National Institute on Drug Abuse

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# Acute Cocaine Intoxication: Current Methods of Treatment

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# Acute Cocaine Intoxication: Current Methods of Treatment

**Editor:**

**Heinz Sorer, Ph.D.**

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# Contents

# The Medications Development Program: A New Initiative of the National Institute on Drug Abuse

*Heinz Sorer*

## INTRODUCTION

The National Institute on Drug Abuse (NIDA) plays a leading role in the Federal research effort to increase knowledge about the causes and treatment of drug abuse and addiction and to identify means of preventing and controlling drug abuse and ultimately to eliminate the demand for illicit drugs in this country.

Congress passed the Anti-Drug Abuse Act of 1988 as a legislative response to the drug abuse epidemic. Cocaine and crack use were important considerations in the development and passage of this legislation, which authorized up to $2.7 billion for all Federal activities in the War on Drugs. NIDA received almost $300 million for use in data collection, treatment evaluation, demonstration projects, and for the first time, the development of new and improved medications to fight drug abuse. Of this $2.7 billion, $10 million was allocated for medications development. In subsequent years, the budget for medications development has increased as programs were initiated and studies funded.

The 1988 act also entailed the setting up of a new division within NIDA, the Medications Development Division (MDD), which was outlined in 1989 although it did not become official until 1990. Its goals include:

- Conducting necessary studies to identify, develop, and obtain Food and Drug Administration (FDA) marketing approval for new medications for the treatment of drug addiction and other brain and behavioral disorders

- Developing and administering a national program of basic and clinical pharmaceutical research designed to develop innovative biological and pharmacological treatment approaches for addictive disorders

- Establishing a close working relationship with pharmaceutical and chemical companies in the United States and abroad and with medications development programs in other agencies in the United States and abroad

Figure 1 shows the current organization of NIDA. MDD is one of six research divisions within the Institute.

Figure 2 shows the organization of MDD. Its setup is much like that of a minipharmaceutical company, with the same branches or departments that are found at a large pharmaceutical manufacturer. The Division consists of the following branches: Chemistry/Pharmaceutics, Pharmacology/Toxicology, Clinical Trials, Regulatory Affairs, and Biometrics. Since 1989 MDD has grown to 33 employees and a budget of $30 million. The Division is expected to reach its projected size of 35 to 40 staff members within one year, with a growing budget to meet its expanding needs and capabilities.

By hiring staff and contracting for scientific services, NIDA has the capacity to develop medications from the point of discovery to preclinical studies to clinical testing. By means of the Government contracting process, MDD is developing the intrinsic capacity to perform all necessary chemistry, pharmacokinetic, pharmacology, and toxicology studies necessary to support clinical trials to treat substance abuse.

The Division has established a close working relationship with FDA and the Pharmaceutical Manufacturers Association.

When used appropriately, medications work in the treatment of addiction. There is a need to increase treatment capacity and effectiveness, and medications are tools in this effort. NIDA is providing leadership by committing itself on a long-term financial, programmatic, and scientific basis to the development of such medications.

These medications will not be magic bullets; rather, they will be part of a comprehensive treatment program addressing the psychological, social, and behavioral aspects of addiction. It is hoped that the medications will be able to normalize an individual whose brain has been biochemically deranged by drugs. The aim is to bring as many patients as possible to a drug-free state; the pharmacologic agents will act as bridges to such a state.

MDD is not focused solely on drug abuse treatment. It also coordinates medications development with NIDA's sister research institutes, the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Mental Health. In this case, MDD will assist in developing studies of medications to

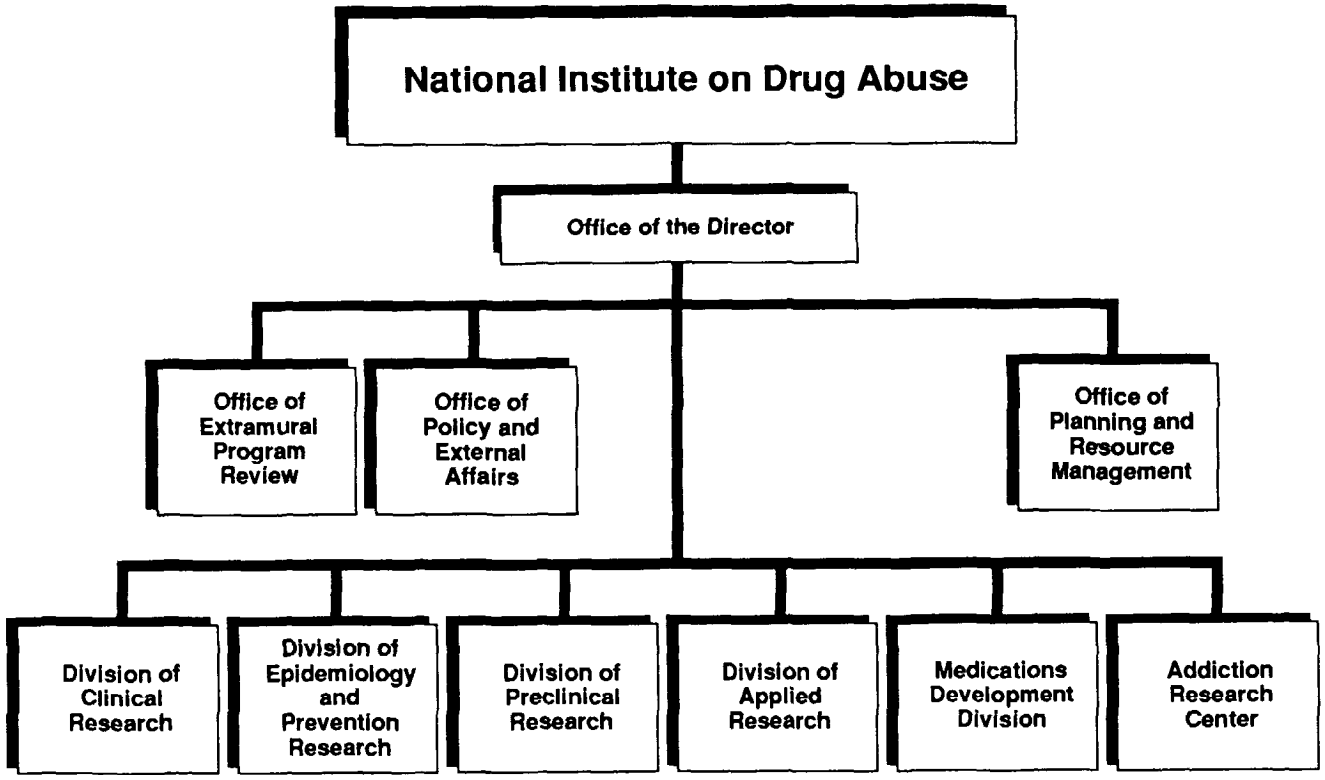


**FIGURE 1.** *Current organization of NIDA*

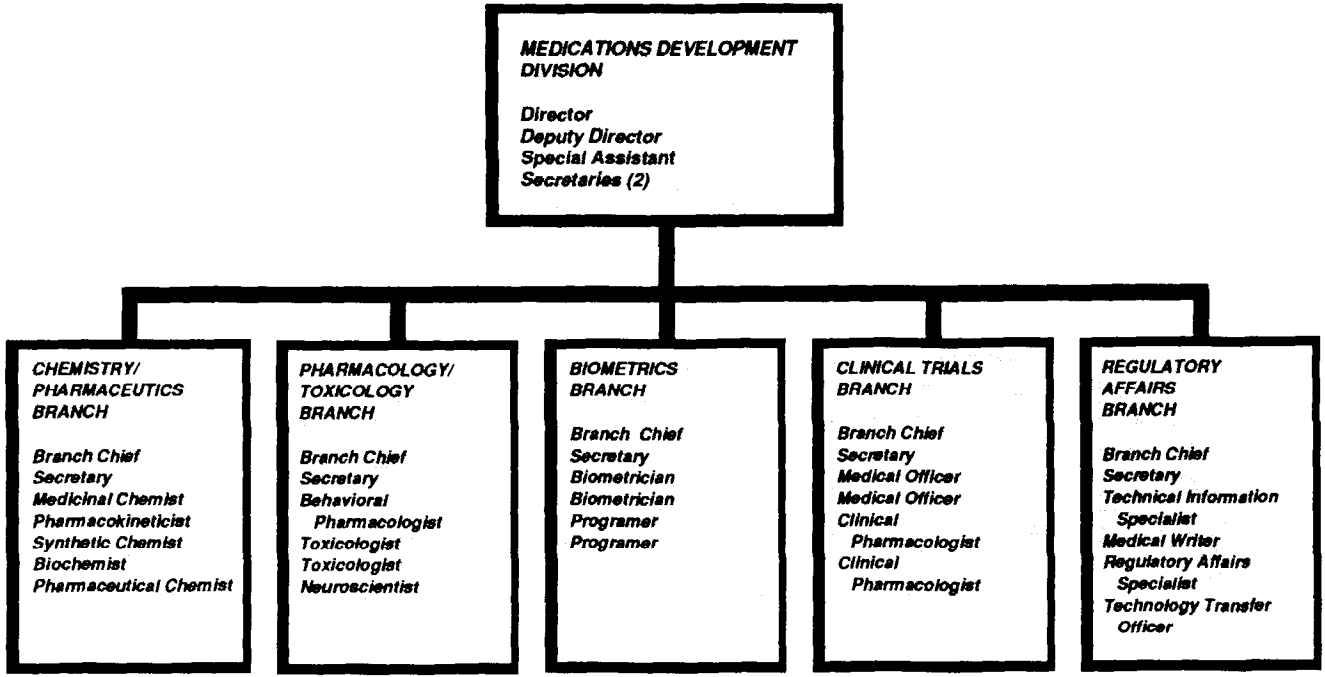


**FIGURE 2.** *Current organization of MDD*

treat alcoholism and less studied forms of mental illness, such as refractory depression, a form of depression unresponsive to any marketed medications.

In fiscal year (FY) 1991, the budget for the Medications Development Program was about $40 million, or about 9.5 percent of NIDA's budget.

MDD has been using a multipronged approach to medications development to help speed up the process. By hiring staff and contracting for scientific services, NIDA has the capacity to develop medications from the point of preclinical studies to clinical testing. By means of the Government contracting process, MDD has developed the intrinsic chemistry, pharmacokinetic, pharmacology, and toxicology studies necessary to support clinical trials for medications to treat substance abuse.

The Division has brought together the Federal Government, pharmaceutical companies, and academia in new and innovative cooperative ventures. Specifically, the Division has expanded NIDA's pharmacologic research capabilities, forged drug development agreements with pharmaceutical firms, and established a network of clinical research sites at universities and Department of Veterans Affairs (DVA) medical centers nationwide.

The following are brief descriptions of some of the ongoing MDD programs. This survey provides an overview and is not all inclusive.

## COCAINE TREATMENT DISCOVERY PROGRAM

The goal of the program is to identify new pharmacologic entities that may be of use in the treatment of cocaine abuse, which has proven to be refractory to most standard methods of treatment.

Critical reviews of the current scientific literature are being carried out to identify potential treatment medications. Efforts also are being directed toward understanding the types of physiological mechanisms that mediate the effects of cocaine to identify additional drug classes that might serve as useful medications. These functions are being accomplished through the efforts of a compound identification team, which draws on the expertise of individuals with chemistry and pharmacology backgrounds.

Once specific compounds have been targeted, a compound acquisition team contacts the appropriate commercial or academic concerns to secure the compound for testing. Agreements are also established with industry to provide incentives for the development of compounds identified as potential treatments of cocaine abuse. These incentives are in place primarily to ensure

that proprietary rights to the compound are retained by the pharmaceutical company and that the rights to the development and marketing of promising compounds will rest with the company. Another significant incentive is that preclinical testing (and, potentially, clinical testing) is carried out with minimal expense to the company.

A decision tree has been established to determine the sequence of preclinical tests to be conducted. This testing scheme has been designed to distinguish those compounds that show promise as potential therapeutic agents from those that do not. Two types of therapeutic approaches have been identified according to how they decrease the effects of cocaine, and the decision tree has been organized to identify compounds that possess the pharmacological profile necessary for either treatment strategy. In one approach, medications that antagonize the effects of cocaine are identified. In the other, compounds are identified for their ability to substitute for cocaine, in much the same manner as methadone is used to substitute for heroin. Pharmacokinetic characteristics of the medications are of critical importance for the success of either type of treatment program. For example, the duration of action of the medication must be of sufficient length to make the treatment practical. Substitution medications have some unique pharmacokinetic requirements. Such a medication should have a slow onset of action so that it does not produce a rapid “high” associated with its administration. A rapid onset may confer abuse liability to the medication itself. An additional feature of a substitution medication is that it should have less activity than cocaine, to further limit its abuse liability.

Testing is conducted at several different facilities, including universities under contractual arrangements and Government laboratories under interagency agreements. These sites test compounds by means of several testing procedures using protocols outlined by the Cocaine Treatment Discovery Program. The sequence for conducting the various tests is determined by the decision tree. The initial testing, which involves in vitro receptor binding assays as well as associated functional assays, is conducted as a means of pharmacologically profiling new compounds. Since specific neurochemical mechanisms of action have been targeted as potential leads for medication development, the results obtained from these in vitro assays are used to prioritize compounds for subsequent in vivo behavioral testing.

Three primary behavioral tests have been shown to be reliable in measuring cocaine effects and are thought to be valid measures of the abuse potential of cocaine. The initial assay is *stimulation of locomotor activity.* Those compounds that stimulate activity in a manner similar to cocaine are not subjected to further testing. Compounds that do *not* stimulate behavior,

or show weak stimulant effects, are examined further. Subsequent testing is directed toward assessing whether these potential medications are effective in blocking or attenuating the effects of cocaine, including the ability of the compounds to attenuate cocaine-induced stimulation of locomotor compounds. Other assays involve more complex behavioral effects of cocaine. Another test, cocaine discrimination, examines interoceptive cues, which are thought to be analogous to the use of cocaine in humans, and determines whether medications alter or attenuate those effects. *Cocaine self-administration* examines the rewarding effects of cocaine and determines how frequently subjects take cocaine when being treated with the medication. Although most of these experiments are conducted in rodents, additional cocaine discrimination and self-administration studies will be conducted in primates to provide information for investigational new drug application (IND) submissions.

Once a compound has been examined in all tests as determined by the decision tree, the results are evaluated and recommendations are made regarding its status as a clinical trials candidate. In addition, both positive and negative results are further considered by the Cocaine Treatment Discovery Program. The information is of considerable use in providing insights into new directions and approaches as well as in determining which directions are not likely to be profitable.

At present, attention is directed toward examining compounds with particular mechanisms of action that have been identified by examining the scientific literature. According to this literature, there are three basic physiological systems on which drugs might act to attenuate the effects of cocaine: the neurotransmitters dopamine and serotonin as well as receptors for $\sigma$-ligands. The Cocaine Treatment Discovery Program has prioritized drugs that act according to these mechanisms for immediate and close examination. There are also indications, based on more preliminary data, that compounds acting via different mechanisms may be of some consequence in modifying the effects of cocaine; these compounds also are being tested. Some drugs with mechanisms of action of unknown utility in treating cocaine abuse are also being evaluated, since the results from such tests can be of value in serving as pharmacological standards. In addition, these drugs may have unexpected activity in altering the effects of cocaine.

## DEVELOPMENT OF NEW AND NOVEL DOSAGE FORMS TO IMPROVE COMPLIANCE, MINIMIZE DIVERSION, AND IMPROVE EFFICACY

Recent advances in pharmaceutical technology make it possible to develop controlled-release delivery systems that provide optimum drug effects by

controlling the rate at which a drug enters the body. Of particular interest among the controlled-release systems are the injectable/implantable depot formulations to reduce dosing frequency, thus improving treatment compliance and reducing the necessity for frequent clinic visits. In addition, the diversion problems associated with take-home doses are eliminated.

NIDA has supported research in this area by means of grants and contracts. An injectable naltrexone depot preparation has been developed and will soon be tested in humans for safety and efficacy. In addition, efforts on the development of 1 -week sustained-release dosage forms for narcotic agonists (methadone) and l-month systems for antagonists (naltrexone and nalmefene) and a mixed agonist/antagonist (buprenorphine) are ongoing and currently funded.

## PRECLINICAL TOXICOLOGY PROGRAM

Inherent in the development of any new medication is a series of studies designed to determine medication safety for ethical reasons. These studies must be conducted in animals before the medication is given to humans. Generally, toxicity studies are tests that directly identify and quantify the adverse effects, at high doses, that a drug is capable of producing. The results of these studies in animals are of great assistance to the clinician in monitoring the subjects for potential adverse effects of the drug in clinical trials. The studies are classified by the number of doses administered to the animal: For example, acute is a single dose, subchronic (also called subacute) is usually 2 to 14 weeks of continuous dosing, and chronic studies are usually for 1 year. In addition, evaluation of the carcinogenic potential, conducted in rodents, requires 18 to 24 months of dosing. The cost and amount of time to conduct these studies are directly proportional to the duration of dosing and the number of animals required. An acute study can be conducted for $20,000, whereas a carcinogenicity study in a rodent costs more than $2 million.

To ensure that resources are used wisely and that the toxicology studies are conducted well in advance of the clinical investigations, MDD has established a formal peer review committee that develops a long-range plan for new studies, including the development of interagency agreements and contracts. Furthermore, the peer review committee finalizes all new protocols, assists the project officer in monitoring the studies, and reviews all final reports. The time to conduct a complete series of tests—starting with the acute study and finishing with the carcinogenicity evaluation—typically covers at least 5 years. The studies are conducted to set meaningful dose levels for longer term studies.

To ensure the safety of the drugs to women of childbearing potential, reproductive and teratology testing in rats and rabbits must be conducted to assess any adverse effects.

Although the technology of toxicology testing in the development of new medications is not anticipated to change substantially, consideration must be given to the interactions between abused drugs and new medications. This is particularly important in medications to be tested for the treatment of cocaine addiction, since the mechanisms of cocaine's effects on human organs are more complex than the effects of opiates. MDD has developed a paradigm to address the issue of adverse drug interactions. These studies will likely be included in INDs to support safety of medications to treat cocaine addiction. The cost of providing additional toxicology testing services (including interaction studies) must be borne in the development of new medications.

Toxicology studies (in animals) must be conducted prior to conducting clinical trials. The duration and the type of toxicology study are dependent on the type of trial (i.e., number of days dosed).

**PHARMACOKINETICS AND PHARMACODYNAMICS**

Pharmacokinetics is a quantitative description of the processes-absorption, distribution, metabolism, and excretion (ADME)-that a drug undergoes in the body. Pharmacodynamics is a quantitative description of the time course of drug effects. Since the effects of a drug are in general related to the quantity of a drug that reaches the site of action and how long it remains there, the integration of pharmacokinetics and pharmacodynamics is of significant importance in enhancing the understanding of basic mechanisms governing drug action and provides a means to establish the correlation of drug responses with the concentration in biological fluids.

Thus, pharmacokinetic/pharmacodynamic information is essential in every phase of medication development such as the selection of the drug, route and dose of administration for pharmacology/toxicity assessments, design and evaluation of dosage forms, and establishment of dosage regimens for clinical use. In addition, the pharmacokinetic/pharmacodynamic information is required by FDA for the approval of INDs and new drug applications (NDAs).

NIDA has supported pharmacokinetic/pharmacodynamic studies in both animals and humans for potential treatment drugs through contracts and interagency agreements with DVA. The pharmacokinetic/pharmacodynamic information covering the dose range proposed for pharmacological/toxicological and clinical studies is generated for candidate treatment drugs following single

and multiple doses. When appropriate, interaction studies of the drugs with alcohol, cocaine, and other drugs will be conducted to determine if there is any pharmacokinetic or pharmacodynamic interaction. The work involved in these studies includes the development of analytical methods; identification of metabolites; quantification of drugs/metabolites in biological samples; determination of pharmacokinetic parameters such as bioavailability, volume of distribution, protein binding, clearance, and half-life monitoring pharmacological responses; and establishment of correlation of pharmacological responses with drug plasma level/pharmacokinetic parameters. Pharmacokinetic/ pharmacodynamic studies are in progress for *l*-alpha-acetyl methadol (LAAM), naloxone, and buprenorphine. Studies with ibogaine are planned.

The utility of pharmacodynamic/pharmacokinetic studies in relation to clinical studies is illustrated by the following examples.

The results of a study on buprenorphine indicate that it is quickly absorbed following the sublingual route of administration. These data provide the basis for the establishment of a sound clinical protocol regarding the time required for holding buprenorphine under the tongue for a pivotal clinical trial (N. Chiang, personal communication, February 1992).

Pharmacokinetic and pharmacodynamic data indicate that buprenorphine (a mixed opioid agonist) is much more bioavailable than naloxone (an opioid antagonist) following the sublingual route of administration (N. Chiang, personal communication, February 1992). One can take advantage of this differential in bioavailability between buprenorphine and naloxone in such a manner that buprenorphine effects are predominant (only slightly attenuated by naloxone) following the prescribed sublingual route of administration, whereas naloxone effects are predominant following the illicit parenteral route of administration. Consequently, when given by the prescribed route, buprenorphine will be effective for addiction treatment, whereas taken by the illicit intravenous route, it may be ineffective or may precipitate withdrawal in opiate-dependent patients. Therefore, this product will have very low abuse potential and can be dispensed as a “take-home” drug. Clinical pharmacokinetic and pharmacodynamic studies are in progress to determine the optimal doses of buprenorphine and naloxone for the development of such a combination sublingual product.

## REGULATORY AFFAIRS

A major role in the development of new medications has been assumed by FDA since the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act were passed by Congress in 1962. All sponsors are required to submit an IND before embarking on research in humans with a nonmarketed drug or a

marketed drug for a new indication or a new medication; throughout the entire development of a new medication, numerous INDs and eventually an NDA will be filed. The sponsor and FDA interact frequently (e.g., in the pre-IND and pre-NDA meetings) to ensure a thorough mutual understanding and productive collaboration.

The MDD Regulatory Affairs Branch prepares and files INDs involving chemistry, formulation, pharmacology, toxicology, and clinical data and serves as liaison with the relevant FDA reviewing division, including arranging all necessary pre-IND and end of Phase I and II trial meetings for non-Government sponsors working with NIDA in obtaining approval for an indication of drug abuse or addiction. The Branch also performs liaison with other essential U.S. Public Health Service agencies to secure the regulatory approvals necessary to undertake Government-sponsored or cosponsored trials.

The Regulatory Affairs Branch is responsible for implementating the Federal Technology Transfer Act for NIDA. In this role, the Branch examines invention reports submitted by intramural scientists and makes recommendations regarding domestic and foreign patent filings, material transfer agreements, and licensing provisions to the National Institutes of Health Office of Technology Transfer. The Branch also provides technical assistance and primary review of intramural Cooperative Research and Development Agreements (CRADAs) and is the progenitor of extramural CRADAs involving attempts to commercialize new medications and dosage form technologies.

In line with its responsibilities involving technology transfer, interagency liaison, and regulatory filings, the Branch serves as the contact point for all entities (governmental and nongovernmental) that wish to explore the possibility of pursuing development of medications to treat addiction. The Branch not only provides guidance in the area of interacting with MDD on projects of mutual interest but also serves as a broker in suggesting alternative resources that may be available to meet the needs of investigators and sponsors when MDD cannot provide these services or cannot provide them in a timely manner. MDD considers these activities, which may potentially expedite development of new addiction treatment medications, to be worthwhile regardless of the level of MDD involvement.

**BIOMETRICS BRANCH**

The Biometrics Branch is engaged in the design and formulation of research protocols and the collection, computer entry, management, and analysis of data of preclinical and clinical studies. The objectives of these studies include

the identification of potential medications and, by means of appropriate clinical trails, the preclinical and clinical development of new medications useful in the treatment of drug dependency and addiction.

## CLINICAL TRIAL PROGRAM

The purpose of the clinical trial is to determine—by means of the collection of clear and well-documented evidence—whether the investigational medication is effective and safe when used according to the manner intended. Clinical evaluation of a compound is initiated when there are adequate, sufficient, and appropriate preclinical data to support the investigation in humans. An IND must be filed with FDA prior to initiation of the trials. Conventionally, clinical trials are conducted according to the following approach:

Phase I trials establish the human dose range and the ADME profile as well as any adverse reaction to the new medication in normal, healthy volunteers. Such studies are open (i.e., not blinded) and are often carried out in clinical research centers by a clinical pharmacologist.

Phase II trials test the medication in a small population of patients with the target disease to determine efficacy and to develop additional safety data. Studies are carried out under controlled double-blind conditions.

In Phase III trials the medication is evaluated in a wider range of patients to substantiate further the efficacy of the medication. These trials are usually conducted in clinical settings similar to those anticipated for the ultimate use of the medication. The investigators are usually specialists in the treatment of the targeted disease.

The implementation of clinical trials for the development of drug abuse treatment medications is a highly complex task. It requires an integrated effort of multidisciplinary expertise with resources. These activities may be described as the development of (1) sensitive clinical efficacy trial methodology, (2) clinical trial infrastructure and resources, and (3) clinical data management.

Clinical trials for the development of new medications are highly focused activities with safety and efficacy as the common primary outcomes. The design of the trial is of great importance in achieving these goals. By optimizing the sensitivity of the trial, highly predictive clinical efficacy data will be generated.

Currently, the treatment of cocaine abuse and dependence is an area of controversy. Basically, there is a lack of consensus in the field about (1) the

perception of the biological nature of the disorder as well as a treatment rationale, (2) a well-accepted and widely utilized effective treatment paradigm, and (3) possible useful medications as adjunctive therapy.

MDD is seeking medications that will treat overdose, reduce use, initiate abstinence, and/or prolong abstinence or prevent relapse of cocaine abuse. In recent years, a variety of pharmacological approaches have been introduced to reduce cocaine craving and use. Most of these have been tested in open-label, noncontrolled trials with little value for assessing the aforementioned efficacy outcome of the medications. Several clinical pharmacology trial paradigms have been used by researchers to explore a medication's effect on human drug discrimination, drug self-administration, or drug-seeking behavior. However, the clinical implications of such study results in predicting the aforementioned efficacy outcome of the investigational medications are not clear.

MDD has created a diverse portfolio of clinical capabilities. NIDA's Addiction Research Center (ARC) in Baltimore, MD, maintains a 24-bed inpatient unit and an outpatient clinic. This facility has pioneered the testing of medications for the treatment of narcotic and stimulant abuse. Medication development studies have included opiate agonists and antagonists, antidepressants, dopaminergic agents, calcium channel blockers, and antiepileptic medications. ARC has the capacity to conduct Phase I and early Phase II trials with new medications selected by MDD for possible development. A Phase I pilot study of depot naltrexone is being conducted at ARC for MDD.

By means of grants, MDD and the Division of Clinical Research support several well-recognized Treatment Research Units (TRUs) around the United States, which are well respected in the field of pharmacotherapy of substance abuse disorders. Several marketed compounds with central nervous system activity were studied for efficacy of cocaine abuse treatment in various TRUs in 1991.

Under an interagency agreement between NIDA and the Washington, DC, DVA Medical Center, the Institute supports a 24-bed inpatient/outpatient facility for the conduct of clinical trials of medications to treat substance abuse disorders. Operated by the Psychiatry Service, the unit became operational in April 1991. Both Phase I and early Phase II trials may be performed at this facility. Interagency agreements between NIDA and two other DVA medical centers have also been developed with the goal of developing the capacity for multicenter trials. Existing agreements involve the DVA medical centers in Philadelphia and West Los Angeles.

In addition to developing these DVA sites, MDD also developed an interagency agreement with the DVA's Cooperative Studies Program (CSP) to conduct clinical trials. Under this agreement, CSP will select participating DVA medical centers to provide inpatient and outpatient facilities and services necessary for the implementation of clinical trials. Currently, MDD has two multicenter clinical trials planned on buprenorphine, as well as a multicenter study on LAAM. Both projects will utilize a combination of the DVA, the DVA CSP, and some of the TRU sites.

**Clinical Data Management**

Clinical trials are focused, organized research studies conducted in humans to determine the risk or benefit ratio of a new therapeutic agent. These studies must be conducted under FDA regulations. The end products of clinical trials are data and observations, which are analyzed according to preselected statistical tests. To ensure the integrity of the study database and the consistency between and among different study sites, the need for proper and effective *study monitoring* and *data management* cannot be overemphasized.

The scope of clinical data management activities includes:

- Carefully designed clinical protocol and case report forms
- Efficient management of clinical data
- Quality assurance of the consistency and documentation of all modification and transformation of data

The objectives of clinical data management are to maximize the accuracy, speed, and cost-effectiveness of data transfer from the case report forms to the study master file that is appropriate for the statistical analysis that will be used to support the efficacy of the drug under study. During the process, the data must be verified by quality control audit prior to the submission of each report. For various management and analytical purposes, the study master file and its subsets must be organized in a manner readily available to retrieval and manipulation for an extended period.

To ensure smooth clinical data flow and accurate recordkeeping, clinical data management involves not just statistical design and analysis of the clinical trial but also development of software for data collection, storage and retrieval, encoding, and entry; database validation; and generation of listings, reports, and summaries. This activity usually involves such personnel as physicians, clinical data processors, computer specialists, and statisticians.

At the present time, MDD is utilizing the Perry Point, MD, Data Coordinating Center, DVA, via the DVA CSP agreement, to manage the buprenorphine and LAAM multicenter trials.

### Clinical Study Monitoring

The function of clinical study monitoring is to ensure smooth and productive interactions among the study sponsor, MDD, study investigators (e.g., ARC, TRUs, DVA, medical centers, or other sites), and the regulatory body (FDA). Each party has a scientific as well as a societal role in the process of medications development and use. Since each tends to see its roles differently, conflicting views are inevitable. Therefore, the clinical monitors must ensure that the study is conducted according to the protocol in compliance with Good Clinical Practices and FDA regulations and that each clinical study conforms to accepted medical standards for the protection of subjects. The investigators and their associates must be thoroughly instructed in their responsibilities, including reporting procedures and study drug accountability. All relevant data must be accurately recorded when the study has been completed. Any side effects are promptly evaluated and communicated as appropriate to other investigators and regulatory agencies. Thus, clinical study monitoring is an important, continual effort during the life of a clinical trial. The effort is much more extensive if the trial is a large multicenter trial.

## COMPOUNDS CURRENTLY IN CLINICAL DEVELOPMENT

### Opiate Treatment Compounds

**LAAM.** Although methadone maintenance had been shown repeatedly to be the most effective treatment of opiate addiction in the late 1960s, several investigators realized that significant problems existed with regard to the pharmacology of methadone. At the doses used, methadone did not suppress the narcotic craving for a full 24 hours in many addicts. Very large doses of methadone were necessary to provide sustained relief of abstinence symptoms for sedation, which caused the patient to “nod” for the first several hours after consumption.

Furthermore, the patient was required to attend a methadone dispensing clinic daily to consume his or her medication under staff supervision. This inconvenient and burdensome time and travel demand was often draining physically and emotionally. When the patient was assuming responsibility and trying to engage in work, this requirement was considered by some to be antitherapeutic. A compromise solution was reached. After demonstrating satisfactory adherence to the program regulations for at least 3 months and

showing substantial progress in rehabilitation by participating in educational, vocational, and homemaking activities, those patients whose employment, education, or homemaking responsibilities would be hindered by daily attendance may be permitted to reduce to three times weekly the times when they must ingest the drug under observation (Federal Register 1972). Take-home doses could be dispensed for the other 4 days after this regulation was implemented.

The practice of permitting take-home supplies of methadone for unsupervised self-administration contributed to new problems. Accidental ingestion of methadone by nontolerant persons, especially children, led to an alarming increase in toxic reactions and overdose fatalities. Also, a market developed for the illicit sale and redistribution of methadone to heroin addict peers suffering from withdrawal or to nonaddict drug users seeking a new euphoriant. The treatment agent was becoming a new source of addiction. Finally, the patient might skip or delay a dose of methadone to "shoot up" with heroin after the blockade had diminished. Thus, the take-home privileges inadvertently negated much of the usefulness of random urine monitoring for illicit heroin use. Furthermore, an adversary system or "game" was created in which the patient might attempt to deceive the treatment staff to gain or retain take-home privileges. These issues demonstrated the need for opioid maintenance pharmacotherapy.

In 1969, LAAM was tested in a clinical narcotic treatment program. LAAM was selected because of its long duration of action. It also offered the patient a smoother, sustained effect, appeared to have fewer sedative properties, and produced a lower degree of euphoria. Patients could be maintained on a three-times-weekly dosage schedule that eliminated the daily necessity of engaging in drug-seeking and drug-taking behavior. This approach represents an important therapeutic advance because the destructive, habitual pattern of behavior associated with the heroin addict lifestyle is broken. The patient is less psychologically and physically dependent when not involved with daily drug taking; this can strengthen the addicts identification with the drug-free population and break association with the drug culture.

LAAM offers a practical answer to the problems related to take-home methadone. Illicit redistribution can be reduced because three-times-weekly LAAM reduces the amount of take-home medication a clinic must provide patients for out-of-clinic administration. If necessary, a no-take-home policy can be established by a clinic or program where redistribution and accidental overdose is especially prevalent.

Furthermore, several pharmacological properties make LAAM less prone to abuse than methadone. LAAM is one-tenth as active as its metabolites. Because metabolism requires time, several hours pass between taking LAAM and the onset of psychoactivity. Therefore, LAAM is less likely to be a reinforcer of drug-taking behavior because substances with a rapid, immediate onset of euphoric effects are much more desired by drug users. LAAM has another unique characteristic that makes it less desired: Its onset of action is more rapid when administered orally than intravenously, the preferred route of heroin addicts, which makes it different from opiates abused by the intravenous route, namely, heroin.

LAAM may offer treatment programs advantages over methadone by improving the logistics of drug distribution. A three-times-weekly dosage allows for more controlled drug delivery to increasingly large numbers of patients. By reducing the required number of clinical visits, efficiency of treatment may be increased because fewer staff members are needed to dispense drugs and provide pharmacy services. Thus, conversion either reduces the cost of treatment or increases the number of available treatment slots.

MDD has reviewed preclinical and clinical data generated in the 1970s and early 1980s and is working with a contractor to bring them into a suitable format for assessment of an NDA. An observational labeling assessment study with LAAM is planned in 15 to 30 methadone treatment clinics. Preclinical toxicity studies are being reviewed to determine what deficiencies, if any, still exist, and steps are being taken to address these. Current plans focus on a December 1992 “NDA Day for LAAM” with FDA.

**Buprenorphine.** Buprenorphine is a member of a relatively new class of chemical compounds, a so-called partial p-agonist. It combines some of the best attributes of medications such as methadone and naltrexone in a single compound. The Medications Development Program is examining buprenorphine as a maintenance and detoxification agent for opiate dependence, and initial findings appear promising. Results of a study performed at ARC show that an 8-mg dose of buprenorphine was as effective as 60 mg (recommended therapeutic dose) of methadone in retaining clients in treatment and in preventing illicit opiate use. On standard addiction rating tests, the patients on buprenorphine scored as having less need for, less liking of, and were less “hooked” on buprenorphine than patients on methadone. Other trials are being initiated by MDD at NIDA-funded TRUs and at DVA medical centers. MDD has prepared a comprehensive development plan for additional clinical trials and related research necessary to obtain FDA approval of buprenorphine for treatment of heroin addiction. Buprenorphine should be superior to methadone in other ways. It produces significantly less physical dependence;

it is much easier to withdraw someone from the medication; and it should have less abuse liability and overdose potential. NIDA has begun a 12-site, 500- to 700-subject clinical trial of buprenorphine in FY 1992. If this trial produces confirmatory results, NIDA will also pursue the development of buprenorphine combined with a suitable antagonist. Such a combination product would precipitate withdrawal in addicts who have not been carefully acclimated to buprenorphine, thus greatly reducing its desirability for diversion for illicit use and potentially making this form of treatment available through a wider range of providers than is possible under the current law regarding treatment with narcotic agonist medications such as methadone. If a full development program with an antagonist combination were to be pursued, it would require 2 to 3 years of intensive effort and a commitment of several million dollars. As mentioned previously, the buprenorphine/naloxone combination would be targeted for take-home use.

**Depot Naltrexone.** Naltrexone is an opiate antagonist currently marketed in an oral dosage form that blocks the effects of opiates such as heroin. However, patient compliance is low. Therefore, NIDA has developed a preliminary version of a time-release depot dosage form to increase patient compliance. A single injection of naltrexone utilizing this dosage form has blocked the effects of opiate challenges for up to 7 weeks in rhesus monkeys. It is hoped that this formulation may provide opiate blockade for periods of at least 30 days in humans. NIDA has recently initiated a Phase I clinical trial in normal volunteers at ARC to determine tolerance levels to various amounts of this new dosage form. Additional funding will be needed to bring this dosage form to the stage necessary to attract a commercial sponsor.

**Ibogaine.** NIDA has received information from individuals and groups of former addicts concerning ibogaine. These individuals and groups have presented anecdotal evidence of successful treatment of addiction to opiates and other drugs in Europe using ibogaine, although these trials have not been run in accordance with standards recognized by FDA or MDD. MDD has met with these individuals and groups to discuss the types and quality of data that must be generated to substantiate any of the claims made for this compound. NIDA has agreed to pursue research on the pharmacology and toxicology of this compound. The results of these studies will indicate whether clinical trials with ibogaine are warranted.

## SUMMARY

The NIDA Medications Development Program involves the discovery and development of pharmacotherapies for drug dependence. The program is proceeding along two fronts: development of pharmacotherapies for

(1) cocaine abuse and (2) opiate abuse. Discovery and development of pharmacotherapies for cocaine abuse is a relatively new initiative being vigorously and systematically pursued. Discovery and development of pharmacotherapies for opiate abuse has been ongoing for more than 40 years; knowledge in this area is greater than that for cocaine abuse. Nevertheless, this effort will continue as the demand for new and nonaddicting analgesic agents and pharmacotherapies for opiate abuse continues. It is expected that MDD will grow as efforts to reduce cocaine and opiate continue.

## REFERENCE

*Federal Register.* 37(242):26790, December 15, 1972.

## AUTHOR

Heinz Sorer, Ph.D.
Pharmacologist
Medications Development Division
National Institute on Drug Abuse
Parklawn Building, Room 11A-55
5600 Fishers Lane
Rockville, MD 20857

# Cocaine-Related Medical Crises: Evidence From the Drug Abuse Warning Network

*James D. Colliver, Andrea N. Kopstein, and Arthur L. Hughes*

## INTRODUCTION

This chapter presents information on cocaine-related emergency room (ER) episodes that occurred in the United States during 1989 and 1990. It is based on data from the Drug Abuse Warning Network (DAWN) sponsored by the National Institute on Drug Abuse (NIDA). Supplementary data on cocaine-related deaths seen by medical examiners (MEs) participating in DAWN also are discussed. The rather restricted period of the trend analysis is necessary because the ER data presented are weighted estimates from the new DAWN sample of hospitals; comparable estimates for years prior to 1989 are not available.

Trends in cocaine-related ER episodes in DAWN over longer periods have been studied using raw data from hospitals that reported consistently (figure 1). In the decade from 1976 through 1985, cocaine-related ER episodes increased more than ninefold (National Institute on Drug Abuse 1987). From 1985 to 1988, these episodes underwent a further increase of more than fourfold (Adams et al. 1990). In the second half of 1986, cocaine overtook both heroin/morphine and alcohol-in-combination to become the most frequently reported drug in the DAWN ER data (National Institute on Drug Abuse 1989). More recently, unpublished trend analyses—based first on raw data from consistently reporting hospitals and later on weighted estimates from the new statistical sample—showed that cocaine mentions in ER episodes leveled off from the second quarter to the third quarter of 1989 and then dropped 25 percent in the fourth quarter of that year. Subsequent data through the end of 1990 show additional, less dramatic decreases in cocaine mentions in ER drug abuse episodes.

The first objective of this chapter is to examine this decrease in cocaine mentions in the DAWN ER data to ascertain whether it can be credibly

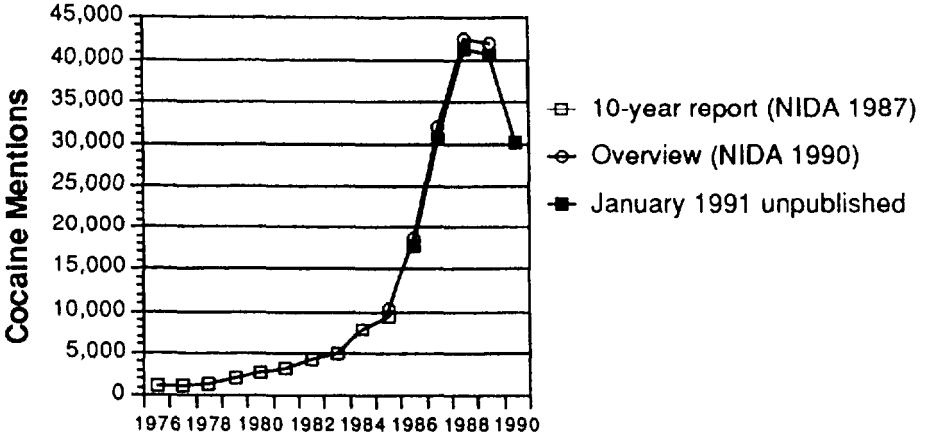


**FIGURE 1.** *Annual ER mentions of* cocaine *based on raw data from different consistent panels, DAWN, 1976-90*

interpreted as an actual decline in acute morbidity associated with cocaine use or whether some other explanation would be consistent with the facts.

A second objective of the chapter is to examine cocaine-related episodes that are reported as overdoses and compare these cases with other episodes in which cocaine is mentioned. Overdose episodes-particularly those in which cocaine is the only drug reported-would appear to most closely approximate cases of acute cocaine intoxication, which is the topic of this monograph. In addition to overdoses, DAWN collects data on drug-related episodes where the reason for the ER visit is an unexpected reaction to the drug, chronic effects of use, withdrawal, an accident or injury related to drug use, or to obtain medical clearance or prior treatment in preparation for entry into a drug detoxification program. However, DAWN data are collected through a record review system, and information on factors such as the reason for the ER visit is frequently unavailable or inconclusive. Therefore, it is important to look at both the overall data on cocaine-related episodes and those episodes that involve an overdose.

In addition to ER data, this chapter provides information on cocaine-related deaths reported by MEs affiliated with DAWN. Excluding data from the New York and Newark metropolitan areas, which were incomplete, DAWN ME cases involving cocaine increased from 53 in 1975 to 2,332 in 1989, a 44-fold increase (National Institute on Drug Abuse 1987, 1990).

## BACKGROUND AND METHOD

### General Information on DAWN

DAWN is a large, ongoing data collection system designed to identify emerging drug problems, monitor drug abuse patterns and trends, and identify substances associated with acute morbidity and mortality. Morbidity data are obtained from hospital ERs, and mortality data are collected from MEs' offices. Hospitals in 21 large metropolitan areas and a national panel of facilities from outside those areas participate in DAWN on a voluntary basis. ME facilities affiliated with DAWN are located in 27 metropolitan areas. The data are collected by a reporter, generally a member of the facility staff, using a record review procedure. Reportable cases are defined as those in which a substance is used nonmedically to achieve psychic effects, because of dependence, or in a suicide attempt or gesture. Nonmedical use includes (1) use of a prescription drug in a manner inconsistent with accepted medical practice, (2) use of an over-the-counter (OTC) drug contrary to approved labeling, or (3) any use of another substance (such as an illicit drug) for psychic effect, dependence, or suicide. As the DAWN data reflect only those instances of drug abuse that have resulted in a medical emergency or death, patterns in the DAWN data do not necessarily reflect profiles in the prevalence of drug use in the general population. However, they are regarded as valid indicators of acute health consequences of drug use.

### New DAWN Statistical Sample and Estimates

DAWN was begun in 1972 by the Drug Enforcement Administration. A representative statistical sample of hospitals was selected at the outset, but over the ensuing years, attrition and recruitment of additional sample units that had not been selected randomly caused the DAWN ER reporting base to become nonrepresentative. During those years, data from DAWN did not reflect total drug abuse ER episodes in the Nation or the respective DAWN metropolitan areas. The trends and profiles of drug abuse cases were not necessarily representative of such cases occurring at hospitals that did not report to DAWN.

NIDA assumed responsibility for DAWN in 1980. One of its objectives was to implement a new sample that could be used to produce representative estimates for the Nation as a whole and for the separate DAWN metropolitan areas. The project started in 1982 with the development of a sampling plan. This plan required the recruitment of 300 new hospitals but was delayed until 1985 because of budgetary constraints. Recruitment of new sample hospitals is now complete enough for the data to be used, and the weighting and

estimation procedures have been developed and refined. The annual ER data report for 1990 (National Institute on Drug Abuse 1991 a) was the first such document to be based on the weighted estimates, which represent NIDA's best estimate of the total number of drug abuse-related ER cases in the coterminous United States (i.e., the 48 contiguous continental States and the District of Columbia) and the 21 oversampled DAWN metropolitan areas.

The new sample provides weighted estimates for ER episodes starting with the first quarter of 1989. Estimates produced for earlier periods are not directly comparable with the weighted estimates because they were not based on a representative sample of hospitals and because they were based on raw, unweighted data. In both the old hospital reporting base and the new sample, there are more facilities from the oversampled DAWN metropolitan areas than from outside those areas (i.e., the national panel). In the new sample, for example, about 18 percent of hospitals are in the national panel. However, the territory covered by the national panel includes about 84 percent of all eligible hospitals in the Nation. Thus, without the weights, the raw data overemphasize cases occurring in the DAWN metropolitan areas. The new estimates are calculated using weights that compensate for the different sampling rates, nonresponse, and other factors. The data released by NIDA in past years do not include these adjustments and also were not based on a representative sample.

Important changes in the profile of DAWN cases occur when the weights are used to create the estimates. In the unweighted data for 1989, for example, cocaine was reported in 40.1 percent of ER episodes (National Institute on Drug Abuse 1990). With the new estimates, the proportion of cocaine-related episodes for 1989 was 25.8 percent based on weighted data from sample hospitals. This change reflects the effects of properly weighting the data from hospitals outside the 21 oversampled metropolitan areas. Transition to the weighted data from the new sample changed the distributions for many variables, including sex, age, race/ethnicity, and motive for drug use.

Although estimation procedures for the new sample have been developed, variance estimation is expensive and somewhat difficult because of the complex nature of the sample and the use of direct variance estimation methods. In the tables in this chapter, estimates with a relative standard error (RSE) of 50 percent or higher are suppressed; refer to the Annual Emergency Room Data 1990 report (National Institute on Drug Abuse 1991a) for further information about RSEs and the implications of the 50-percent criterion. Statistical tests of selected differences have been performed as part of the analysis.

## Method

Information on the general methods used in analyzing DAWN data can be found in the Annual Emergency Room Data 1990 (National Institute on Drug Abuse 1991 a) and Annual Medical Examiner Data 1990 reports (National Institute on Drug Abuse 1991b). For this study, episodes involving cocaine have been extracted from the overall files. Data on mentions of other drugs in combination with cocaine are included in the analysis, and it should be recognized that some of the patterns seen in the data for cocaine may be more related to these other drugs than to cocaine.

A variety of drug coding schemes are used in DAWN, but the data that are published usually show aggregate drug groups and therapeutic classes. The DAWN drug vocabulary contains 46 separate substance, street, or metabolite names for cocaine, but only 15 of these names were reported to DAWN during 1989-90. In 81.4 percent of cocaine-related emergencies, the substance reported was simply cocaine. For the majority of the remaining cases, the street name “crack” was reported to DAWN (18.0 percent). Other street names reported for cocaine-related emergencies included “coke” (0.4 percent) and “rock” cocaine (0.07 percent). Benzoylecgonine, a metabolite of cocaine, was reported in 0.07 percent of cases.

In accordance with the focus on acute cocaine intoxication, special analyses on cases reported as overdoses are included. However, in the numerous episodes in which other drugs are mentioned in combination with cocaine, attribution of causality is uncertain. In analyzing the contribution of cocaine as a causal agent, it would be possible to select overdose cases involving cocaine and no other drug. In 1990, 3,405 weighted cases (4 percent of all cocaine cases) met this criterion. However, this procedure was not followed because reducing the number of cases in this way increases the sampling variability of the estimates to an unacceptably high level.

The ER and ME data presented in this chapter are based on records received by the end of May 1991 and correspond to the data used for the 1990 annual reports (National Institute on Drug Abuse 1991a, 1991b). The ME data exclude cases in which the manner of death was reported as homicide and cases in which acquired immunodeficiency syndrome was noted on the form.

## FINDINGS

### Recent Trends in Cocaine-Related ER Episodes

Figure 2 shows quarterly provisional estimates of cocaine-related ER episodes in the total coterminous United States for 1989 and 1990. These episodes rose

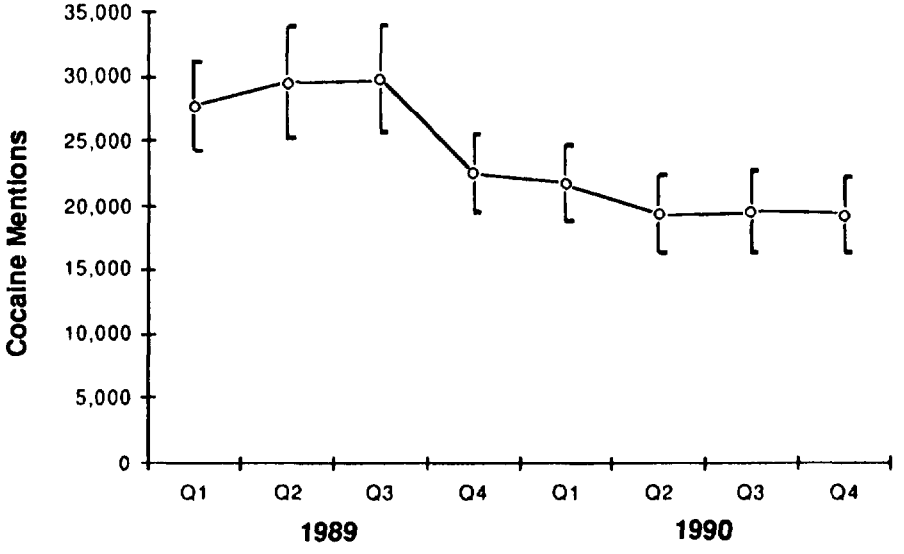


**FIGURE 2.** *Estimates of quarterly ER cocaine mentions (95-percent confidence interval) in total coterminous United States, DAWN, first quarter 1989 through fourth quarter 1990*

from 27,803 in the first quarter of 1989 to 29,939 in the third quarter of that year then dropped sharply to 22,646 in the fourth quarter. This decrease was followed by two additional quarterly declines, and cocaine cases reached a 2-year low of 19,381 in the fourth quarter of 1990.

The sharp decrease from the third to the fourth quarter of 1990 could not be accounted for by data from just a few hospitals because it was widespread across the 21 metropolitan areas. Table 1 examines the estimates for calendar years 1989 and 1990 by metropolitan area and includes a test of the differences between the two years. In 1990 New York led the other metropolitan areas with 12,633 cocaine episodes, followed by Philadelphia with 8,920. Trailing behind were Chicago with 4,904 cocaine-related episodes, Washington, DC, with 4,788, and Los Angeles-Long Beach with 4,129. The largest decreases in cocaine-related cases were in Seattle (down 54 percent) and Minneapolis-St. Paul (down 46 percent). Decreases of 35 percent or more also were observed in the Detroit, Los Angeles-Long Beach, and Washington, DC, areas. In stark contrast to the national trend, cocaine cases in Baltimore increased 64 percent, from 1,839 in 1989 to 3,023 in 1990. Data by quarter (not shown) revealed a steady increase in cocaine cases in Baltimore from the fourth quarter of 1989 through the fourth quarter of 1990.

**TABLE 1.** *Estimate of the number of ER episodes involving cocaine in 1989 and 1990 and percent change from 1989 to 1990, by metropolitan area*

| Metropolitan Area | 1989 | 1990 | Percent Change 1989-90 |
|---|---|---|---|
| Total coterminous U.S. | 110,013 | 80,355*** | -27.0 |
| Atlanta | 3,315 | 2,743*** | -17.3 |
| Baltimore | 1,839 | 3,023*** | 64.4 |
| Boston | 2,550 | 1,961** | -23.1 |
| Buffalo | 297 | 282 | -5.1 |
| Chicago | 6,509 | 4,904*** | -24.7 |
| Dallas | 1,314 | 1,028*** | -21.8 |
| Denver | 870 | 569*** | -34.6 |
| Detroit | 6,324 | 3,888* | -38.5 |
| Los Angeles-Long Beach | 6,999 | 4,129*** | -41.0 |
| Miami-Hialeah | 974 | 748*** | -23.2 |
| Minneapolis-St. Paul | 551 | 299*** | -45.7 |
| New Orleans | 3,608 | 3,397 | -5.8 |
| New York | 14,926 | 12,633 | -15.4 |
| Newark | 4,618 | 3,752* | -15.4 |
| Philadelphia | 12,688 | 8,920* | -29.7 |
| Phoenix | 943 | 614*** | -34.9 |
| St. Louis | 709 | 700 | -1.3 |
| San Diego | 715 | 725 | 1.4 |
| San Francisco | 3,180 | 2,297*** | -27.8 |
| Seattle | 1,680 | 777*** | -53.8 |
| Washington, DC | 7,854 | 4,788* | -39.0 |
| National panel | 27,548 | 18,177*** | -34.0 |

NOTE: These estimates are based on a representative sample of non-Federal short-stay hospitals with 24-hour ERs.

Significance level of difference from 1989 to 1990: *p<.05; **p<.01; ***p<.001.

SOURCE: NIDA, DAWN (May 1991 files)

The distribution of cocaine patients by race/ethnicity changed from 1989 to 1990. As shown in figure 3 and table 2, black patients outnumbered white patients in cocaine-related cases throughout the period. Considering the estimates by quarter (figure 3), the sharp decrease in cocaine cases from the

third to the fourth quarter of 1989 occurred for both black and white patients. However, subsequent decreases across quarters in 1990 occurred for white patients, whereas cases involving black patients remained about the same. Analysis of the distributions across the two calendar years (table 2) shows that the proportion of white patients decreased from 35 percent in 1989 to 30 percent in 1990 ($p<.001$), whereas the proportion of black patients increased from 46 to 54 percent ($p<.001$). The proportion of Hispanic patients held steady at 8 to 9 percent.

From 1989 to 1990 the age distribution of patients in cocaine-related ER episodes shifted slightly upward (table 2). The proportion of patients 18 to 25 years old decreased from 29 to 24 percent ($p<.001$); the proportion ages 35 to 44 years increased from 20 to 24 percent ($p<.001$); and the proportion 45 years of age and older increased from 3.7 to 4.8 percent ($p<.01$).

There was no significant change in the sex distribution of cocaine patients from 1989 to 1990. In each year 65 percent of these patients were male and 34 percent were female.

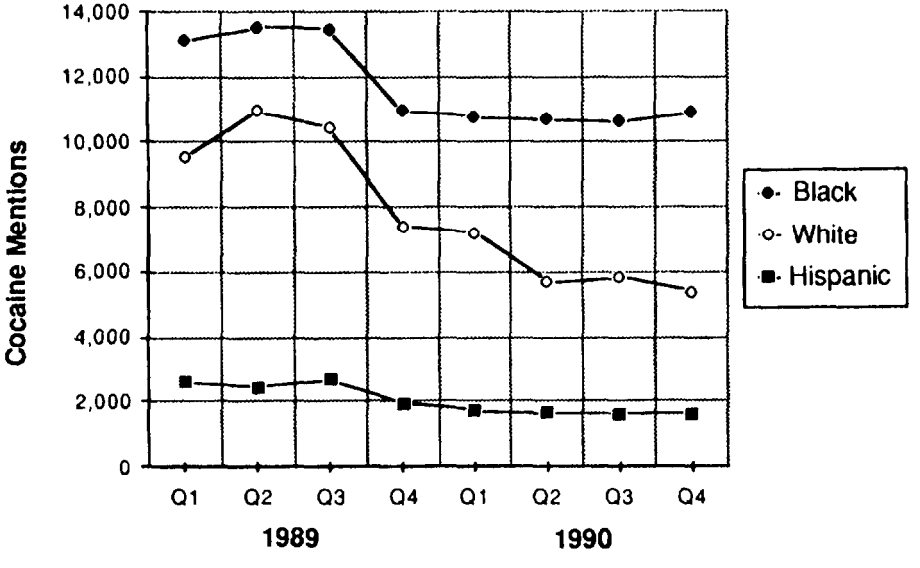


**FIGURE 3.** *Estimates of quarterly ER cocaine mentions involving white, black, and Hispanic patients, DAWN, first quarter 1989 through fourth quarter 1990*

**TABLE 2.** *Estimate of the number and percentage of cocaine-related ER episodes by selected demographic and episode characteristics, 1989 and 1990*

| Selected Demographic and Episode Characteristics | 1989 | | 1990 | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Total cocaine episodes[a] | 110,013 | 100.0 | 80,355 | 100.0 |
| Sex[a] | | | | |
| Male | 71,964 | 65.4 | 52,213 | 65.0 |
| Female | 37,084 | 33.7 | 27,150 | 33.8 |
| Race/ethnicity[a] | | | | |
| White | 38,349 | 34.9 | 24,100 | 30.0 ** |
| Black | 51,052 | 46.4 | 43,010 | 53.5 ** |
| Hispanic | 9,710 | 8.8 | 6,627 | 8.2 |
| Other | 395 | 0.4 | 344 | 0.4 |
| Age[a] | | | | |
| 6-17 years | 2,555 | 2.3 | 1,877 | 2.3 |
| 18-25 years | 31,600 | 28.7 | 19,614 | 24.4 ** |
| 26-34 years | 49,818 | 45.3 | 35,639 | 44.4 |
| 35-44 years | 21,529 | 19.6 | 19,186 | 23.9 ** |
| 45 years and older | 4,099 | 3.7 | 3,868 | 4.8 * |
| Drug concomitance | | | | |
| Mentioned alone | 50,644 | 46.0 | 33,787 | 42.1 ** |
| Mentioned in combination | 59,369 | 54.0 | 46,568 | 57.9 ** |

NOTE: These estimates are based on a representative sample of non-Federal short-stay hospitals with 24-hour ERs in the coterminous United States.

[a]Total includes unknown sex, race/ethnicity, and age categories that are not shown separately. Percentages for these variables will not sum to 100.

Significance level of difference from 1989 to 1990: *p<.01; **p<.001

SOURCE: NIDA, DAWN (May 1991 files)

Data on cocaine-related episodes by drug use motive reveal that the proportion of cases in which drugs were taken to achieve psychic effects (e.g., recreational use) decreased from 22 percent in 1989 to 18 percent in 1990 (p<.01, data not shown). The proportion of dependence cases increased slightly from 60 to 63 percent (not significant). Increases in the proportion of dependence cases

among cocaine episodes have been noted in previous studies (e.g., Colliver and Kopstein 1991; National Institute on Drug Abuse 1987).

Overdoses accounted for 14 percent of cocaine-related episodes in both 1989 and 1990. Among other categories of reason for ER contact, the only statistically significant difference between the two years was observed for the proportion of unexpected reaction cases, which decreased from 26 percent in 1989 to 23 percent in 1990 ($p<.05$). Patients seeking detoxification accounted for 27 to 28 percent of cocaine-related episodes, and those experiencing chronic effects accounted for 18 to 19 percent.

Cocaine was smoked in approximately 28 percent of the cases in 1990, injected in 22 percent, and sniffed or snorted in 12 percent. These proportions were not significantly different from those observed in 1989.

Drug concomitance is one of the key moderating variables in this analysis. In single-drug episodes, the role of cocaine as a causal factor is clearer than when other drugs are mentioned in combination. In 1989 other drugs were reported in combination with cocaine in 54 percent of the episodes in which it was mentioned, and this proportion increased to 58 percent in 1990 ($p<.001$, table 2). Complementing this increase, the proportion of cases in which cocaine was mentioned alone decreased from 46 to 42 percent ($p<.001$).

The specific drugs mentioned in combination with cocaine may be important in making decisions regarding clinical strategies in treating emergency cases (discussed in the next section). For the most part, the proportions of cases involving specific combination drugs did not differ greatly from 1989 to 1990. One exception is that mentions of alcohol-in-combination increased from 38 percent of cocaine-related episodes in 1989 to 43 percent in 1990 ($p<.001$, data not shown).

**All Cocaine-Related Cases vs. Cocaine-Related Overdoses**

As indicated above, overdose was the reported reason for ER contact in approximately one cocaine-related episode in seven (14 percent) in 1990. Many of these cases involved other drugs in addition to cocaine, and in some instances, the overdose may be related primarily to these other drugs rather than to cocaine.

Figure 4 shows the volume and trends of overdose cases in relation to the overall cocaine-related cases for the quarters of 1989 and 1990. Cocaine overdoses increased from 3,617 in the first quarter of 1989 to 4,389 in the third quarter of 1989 then decreased sharply in the fourth quarter of 1989 to 3,011.

In the next quarter, they reached a 2-year low of 2,607. Subsequently, cocaine-related overdose cases increased to 2,964 in the second quarter of 1990 and then decreased to 2,620 in the fourth quarter of 1990.

In tables 3 through 6, data for overdose cases are compared with data for all cocaine-related episodes based on demographic, episode, and drug use characteristics. Percent distributions of these variables in all cocaine-related episodes are compared with the corresponding percentages among cocaine-related overdose episodes. The data shown are weighted estimates for 1990.

Across the 21 DAWN metropolitan areas (table 3), ER overdose episodes involving cocaine were most numerous in Philadelphia (1,400). New York, Los Angeles-Long Beach, and Chicago trailed far behind Philadelphia with 641, 574, and 502 cases, respectively. Hospitals in the national panel accounted for 42 percent of cocaine mentions in overdose episodes but for only 23 percent of all cocaine mentions. Considered in relationship to all cocaine-related episodes, Minneapolis-St. Paul had the highest proportion

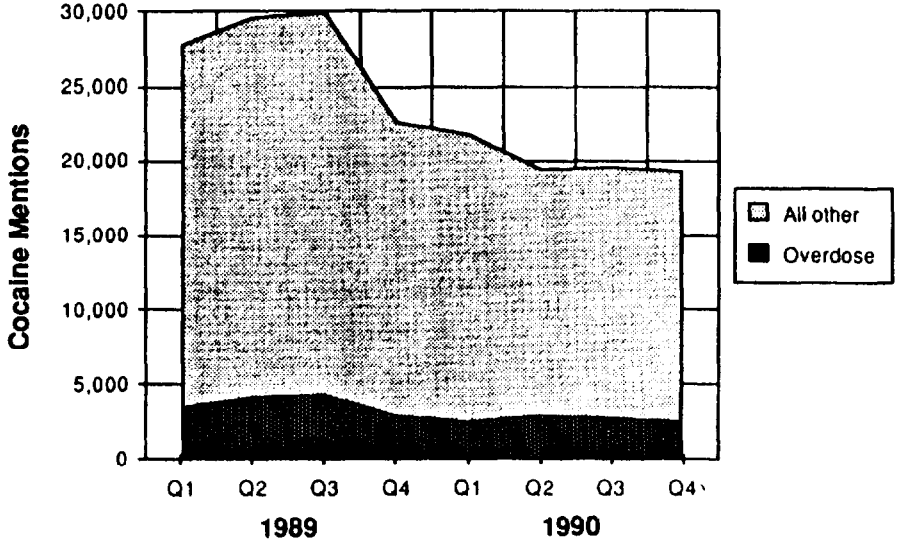


**FIGURE 4.** *Estimates of quarterly ER cocaine mentions involving overdose and other reasons for visit, DAWN, first quarter 1989 through fourth quarter 1990*

**TABLE 3.** *Estimate of all ER episodes involving cocaine and overdose episodes involving cocaine by metropolitan area, 1990*

| Metropolitan Area Episodes | All Episodes involving Cocaine | Overdose Episodes Involving Cocaine | Percent Overdose |
|---|---|---|---|
| Total coterminous U.S. | 80,355 | 11,022 | 13.7 |
| Atlanta | 2,743 | 183 | 6.7 |
| Baltimore | 3,023 | 220 | 7.3 |
| Boston | 1,961 | 371 | 18.9 |
| Buffalo | 282 | 43 | 15.2 |
| Chicago | 4,904 | 502 | 10.2 |
| Dallas | 1,028 | 239 | 23.2 |
| Denver | 569 | 131 | 23.0 |
| Detroit | 3,888 | 341 | 8.8 |
| Los Angeles-Long Beach | 4,129 | 574 | 13.9 |
| Miami-Hialeah | 748 | 138 | 18.4 |
| Minneapolis-St. Paul | 299 | 113 | 37.8 |
| New Orleans | 3,397 | 200 | 5.9 |
| New York | 12,633 | 641 | 5.1 |
| Newark | 3,752 | 161 | 4.3 |
| Philadelphia | 8,920 | 1,400 | 15.7 |
| Phoenix | 614 | 155 | 25.2 |
| St. Louis | 700 | 65 | 9.3 |
| San Diego | 725 | 82 | 11.3 |
| San Francisco | 2,297 | 390 | 17.0 |
| Seattle | 777 | 99 | 12.7 |
| Washington, DC | 4,788 | 318 | 6.6 |
| National panel | 18,177 | 4,659 | 25.6 |

NOTE: These estimates are based on a representative sample of non-Federal short-stay hospitals with 24-hour ERs.

SOURCE: NIDA, DAWN (May 1991 files)

of overdose cases (38 percent), whereas Newark had the lowest (4.3 percent). In addition to Minneapolis-St. Paul, areas with at least 20 percent overdose cases were Dallas, Denver, and Phoenix. The Atlanta, Baltimore, Chicago, Detroit, New Orleans, New York, Newark, St. Louis, and Washington, DC, areas had 10 percent or less overdose episodes among cocaine-related cases.

Based on the data for 1990, male patients accounted for 65 percent of all cocaine cases and 61 percent of cocaine-related episodes involving an overdose (table 4). The race/ethnicity distribution of patients in cocaine overdose cases was different from that in all cocaine cases. Patients were

**TABLE 4.** *Estimate of all ER episodes involving cocaine and overdose episodes involving cocaine by selected demographic characteristics, 1990*

| Selected Demographic Characteristics and Facility Location | All Episodes Involving Cocaine | | Overdose Episodes Involving Cocaine | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Total cocaine episodes[a] | 80,355 | 100.0 | 11,022 | 100.0 |
| Sex[a] | | | | |
| Male | 52,213 | 65.0 | 6,732 | 61.1 |
| Female | 27,150 | 33.8 | 4,199 | 38.1 |
| Race/ethnicity[a] | | | | |
| White | 24,100 | 30.0 | 4,733 | 42.9** |
| Black | 43,010 | 53.5 | 4,378 | 39.7** |
| Hispanic | 6,627 | 8.2 | 870 | 7.9 |
| Other | 344 | 0.4 | 92 | 0.8 |
| Age[a] | | | | |
| 6-17 years | 1,877 | 2.3 | 540 | |
| 18-25 years | 19,614 | 24.4 | 3,012 | 4.9 |
| 26-34 years | 35,639 | 44.4 | 4,632 | 42.0 |
| 35-44 years | 19,186 | 23.9 | 2,444 | 22.2 |
| 45 years and older | 3,868 | 4.8 | 359 | 3.3 |
| Facility location[b] | | | | |
| Central city | 45,361 | 73.0 | 4,283 | 67.3 |
| Outside central city | 16,816 | 27.0 | 2,080 | 32.7 |

NOTE: These estimates are based on a representative sample of non-Federal short-stay hospitals with 24-hour ERs in the coterminous United States.

[a]Total includes unknown age, sex, and race/ethnicity categories that are not shown separately. Percentages will not sum to 100.

[b]Excludes data from the national panel.

Significance level of difference between percentages in all episodes and overdose episodes: *p<.05; **p<.01.

SOURCE: NIDA, DAWN (May 1991 files)

white in 43 percent of cocaine-related overdose cases, compared with 30 percent of all cocaine-related cases ($p<.01$). Black patients accounted for 40 percent of cocaine-related episodes in which the reason for contact was an overdose, compared with 54 percent of all cocaine-related episodes ($p<.01$). The proportion of Hispanics was 8.2 percent for all episodes and 8 percent for overdose episodes.

Patients in cocaine-related overdoses seen in hospital ERs in 1990 were, on average, somewhat younger than those involved in all cocaine episodes in that year (table 4). Patients 6 to 25 years old accounted for 32 percent of cocaine-related overdose cases, compared with 27 percent of all cocaine-related ER episodes. At the opposite end of the age spectrum, the proportion of patients 45 years of age and older was 3.3 percent among cocaine-related overdose cases, compared with 4.8 percent of all cocaine-related cases ($p<.05$).

Among all cocaine-related cases in the 21 DAWN metropolitan areas, 73 percent were reported by central city hospitals and 27 percent by hospitals in the suburbs (table 4). Among overdose cases, the comparable proportions were 67 percent for central city hospitals and 33 percent for suburban hospitals,

A reversal in the distribution of cocaine cases by drug use motive is seen when all episodes are compared with overdose episodes (table 5). In 1990, dependence was the drug use motive in 63 percent of all cocaine-related episodes but in only 29 percent of cocaine-related episodes that involved a drug overdose ($p<.001$). Conversely, suicide was reported as the drug use motive in 7 percent of all cocaine cases compared with 37 percent of cocaine-related overdose cases ($p<.001$). Although drug use motive is reported once for an episode regardless of the number of drugs mentioned, the actual motive may differ for the separate drugs. Thus, when multiple drugs are involved, it is possible to misinterpret the data on motive when looking at any particular drug. Although statistically nonsignificant, the proportion of cases with unknown drug use motive, which occurred frequently enough to affect the interpretation of the data, was 4 percentage points higher in the overdose cases than in all cocaine-related episodes (16 vs. 12 percent).

The distribution of cocaine patients by disposition (episode outcome) was different for overdose episodes compared with all episodes (table 5). Patients were admitted as inpatients in 47 percent of overdose cases compared with 37 percent of all cases ($p<.01$). Patients who had overdosed died in the ER in 1.7 percent of cases compared with 0.4 percent among all cocaine-related cases.

Smoking was less likely to be the route of administration of cocaine in overdose cases than in all cases in which cocaine was mentioned ($p<.001$, table 5). In

**TABLE 5.** *Estimate of all ER episodes involving cocaine and overdose episodes involving cocaine by selected episode and drug use characteristics, 1990*

| Selected Demographic Characteristics and Facility Location | All Episodes Involving Cocaine | | Overdose Episodes Involving Cocaine | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Total cocaine episodes[a] | 80,355 | 100.0 | 11,022 | 100.0 |
| Drug use motive | | | | |
| Psychic effects | 14,687 | 18.3 | 2,031 | 18.4 |
| Dependence | 50,831 | 63.3 | 3,176 | 28.8** |
| Suicide | 5,203 | 6.5 | 4,035 | 36.6** |
| Unknown/other | 9,634 | 12.0 | 1,780 | 16.1 |
| Disposition[a] | | | | |
| Treated and released or referred | 47,795 | 59.5 | 5,281 | 47.9* |
| Admitted to hospital | 29,336 | 36.5 | 5,120 | 46.5* |
| Left against advice | 2,206 | 2.7 | 396 | 3.6 |
| Died | 299 | 0.4 | 192 | 1.7 |
| Route of administration | | | | |
| Injected | 17,301 | 21.5 | 2,921 | 26.5 |
| Smoked | 22,696 | 28.2 | 1,906 | 17.3** |
| Sniffed/snorted | 9,661 | 12.0 | 1,478 | 13.4 |
| Unknown | 25,722 | 32.0 | 3,796 | 34.4 |
| Other/multiple | 4,975 | 6.2 | 922 | 8.4 |
| Drug concomitance | | | | |
| Mentioned alone | 33,787 | 42.0 | 3,405 | 30.9* |
| Mentioned in combination | 46,568 | 58.0 | 7,617 | 69.1* |

NOTE: These estimates are based on a representative sample of non-Federal short-stay hospitals with 24-hour ERs in the coterminous United States.

[a]Total includes unknown categories of reason for ER visit, disposition, and route of administration that are not shown separately. Percentages will not sum to 100.

Significance level of difference between percentages in all episodes and overdose episodes: *p<.01; **p<.001.

SOURCE: NIDA, DAWN (May 1991 files)

1990 cocaine-related ER episodes involving a drug overdose, the drug was injected in 27 percent of cases, smoked in 17 percent, and sniffed or snorted in 13 percent. Among all cocaine-related episodes, the drug was injected in 22 percent of cases, smoked in 28 percent, and sniffed or snorted in 12 percent. It should be noted, however, that route of administration was unknown in approximately one-third of cocaine mentions. Although the proportion of unknowns did not differ significantly between all cocaine episodes and cocaine episodes involving an overdose, the magnitude of the unknowns makes the interpretation of the data on route of administration uncertain.

Overdose cases were more likely than other episodes to involve additional drugs in combination with cocaine (table 5). In 69 percent of cocaine-related overdose episodes, the drug was reported in combination with other substances; the comparable figure among all cocaine-related episodes was 58 percent ($p<.01$). This information raises the question of how often one of the other drugs or the combination of drugs, rather than cocaine alone, was responsible for the overdose.

As shown in table 6, alcohol was the drug most frequently mentioned in combination with cocaine, both in all cocaine-related episodes (43 percent) and in cocaine-related overdose episodes (46 percent). Heroin/morphine ranked second and was reported in 12 percent of all cocaine episodes and in 11 percent of overdoses involving cocaine. Marijuana/hashish was reported in 7.4 percent of all cocaine cases and in 6.7 percent of cocaine-related overdoses. Phencyclidine (PCP) was mentioned in 1.6 percent of all cocaine cases and in 1.1 percent of overdose cases involving cocaine. Diazepam was more likely to be reported in cocaine-related overdose cases than in all cocaine-related episodes (3.2 vs. 1.2 percent, respectively, $p<.05$). Ibuprofen was reported in 2.6 percent of cocaine-related overdoses, compared with 0.4 percent of all cocaine-related cases ($p<.01$). Unspecified benzodiazepines were more frequently reported when overdose was the reason for the ER visit than overall (1.6 vs. 0.7 percent, respectively, $p<.05$). The same was true of alprazolam (1.5 percent in cocaine-related overdoses vs. 0.4 percent in all cocaine-related cases, $p<.05$) and acetaminophen (1.4 vs. 0.3 percent, $p<.001$).

**Cocaine-Related ME Cases**

As indicated previously, DAWN ME cases involving cocaine increased 44-fold between 1975 and 1989. Quarterly trends for 1986 to 1990 are shown in figure 5. Although the file was held open for 5 months to include all records received by the end of May 1991, the data for the last one or two quarters may still be somewhat incomplete. In addition, it should be noted that the trends are shown with and without data for the New York metropolitan area because ME data for

**TABLE 6.** *Drugs mentioned in combination with cocaine in all ER episodes and overdose episodes, 1990*[a]

| Combination Drug | Percent Among All Episodes Involving Cocaine[b] | Percent Among Overdose Episodes Involving Cocaine[b] |
|---|---|---|
| Alcohol-in-combination | 42.5 | 46.0 |
| Heroin/morphine | 12.4 | 10.9 |
| Marijuana/hashish | 7.4 | 6.7 |
| PCP/PCP combinations | 1.6 | 1.1 |
| Diazepam | 1.2 | 3.2* |
| Methamphetamine/speed | 1.1 | 1.2 |
| LSD | 0.8 | 1.8 |
| Amphetamine | 0.7 | 1.7 |
| Unspecified benzodiazepine | 0.7 | 1.6* |
| Alprazolam | 0.4 | 1.5* |
| Ibuprofen | 0.4 | 2.6** |
| Codeine | 0.3 | —[c] |
| Acetaminophen | 0.3 | 1.4*** |
| Diphenhydramine | 0.3 | 1.4 |
| Lorazepam | 0.3 | 1.0 |
| Clonazepam | 0.3 | 1.5 |
| Acetaminophen with codeine | 0.2 | 1.3 |
| Phenobarbital | 0.2 | 1.4 |
| Propoxyphene | 0.2 | 1.0 |
| OTC sleep aids | 0.2 | —[c] |
| Aspirin | 0.2 | 1.0*** |
| Fluoxetine | 0.2 | —[c] |
| Desipramine | 0.2 | 1.0 |

NOTE: These estimates are based on a representative sample of non-Federal short-stay hospitals with 24-hour ERs in the coterminous United States.

[a]Includes drugs mentioned in at least 1.0 percent of all episodes involving cocaine or 1.0 percent of overdose episodes involving cocaine.

[b]Because up to three drugs can be reported in combination with cocaine, these percentages could sum to more than 100.

[c]Figure does not meet standard of precision (RSE ≥ 50 percent).

Significance level of difference between percentages in all episodes and overdose episodes: *p<.05; **p<.01; ***p<.001

SOURCE: NIDA, DAWN (May 1991 files)

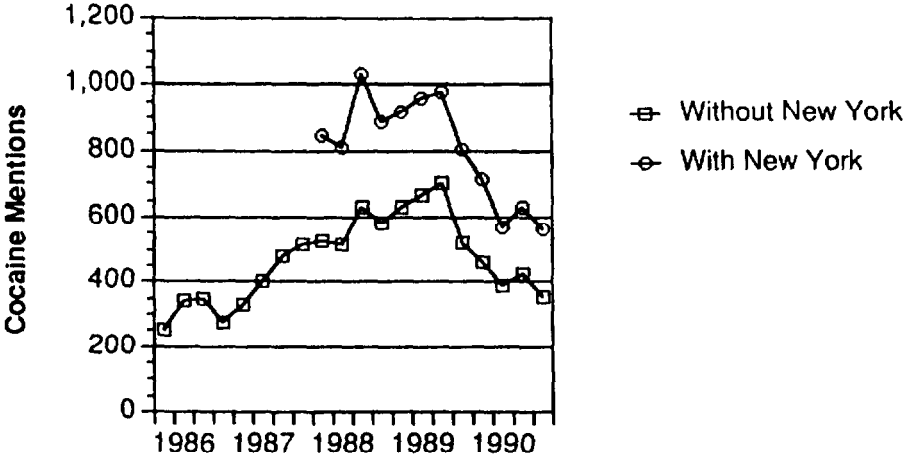


**FIGURE 5.** *Quarterly number of cocaine mentions reported by DAWN MEs, first quarter 1986 through fourth quarter 1990*

New York City were not available for the first 2 years shown in the graph. What is most notable, however, is that the trends show a sharp drop in cocaine-related cases between the third and fourth quarters of 1989, the same time the drop in ER cases occurred.

Table 7 shows the number of cocaine-related ME cases in 1989 and 1990 and the percent change according to metropolitan area. Overall, cocaine-related deaths decreased 32 percent from 3,663 in 1989 to 2,483 in 1990. Most of the 27 metropolitan areas experienced decreases in deaths involving cocaine. Two exceptions were Atlanta, where these cases increased from 67 in 1989 to 73 in 1990, and San Francisco, where they increased from 138 to 143.

The key variable distinguishing ME cases according to the causal role of the reported drug(s) is concomitance/cause of death. Directly caused, drug-induced deaths are distinguished from indirectly caused, drug-related deaths; in these latter cases, the drug interacts with a physiological condition, physical event, or medical disorder to cause the death. Drug-induced deaths are further categorized as single- and multiple-drug cases. Of the 2,483 DAWN ME cases in 1990 in which cocaine was mentioned, 64 percent were direct, drug-induced cases. Seven percent (172 deaths) involved only cocaine. In table 8, the data for these single-drug, cocaine-induced cases are compared with the data for all cases in which cocaine was reported.

**TABLE 7.** *Number of cocaine-related deaths reported by MEs participating in DAWN, 1989 and 1990*

| Metropolitan Area | 1989 | 1990 | Percent Change |
|---|---|---|---|
| Total DAWN system | 3,663 | 2,483 | -32.2 |
| Atlanta | 67 | 73 | +9.0 |
| Baltimore | 47 | 29 | -38.3 |
| Boston | 113 | 51 | -54.9 |
| Buffalo | 7 | 5 | —* |
| Chicago | 219 | 126 | -42.5 |
| Cleveland | 20 | 13 | -35.0 |
| Dallas | 74 | 39 | -47.3 |
| Denver | 14 | 13 | -7.1 |
| Detroit | 124 | 74 | -40.3 |
| Indianapolis | 2 | 1 | —* |
| Kansas City | 15 | 8 | -46.7 |
| Los Angeles/Long Beach | 630 | 422 | -33.0 |
| Miami | 73 | 29 | -60.3 |
| Minneapolis/St. Paul | 11 | 2 | -81.8 |
| New Orleans | 43 | 35 | -18.6 |
| New York | 1,141 | 848 | -25.7 |
| Newark | 148 | 81 | -45.3 |
| Norfolk | 5 | 5 | —* |
| Oklahoma City | 16 | 10 | -37.5 |
| Philadelphia | 324 | 215 | -33.6 |
| Phoenix | 35 | 24 | -31.4 |
| St. Louis | 45 | 38 | -15.6 |
| San Antonio | 18 | 17 | -5.6 |
| San Diego | 81 | 53 | -34.6 |
| San Francisco | 138 | 143 | +3.6 |
| Seattle | 38 | 29 | -23.7 |
| Washington, DC | 215 | 100 | -53.5 |

*Denominator for percent change is less than 10.

SOURCE: NIDA, DAWN (May 1991 files)

Data on race/ethnicity show that 34 percent of all decedents in cocaine-related cases were white, 44 percent were black, and 20 percent were Hispanic (table 8). However, in the data for single-drug, cocaine-induced deaths, 57 percent were black and 8 percent were Hispanic. The proportion of white decedents, 32 percent, was similar to that in all cocaine-related ME cases.

Data on cocaine-related deaths according to sex show a slightly higher proportion of female decedents among single-drug, cocaine-induced cases than among all cocaine-related cases (27 vs. 23 percent, respectively).

**TABLE 8.** *Number of cocaine-related deaths and number of direct, single-drug, cocaine-induced deaths reported by DAWN MEs by decedent demographic characteristics and cause of death, 1990*

| Demographic and Case Characteristics | All Cases Involving Cocaine | | Single-Drug, Cocaine-Induced Deaths | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| Total cocaine-related cases | 2,483 | 100.0 | 172 | 100.0 |
| Race/ethnicity* | | | | |
| White | 837 | 33.7 | 55 | 32.0 |
| Black | 1,098 | 44.2 | 98 | 57.0 |
| Hispanic | 502 | 20.2 | 13 | 7.6 |
| Sex' | | | | |
| Male | 1,904 | 76.7 | 125 | 72.7 |
| Female | 570 | 23.0 | 46 | 26.7 |
| Age* | | | | |
| 6-17 years | 14 | 0.6 | 2 | 1.2 |
| 18-25 years | 306 | 12.3 | 17 | 9.9 |
| 26-34 years | 955 | 38.5 | 61 | 35.5 |
| 35-44 years | 848 | 34.2 | 67 | 39.0 |
| 45 years and older | 344 | 13.9 | 22 | 12.8 |
| Concomitance/cause of death' | | | | |
| Direct-single drug | 172 | 6.9 | 172 | 100.0 |
| Direct-multiple drug | 1,410 | 56.6 | NA | NA |
| Drug(s) and physiological condition | 115 | 4.6 | NA | NA |
| Drug(s) and physical event | 560 | 22.6 | NA | NA |
| Drug(s) and medical disorder | 212 | 8.5 | NA | NA |

*Total includes other and/or unknown concomitance/cause of death, sex, age race ethnicity categories that are not shown separately. Percentages will not sum to 100.

NA=not applicable

SOURCE: NIDA, DAWN (May 1991 files)

The age distribution of single-drug, cocaine-induced deaths shows a somewhat higher proportion in the 35 to 44-year age group than among all deaths in which cocaine was mentioned (39 vs. 34 percent). However, the two distributions were similar.

Table 9 presents information on drugs mentioned in combination with cocaine in all ME cases in 1990. Alcohol ranked first and was reported in 41 percent of cases involving cocaine. Heroin/morphine (including unspecified opiates) ranked second with 29 percent. These drugs were followed by codeine and methadone with 8.1 and 6.9 percent, respectively. Diazepam was reported in 4.1 percent of cocaine-related cases.

## SUMMARY AND DISCUSSION

The most important findings of this study relate to the recent decrease in cocaine-related ER episodes and ME cases. First, decreases starting in the fourth quarter of 1989 for most of the 21 DAWN metropolitan areas as well as in the total data suggest, as previously indicated, that the changes are not isolated and could not have been associated with changes affecting just a few hospitals. If only a few hospitals or metropolitan areas had been involved, the drop in cocaine cases might be argued to have resulted from factors such as administrative changes initiated to deal with ER overcrowding. Because the decrease was widespread, however, such an explanation seems less likely.

The second finding related to recent trends is the simultaneous decrease in ER and ME cases related to cocaine. Both types of cases showed decreases beginning in the fourth quarter of 1989 and continuing into 1990. This, too, suggests that the change is real.

A third point related to these trends is that, for the most part, decreases occurred for all demographic groups and all categories of episode and drug use variables. However, some differences in trends were observed. Notably, the secondary decreases in cocaine-related ER episodes that occurred in the first two quarters of 1990 affected white patients to a far greater extent than black patients. The increase in the Baltimore area, which is quite significant, occurred after the initial wave of decreases.

Another point related to recent trends is the increasing involvement of other drugs mentioned in combination with cocaine. Assuming that the decrease in the overall numbers of cocaine-related medical emergencies is real, this pattern, together with the slight aging trend, might be consistent with the hypothesis of reduced current use of cocaine by casual users but continued use by individuals more dependent on it. These latter users might be more likely than casual users to have a secondary drug problem. Recent increase in the proportion of dependence cases among cocaine-related episodes, though not statistically significant in the present analysis, are also consistent with this hypothesis.

**TABLE 9.** *Drugs most frequently mentioned in combination with cocaine in ME cases reported to DAWN, 1990*

| Combination Drug | Number of Mentions | Percent of Cases |
|---|---|---|
| Alcohol | 1,005 | 40.5 |
| Heroin/morphine* | 726 | 29.2 |
| Codeine | 200 | 8.1 |
| Methadone | 172 | 6.9 |
| Diazepam | 103 | 4.1 |
| Lidocaine | 81 | 3.3 |
| Amitriptyline | 69 | 2.8 |
| Nortriptyline | 58 | 2.3 |
| Marijuana/hashish | 47 | 1.9 |
| Diphenhydramine | 45 | 1.8 |
| PCP/PCP combinations | 37 | 1.5 |
| Propoxyphene | 34 | 1.4 |
| Methamphetamine/speed | 33 | 1.3 |
| Acetaminophen | 32 | 1.3 |
| Quinine | 23 | 0.9 |
| Unspecified benzodiazepine | 23 | 0.9 |
| Phenobarbital | 22 | 0.9 |
| Doxepin | 20 | 0.8 |
| Chlordiazepoxide | 16 | 0.6 |
| Amphetamine | 13 | 0.5 |
| Chlorpheniramine | 13 | 0.5 |
| Caffeine | 12 | 0.5 |
| Hydantoin | 12 | 0.5 |
| Aspirin | 11 | 0.4 |
| Doxylamine succinate | 11 | 0.4 |
| Desipramine | 10 | 0.4 |
| Thioridazine | 10 | 0.4 |

*Includes opiates not specified as to type.

SOURCE: NIDA, DAWN (May 1991 files)

The slight plurality of white patients in overdose episodes, with black patients predominating in cocaine-related episodes overall, has several possible explanations. For example, smoking is less likely to be the route of administration in overdose episodes than in other episodes (table 5), and other studies (e.g., Colliver and Kopstein 1991) have shown that ER patients who smoke cocaine are more likely to be black. However, if there is an association here, the direction of causality, if any, is uncertain.

The high proportion of suicide cases among overdose episodes involving cocaine also is curious. It may be that the overdose in these cases was

associated with another drug rather than cocaine. That overdose cases are more likely to involve other drugs is consistent with the pattern of suicides, in which individuals take whatever is available. Together with the possible involvement of individuals receiving medication under a physician's direction and persons self-medicating for emotional difficulties, this availability factor may partially account for the high proportion of drugs such as diazepam, unspecified benzodiazepines, and alprazolam in overdose cases. The differential involvement of drugs such as ibuprofen and acetaminophen in overdose cases are particularly suggestive of the "take-anything" suicide syndrome. An alternative explanation, of course, is that cocaine may disinhibit latent suicidal tendencies.

It is uncertain how many overdoses result from cocaine and how many from another drug mentioned in combination with it. The blame clearly rests with cocaine in the 31 percent of overdoses in which it was the only drug reported (3,405 weighted emergency cases in 1990 or 4 percent of all cocaine cases in that year). Unfortunately, data in DAWN do not provide adequate information to answer this question for the remaining 69 percent of overdoses, and researchers are left to make what they can of the drug combination data.

In practice, the ER staff must distinguish between symptoms of cocaine overdose and opiate or other drug overdoses and select a treatment strategy commensurate with the diagnosis. In selecting medications in these situations, physicians must consider possible interaction with any other drugs the patient might have taken in addition to cocaine. Acutely intoxicated patients may be unable to respond to questions about the drugs they have taken. In these cases, information on other drugs frequently reported in combination with cocaine, provided by studies such as this one, may be useful in suggesting the types of interactions that must be anticipated. Possible interactions with other drugs patients may have taken also must be considered in any effort to develop new medications to combat cocaine intoxication.

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**AUTHORS**

James D. Colliver, Ph.D.
Senior Research Analyst
CSR, Incorporated
Suite 600
1400 I Street, NW
Washington, DC 20005

Andrea N. Kopstein, M.P.H.
Statistician

Arthur L. Hughes, M.A.
Mathematical Statistician

Division of Epidemiology and Prevention Research
National Institute on Drug Abuse
Rockwall II, Suite 620
5600 Fishers Lane
Rockville, MD 20857

# Preclinical Assessment of Cocaine Toxicity: Mechanisms and Pharmacotherapy

*Jeffrey M. Witkin and Jonathan L. Katz*

## INTRODUCTION

Data on emergency room admissions and cocaine-related deaths document the toxic consequences of cocaine abuse. In 1990 approximately 20,000 individuals required emergency treatment for cocaine toxicity (Colliver et al., this volume). Of these, most were treated by relatively standard emergency medical procedures and released without hospital admission (Schrank, this volume). Nonetheless, some cocaine toxicities result in cardiovascular abnormalities, central nervous system (CNS) damage, neurological impairment, and death (see Miller et al.; Rowbotham; and Wetli, this volume).

Pharmacotherapy currently used to treat cocaine toxicity generally involves standard emergency medications directed at the specific symptomotologies listed below (e.g., arrhythmias, high blood pressure, convulsions). Although many of the symptoms of cocaine toxicity can be managed with existing medications, new compounds to treat cocaine overdose could improve on efficacy, provide more rapid control of acute cocaine toxicity, or treat symptoms or sequelae (e.g., kindling, neurotoxicity) for which there are currently no treatments.

- Acute behavioral toxicity
  —Psychosis
  —Agitation
  —Delirium

- Long-term toxicity
  —Neurotoxicity
  —Kindling (seizures, psychosis)
  —Stroke damage

- Convulsions
  —Anticonvulsant resistant

- Lethality
  —Cardiovascular
  —Respiratory
  —Thermoregulatory

The acute behavioral toxicities associated with cocaine abuse are not well controlled by haloperidol or chlorpromazine and appear to be best controlled by heavy sedation induced with benzodiazepines or barbiturates (Schrank, this volume). Thus, improvements in the pharmacological specificity of control over these toxic symptoms may have some utility in increasing the degree of treatment specificity. Until such sedation can be achieved, the physical restraint sometimes needed by patients suffering from cocaine toxicity, typically requiring several people, suggests that a more rapid means of drug delivery could be designed (suggested by Dr. Charles Wetli) that would avoid injury to the patient and to those in attendance.

Several potential outcomes of a toxic episode currently have no specific pharmacological treatment. For example, there can be a progression of neural damage from ischemia and stroke related to cocaine use. Excitatory amino acid antagonists could be useful for minimizing neurological impairment (Meldrum and Garthwaite 1990). Ketamine is clinically available and could provide such protection, although better experimental agents likely will be forthcoming. Compounds also might be developed that block the development of the kindled seizures and psychosis that can result from repeated high-dose cocaine exposure (see below). Convulsions resistant to standard anticonvulsant therapy can be life threatening and require severe treatment measures. Therefore, novel anticonvulsant agents that are effective against these resistant convulsions would appear to have some utility. Finally, compounds that improve the chances of survival after life-threatening cocaine toxicities, regardless of the mechanisms of lethality or protection, also would be welcome improvements.

Preclinical studies of cocaine overdose can provide valuable assistance for drug development in three major areas. First, these studies can advance understanding of the clinical phenomena associated with cocaine toxicity by investigating the basic mechanisms involved with cocaine toxicity. This includes the development of preclinical models to evaluate specific aspects of the clinical state. Second, these studies can evaluate treatments using appropriate preclinical models; existing compounds, new molecular entities, and adjunct therapies can be investigated. Third, they can evaluate the safety

of proposed cocaine abuse and cocaine toxicity treatments. This work includes an assessment of the effects of the drugs in combination with cocaine and, as dictated by known mechanisms, other drugs of abuse.

## ACUTE COCAINE TOXICITY: MODELS

Various classes of models can be used for preclinical investigation, although discussion of these are beyond the scope of this chapter (for an overview, see Witkin, in press; Witkin and Katz 1990). For the present purposes, it is important to distinguish predictive models from functional models. Predictive models are those that generate data that are predictive of clinical efficacy or safety but need not be functionally equivalent to the clinical state (i.e., preclinical signs and clinical symptoms controlled by the same mechanism). Predictive models are not required to resemble the clinical situation. If novel anticonvulsants block convulsions in mice after acute doses of cocaine and these compounds are clinically effective, the model is predictive regardless of whether the preclinical and clinical phenomena are mediated by similar mechanisms. In this example, there is often a delay in convulsions after cocaine administration in humans that does not occur in the preclinical model, suggesting some differing mechanisms that do not detract from the predictive validity of the model. Functional models are those in which the mechanisms underlying the preclinical and the clinical phenomena are the same. Thus, functional models are typically predictive models, whereas the converse is not necessarily true. The primary difficulty in obtaining adequate functional models is the lack of understanding of the mechanisms underlying the clinical symptoms of cocaine toxicity.

In many of the animal models of cocaine toxicity, the choice of an appropriate species or procedure is not straightforward. For example, significant variation in the acute sensitivity to cocaine convulsions can be observed even across mouse strains (Marley et al. 1991). Other experimental procedures, albeit important in their own right, do not appear to adequately model specific clinical features of cocaine toxicity. For example, Tella and colleagues (1991) have shown that prazosin can increase the dose of intravenously infused cocaine required to produce convulsions and lethality in rats; however, observation of cardiovascular function and body temperature with cocaine either alone or in conjunction with prazosin did not suggest any direct involvement of these systems in the pathological effects of cocaine. Other species or procedures will be necessary to model the specific cardiovascular changes (e.g., arrhythmias, ventricular tachycardia, ventricular fibrillation, vesicular spasms) that have been associated with the toxic effects of cocaine in human drug abusers (Nadeemanee 1991).

## ACUTE COCAINE TOXICITY: MECHANISTIC STUDIES

High-bolus doses of cocaine produce dose-dependent increases in convulsions and lethality in rodent models of acute toxicity. Under these conditions, convulsions and lethality are described by different functions, with convulsions being produced at significantly lower doses than those producing death (Witkin and Katz 1991). These data, in addition to drug-interaction information described below, provide the first indication that convulsions, often associated with cocaine lethality, are not inextricably linked mechanistically to lethality (Witkin et al. 1989a).

### Stereospecificity

Using optically pure samples of the unnatural (+)-enantiomer of cocaine, Katz and colleagues (1990) showed that only the natural isomer of cocaine possesses behavioral activity. Doses of (+)-cocaine were devoid of behavioral effects across a range in excess of 200 times those of active doses of (-)-cocaine. This dose range of the (+)-isomer was sufficient to ensure that differences in affinities of the isomers for the dopamine or serotonin transporters were not responsible for the lack of activity observed (see Katz et al. 1990 for discussion). In contrast, convulsions and lethality were produced with only a tenfold difference in potency of the two enantiomers (figure 1). These results suggest that the acute toxic effects of bolus (-)-cocaine may be due to mechanisms different from those that mediate its behavioral activity. The toxicity of cocaine may be due to actions of cocaine other than or in addition to its ability to block catecholamine and indoleamine uptake processes.

#### Dopamine Receptor Subtypes

The role of specific dopamine receptor subtype blockers in the toxicity of cocaine has been evaluated. Haloperidot, a preferential antagonist at dopamine $D_2$ receptors, is ineffective in altering the lethal effects of cocaine in rodents (figure 2, left panel) (Derlet et al. 1989; Witkin et al. 1989a; Witkin and Katz 1991). Other $D_2$ antagonists also have been reported to be inactive against the lethal effects of cocaine (see references in Witkin et al. 1989a). Likewise, haloperidol does not prevent the development of cocaine-kindled seizures (Karler et al. 1989). However, haloperidol effectively prevents the lethal effects of amphetamines (figure 2, right panel) (Derlet et al. 1989; Witkin et al. 1990). The contrasting effects of haloperidol against cocaine- or amphetamine-induced lethality points to the difficulty in extrapolating from one class of psychomotor toxicant to another.

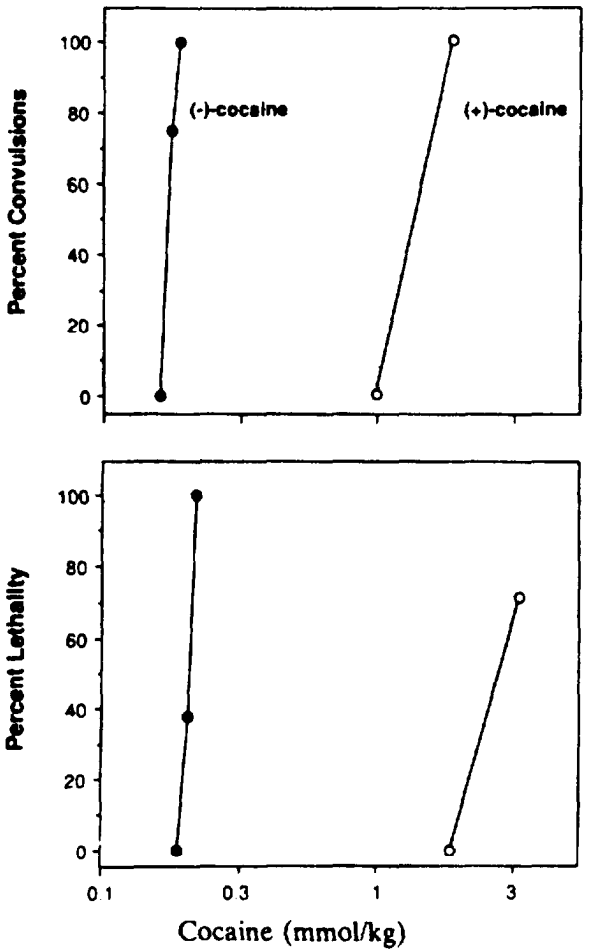


**FIGURE 1.** *Convulsive and lethal effects of the stereoisomers of cocaine. Both isomers produced dose-dependent increases in convulsions and lethality, with (-)-cocaine tenfold more potent than (+)-cocaine.*

SOURCE: Katz et al. 1990. Copyright 1990 by Clinical Neuroscience Publishers (London).

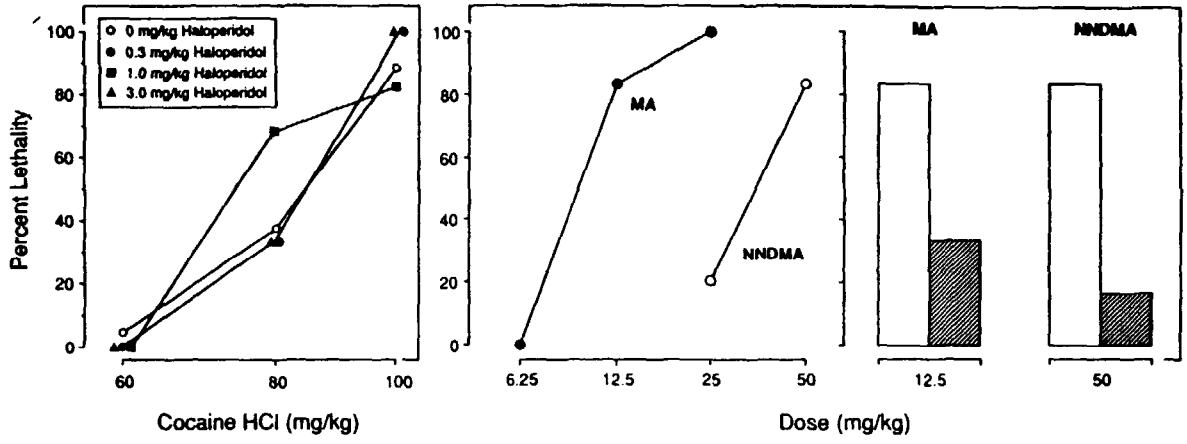




**FIGURE 2.** *Left panel: Haloperidol does not prevent the lethal effects of cocaine in rats. Middle panel: Lethal effects of methamphetamins (MA) and N,N-dimethylamphetamine (NNDMA) in rats. Right panel: Protection against the lethal effects of MA and NNDMA by 1.0 mg/kg haloperidol in rats.*

SOURCE: Left: Witkin et al. 1989a. Reprinted with permission from Life Sciences, vol. 44, Witkin, J.M.; Goldberg, S.R.; and Katz, J.L. Lethal effects of cocaine are reduced by the dopamine-1 receptor antagonist SCH 23390 but not by haloperidol. Copyright 1989 by Pergamon Press plc (Elmsford, NY). Middle and right: Witkin, J.M.; Ricaurte; G.A.; and Katz, J.L. Behavioral effects of N-methylamphetamine and N,N-dimethylamphetamine in rats and squirrel monkeys. J Pharmacol Exp Ther 253:466-474, 1990. Copyright 1990 by American Society for Pharmacology and Experimental Therapeutics (Baltimore, MD).

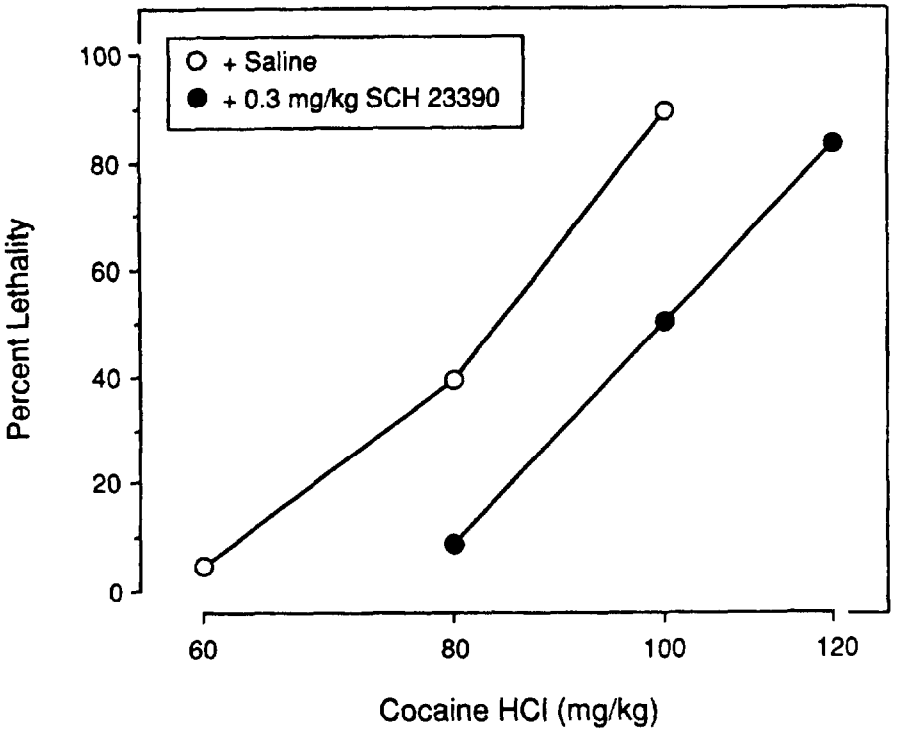


**FIGURE 3.** *Protection against the lethal effects of cocaine by the $D_1$ dopamine antagonist SCH 23390 in rats*

SOURCE: Witkin et al. 1989a. Reprinted with permission from *Life Sciences,* vol. 44, Witkin, J.M.; Goldberg, S.R.; and Katz J.L. Lethal effects of cocaine are reduced by the dopamine-1 receptor antagonist SCH 23390 but not by haloperidol. Copyright 1989 by Pergamon Press plc (Elmsford, NY).

In contrast to haloperidol, lethal effects of cocaine have been reported to be blocked by the $D_1$ antagonist SCH 23390 (figure 3) (Derlet et al. 1990; Witkin et al. 1989a; Witkin and Katz 1991). Interestingly, neither SCH 23390 nor related $D_1$ antagonists alter the convulsive effects of cocaine, and yet they increase the $LD_{50}$ for cocaine in rats and mice. Specific $D_1$ antagonists also have been suggested as potential candidates for use in the treatment of cocaine abuse based on their efficacy in preclinical studies of the discriminative and reinforcing effects of cocaine and their potentially low side-effect profile (Kleven et al.

1990; Witkin, in press). For example, SCH 23390, but not haloperidol, partially prevented the discriminative stimulus effects of cocaine in a rodent model predictive of the subjective effects of cocaine in humans (Witkin et al. 1991a).

The involvement of $D_1$ receptors in the lethal effects of cocaine is further documented by results of experiments with other compounds (Witkin and Katz 1991). Similar protection against cocaine lethality is conferred by the $D_1$ antagonists SCH 39166 and SKF 83566. The effects of SCH 23390 are stereospecific; the inactive enantiomer SCH 23388 does not protect even when given in doses 30 times those of SCH 23390 required to prevent lethality. The pharmacological specificity of $D_1$ antagonists for cocaine was demonstrated by the lack of effect of 23390 against lethal effects of the local anesthetic lidocaine, a compound relatively devoid of dopaminergic activity. Thus, although lidocaine and cocaine may share local anesthetic mechanisms, only the dopaminerigically triggered toxic events are prevented with $D_1$ antagonists.

Dopamine antagonists appear to play a limited role in modifying the cardiovascular effects of cocaine. Schindler and colleagues (1991) showed that haloperidol attenuated cocaine-induced tachycardia in squirrel monkeys but did not block the increases in blood pressure produced by intravenous cocaine. SCH 23390 was ineffective in altering either effect of cocaine on cardiovascular function despite its ability to attenuate the pressor effects of the D, agonist SKF 38393. However, evaluation of these drugs in other cardiovascular models (e.g., vascular spasms, arrhythmias) will be useful in defining the role of cardiovascular events in the $D_1$ receptor-sensitive lethality.

**Noradrenergic Mechanisms**

Neurotransmitter depletion studies have suggested a modulatory role for norepinephrine but not dopamine in seizure susceptibility to some convulsants but not to cocaine (Mason and Corcoran 1979). Nonetheless, several antagonists, including prazosin, propranolol, and labetalol, protected against the lethal effect of cocaine in rats, but additional protection was not afforded by combined treatment with prazosin and propranolol (Derlet and Albertson 1990a). However, combined treatment with propranolol and phentolamine (but not separate treatment) was found to protect against the lethal effects of cocaine in mice without affecting convulsions (figure 4). The combined $\alpha$- and ß-noradrenergic antagonist labetalol has found clinical use in the medical management of cardiovascular toxicity induced by cocaine (Gay and Loper 1968). The $\alpha$-2 antagonists idazoxan and RX811059A did not alter the convulsive or lethal effects of cocaine in mice (Jackson et al. 1990). In squirrel monkeys, cocaine-induced pressor activity (tachycardia in rats) (Jones and

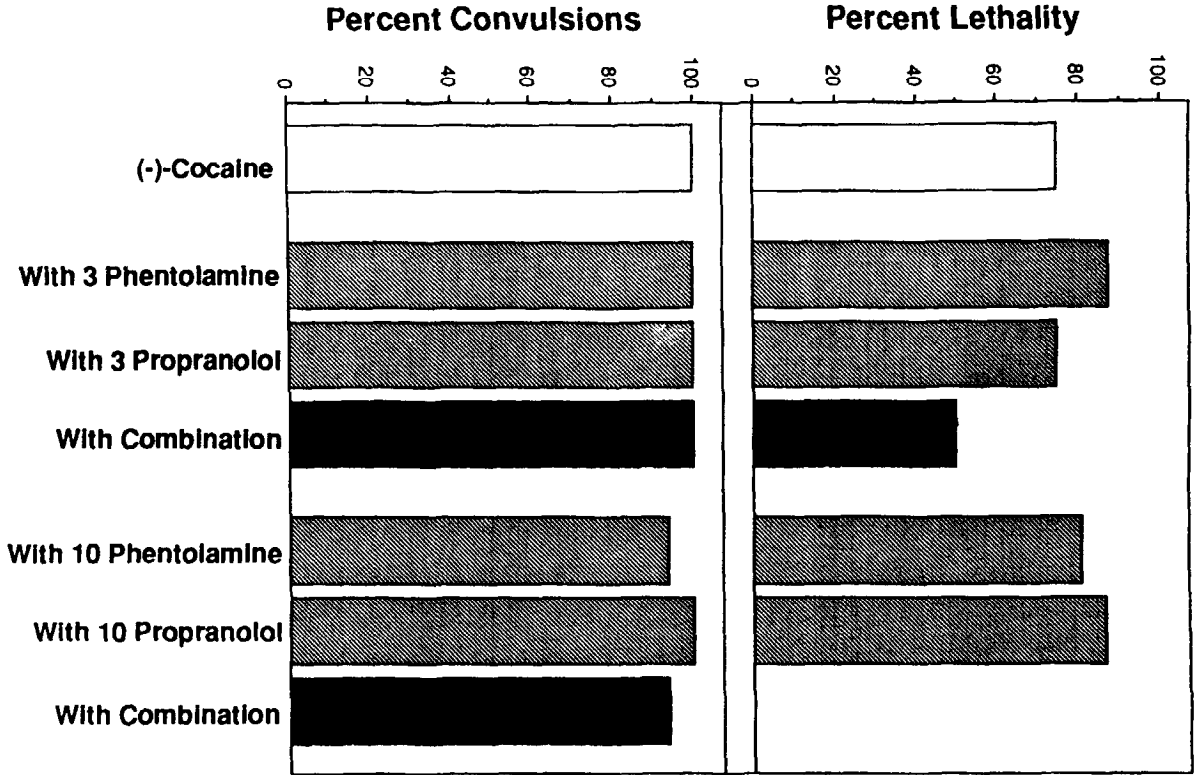


**FIGURE 4.** *Protection by combined α-and ß-adrenergic blockade against the lethal but not the convulsive effects of cocaine. Data represent effects observed in groups of at least eight male Swiss Webster mice each.*

Tackett 1990) was antagonized by $\alpha$-blockade with phentolamine, and the tachycardiac response to cocaine was antagonized with propranolol (Tella et al. 1990). However, in rat models of acute toxicity in which cocaine is infused intravenously until death, protection against the cardiovascular consequences of cocaine with noradrenergic blockers is not inextricably linked to protection against lethality (Tella et al. 1991).

### Cholinergic Mechanisms

Sharkey and coworkers (1988) demonstrated that cocaine binds to muscarinic receptors and has weak antimuscarinic actions in vitro. Based on these results, the authors suggested that cocaine at high doses may interfere with the dampening of sympathetic cardiac influences, thereby rendering the cardiovascular system vulnerable to potentially lethal consequences. Increases in the cardiotoxic effects of cocaine have been reported in dogs treated with atropine (Wilkerson 1989). Similar enhancement was reported with the quaternary antimuscarinic, scopolamine methylbromide, suggesting a peripheral influence of anticholinergics in the cardiotoxicity of cocaine. In other studies, it has been shown that physostigmine could significantly protect rats against the acute lethal effects of cocaine (Witkin et al. 1989b). This effect was additionally surprising since physostigmine would be anticipated to block the plasma hydrolysis of cocaine (Stewart et al. 1977). However, the mechanism of protection did not appear to be via the indirect muscarinic agonist actions of physostigmine, since direct-acting muscarinic agonists were ineffective and the protection was not sensitive to atropine.

### Calcium Channels

Results of studies with calcium channel antagonists on cocaine toxicity have been mixed. Trouve and Nahas (1986) report significant protection against the cardiotoxic effects of cocaine and increases in survival time with nitrendipine pretreatment in rats. Rats pretreated with diltiazem, nifedipine, or verapamil exhibited shortened onset to convulsions and, at some doses, increased lethality induced by cocaine (Derlet and Albertson 1989). In both squirrel monkeys and rats, calcium channel antagonists only blocked the pressor effects of cocaine and did not afford protection against cocaine-induced lethality in rats (C.W. Schindler, personal communication, July 1991; Tella et al. 1991).

### Peripheral Mechanisms

To evaluate the contribution of peripheral actions of cocaine to its toxicity, the stable charged methiodide analog of cocaine (Shriver and Long 1971; Tessel

et al. 1978) was used to mimic the peripheral actions of cocaine. The lack of CNS actions of cocaine methiodide was verified by bioassay. In mice, cocaine methiodide was devoid of locomotor stimulatory actions (Witkin and Katz 1991) and did not fully reproduce the discriminative stimulus effects of cocaine in rats (Witkin et al. 1991a). In contrast, lethal effects of cocaine and cocaine methiodide showed a relative potency close to one with parallel dose-response curves suggesting comparable mechanisms of action. Doses of the $D_1$ antagonists about two orders of magnitude lower than those effective against cocaine lethality were effective in preventing death from cocaine methiodide; haloperidol did not alter the lethal effects of cocaine methiodide despite complete protection against convulsions at neuroleptic doses of haloperidol (Witkin and Katz 1991). These data suggest that peripheral mechanisms significantly contribute to cocaine lethality. The mechanism by which $D_1$ antagonists protect against the peripheral manifestations of cocaine toxicity (cocaine methiodide) or the combined peripheral/central actions of cocaine are not known. Wilkerson (1988) and Tella and colleagues (1990) have provided evidence to suggest that the cardiovascular effects of cocaine are controlled by both central and peripheral actions and that some of these peripheral effects of cocaine may be centrally driven. The discovery of a peripherally acting, selective $D_1$ antagonist would be a useful research tool in this regard.

**Metabolites**

Cocaine metabolites, although generally thought to be behaviorally inactive, may have toxic actions that act alone or in concert with the parent compound. Benzoylecgonine has been reported to be a potent vasoconstrictor in isolated cat cerebral arteries and to display greater efficacy than cocaine (Madden and Powers 1990). The recently identified metabolite of cocaine, cocaine ethyl-ester (cocaethylene), is formed in liver in the presence of alcohol. Cocaethylene has been associated with emergency room admissions related to cocaine and with cocaine-related deaths (Hearn et al. 1991a). The pharmacology of cocaethylene appears to be very similar to that of cocaine (Hearn et al. 1991a; Jatlow et al. 1991). However, compared with cocaine, cocaethylene is slightly less potent in stimulating locomotor activity in mice and in producing discriminative stimulus effects comparable to cocaine in squirrel monkeys (Katz and Witkin, in press). The toxicity of cocaethylene, on the other hand, is at least as potent as that of cocaine. The compounds are equipotent in producing clonic convulsions in mice (Katz and Witkin, in press), whereas cocaethylene is more potent in producing lethality (Katz and Witkin, in press; Hearn et al. 1991b). Thus, given the high incidence of alcohol use in association with cocaine toxicity (Colliver et al., this volume), the contribution of cocaethylene to the toxicity of cocaine cannot be ignored.

## SAFETY EVALUATION OF PROPOSED COCAINE ABUSE TREATMENT AGENTS

Preclinical evaluation of the potential toxicity of treatment compounds must provide safety assurance before Phase I clinical evaluations can begin. In the case of drugs of abuse, new potential therapeutic entities also must be scrutinized closely for drug interactions, primarily with the target drug of abuse. However, given the prevalence of polydrug abuse, certain drug interactions guided by known mechanisms of action cannot be neglected. An additional concern of drug abuse treatment agents stems from the potential sensitization to the toxic effects of cocaine induced by repeated treatment with the therapeutic agent. For example, repeated treatment with a dopamine receptor blocking agent may increase the likelihood of a toxic cocaine episode due to adaptive CNS mechanisms.

### Drug Interactions

Safety evaluation and drug-interaction studies can be approached from a number of angles (see Pentel and Thompson, this volume). One approach is to give the test compound in conjunction with relatively low, yet psychoactive doses of cocaine (e.g., doses that increase locomotor activity but are far from the lethal range). Indications of toxicity from the combined treatment can be gleaned by close observation of the animals. However, if the dose of cocaine is too low, enhanced toxicity may not be observed. For example, if the $ED_{50}$ for behavioral activity of cocaine is used (e.g., for locomotor stimulation, the $ED_{50}$ is about 10 mg/kg in mice), an additional amount of test substance with an effect equivalent to about 45 mg/kg of cocaine (based on data of Witkin and Katz 1991) would be needed to observe the first dramatic overt signs of toxicity due to the drug interaction (convulsions).

Figure 5 illustrates some potential interactions of cocaine with hypothetical treatments using $ED_{50}$ values and slopes of dose-effect curves that correspond to actual data. The $ED_{50}$ for behavioral effects is shown as X, whereas that for convulsions is 6X. Thus, large alterations in the convulsive threshold for cocaine would be required to observe convulsions if the $ED_{50}$ dose of cocaine for behavioral activity were given in conjunction with the test compound. A shift in convulsive threshold in the presence of treatment would have to be on the order of sixfold to detect convulsions at the behavioral $ED_{50}$. Furthermore, assuming that the treatment doubles the sensitivity of the subjects to convulsions ($ED_{50}$ for convulsions now equals 3X, Rx 1 in figure 5), administration of the behavioral or twice the behavioral $ED_{50}$ of cocaine still would not result in convulsions in any animal. However, since the slope of the dose-response function for behavioral activity is less than that for convulsions,

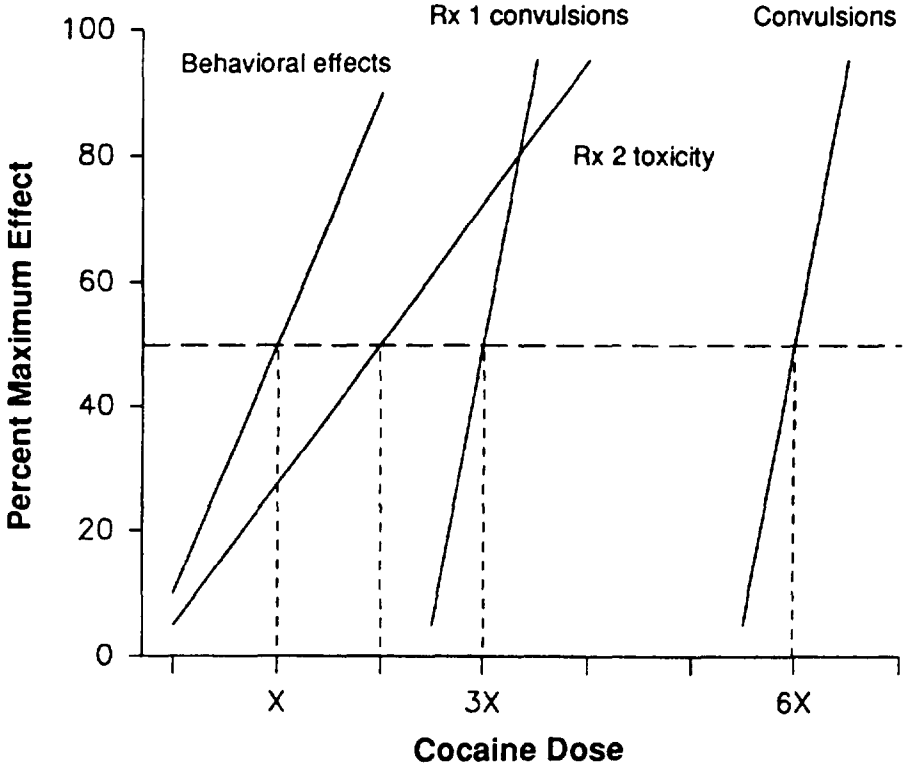


**FIGURE 5.** *Theoretical data illustrating dose-effect functions for the behavioral effects of cocaine (e.g., with the range of abused doses; curve at far left) and the convulsanf effects of cocaine (curves at the far right). Also shown are hypothetical dose-effect functions for interactions of cocaine with two hypothetical drug abuse treatments.*

large, behaviorally active doses of cocaine would result in convulsions in some animals when given in combination with this treatment. For other toxic effects, such as lethality, that occur at even greater cocaine doses, detection of toxicity is even more difficult when examining behaviorally active cocaine doses in combination with the treatment. However, if appropriate animal models could predict toxicity from low doses of cocaine (e.g., cardiac arrhythmias, severe blood pressure changes), this model of test drug evaluation could be very useful. Thus, if the treatment interaction toxicity (Rx 2 toxicity) can be modeled preclinically and validated as a predictor of clinical toxicity, then even small

changes in the toxicity of behaviorally active doses would be detected and predictive of increased clinical risk.

Adequate safety evaluation can be achieved by examining the effects of lower doses of cocaine in combination with the treatment, given adequate monitoring of low-dose toxicity signs. In the absence of models predictive of toxicity from low doses, direct observation of toxicity induced by cocaine alone and in the presence of the treatment is needed. Appropriate toxicological assessment requires more complete dose-effect analysis. Figure 5 shows theoretical dose-effect functions for convulsions alone and in the presence of a fixed dose of a test compound (Rx 1 convulsions). In evaluating preclinical data of this nature, the relationships among dose-effect curves are predictive of clinical toxicity. Treatment 1 shifts the $ED_{50}$ for convulsions to the left twofold. The degree of that shift alone is probably not helpful in evaluating the magnitude of concern over clinical toxicity. Instead, one must evaluate this shift relative to the ratio of potencies of cocaine for inducing its behavioral effects and convulsant effects. In this case, although only a twofold increase in sensitivity of cocaine is added with the treatment, this is one-third of the original difference between behavioral and toxic effects.

Furthermore, the toxicity and therapeutic potency of the treatment must be known to evaluate its interactive effects with cocaine. Thus, if the therapeutic dose of the treatment produces a shift of the convulsant effects of cocaine to one-third of that of its behaviorally active dose range (e.g., range of abused doses), the likelihood of clinical enhancement of convulsions is high. Although safety evaluation should stay within the therapeutic dose range of the treatment, this range is sometimes difficult to anticipate or to extrapolate. Thus, the dose used preclinically relative to the therapeutic dose range may not always be known. Under these conditions, interpretation of the dose-effect curves can be made, given available information on the toxicity of the treatment when given alone. For example, if the dose of the treatment is near its own convulsant threshold, such a twofold shift in the cocaine dose-response function is probably indicative of a minor clinical hazard since toxic doses of the treatment would not realistically be within the clinically prescribed dose range.

Finally, it must be acknowledged that any preclinical safety data must be considered as only a rough guideline for clinical investigation. A host of differences between the effects of the test compound alone and in combination with cocaine in experimental animals and humans necessitates the use of carefully monitored clinical trials to ultimately establish safety of new medications.

### Mazindol

Mazindol was reported in open trials to reduce cocaine intake and craving for cocaine in methadone maintenance patients (Berger et al. 1989). Given the overlapping pharmacological profile of mazindol and cocaine, it was anticipated that the two compounds may exacerbate the toxicity of one another. In mice, mazindol has been shown to enhance both the convulsive and lethal effects of cocaine at doses that are not toxic when given alone (figure 6). These data have suggested caution in the use of mazindol in outpatient treatment (Jaffe et al. 1989). However, the shifts in the dose-response functions were relatively small (about twofold), and the dose of mazindol used in these experiments was only one log-unit lower than the convulsant and lethal doses of mazindol. Since the therapeutic dose range for mazindol would be estimated to be below that used here, the potential for drug-interaction toxicity may be relatively small.

### Tricylic Antidepressants

Although not without problems of compliance, side effects, and imperfect overall treatment outcomes, desmethylimipramine is one of the most used pharmacological treatments for cocaine abuse (Gawin et al. 1989; Johanson and Fischman 1989; McElroy et al. 1990; O'Brien et al. 1988). Tricyclic antidepressants might be anticipated to increase toxicity problems of cocaine abuse, and cardiovascular toxicity has been noted (Fischman et al. 1990). However, Jackson and coworkers (1990) noted that desmethylimipramine afforded significant protection against the lethal effects of high doses of cocaine in mice.

### Opioids

The partial opioid agonist buprenorphine has been reported in both preclinical studies and in open clinical trials to display efficacy in decreasing cocaine self-administration (Kosten et al. 1989a, 1989b; Mello et al. 1989, 1990; Carroll and Lac, in press; see Witkin, in press, for summary). Buprenorphine has been shown to produce a dose-dependent protection against the lethal effects of cocaine (Witkin et al. 1991b; figure 7, top panel). Although buprenorphine protects against cocaine lethality, the convulsant effects of cocaine are unaltered by buprenorphine treatment.

Further investigation suggested that the protection provided by buprenorphine was due to μ-opioid agonist actions of buprenorphine. Other μ-opioids also confer protection at relative potencies that are consistent with their affinities for μ-opioid receptors. In addition, the unnatural (+)-enantiomer of buprenorphine is devoid of activity; protection is blocked by relatively low doses of naloxone

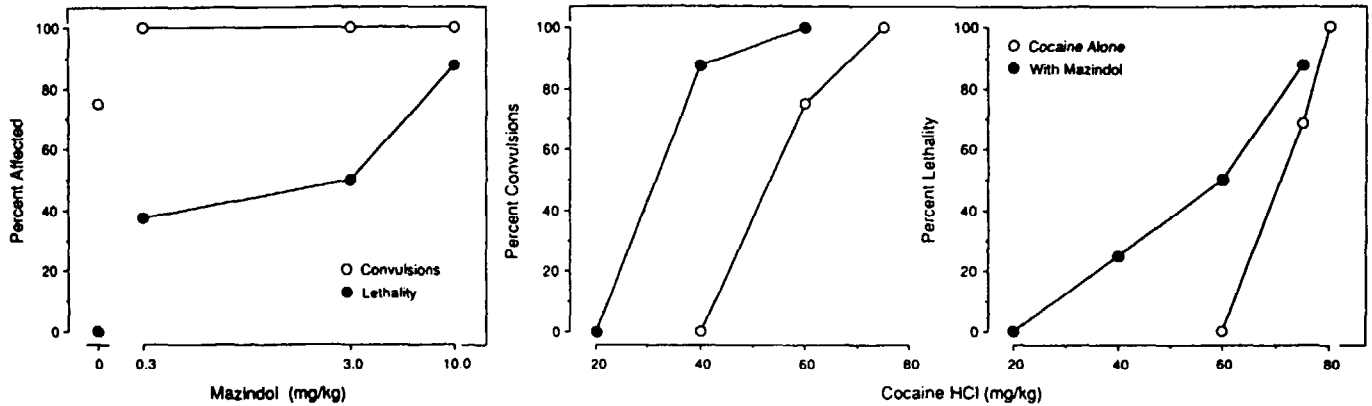




**FIGURE 6.** *Enhancement of the convulsant and lethal effects of cocaine by mazindol. Left panel: Effects of increasing doses of mazindol against a fixed dose of cocaine (60 mg/kg) that was not lethal when given alone. Right panels: Effects of cocaine alone and in the presence of 3 mg/kg mazindol on the convulsant and lethal effects of cocaine. Mazindol alone did not induce convulsions or lethality at doses below 30 mg/kg. Each point represents effects observed in at least eight male Swiss Webster mice.*

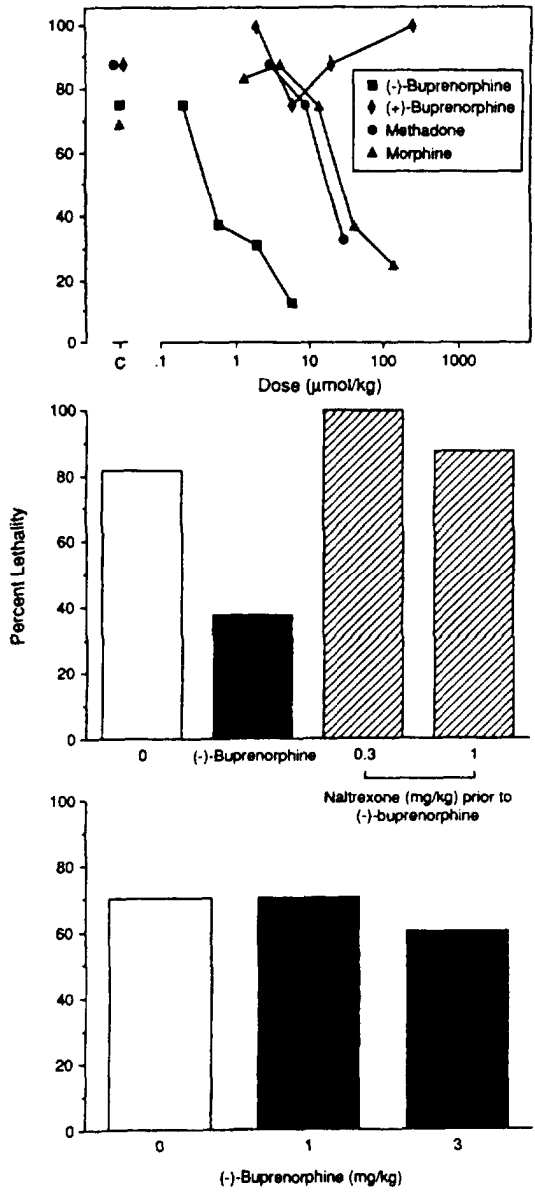


**FIGURE 7.** *Top panel: dose-dependent protection against cocaine-induced lethality by several µ-opioids, but not by (+)-buprenorphine, which does not interact with opioid receptors. Respective control effects of cocaine alone (75 mg/kg) are shown by the*

*unconnected points above C. Middle paneL: antagonism by naltrexone of the protection against cocaine-induced lethality conferred by buprenorphine. Unfilled bar: cocaine alone (75 mg/kg); solid bar: (-)-buprenorphine (1.0 mg/kg) administered 30 minutes before cocaine; striped bars: naltrexone (0.3 or 1.0 mg/kg) administered 15 minutes before (-)-buprenorphine, which was given 30 minutes before cocaine. Bottom panel: lack of effect of (-)-buprenorphine on cocaine-induced lethality in CXBK mice, Unfilled bar: cocaine alone (100 mg/kg); solid bars: (-)-buprenorphine (1.0 or 3.0 mg/kg) administered 30 minutes before cocaine.*

SOURCE: Witkin et al. 1991b. Copyright 1991 by Elsevier Scientific Publishers Ireland Ltd. (Shannon).

(figure 7, middle panel); and buprenorphine does not induce protection in CXBK mice, a recombinant inbred mouse strain relatively devoid of μ-opioid receptors (figure 7, bottom panel).

**Carbamazepine**

Carbamazepine recently has received attention as a potential cocaine treatment agent based on the preclinical observations of Post and Weiss (1989) and the initial positive clinical findings of Halikas and coworkers (1989). Post and Weiss (1989) drew parallels between the sensitization that develops to the stimulatory, seizurogenic effects and mania induced by cocaine, as well as manic-depressive psychosis. Since carbamazepine has been used in the treatment of manic-depressive psychosis, these authors suggest it also may be useful in the treatment of cocaine abuse. Data indicate that carbamazepine can attenuate the development of cocaine-kindled seizures but not sensitization to the locomotor stimulatory effects of cocaine in rats; however, carbamazepine does not alter the convulsions induced by high doses of cocaine once kindling has progressed (Post and Weiss 1989; Weiss et al. 1990). Substantial differences in the degree to which carbamazepine confers protection against both acute and kindled convulsions and lethality have been reported across mouse strains (Marley and Goldberg 1991). The relevance of these observations to an understanding of the mechanisms of action of carbamazepine as a blocker of effects of cocaine will require further detailed study.

## ANTICONVULSANT DEVELOPMENT

Convulsions associated with cocaine abuse can be life threatening and resistant to standard anticonvulsant drugs. In some models of cocaine seizures, even high, incapacitating doses of diazepam are ineffective against cocaine convulsions (Witkin and Tortella 1991). In this model, high doses of cocaine (75 mg/kg, intraperitoneally [IP]) produced *diazepam-insensitive* convulsions, whereas somewhat lower doses (60 mg/kg, IP) produced *diazepam-sensitive* convulsions (see also Derlet and Albertson 1990b). A host of other compounds are also inactive against diazepam-insensitive cocaine convulsions. These compounds include the nonopioid antitussive anticonvulsants (caramiphen, carbetapentane, and dextromethorphan), $D_1$ dopamine receptor antagonists, noradrenergic antagonists, various opioids, and 5-$HT_2$ serotonin antagonists (Tortella et al., in press).

In contrast, noncompetitive N-methyl-D-aspartate (NMDA) antagonists dose-dependently blocked the diazepam-insensitive convulsions (figure 8, left panel). In addition, protection against diazepam-sensitive convulsions also was conferred by antagonists that act competitively at the NMDA receptor. Importantly, competitive antagonists generally have been found to be devoid of the phencyclidine-like behavioral effects associated with the noncompetitive antagonists (Willetts et al. 1990).

The relation of these data to the NMDA receptor is strengthened by observations that drugs that act at other sites on the NMDA receptor complex also modify the convulsant effects of cocaine. The NMDA receptor is coupled allosterically to a strychnine-insensitive glycine receptor. An antagonist (7-chlorkynurinic acid) and a partial agonist (ACPC) at this site also were evaluated for anticonvulsant efficacy against cocaine since they attenuate the convulsant and lethal effects of exogenously administered NMDA at doses well below those producing behavioral incapacitation. Figure 8 (right panel) shows that these compounds also produce protection against diazepam-sensitive cocaine convulsions. Further results suggest that some of these compounds may be useful adjuncts to standard anticonvulsant therapy. For example, caramiphen and diazepam are devoid of activity against diazepam-insensitive convulsions when given alone; in conjunction with low doses of diazepam, caramiphen dose-dependently protected against diazepam-insensitive cocaine convulsions (Tortella et al., in press).

## ANTIPSYCHOTIC DEVELOPMENT

Compounds that bind to o-receptors are being developed as novel antipsychotic agents that may be devoid of the side effects associated with conventional

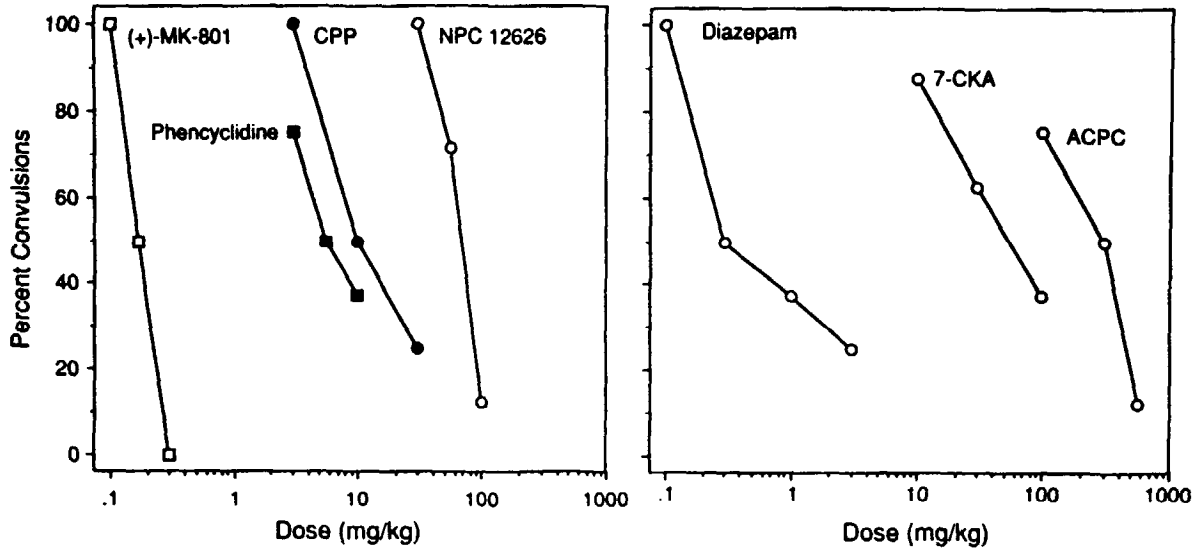


**FIGURE 8.** *Left panel: dose-dependent attenuation of the diazepam-insensitive convulsive effects of 75 mg/kg cocaine by competitive (CPP, NPC 12626) and noncompetitive (MK-801, phencyclidine) NMDA antagonists. Right panel: prevention of the convulsions induced by 60 mg/kg cocaine by diazepam and two ligands of the strychnine-insensitive glycine site of the NMDA receptor/ion complex.*

SOURCE: Witkin and Tortella 1991. Reprinted with permission from *Life Sciences-Pharmacology Letters, vol. 48,* Witkin, J.M., and Tortella, F.C. Modulators of N-methyl-D-aspartate protect against diazepam- or phenobarbital-resistant cocaine convulsions. Copyright 1991 by Pergamon Press plc (Elmsford, NY).

antipsychotics, such as haloperidol. The ability of the selective σ-ligands BMY 14802 and rimcazole to block the locomotor stimulant effects of cocaine was compared with that of haloperidol and (+)-3-PPP, which have both dopamine and σ-receptor affinity, and the novel non-σ antipsychotic clozapine. Each of the selective σ-ligands produced a significant shift in the cocaine dose-effect functions at doses that did not have significant behavioral effects of their own. In contrast, haloperidol, (+)-3-PPP, and clozapine were inactive as antagonists of the locomotor stimulant effect of cocaine at doses that were behaviorally inactive. At higher doses, all of these drugs except (+)-3-PPP also blocked the locomotor stimulant effects of cocaine (Menkel et al. 1991). Interestingly, (+)-3-PPP completely protected against the convulsant effects of cocaine, whereas other σ-ligands were only moderately effective, if at all (Tortella et al., in press).

The attenuation of the stimulant effects of cocaine by the selective σ-compounds suggests a novel approach to the development of drugs that may be useful in the treatment of cocaine abuse and psychotic symptomatology. The activity of these σ-ligands against cocaine at doses without significant behavioral activity of their own suggests that these compounds might specifically block the psychotropic effects of cocaine without interfering with ongoing behavior. The discovery and evaluation of other σ-site-selective ligands will help clarify questions of mechanism and may foster development of antagonists with therapeutic efficacy in the treatment of cocaine abuse and toxicity.

## CONCLUSIONS

The acute and chronic toxicity of cocaine is not fully understood. Treatment strategies, although generally effective, remain imperfect. There are several areas in which improved medications could be clinically useful. Preclinical drug development efforts can increase understanding of the mechanisms underlying cocaine toxicity, develop functional and predictive models, establish safety of cocaine abuse treatments, and provide new leads in the development of more effective medications to be used in the treatment of drug overdose toxicity and drug abuse.

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**AUTHORS**

Jeffrey M. Witkin, Ph.D.
Head
Drug Development Group
Psychobiology Laboratory

Jonathan L. Katz, Ph.D.
Chief
Psychobiology Laboratory

Preclinical Pharmacology Branch
Addiction Research Center
National Institute on Drug Abuse
P.O. Box 5180
Baltimore, MD 21224

# The Cardiovascular Effects of Cocaine—Update 1992*

*Lewis R. Goldfrank and Robert S. Hoffman*

## INTRODUCTION/EPIDEMIOLOGY

In 1974 the National Institute on Drug Abuse (NIDA) estimated that 5.4 million Americans had used cocaine at some time in their lives (Abelson and Miller 1985; Johnston et al. 1987). This number increased dramatically so that by 1985 there were 25 to 40 million Americans who had used the agent, 3 million of whom could be considered cocaine dependent (Abelson and Miller 1985; Johnston et al. 1987). In 1988 there were 3.5 million Americans between the ages of 18 and 25 who admitted to frequent use of cocaine (National Institute on Drug Abuse 1989). Similar studies, including that of the NIDA-sponsored Drug Abuse Warning Network (DAWN), have demonstrated a tenfold to twentyfold increase in emergency department utilization for cocaine-related problems (Colliver 1987; National Institute on Drug Abuse 1987a, 1987b; Adams and Durell 1984; Jekel et al. 1986). Cocaine use is commonly associated with the concomitant administration of other substances of abuse such as ethanol, opioids (typically heroin), marijuana, and sedative hypnotics (typically benzodiazepines). Current data suggest a marked increase in cocaine use and complications. For example, in 1980 cocaine was the 10th most commonly used drug in patients presenting to the Bellevue Hospital Emergency Department; however, by 1989 it became the most commonly used agent (unpublished data). As of 1986 cocaine use was the most frequent drug-related cause of U.S. emergency department visits and ranked third behind opioids and drugs combined with ethanol as the cause of drug-related mortality (MacDonald 1987). Finally, between 1985 and 1988 cocaine-related mortality increased from the fourth to the second most common cause of death (accounting for more than 11.5 percent of the total fatalities) reported to the American Association of Poison Control Centers National Data Collection System (Litovitz et al. 1986, 1989).

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The first systematic study designed to validate drug abuse mortality data, from either national vital statistics (maintained by the Centers for Disease Control's National Center for Health Statistics [NCHS]) or DAWN, by means of a comparison with a supplemental cause of death database was undertaken between 1983 and 1988 in 25 metropolitan areas (Pollack et al. 1991). During this 6-year period, DAWN reported 6,057 cocaine-related fatalities, and NCHS reported 3,466. Depending on the database utilized, the differences in individual cities were as great as 600 percent. In addition, Pollack and colleagues (1991) demonstrated that mortality rates exceeded the number of deaths reported to NCHS in six of seven forensic case series studied. When not attributed to trauma or human immunodeficiency virus infection, the marked increase in fatalities described in all the current series is ascribed to cardiovascular causes (National Institute on Drug Abuse 1987b).

Despite their limitations, these reports demonstrate evolving patterns of utilization, showing that intranasal cocaine (insufflation), which was the primary route of delivery in the early 1980s, was replaced largely by intravenous (IV) cocaine in the mid-1980s and by smoking the alkaloid form of cocaine known as "crack" in the late 1980s (Abelson and Miller 1985; Johnston et al. 1987; Colliver 1987; National Institute *on* Drug Abuse 1987a, 1987b; Jekel et al. 1986). The myriad clinical manifestations of cocaine intoxication include systemic complications such as malnutrition and exhaustion as well as neurologic, psychiatric, cardiovascular, venous, musculoskeletal, dermatologic, gastrointestinal, pulmonary, infectious, obstetrical, and neonatal manifestations. There is no current evidence to suggest that the presence of preexistent vascular disease or other abnormalities are essential prerequisites for the development of a cocaine-related cardiovascular event. This chapter emphasizes the cardiovascular and systemic vascular characteristics of cocaine utilization and their therapeutic implications; it also attempts to minimize reliance on the reported rates of cocaine drug use, complication, and death due to the demonstrated unreliability of the current databases (Kleber 1991; Schuster 1991; Weisman and Goldfrank 1991).

## PHARMACOLOGIC PRINCIPLES

The white crystalline powder benzoylmethylecgonine (cocaine) is widely used (by insufflation or IV route) as the highly water-soluble hydrochloride salt or (by smoking) as the free base (or crack) form, which has limited water solubility but is more volatile, vaporizable, and stable to pyrolysis when compared with the hydrochloride salt. Cocaine's pharmacologic effects are unusual in that it (1) can inhibit the initiation or conduction of nerve impulses (anesthetic effect) and (2) has both centrally and peripherally mediated vasoconstrictor effects (Ritchie and Greene 1990). The pharmacologic effects of cocaine are discussed from a

theoretical perspective and often differ from the reported clinical responses. Patients invariably utilize multiple other substances that alter the normal end organ manifestations and potential adverse effects. The neuropharmacologic drug interactions, the pharmacokinetic changes, and the development of new metabolites have not been studied in detail.

Cocaine is a central nervous system (CNS) stimulant. Cocaine use is associated with a general feeling of well-being, manifested by enhanced alertness, self-confidence, reduction in social inhibitions, euphoria, and dysphoria (Gawin 1991). The vasomotor center is initially stimulated producing hypertension and tachycardia; however, later these same medullary centers are depressed with the resultant development of respiratory depression and possible death (Tseng et al. 1991). Small doses of cocaine slow the heart due to a central vagally mediated effect (Ritchie and Greene 1990), whereas larger doses produce tachycardia by direct central stimulation and also by increasing peripheral catecholamine levels (Ritchie and Greene 1990). This latter effect results from cocaine-induced blockade of norepinephrine reuptake, one of the mechanisms normally responsible for limitation of peripheral catecholamine effects. Cocaine also may alter neurotransmission of histamine, acetylcholine, and phenylethylamine (Gawin 1991). Alternatively, cocaine's stimulatory effects may be mediated through the release of the excitatory amino acids aspartate and glutamate (Rockhold 1991). Although cocaine also affects the release and reuptake of serotonin and dopamine, which are the major determinants of stimulant abuse, psychiatric complications, and withdrawal manifestations (Gawin and Ellinwood 1988) this chapter does not focus on these pharmacological effects. Possible alterations in plasma cholinesterase (Van Dyke et al. 1978) (the major enzyme responsible for cocaine metabolism) as well as the development of an incomplete form of tolerance (Ambre et al. 1988) play a role in the adaptive process. This adaptive process, which allows for the euphoria and cardioacceleratory effects to diminish at a more rapid rate than the plasma cocaine levels, has been demonstrated by several researchers (Javaid et al. 1978; Zahler et al. 1982; Chow et al. 1985). That a second dose of cocaine delivered within an hour of the initial dose induces a lesser response is suggestive of highly effective homeostatic negative feedback mechanisms or acute tolerance (Chow et al. 1985; Fischman and Schuster 1981).

The initial effect on blood pressure is directly related to sympathetically induced tachycardia and vasoconstriction. A subsequent fall in blood pressure may follow as massive cocaine doses probably result in direct toxic effects on the myocardium. These manifestations of homeostasis, adaptation, and tolerance play a substantial role in the diverse pathophysiologic characteristics of cocaine toxicity, in addition to those that are specifically cardiovascular in nature (Fischman and Schuster 1981).

Cocaine is absorbed by all sites (typically the mucous membranes but also the respiratory, gastrointestinal, cutaneous, and genitourinary tract routes), and it is absorbed whether in the hydrochloride or the free base form. The rapidity of peak onset of action from the IV and inhalation routes are approximately 30 seconds to 2 minutes, whereas intranasally the peak effect may be achieved within one-half hour. Gastrointestinal peak absorption may be delayed for up to 90 minutes (Van Dyke et al. 1978). The duration of effect is directly related to onset of effect and is approximately 15 to 30 minutes by IV or inhalation route, 1 hour by intranasal exposure, and as long as 3 hours after gastrointestinal absorption (Resnick et al. 1977). Following the IV or inhalational administration of cocaine the plasma half-life approximates 60 minutes, but because of cocaine's vasoconstrictor effect its absorption is inhibited by the intranasal route, and the apparent half-life approaches 2 to 3 hours (Javaid et al. 1978; Zahler et al. 1982).

Cocaine is rapidly metabolized in great part by plasma (and somewhat by hepatic) cholinesterases to an inactive metabolite, ecgonine methyl ester (Inaba et al. 1978). Human and animal evidence suggests that an association exists between the manifestations of cocaine intoxication and plasma cholinesterase activity such that low plasma cholinesterase activity increases the risk for life-threatening cocaine toxicity (Hoffman et al. 1991, 1992; Devenyi 1989). Benzoylecgonine, the other major inactive metabolite of cocaine, is formed as the result of nonenzymatic hydrolysis in the blood (Stewart et al. 1977, 1979). Norcocaine, an active metabolite, is formed by an N-demethylation reaction and usually represents less than 5 percent of the total quantity of cocaine metabolites (Inaba et al. 1978). At most, 5 to 10 percent of the total cocaine dose is excreted unchanged in the urine. Unmetabolized cocaine is not usually present in the serum after 6 hours, whereas the metabolites can usually be found for at least 48 hours (Verebey 1987). Actually, the ratio of cocaine to its metabolites in the urine has been used to predict the time of exposure (Ambre 1985). Recently, benzoylecgonine has been detected in the urine as late as 22 days after the last intoxication in three asymptomatic patients with histories of substantial cocaine use (Weiss and Gawin 1988). Although it is unclear whether this is related to storage in body tissues or to abnormal metabolism, this finding may have important clinical implications if active cocaine metabolites may also be delayed in their metabolism and/or excretion.

## CARDIOVASCULAR MANIFESTATIONS OF COCAINE

The toxic vascular effects of cocaine in humans are due largely to direct stimulation of the central nervous, cardiovascular, and respiratory systems Concomitant inhibition of catecholamine reuptake serves to amplify and perpetuate these effects. Overstimulation and subsequent catecholamine

depletion may produce central nervous, cardiovascular, and respiratory system depression. This section deals in greatest detail with the heart, great vessels, and CNS but will also focus on the vascular effects of the pulmonary skeletal musculature, dermatologic, gastrointestinal, uterine, placental, and fetal systems. A summary of the vascular effects of cocaine can be found in table 1.

**The Heart**

There are now numerous reports documenting myocardial ischemia and infarction during cocaine intoxication (Coleman et al. 1982; Kossowsky and

**TABLE 1.** *Summary of vascular complications of cocaine toxicity*

| System | Complication |
|---|---|
| Neurologic | Intracerebral hemorrhage, cerebral infarction, seizures, migraine headache, vasculitis, blindness |
| Cardiac | Myocardial infarction, myocardial ischemia, coronary vasospasm, arrhythmias myocarditis, cardiomyopathy |
| Great vessels | Aortic dissection and rupture, hypertension |
| Gastrointestinal | Mesenteric ischemia and infarction, gastrointesinal perforation, hepatic failure, splenic infarction |
| Pulmonary | Pulmonary edema, infarction |
| Musculoskeletal | Rhabdomyolysis |
| Dermatologic | Ischemia |
| Uterine, placental, obstetrical, and neonatal | *Abruptio placentae,* spontaneous abortion, prematurity, developmental delays, growth retardation, congenital abnormalities |
| Genitourinary | Renal and testicular infarction, myoglobinuric renal failure |
| Venous | Vasculitis, superficial and deep venous thrombosis and thrombophlebitis |

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Lyon 1984; Schachne et al. 1984; Cregler and Mark 1985; Howard et al. 1985; lsner et al. 1986; Pasternack et al. 1985; Mathias 1986; Simpson and Edwards 1986; Weiss 1986; Smith et al. 1987; Frishman et al. 1989; Stenberg et al. 1989; Amin et al. 1990; Minor et al. 1991; Zimmerman et al. 1991; Brody et al. 1990a; Tokarski et al. 1990; Gitter et al. 1991) or withdrawal (Nademanee et al. 1989). These case reports have demonstrated that infarctions frequently occur in patients in the 19- to 40-year-old range without apparent massive exposures (Schachne et al. 1984) to cocaine or without concurrent seizures or agitation. Patients with cocaine-associated myocardial infarctions frequently have either atypical chest pain, no chest pain, or chest pain delayed for hours to days after their most recent use of cocaine (Amin et al. 1990; Zimmerman et al. 1991; Brody et al. 1990a; Tokarski et al. 1990; Gitter et al. 1991). The electrocardiograms revealed abnormalities consisting of ST segment elevation and T-wave inversions that persisted during hospitalization. Electrocardiographic abnormalities were noted in many, but not all, patients with acute myocardial infarctions (Amin et al. 1990; Tokarski et al. 1990). In addition, no predeliction for a specific coronary artery distribution was shown, and Q-wave or non-Q-wave infarctions were equally frequent (Amin et al. 1990). These researchers offer varying analyses of the pathogenesis of these events. Mechanisms of pathogenesis under consideration include tachyarrhythmias, systemic arterial hypertension, increased myocardial oxygen demand, immediate or delayed coronary vasospasm, predisposition due to underlying coronary artery stenosis, increased platelet aggregation, and accelerated atherogenesis. There has been no evidence correlating blood levels or route of administration to the development of cocaine-induced myocardial ischemia or infarction (Mittleman and Wetli 1984). Autopsy and angiographic studies have demonstrated myocardial infarction in the absence of atherosclerotic disease and any other evidence of underlying heart disease (Cregler and Mark 1985; Howard et al. 1985; lsner et al. 1986; Pasternack et al. 1985; Minor et al. 1991). Minor and coworkers (1991) performed a comprehensive review of all 35 reported cases of myocardial infarction temporally related to the use of cocaine in the presence of normal coronary arteries. These patients, with an average age of 32 years (range 21 to 60 years), experienced myocardial infarction involving the anterior left ventricular wall 77 percent of the time, Focal coronary vasospasm was found in 2 cases, and an intracoronary thrombus was found in 9 of 11 patients studied within 12 hours of infarction. Angiography done shortly after infarction has demonstrated acute thrombotic occlusion, which, after being treated with thrombolytic agents, has shown no underlying atheromatous disease (Smith et al. 1987). However, in an autopsy study of 17 non-cocaine-related fatalities in young (average age 32 years) cocaine abusers, coronary artery narrowing of greater than 75 percent of luminal diameter was found in approximately 50 percent of cases (Dressler et al. 1990).

In 90 percent of patients with variant angina (Prinzmetal's), ergonovine challenge tests normally lead to a rise in systemic pressure, diffuse coronary artery narrowing, and focal vasospasm (Isner et al. 1986). However, administration of ergonovine in patients with cocaine-induced myocardial infarctions uniformly fails to produce focal vasospasm (Howard et al. 1985; Isner et al. 1986; Pasternack et al. 1985), although Chokshi and colleagues (1989a) described a patient with a history of a cocaine-related ischemic event who had a negative ergonovine provocation test and severe coronary vasospasm when provoked with intranasal cocaine. Thus, the absence of a response to standard testing techniques cannot be used to exclude the possibility that cocaine-induced vasospasm occurred.

In the normal myocardium, increased oxygen demand stimulates coronary vasodilation through an autoregulatory mechanism (Marcus 1983). In the presence of cocaine and the marked increase in sympathetic activity, this autoregulation may be lost and vasoconstriction may take precedence (Mathias 1986) as has been noted in those with established atherosclerotic lesions (Mudge et al. 1976). Although many of the patients studied also smoked cigarettes and used other drugs as well as cocaine admixed with numerous contaminants, these episodes have also occurred when cocaine was smoked exclusively, which is usually considered to be a relatively pure intoxication (Smith et al. 1987). The strongest correlation can be made in individuals when there is a temporal relationship between the use of cocaine and the myocardial infarction or the recurrent episode of ischemia.

Ventricular wall akinesis and dyskinesis have been demonstrated in the distribution of the infarction. Infarctions have been anterior, inferior, and anterolateral, with the left anterior descending coronary artery being most frequently affected (Smith et al. 1987; Frishman et al. 1989). In many of the affected individuals, ischemia recurred in those who continued to utilize cocaine (Smith et al. 1987), with subsequent reinfarction (Simpson and Edwards 1986; Weiss 1986) and death being described (Simpson and Edwards 1986). In certain patients with cocaine-induced myocardial infarctions, normal stress electrocardiograms and thallium studies have been subsequently documented (Isner et al. 1986).

The sympathomimetic action of cocaine and the effects of epinephrine and norepinephrine are postulated to initiate platelet adherence and aggregation (Tonga et al. 1985). In cocaine-associated deaths some researchers (Tazelaar et al. 1987) have demonstrated a marked increase ($p<.001$) in myocardial contraction band necrosis (93 percent) at autopsy when compared with a control population of sedative-hypnotic drug-associated deaths (45 percent). However, Virmani and colleagues (1988) were unable to demonstrate any

statistically significant relationship, with a 25-percent incidence of contraction band necrosis being found in those patients with cocaine-associated deaths and a 41-percent incidence in those patients with sudden traumatic death. Contraction band necrosis is pathologically defined by the hypercontracted sarcomere and myofibrillar disruption commonly occurring in patients in the presence of high catecholamine levels, such as with pheochromocytomas (Rosenbaum et al. 1987; Reichenbach and Benditt 1970) or in the presence of cocaine (Karch and Billingham 1986). Myocyte necrosis occurs, and this tissue is ultimately replaced by fibrous tissue. Karch and Billingham (1986) suggest that this myofibrillar degeneration may indicate reperfusion injury. Direct cocaine-induced coronary vasospasm has been suggested in a human angiography study with patients receiving 2 mg/kg cocaine intranasally (Lange et al. 1989). In these patients with no prior use of cocaine, diffuse coronary artery constriction occurred in the absence of associated chest symptoms or pain. The heart rate and arterial blood pressure increased while the coronary sinus blood pressure and the diameter of the left coronary artery fell. All these parameters returned to normal when an intracoronary infusion of the $\alpha$-adrenergic blocker phentolamine was given. Another study demonstrated enhanced evidence of vasoconstriction at sites of significant coronary artery stenosis (Flores et al. 1990). This vasospasm was exacerbated by the administration of propranolol, which produced anginal symptoms and ST-segment elevation in one of the study patients, Animal experimental models that support the theory of cocaine-induced coronary vasospasm are reviewed by lsner and Chokshi (1989).

Chronic alterations in catecholamine levels may produce coronary vasospasm, thereby making the individual prone to ischemia and infarction by simultaneously increasing myocardial oxygen demand and decreasing oxygen supply. Nademanee and coworkers (1989) recently demonstrated with ambulatory electrocardiographic monitoring that individuals had spontaneous ischemic episodes during the first weeks of undergoing withdrawal from cocaine. They postulate that patients in cocaine withdrawal manifest a dopamine-depleted state, which results in intermittent coronary spasm. Del Aguila and Rosman (1990) recently documented a myocardial infarction that occurred 3 days after cocaine use in a 42-year-old male with normal coronary arteries. The researchers postulated a state of increased adrenergic receptor sensitivity and catecholamine replenishment during the cocaine withdrawal period as an explanation for their findings. Further understanding of the pharmacologic characteristics of cocaine withdrawal may better explain these events.

## Myocarditis

Although Virmani and colleagues' (1988) study did not demonstrate myocardial contraction band necrosis, it did demonstrate mononuclear myocarditis in 20 percent of those patients who died with detectable cocaine in body fluids, whereas only 3.7 percent of those without cocaine who succumbed to a traumatic death had similar findings. The study suggests that mononuclear myocarditis may represent the result of microvascular injury. One of the patients reported by Isner and colleagues (1986) also had myocarditis with a characteristic eosinophilic leukocytic infiltration, as did two additional patients in the Virmani group and several patients in other studies, suggesting a hypersensitivity reaction to cocaine, its metabolites, or contaminants (Karch and Billingham 1988).

Striking similarities have been noted in patients with ineffectively treated or untreated pheochromocytomas or in animals exposed to norepinephrine. Examination of the hearts of 26 patients who died with pheochromocytoma demonstrated an active myocarditis in 58 percent, and two-thirds of these patients died of left ventricular failure (Van Vliet et al. 1966). These researchers characterized the focal degeneration and necrosis of myocardial fibers with foci of histiocytes, plasma cells, and polymorphonuclear leukocytes as an "active catecholamine myocarditis." In a preliminary rat study, 40 percent of 60 rats died within 72 hours after being given 1 to 2 subcutaneous injections of 2 mg of norepinephrine per kilogram body weight (Van Vliet et al. 1966). All these animals were found to have an active myocarditis; those rats sacrificed during the first 5 days following the experiment also showed an active myocarditis, whereas those that were sacrificed 3 to 8 weeks later showed myocardial fibrosis.

## Arrhythmias

Low-dose cocaine may result in bradycardias, whereas higher doses have been associated with virtually all other arrhythmias. Sinus tachycardia, atrial fibrillation, ventricular extrasystoles, accelerated idioventricular rhythms, and ventricular tachycardia and fibrillation may follow exposure to cocaine and may be directly related to increased catecholamine levels from effects on the central and peripheral sympathetic nervous systems. In addition, cocaine-induced myocardial ischemia or infarction may produce secondary cardiac arrhythmias that are indistinguishable from those arrhythmias produced from atherosclerotic heart disease. Recent work has concentrated on cocaine's direct effects on myocardial conduction and arrhythmogenesis. In dogs, Schwartz and coworkers (1989) demonstrated that, although low doses of cocaine produced increases in blood pressure, higher doses resulted in hypotension, infranodal

and interventricular conduction delays, and lethal ventricular arrhythmias. In this study the QRS and QT intervals were markedly prolonged, and PR intervals remained unchanged. Similar effects were noted by Parker and colleagues (1989a), who suggested that cocaine demonstrated electrophysiologic properties similar to type I antiarrhythmics, producing classic QRS and QT prolongation. This probably occurs through blockade of sodium channels and may help to explain why increasing doses of cocaine appear to have a direct myocardial depressant effect (Perreault et al. 1989; Hale et al. 1989). Some of these arrhythmias may lead to a cerebral hypoperfusion and a transient loss of consciousness, a common finding in the cocaine-overdosed patient. Clinically, this presentation must be differentiated from a seizure disorder or a cerebrovascular catastrophe. A schematic representation of the mechanisms that lead to myocardial ischemia *or* arrhythmias is shown in figure 1.

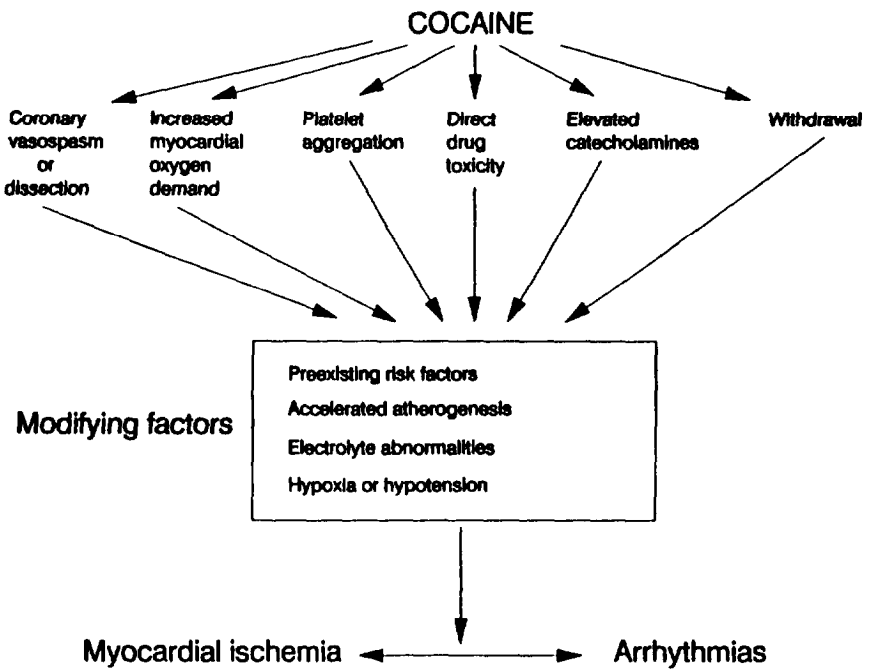


**FIGURE 1.** *Mechanism of acute cocaine-induced arrhythmias and myocardial ischemia*

## Cardiomyopathy

Long-term cocaine use predisposes to the development of a dilated cardiomyopathy and recurrent myocardial infarction even in the absence of atherosclerotic epicardial coronary artery disease. Although this form of dilated cardiomyopathy may result from ischemia and the induction of a "stunned" myocardium secondary to protracted coronary vasospasm (Weiner et al. 1986), recent work has suggested that cocaine may have a direct effect on contractility independent of its ischemic effects (Johnson et al. 1989). Chokshi and colleagues (1989b) described a patient who developed a dilated cardiomyopathy temporally related to using free base cocaine. With noninvasive studies, this patient's left ventricular systolic function was demonstrated to improve during a 2-week period of cocaine abstinence. More recently, Van De Bor and associates (1990) demonstrated that infants born to cocaine-using mothers had statistically lower cardiac outputs in the first day of life when compared with control infants; the differences resolved by the second day of life. These results are quite comparable with the catecholamine-induced reversible cardiomyopathies reported to be associated with pheochromocytomas (Imperato-McGinley et al. 1967) and methamphetamine use (Hong et al. 1991).

## Endocarditis and Endothellal Injury

An increased risk of upper extremity deep vein thrombosis (Lisse et al. 1989a, 1989b) and bacterial endocarditis (Chambers et al. 1987) has been noted to be associated with IV cocaine use. This risk of endocarditis seems to be higher than that for a similar population of IV heroin users and may result from the increased frequency of injections in cocaine users or from direct effects of cocaine on endovascular tissues and the immune system (Chaisson et al. 1989; Weiss 1989). The normal functioning of the coronary artery endothelial cells is dependent on the release of endothelium-derived releasing factor. This agent is recognized as nitric oxide (Palmer et al. 1987) or another nitrosothiol compound. Endothelial dysfunction has been noted in individuals with coronary risk factors. Dysfunction also has been noted in humans who are hypersensitive to catecholamines with vasoconstrictor properties such as serotonin, which, in the presence of endothelial dysfunction, also causes intense vasoconstriction of vascular smooth muscle, potentially resulting in coronary vasospasm (Vanhoutte and Shimokawa 1989). Minor and coworkers (1991) also suggest that an endothelial-derived contracting factor may play a role in vasospasm. All these factors represent a potential for endothelial injury and dysfunction, which may result in platelet-mediated vasoconstriction and aggregation.

## The Great Vessels

Several cases of cocaine-induced aortic dissection and rupture have been reported (Tardiff et al. 1989; Barth et al. 1986; Gadaleta et al. 1989; Edwards and Rubin 1987). In one pathologic report a medial dissection ruptured proximally to the level of the aortic valve cusps in a man who had been smoking free base cocaine (Barth et al. 1986). It is presumed that dissection and rupture result from the increase in shear forces that result from cocaine-induced hypertension and tachycardia. This is supported by the lack of pathological correlates of aortic dissection (e.g., atherosclerotic aneurysms, syphilitic aortitis, cystic medial necrosis, Marfan's syndrome). To date, no cases of rupture of abdominal aneurysms, which are typically atherosclerotic in nature, have been reported to be associated with cocaine use.

## Cerebral Vasculature

Cerebrovascular accidents, including subarachnoid hemorrhage (Lichtenfeld et al. 1984; Schwartz and Cohen 1984), intracerebral hemorrhage (Wojak and Flamm 1987), cerebral infarction (Seaman 1990; Brust and Richter 1977; Levine et al. 1987, 1990; Golbe and Merkin 1986) transient ischemic attacks (Mody et al. 1988), migraine-like headache syndromes (Satel and Gawin 1989), seizures (Choy-Kwong and Lipton 1989a), cerebral vasculitis (Kaye and Fainstat 1987), anterior spinal artery syndrome (Mody et al. 1988), and the more common psychiatric manifestations (Lowenstein et al. 1987), have been reported with increasing frequency. In all but one of these case reports or series there was no correlation with the route of cocaine delivery, the amount taken, or prior exposure (Levine et al. 1990). Levine and coworkers (1990) found that ischemic and hemorrhagic strokes were reported with nearly equal frequency in association with the use of alkaloidal cocaine, whereas cocaine hydrochloride was associated with approximately 80 percent of the intracranial hemorrhages, and in 50 percent of these cases ruptured cerebral saccular aneurysms or vascular malformations were noted.

Although some patients have evidence of underlying cerebrovascular disease such as rupture of preexisting unsuspected aneurysms or arteriovenous malformations under the influence of cocaine-induced hypertension, reports have failed to demonstrate underlying disease in most patients (Wojak and Flamm 1987; Satel and Gawin 1989; Henderson and Torbey 1988). Other mechanisms have been proposed for stroke associated with cocaine use and include increased coagulability, impaired cerebrovascular autoregulation from increased cerebrovascular resistance (Levine et al. 1987, 1990), vasospasm (Golbe and Merkin 1986), embolism of particulate matter, and immunologically mediated arteritis or vasculitis (Caplan et al. 1982; Krendel et al. 1990).

Recently, the finding of a high incidence of anticardiolipin antibodies in the serum of cocaine users has led some researchers to conclude that the immunologic mechanisms may play a greater role in cocaine toxicity than previously assumed (Fritsma et al. 1991).

The visual system has also been affected by cocaine. Direct instillation into the conjunctival sac denudes the corneal epithelium (Ravin and Ravin 1979). Toxicity from particulates in smoke and irritation produce corneal abrasions and ulcerations in a syndrome known as "crack eye" (McHenry et al. 1989). Vascular effects, including central retinal artery occlusion (Devenyi et al. 1988) and bilateral blindness from diffuse vasospasm (Reimer and Hoffman 1991) have also been noted.

**Pulmonary Vasculature**

The possibility of a direct effect of cocaine on the pulmonary vasculature has not been thoroughly evaluated. This is extremely important in view of the highly concentrated heated cocaine alkaloid that is frequently used and directly delivered into the pulmonary circulation. Ettinger and Albin (1989) suggest that cocaine may induce an increase in systemic vascular resistance, with resultant left ventricular dysfunction and pulmonary edema. Murray and colleagues (1988a) have shown that pulmonary artery hypertrophy, in the absence of foreign particle embolization, may occur with chronic cocaine use. Other authors have described alveolar hemorrhage following the use of free base cocaine, which may result from extreme vasoconstriction of the pulmonary vasculature with ensuing tissue hypoxia (Godwin et al. 1989; Murray et al. 1988b). More recently, a clinical presentation of pulmonary embolus in association with crack use was reported (Delaney and Hoffman 1991). After all sources and common risk factors for pulmonary embolus were excluded, the pulmonary infarction that resulted was presumed to be the consequence of in situ vasospasm and thrombosis.

**Skeletal Muscle Vasculature**

Numerous recent reports of cocaine-related rhabdomyolysis involving all routes of exposure have recognized the association with massive creatine phosphokinase levels, acute renal failure, profound hypotension, and hyperthermia (Roth et al. 1988; Merigian and Roberts 1987; Herzlich et al. 1988; Menashe and Gottlieb 1988; Anand et al. 1989; Pogue and Nurse 1989; Rubin and Neugarten 1989; Singhal et al. 1989; Brody et al. 1990b; Welch et al. 1991). However, seizures, hyperthermia, hypotension, or prolonged unconsciousness were not requirements for the production of rhabdomyolysis (Zamora-Querzada et al. 1988), which suggests that cocaine may act as a

direct muscle toxin. The mean serum creatine phosphokinase levels were 28,084 U/L in patients who subsequently developed renal failure. Fatalities occurred in 6 of 13 patients with renal failure and 6 of 11 who developed hepatic compromise. This high fatality rate may be related to concomitant disseminated intravascular coagulation and severe, probably ischemic, hepatic dysfunction seen in these patients (Roth et al. 1988). It was postulated that rapid delivery of cocaine to the skeletal muscle vasculature led to arterial vasoconstriction, tissue ischemia, and rhabdomyolysis (Roth et al. 1988). Although rhabdomyolysis is often associated with myoglobinuric renal failure, there is no evidence that cocaine has a direct renal toxic effect. However, it is likely that cocaine's vasoconstrictive effect would concomitantly impair renal vasculature, thus altering renal hemodynamics and making myoglobinuric renal failure more likely (Singhal et al. 1989). Additional suggestive data is represented by the development of renal infarction in a 32-year-old male within minutes after using IV cocaine (Sharff 1984). Sharff presumes that increased $\alpha$-adrenergic stimulation and a possible preexisting thrombus were responsible for the patients infarction.

**Uteroplacental Vasculature**

Maternal cocaine use has recently been recognized as an increasing problem for the successful continuation of the pregnancy (Cherukuri et al. 1988; Chasnoff et al. 1985; Acker et al. 1983; MacGregor et al. 1987; Barnwell and Ramasastry 1983; Chouteau et al. 1988) as well as the subsequent fetal growth and development (Chavez et at. 1989; Doberczak et al. 1988). An increased incidence of spontaneous abortions, abruptio placentae, fetal prematurity, and intrauterine growth retardation has been documented clearly. Experimental evidence in pregnant ewes demonstrated dose-dependent increases in maternal blood pressure with concomitant decreases in uterine blood flow (Moore et al. 1986; Woods et al. 1987). Uterine vascular resistance increased with increasing doses of cocaine. These vascular changes were accompanied by marked fetal tachycardia, hypertension, and hypoxemia (Woods et al. 1987). Direct administration of the cocaine into a fetal vein led to smaller increments in pulse and blood pressure and no significant hypoxemia and no effect on the mother (Woods et al. 1987). This study in ewes is based on a single exposure and cannot replicate the exposure of the placenta and fetus in a cocaine-dependent individual.

The increased incidence of spontaneous abortions and *abruptio placentae* with cocaine use appears to relate directly to placental vasoconstriction decreasing placental vascular supply and increasing uterine contractility. These factors, in addition to the marked hypertension associated with cocaine use, may precipitate abruptio placentae (Chasnoff et al. 1985; Acker et al. 1983). Chronic

exposure may result in decreased uteroplacental blood flow and uteroplacental insufficiency. These factors all may play a role in limiting fetal intrauterine growth and development (MacGregor et al. 1987). Cocaine's effect on placental function has been studied in vivo and in vitro, demonstrating reduced vascular supply associated with vasoconstriction as well as limiting cellular amino acid uptake independent of vascular distribution (Barnwell and Ramasastry 1983).

Two cases of unruptured, incidentally diagnosed, ectopic pregnancies developed acute abdominal pain 1 to 2 hours after using cocaine and were found to have ruptured ectopic pregnancies on return to the hospital (Thatcher et al. 1989). Ectopic pregnancies may rupture at any time, but in both these instances the proximity of the abdominal pain and rupture to the use of cocaine is highly suggestive.

**Gastrointestinal, Splenic, and Hepatic Vasculature**

The intestinal vasculature is highly sensitive to catecholamines due to the wide distribution of $\alpha$-adrenergic receptors in the intestinal wall. Acute mucosal ischemia has been demonstrated in several case reports following cocaine use by the oral, IV, or inhalational routes (Nalbandian et al. 1985; Freudenberger et al. 1990; Mizrahi et al. 1988; Endress and Kling 1990; Garfia et al. 1990). In one case report, transplacental cocaine absorption resulted in intestinal ischemia in a term neonate (Telsey et al. 1988). Another syndrome consisting of acute abdominal pain associated with diarrhea and occult blood positive or grossly bloody stools has also been reported. On examination, superficial ulcerations and diffuse areas of hemorrhage and necrosis have also been noted, giving rise to the term "cocaine colitis" (Fishel et al. 1985). More recently, Lee and coworkers (1990) demonstrated an association between gastrointestinal perforations and crack cocaine use; they postulate acute ischemia with subsequent tissue necrosis and perforation as a possible etiology.

Splenic infarction has been reported in only one case; a 38-year-old black woman with sickle cell trait developed left upper quadrant pain immediately after the IV use of cocaine, pentazocine, and methylphenidate (Novielli and Chambers 1991). Computerized tomography demonstrated a large posterior splenic infarction. Although it is suprising that splenic infarction has not been previously recognized, it must be remembered that this patient had numerous potential etiologies for this event. However, clinicians should at least consider this a potential cocaine complication.

In various mice experimental models, cocaine has been demonstrated to be hepatotoxic, possibly through the formation of a reactive metabolite, norcocaine nitroxide (Kloss et al. 1982, 1983; Gottfried et al. 1986; Kanel et al. 1990), or alternatively through the creation of a futile redox cycle that results in glutathione depletion (Kloss et al. 1984). This latter mechanism is of particular interest because it suggests a mechanism for the protective effect of N-acetylcysteine in cocaine-induced mouse hepatotoxicity (Suarez et al. 1986). Human reports have suggested a correlation between cocaine use and liver function abnormalities in mixed drug dependency (Marks and Chapple 1967) and nonparenteral cocaine use (Kothur et al. 1991). These studies are of great importance because any cocaine effect on hepatic metabolism such as the cytochrome p-450 system or the flavin adenine dinucleotide-containing monooxygenase system may subsequently alter cocaine metabolism. Shunting or delay of hepatic metabolism may alter the production of nontoxic metabolites and could result in an increased or novel production of a toxic metabolite with vasoactive characteristics.

The case of a 32-year-old male who died of massive hepatic failure approximately 12 hours after using intranasal cocaine is of great interest (Perino et al. 1987). The pathology was striking for the presence of periportal and midzonal necrosis with the absence of centrilobular destruction. This finding essentially excludes systemic shock, hypoxia, or hyperthermia as etiologies for the hepatotoxicity. In a study of 39 patients with cocaine-related rhabdomyolysis, liver function abnormalities were noted in 11 of 13 with renal failure and in only 2 of 26 without renal failure (Roth et al. 1988). These findings necessitate further investigation with regard to a direct vascular or indirect hepatoxic effect.

## EXPERIMENTAL BASIS FOR THE TREATMENT OF THE VASCULAR MANIFESTATIONS OF COCAINE INTOXICATION

The pharmacologic and toxicologic properties that result in the cardiovascular manifestations of cocaine toxicity have led to several consequential and at times contradictory experimental studies (Catravas et al. 1978; Catravas and Waters 1981; Derlet and Albertson 1989a, 1989b; Derlet et al. 1989; Spivey et al. 1990; Mercuro et al. 1988; Trouve and Nahas 1986; Trouve et al. 1987; Smith et al. 1991. Although many of these studies relate in particular to control of neuropsychiatric manifestations, it is clear even from this conflicting database that the cardiovascular and neuropsychiatric complications are inextricably linked. A logical analysis of these studies is essential to propose an appropriate clinical approach to the cocaine-intoxicated patient in general and the vascular manifestations of cocaine-intoxication in particular.

In the dog model used by Catravas and coworkers (1978) and Catravas and Waters (1981), cocaine-related increases in mean arterial pressure, heart rate, cardiac output, rectal temperature, and systemic pH were studied. All animals administered cocaine developed convulsions and died with a mean lethal dose of 22 mg/kg. In the experimental design, pretreatment antidotal therapy was administered. Although chlorpromazine demonstrated efficacy with regard to vital sign abnormalities and lethality, all animals developed seizures. Pimozide, a specific dopamine-2 ($D_2$) receptor antagonist and adrenergic blocking agent, had no salutary effect on lethality or any other parameter. Although propranolol was efficacious with regard to tachycardia and hypertension, it had an adverse effect on the incidence of seizures and mortality. Pancuronium had no effect on the cardiovascular manifestations but did prevent fatalities. Seizure activity was not evaluated, but as expected, no motor activity occurred. Although sodium bicarbonate corrected the metabolic acidosis associated with cocaine toxicity, it had no effect on seizures or lethality. However, pretreatment with diazepam decreased the cardiovascular manifestations, prevented seizures, and resulted in no fatalities. The use of an ambient environment of -5 °C also led to a diminished cardiovascular effect of the cocaine and the absence of seizures and fatalities.

Derlet and Albertson (1989a) also demonstrated in a rat model that diazepam was effective in preventing the tonic clonic manifestations of seizures and death in spite of a continuum of convulsant-like electrical activity. Witkin and colleagues (1989) further expanded investigations in search of a central dopamine receptor blocking agent. Dopamine antagonists with varying affinities for dopamine-1 ($D_1$) and $D_2$ receptor subtypes were utilized. When the established rat model was pretreated with the $D_2$ antagonist haloperidol, there was no alteration in the lethal effect of cocaine. When SCH 23390, a $D_1$ antagonist, was utilized in pretreatment, the lethal dose was increased. Unfortunately, when SCH 23390 was given 5 minutes after cocaine administration, no appreciable benefits could be discerned.

A subsequent rat model study looked at the role of haloperidol in the treatment of cocaine and amphetamine intoxication (Derlet et al. 1989). Haloperidol was ineffective in preventing amphetamine-related seizures but did lower mortality at most doses. When used for cocaine intoxication, there was a decreased incidence of seizures at the highest doses of cocaine, but there was no evidence of decreased mortality. More recently, when Spivey and associates (1990) compared haloperidol and diazepam in a cocaine-toxic swine model, they found that diazepam offered significant protection from cocaine seizures and lethality, whereas haloperidol offered no protection from either of these effects.

The role of the $D_2$ receptor has been studied by Mercuro and colleagues (1988). When this receptor is activated by dopamine or its agonists, it inhibits the sympathetic release of norepinephrine. Specifically, plasma norepinephrine and epinephrine production was studied in human adult male volunteers while at rest and during exercise (Mercuro et al. 1988). Plasma catecholamines increased significantly at maximum exercise. Whereas administration of a selective $D_2$ antagonist, domperidone, showed no modification of heart rate, blood pressure, or catecholamine levels at rest, a significant increase in plasma catecholamine levels was produced with exercise. The result was statistically greater cardiovascular responses (heart rate, blood pressure, and rate pressure product) and increased oxygen consumption. This study suggests that there is a $D_2$ antagonist-mediated increase in catecholamine release associated with exercise. When these results are combined with an analysis of the effects of chlorpromazine and another $D_2$ antagonist, pimozide (Catravas et al. 1978), they suggest that currently available antidopaminergic agents such as chlorpromazine (a $D_1$ antagonist) and haloperidol (a $D_2$ antagonist) may not be efficacious and in fact may be deleterious in treating cocaine toxicity, particularly when exercise (psychomotor agitation) is occurring. The routine failure of $D_2$ antagonists to treat experimental cocaine toxicity must be considered when evaluating uncontrolled, anecdotal reports of response in situations of mild and non-life-threatening poisoning.

Two models utilizing calcium channel blockers have resulted in divergent analyses. Trouve and Nahas (1986) utilized nitrendipine, an experimentally available calcium channel blocker, as an antagonist to cocaine's cardiac toxicity and as a potential antidote to the lethal effects. Arrhythmia suppression, decreased convulsions, increased survival times, and an increased lethal dose of cocaine were demonstrated in the rats administered nitrendipine. In a second rat model, Trouve and coworkers (1987) compared propranolol to nitrendipine. Propranolol was unable to prevent arrhythmias and decreased coronary blood flow. In this model the calcium channel blocker appeared to prevent the cardiac morphologic changes noted with high-dose cocaine.

In a rat model, Derlet and Albertson (1989b) demonstrated that animals pretreated with intraperitoneal (IP) diltiazem, nifedipine, or verapamil developed seizures more rapidly than did control animals. At any specific dose the fatality rate was higher in the calcium channel blocker pretreatment group. This potentiation of seizures and death was demonstrated at 2 mg/kg nifedipine pretreatment doses with three variable cocaine doses. This study suggests that all the currently available calcium channel blockers may increase the risk and consequences of seizures associated with cocaine intoxication. Derlet and Albertson (1989b) raise the concern of a potential hemodynamic interaction between seizures and mortality in cocaine-intoxicated animals

pretreated with calcium channel blockers. The difference between these two studies (Derlet and Albertson 1989b; Trouve et al. 1987) may reflect the choice of calcium channel antagonists or other variations in experimental design. In Trouve and colleagues' study (1987), the calcium channel antagonist was administered intravascularly, whereas Derlet and Albertson (1989b) pretreated by the IP route. It is possible that IP pretreatment with calcium channel antagonists produced local vasodilation, which increased cocaine bioavailability when cocaine was subsequently administered by the IP route. The pretreatment animals could have done as poorly as the control group because the potential beneficial effects of the calcium antagonist might have been masked by increasing the absorbed doses of cocaine.

Also in the rat, Smith and coworkers (1991) studied the effects of multiple agents, including propranolol, labetalol, and verapamil, on survival following an $LD_{50}$ of cocaine. The ß-blocking agents were shown to adversely affect outcome, whereas verapamil did not affect survival in this posttreatment model. However, verapamil has been shown to increase the threshold for ventricular fibrillation in cocaine-treated rats (Billman and Hoskins 1988). This might have implications on the subset of patients whose manifestation of life-threatening toxicity is ventricular arrhythmias.

Another model utilized anesthetized dogs that were pretreated with nifedipine and then administered 10 mg/kg of cocaine by IV bolus (Hale et al. 1991). Although the study demonstrated that nifedipine prevented cocaine-induced decreases in coronary blood flow and improved left ventricular function and ejection fraction, the use of sodium pentobarbital anesthesia limits the importance of this study. When nifedipine administration followed cocaine infusion, there was no improvement in left ventricular function or coronary blood flow. This study suggests a direct negative inotropic effect of cocaine.

Vicaut and coworkers (1991) performed an in vivo study using a videomicroscopy technique to evaluate the microvascular effects of cocaine in rats. They demonstrated that 10 mg/kg of intraarterial cocaine induced a maximal vasoconstriction of all arterioles studied and within 15 seconds almost complete closure of the most distal arterioles. This vasoconstriction was inhibited at all arteriolar levels by the intraarterial infusion of nitrendipine Furthermore, although the intraarterial use of the angiotension-converting enzyme inhibitor enalaprilat inhibited the vasoconstriction in the largest vessels, it was not effective distally (Vicaut et al. 1991). These results offer further experimental confirmation and theoretical explanation for the authors' previous nitrendipine studies (Trouve and Nahas 1986).

The studies by Catravas and Waters (1981) and Derlet and Albertson (1989a) suggest the importance of sedative-hypnotics such as diazepam, the utility of paralyzing agents such as pancuronium, and the efficacy of ambient cooling in the treatment of cocaine toxicity. The risks of currently available $D_1$ and $D_2$ antagonists, a concern over the merits and risks of currently available calcium channel blockers, and the lack of efficacy of a ß-adrenergic blocker such as propranolol are also noteworthy in the varied experimental models. These studies emphasize the need for further research directed toward defining the effects of neurotransmitters, biogenic amines, sedative-hypnotics, specific $D_1$ and $D_2$ antagonists, and calcium channel and ß-adrenergic blockers (or, more specifically, α-₁, $ß_1$, and $ß_2$-adrenergic receptor blockers) and the use of thermoregulatory control. In spite of these controversial studies several clinicians use haloperidol and 8-adrenergic blockers as therapeutic agents for cocaine intoxication (Rappolt et al. 1976; Gay 1982; Sand et al. 1991).

ß-Adrenergic blockers have not been shown to be efficacious with regard to mortality studies in either the Catravas and Waters (1981) or other experimental designs. Although there have been frequent clinical papers supporting propranolol use, actual use in emergency departments has been infrequent, and the pharmacologic argument against propranolol use is strong. Recent work by Lange and colleagues (1990) demonstrates that administration of intracoronary propranolol to patients undergoing cardiac catheterization potentiates cocaine-induced coronary vasoconstriction, decreased coronary sinus blood flow, and increased coronary vascular resistance. Also, cocaine has a stimulatory effect on the heart, increasing both inotropy and chronotropy. Propranolol blocks $ß_1$-adrenergic receptors, decreasing contractile force and heart rate, which, in the absence of cocaine, should allow for a fall in blood pressure. However, because propranolol also inhibits the $ß_2$-adrenergic receptors, an unopposed α-adrenergic receptor stimulation ensues with peripheral vasospasm and possibly a subsequent increase in blood pressure. This theoretical exacerbation of hypertension would result from the markedly elevated catecholamine levels present in the face of acute cocaine intoxication (Olson and Benowitz 1987; Karch 1987). Unopposed α-adrenergic effect was suggested in a case report by Ramoska and Sacchetti (1985) and supported by some researchers (Dusenberry et al. 1987) but questioned by others (Silverstein et al. 1987; Leikin et al. 1987; Karch 1988) as the cause for an increase in blood pressure with concomitant resolution of the patient's tachycardia. Despite the elevated blood pressure, the increased afterload and decreased inotropy might adversely affect blood flow and tissue perfusion. Ramoska and Sacchetti (1985) and Dusenberry and coworkers (1987) suggest that an agent such as labetalol with combined α- and ß-adrenergic blocking effects or a long-acting agent such as metoprolol or the ultra-short-acting esmolol (Kirshenbaum et al. 1988; Gray 1988; Pollan and Tadjziechy 1989) with relative $ß_1$-adrenergic antagonistic specificity might be more efficacious.

Esmolol was employed by Sand and coworkers (1991) as a possible antagonist to the adverse cardiac effects of cocaine due to the fact that the drug is delivered intravenously and would be metabolized within minutes, thereby diminishing risks if any adverse effects developed. These researchers failed to demonstrate any consistent benefit in control of their patients' hypertension, although heart rate decreased in some of their study patients. Although three of seven patients showed resolution of their clinical symptoms, one hypertensive patient had no fall in blood pressure, and two others showed further exacerbation in hypertension. The remaining patient became significantly hypotensive. In uncontrolled experiments such as this one, it is impossible to distinguish between favorable drug effects and simple resolution of effects of the short-acting agent cocaine.

Similarly, only case reports are offered as arguments in favor of the use of labetalol (Dusenberry et al. 1987; Karch 1988; Gay and Loper 1988), whereas no clinical studies on labetalol's efficacy as an α-adrenergic blocker have been presented. Labetalol has substantially greater nonselective ß-adrenergic blockade that is quantitatively far more potent than the a-adrenergic blocking effects (Sybertz et al. 1981). The ratio of α-adrenergic blocking to ß-adrenergic blocking potency is approximately 1:7. If the cocaine-induced catecholamine ratios are comparable with those produced in the presence of a pheochromocytoma, then the result (a hypertensive crisis) would be expected to be similar to that reported by Briggs and colleagues (1978) when using labetalol for treatment of a pheochromocytoma. Furthermore, evidence has already been given to suggest that propranolol has deleterious effects on cocaine-induced coronary vasoconstriction, seizures, and mortality. No experimental data exist to suggest that the addition of weak a-adrenergic blockade to ß-adrenergic blockade is beneficial in this regard. In fact, in Spivey and colleagues' (1990) swine model that demonstrated the benefits of diazepam administration, no protective effects of labetalol could be shown. In Smith and coworkers' study (1991) labetalol was also without efficacy. The only advantage of labetalol is its theoretical advantage of protection against unopposed a-adrenergic effects, which may in fact be inadequate.

The role, if any, for ß- and mixed α- and ß-adrenergic blockers in the presence of cocaine remains ill defined. Experimental data in animals do not support the use of ß-adrenergic blockers, and the controlled and uncontrolled clinical experiences have been exceedingly limited. The use of nonselective ß-adrenergic blockers has been restricted in most patients with cocaine intoxication to those patients who have already been sedated and who have isolated tachyarrhythmias. The choice of an antihypertensive agent that is rapid acting and easily and reliably controlled leads to the use of vasodilating agents such as nitroprusside or an a-adrenergic blocker such as phentolamine.

## THERAPEUTIC PRINCIPLES FOR THE CARDIOVASCULAR MANIFESTATIONS OF COCAINE INTOXICATION

Based on the direct pharmacologic and toxicologic relationship between cocaine's neuropsychiatric and cardiovascular complications, success in management of the neuropsychiatric manifestations almost invariably has a salutary impact on resolution of the cardiovascular abnormalities, at least from an emergent or initial care perspective. Control of acute psychiatric manifestations of cocaine intoxication should be based on supportive care that minimizes risks to patients and staff and reduces external stimuli. Evidence for the link between the CNS and cardiovascular effects of cocaine intoxication is available in the animal model. Wilkerson (1988) demonstrated in dogs that the site of action of cocaine-induced increases in sympathetic activity is in the CNS, and he concluded that the cardiovascular effects of cocaine can only be expressed fully when the central and peripheral nervous systems are integrated. Similar differences between anesthetized and unanesthetized animals have been described by Schwartz and colleagues (1989). Studies mentioned previously by Catravas and Waters (1981) and Derlet and Albetison (1989a) as well as another by Guinn and coworkers (1980) all demonstrate that sedative-hypnotics are uniformly successful agents for the treatment of cocaine toxicity and the prevention of lethality. The model linking the CNS to the peripheral manifestations of cocaine intoxication is demonstrated in figure 2. Using this model, one might predict the failure of therapeutic interventions directed solely at ameliorating the peripheral manifestations of cocaine toxicity. Thus, sedation with diazepam is chosen due to its demonstrable experimental efficacy (Catravas and Waters 1981; Derlet and Albertson 1989a; Spivey et al. 1990; Guinn et al. 1980) and the substantial experience in its use in other clinical states associated with severe agitation and catecholamine excess, such as sedative-hypnotic or ethanol withdrawal (Sellers et al. 1983; Thompson 1978).

Haloperidol is not recommended due to the lack of experimental support (Catravas and Waters 1981; Spivey et al. 1990; Guinn et al. 1980) and significant clinical difficulties in sedative-hypnotic withdrawal in humans (Greenblatt et al. 1978) and animals (Blum et al. 1976), particularly when treatment is initiated in the presence of agitation and hyperthermia. This is of consequence because loss of thermoregulatory control is a common complication in the acutely agitated or psychotic patient with cocaine intoxication. Another argument against the use of haloperidol is the high frequency of acute dystonic reactions associated with cocaine use (Merab 1988; Choy-Kwong and Lipton 1989b; Farrell and Diehl 1991). In addition, Kumor and colleagues (1986) have noted a further increase in the incidence of dystonic reactions in healthy cocaine addicts who were subsequently given

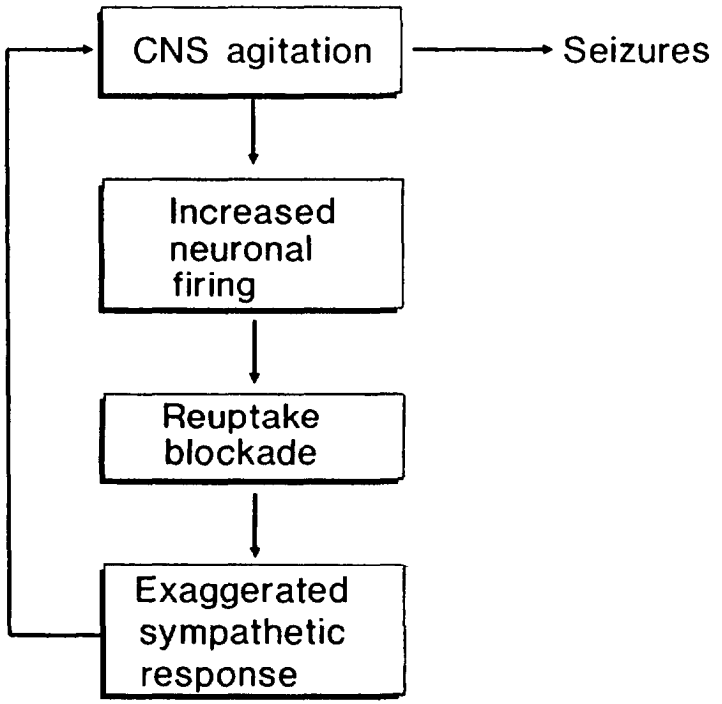


**FIGURE 2.** *A pathophysiologic model for cocaine intoxication*

SOURCE: Goldfrank and Hoffman 1991. Copyright 1991 by *Annals of Emergency Medicine* (Dallas).

haloperidol. These dystonic reactions were often delayed and manifested by torticollis, oculogyric crisis, or truncal or buccolingual symptoms.

Agitation and seizures are managed in the standard manner with a focus on rapid control of motor activity while protecting the patient's airway and achieving adequate ventilation and oxygenation. Restraints should be applied transiently to achieve an IV line. Ideally, if a restraining blanket is used, it should be constructed as a strong netting or a mesh to avoid increasing the patient's temperature by preventing heat dissipation. Diazepam or another benzodiazepine should be used for the initial management of seizures. Although no studies exist that compare phenobarbital to phenytoin for control of cocaine-induced seizures, phenobarbital may be preferable in

that it also produces CNS sedation. If these agents are not rapidly effective, nondepolarizing neuromuscular blockade (e.g., with pancuronium) and general anesthesia may be indicated. Succinylcholine use may be contraindicated because of the risk of hyperkalemia with severe cocaine-induced rhabdomyolysis. It should also be noted that the enzyme plasma cholinesterase is responsible for the metabolism of both succinylcholine and cocaine, so that if these two agents are used simultaneously, prolonged clinical effects of either or both agents might result.

Control of hyperthermia is best achieved by rapid cooling with an ice and water bath or mist and fan technique. Conduction and evaporation prove rapidly efficacious. Control of the associated agitation, psychosis, or seizures is essential to achieve and maintain cooling while avoiding cerebral, hepatic, and muscle cellular destruction. There is no evidence that other pharmacologic agents (such as dantrolene) play a role in enhancing the cooling process in these patients with life-threatening hyperthermia (Fox 1989). Once these more generic approaches are initiated, most patients with cocaine-related cardiovascular manifestations will have begun to improve. The premise chosen is based on the experimental evidence presented above and the model for cocaine intoxication described in figure 2.

Tachyarrhythmias of atrial origin that have not responded to control of the central sympathetic stimulus and cooling should respond to verapamil, esmolol, labetalol, or propranolol. Utilization of these agents in a previously sedated individual limits the risks of unmasking $\alpha$-adrenergic effects and theoretical concerns associated with the risks of seizures when calcium channel or ß-drenergic blockers are given in the animal model. Lidocaine may not be the agent of choice for the treatment of ventricular arrhythmias that develop immediately following cocaine use, such as in an individual with a ruptured bag of cocaine in the gastrointestinal tract. These ventricular arrhythmias should be presumed to occur from either catecholamine excess (in which case sedation and cautious use of mixed $\alpha$-and ß-adrenergic blockade or calcium channel blockade may be indicated) or from cocaine's direct effect on the myocardium. Since this latter effect may be due to cocaine's type I antiarrhythmic properties, the addition of a similar agent (lidocaine) may exacerbate cardiac conduction abnormalities. Furthermore, lidocaine can lower the seizure threshold. The combination of lidocaine and cocaine has been shown to increase the incidence of seizures and death in a rat model (Derlet et al. 1991). Recent evidence suggests that cocaine-induced wide-complex arrhythmias may respond to administration of sodium bicarbonate, in a similar fashion to those arrhythmias produced during intoxication with type IA and type IC antiarrhythmics (Parker et al. 1989b). In an extension of this study, Beckman and colleagues (1991) showed that cocaine-induced QRS prolongation was decreased approximately

to baseline, but no effect was noted on other electrocardiographic or hemodynamic variables. In any other setting, ventricular arrhythmias should be considered to be generated by an ischemic myocardium, and standard management for ventricular arrhythmias (including lidocaine) is indicated.

Initially, myocardial ischemia and infarction should be discriminated from the other common causes of chest pain syndromes in cocaine users such as pneumothorax, pneumomediastinum, dissecting aortic aneurysm, or septic pulmonary emboli from endocarditis. Once myocardial ischemia or infarction is suspected, these atypically young patients should be considered in the same manner as anyone else who is presumed to be at risk for coronary artery disease. The use of nitrates is indicated for cocaine-induced myocardial ischemia, as in those patients with atherosclerotic heart disease. There is substantial human evidence that nitroglycerin alleviates cocaine-induced coronary vasoconstriction in both diseased and nondiseased segments (Brogan et al. 1991). There is no clinical experience with calcium channel blockers (diltiazem or verapamil) in humans with cocaine-related ischemia. ß-Adrenergic blockers, such as propranolol, should not be utilized because of the human data demonstrating enhanced vasospasm. Aspirin should be administered, unless contraindicated, to reduce cocaine-mediated platelet aggregation (Tonga et al. 1985). Thrombolytic therapy has been utilized in spite of previous significant short-term hypertension but should therefore be considered with extreme caution. It should be reserved for those patients who do not respond rapidly to vasodilator therapy, have no suggestion of a cerebrovascular catastrophe clinically, and have no risk of mycotic aneurysm (Bush 1988).

Hypertension unresponsive to sedation should be managed with sodium nitroprusside (0.5 to 10 mcg/kg/min) in a titrated fashion to achieve and maintain a normal blood pressure. Phentolamine is also an effective vasodilator at doses of 5 to 10 mg IV and may improve coronary perfusion (Lange et al. 1989). Cocaine-intoxicated patients should be considered to have an acute elevation in their blood pressure. Unless there is documentation or clinical evidence of long-standing hypertension, there should be no concern of cerebral hypoperfusion subsequent to an immediate lowering of the blood pressure to a normal level.

The other cardiovascular end organ manifestations of cocaine intoxication may necessitate specific intervention. The general strategies for managing catecholamine excess, myocardial ischemia, and hypertension are summarized below and allow for the case-specific approaches to complicated examples such as aortic dissection, mesenteric ischemia, and abruptio placentae. Each

of these cases or the presentation of the patient in shock necessitates a critical understanding of the risk/benefit ratios for pharmacologic, toxicologic, and surgical or obstetrical interventions.

- Hypertension
  —Oxygenation
  —Sedation (benzodiazepine)
  —Vasodilators (nitroprusside or phentolamine)
  —Hydralazine (if associated with pregnancy)

- Myocardial ischemia
  —Oxygenation
  —Sedation (benzodiazepine)
  —Nitrates
  —Aspirin
  —Calcium channel blockers

- Myocardial infarction
  —Oxygenation
  —Sedation (benzodiazepine)
  —Nitrates
  —Aspirin
  —Heparin
  —Calcium channel blockers
  —Opioids
  —Consider thrombolytic therapy

- Tachyarrhythmias
  —Oxygenation
  —Sedation (benzodiazepine)
  —Atrial: Observation, cooling if febrile, consider calcium channel blocker. Cautious use of mixed α–ß-adrenergic blockade may be required.
  —Ventricular: Consider lidocaine or sodium bicarbonate. Try to determine etiology (ischemia vs. direct drug effect). Use standard Advanced Cardiac Life Support approach if ischemia is suspected.

SOURCE: Goldfrank and Hoffman 1991. Copyright 1991 by *Annals of Emergency Medicine* (Dallas).

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## AUTHORS

Lewis Ft. Goldfrank, M.D.
Medical Director
New York City Poison Control Center
Director
Emergency Medical Services
Bellevue Hospital and New York University Medical Center

Robert S. Hoffman, M.D.
Associate Medical Director
New York City Poison Control Center
Director
Medical Toxicology Fellowship
New York City Poison Control Center
Attending Physician
Bellevue Hospital Emergency Medical Services

First Avenue and 27th Street
New York, NY 10016

# Cocaine-Related Emergency Department Presentations

*Kathleen S. Schrank*

## INTRODUCTION

The 1980s saw a dramatic rise in cocaine use throughout the United States. This trend was clearly reflected in emergency departments (EDs) throughout the country, as cocaine became the leading cause of drug-related presentations. The spectrum of emergency medical consequences of cocaine use is quite broad, varying from cardiac arrest with dramatic hyperthermia to relatively minor types of complaints. Fortunately, most medical problems related to cocaine are of short duration and are not imminently life threatening. Unfortunately, many aspects of understanding of this drug's adverse effects and of various treatment options remain ill defined. This chapter discusses the major emergency medical conditions related to cocaine use and clinical approaches and controversies.

## PHARMACOLOGIC ASPECTS OF COCAINE USE

Cocaine hydrochloride is typically used intravenously or by nasal insufflation. Intravenous (IV) use produces immediate clinical effects and peak blood levels; both decline rapidly. Nasal cocaine produces peak blood levels after about 60 minutes, but clinical effects peak much earlier. The alkaloidal form of cocaine (free base or crack) is smoked, with rapid peak effects only a few minutes later than by IV route (Van Dyke and Byck 1982). Smoking crack cocaine is rapidly increasing as the preferred route of ingestion by ED patients in many cities, probably reflecting street popularity; however, this increase may suggest a worrisome higher risk of medical complications. Cocaine also can be administered orally, vaginally, rectally, or sublingually.

Cocaine is metabolized by plasma and liver cholinesterases to compounds, including benzoylecgonine and ecgonine methyl ester, that are excreted by the kidneys along with unmetabolized cocaine. The role of individual variability of plasma cholinesterase activity in terms of risk of adverse reaction to this drug merits further study.

Concomitant use of other drugs along with cocaine is common, but understanding of the ramifications of these mixtures is limited. Users frequently take benzodiazepines to blunt the dysphoric effects of declining cocaine levels. This practice also may serve to enhance respiratory depression and prolong altered mental states but in fact may decrease the risk of seizures. Indeed, animal data indicate a decreased risk of seizure or death if diazepam is given prior to cocaine (Derlet and Albertson 1989a). The combination of alcohol and cocaine also is frequent and may prove to significantly increase the risk of certain adverse reactions. Available evidence shows that concurrent use of ethanol and cocaine leads to hepatic production of a third compound, cocaethylene, via transesterification. Cocaethylene can be measured in blood, urine, and tissues, including brain (Hearn et al. 1991). In animal studies, it appears even more potent than cocaine in lethality; in humans, preliminary data suggest a relationship between cocaethylene and violent agitation (S. Rose, personal communication, May 1991).

The role of adulterants in producing complications attributed to cocaine does not appear significant, though it cannot be fully discounted. The more typical contaminants include other local anesthetics, sugars, inert compounds, and other stimulants. Strychnine, quinine, and hallucinogenic drugs have been reported as well. The presence of adulterants is likely to vary geographically along routes of distribution, but cocaine purity is generally very high, in contrast to other illegal drugs such as opiates or hallucinogenics.

The primary actions of cocaine include central nervous system (CNS) stimulation with increased dopaminergic effect, inhibition of catecholamine reuptake with resultant generalized sympathetic stimulation, alteration of serotonin release and reuptake, and local anesthesia via inhibition of sodium current. Clinically, the adrenergic stimulation produces sinus tachycardia and other arrhythmias, hypertension, hyperthermia, seizures, tremulousness, mydriasis, and death. Sedation with diazepam clinically blunts tachycardia and hypertension, suggesting central mediation of peripheral sympathetic effects. Euphoria, agitation, delirium, insomnia, psychoses, stupor, and coma are mediated through central dopaminergic pathways; effect on serotonin and its significance is not well defined (Spivey and Euerle 1990).

## CARDIOVASCULAR COMPLICATIONS

### Cardiac Arrest

Cocaine may precipitate sudden death through acute cardiovascular, respiratory, or neurologic events. Reported mechanisms of primary cardiac deaths include catecholamine-induced tachyarrhythmias, ischemic

arrhythmias, bradycardias, myocardial depression, and aortic rupture (Gadaleta et al. 1989). Any route of administration may lead to death, and many sudden deaths do not appear to be due to an increased dose of this drug; indeed, cocaine plasma levels in fatalities may be indistinguishable from those in mild intoxications.

Detailed data on cocaine-induced cardiac arrest rhythms and management are lacking. Ventricular fibrillation appears to be the most common rhythm (as in arrests unrelated to drug use), but ventricular tachycardia, primary asystole, bradycardias, and electromechanical dissociation also occur. Current medical management follows standard Advanced Cardiac Life Support algorithms published by the American Heart Association, but in the experience of the author and other staff members at the University of Miami/Jackson Memorial Medical Center, the prognosis is dismal, and modifications may be in order. If the mechanism underlying ventricular fibrillation and ventricular tachycardia (VFNT) is excessive catecholamine action, then the role of epinephrine in these rhythms needs to be explored. Its peripheral vasoconstriction with shunting of blood flow to the coronary and cerebral vessels during arrest remains desirable, but perhaps $\alpha$-receptors are already maximally stimulated by the cocaine, and the direct cardiac effects of epinephrine may be more toxic than helpful in this setting. Alternatively, if the mechanism producing VFNT is either ischemia or direct myocardial depression from cocaine, then epinephrine is indicated. In bradycardic or asystolic arrests, epinephrine remains a vital part of resuscitation efforts.

The optimal antiarrhythmic agent for VFNT in these patients is also unclear; each choice is controversial. Lidocaine generally is still used. However, arrest may be due to a direct depressive effect of cocaine on the myocardium, an effect similar to that of excess Type I antiarrhythmics; lidocaine in theory may exacerbate this (Goldfrank and Hoffmann 1991). In one animal model, high doses of lidocaine (30 or 40 mg/kg) given with cocaine significantly increased the risk of seizures and death (Derlet and Albertson 1991), but extrapolation to clinical dosage (total loading dose 1 to 3 mg/kg) is difficult. ß-Blockade would seem pharmacologically effective if the rhythm is catecholamine induced. However, propranolol is known to exacerbate coronary vasoconstriction (Lange et al. 1990) and therefore decrease coronary blood flow, and P-blockade results in decreased contractility. The majority of animal studies suggest that P-blockade either does not change or may worsen outcome from toxic cocaine doses (Smith et al. 1991), although Robin and colleagues (1989) did show improved survival in one strain of mice given propranolol and massive doses of cocaine. Alkalinization with sodium bicarbonate may be beneficial in VFNT, though again supportive clinical studies are not available. Unfortunately, attempts to provoke malignant arrhythmias by cocaine administration in animal

models have been unsuccessful (Isner and Chokshi 1991), underscoring the limited knowledge base.

Sudden cardiac death is a rare though well-publicized consequence of cocaine use. The vast majority of these deaths occur outside the hospital; arrest following ED arrival with a pulse is extremely rare. Prediction of risk, other than with massive ingestion, is ill defined, but patients who are hyperthermic and whose behavior is agitated are more likely to suffer cardiac arrest. Restoration of spontaneous circulation is uncommon, and the postresuscitation course may be stormy (particularly in the hyperthermic patient) with myocardial failure, hemodynamic instability, hepatic failure, renal failure, and coagulopathy.

**Other Arrhythmias**

Although cocaine may provoke a variety of rhythm disturbances, most are short lived and do not require intervention. Sinus tachycardia is common and usually merits only observation. Volume infusion is appropriate if blood pressure is low, and benzodiazepine sedation is effective in the agitated tachycardic patient.

Supraventricular tachycardia is usually transient but may require treatment if prolonged or if the patient has associated chest pain or hypotension. Sedation of the agitated patient also may slow the rhythm. Electrical cardioversion is preferred for the truly unstable patient. Caution must be exercised in the choice of pharmacologic agent to avoid later bradycardia if the duration of action of the treatment significantly exceeds that of cocaine. Therefore, adenosine may be a logical choice, but clinical experience in this setting is minimal. Esmolol, an “ultra” short-acting cardioselective ß-antagonist, also may be useful, but hypotension is not uncommon as a side effect. Sand and colleagues (1991) found no consistent benefit from esmolol in six patients with sinus tachycardia; the one patient with supraventricular tachycardia became more hypotensive without any effect on rhythm. Other risks of ß-antagonists were discussed above. Also, ß-blockade allows the $\alpha$-stimulation of cocaine to go unopposed, with potentially dramatic hypertension. Calcium channel antagonists may be useful but also are controversial. They may produce hypotension and act much longer than the cocaine. Trouve and coworkers (1987) found that nitrendipine appeared to have beneficial cardiovascular effects and improved outcome in an animal model. However, Derlet and Albertson (1989b) found higher mortality and seizure risk in animals that were pretreated with any of three other calcium blockers.

Bradycardias in the absence of ventilatory problems have been reported, perhaps related to lower doses of cocaine. The patient who is quite symptomatic requires treatment. Temporary support with an external

cardiac pacer is likely the safest approach; atropine also may be used. ED patients who present with a chief complaint of palpitations should be asked about cocaine use. Premature atrial and ventricular contractions are common and rarely require therapy. Cocaine also may unmask underlying heart conditions such as Wolff-Parkinson-White syndrome.

VT with a pulse requires an aggressive approach, but the current level of knowledge does not lead to a clear-cut pharmacologic choice, as discussed above. The unstable patient needed electrical conversion. Sodium bicarbonate may be beneficial (Goldfrank and Hoffman 1991). In the setting of myocardial ischemia, lidocaine is appropriate. Magnesium sulfate also may prove beneficial in these patients, though experience is anecdotal.

**Myocardial lschemia and Infarction**

Cocaine's ischemic effects are well documented and must be suspected in patients of any age who complain of chest pain following drug use. Myocardial ischemia and infarction may occur with or without preexisting atherosclerotic vessels. Cocaine dramatically increases heart rate and blood pressure, is a potent vasoconstrictor, and produces focal coronary vasospasm. Coronary thrombosis may occur at a site of vasospasm, and cocaine-induced platelet aggregation has been seen in vitro. Thus, oxygen demand is significantly increased while coronary supply falls. Any of these actions may result in ischemic damage (Isner and Chokshi 1991), and risk to patients with underlying atherosclerosis is high. Evaluation for acute infarction may be a challenge. Young patients often have repolarization changes that may resemble ischemia and typically have no prior electrocardiograms (ECGs) for comparison. Creatine kinase (CK) may be elevated from skeletal muscle rather than heart, and percentage of MB fraction may be misleading in the patient with both muscle and myocardial injury. lschemic symptoms may begin right after drug use or may be delayed for hours to days.

Currently, anti-ischemic management parallels that for noncocaine users, with supplemental oxygen, nitrates, opiates, benzodiazepine sedation, and consideration of calcium channel or ß-receptor antagonists. The risk of the latter two classes of drugs appears low, since the acute toxic effects of cocaine are usually gone. Tachycardia and severe hypertension should be controlled if present, but sedation and relief of pain may accomplish this without more specific therapy. Patients with cocaine-caused infarcts are certainly candidates for thrombolysis given early in their course. Available data do not yet allow distinction from other myocardial infarction patients in terms of early or late arrhythmias, prognosis, treatment, optimal window of time for thrombolysis, or cardiac rehabilitation plans, Anecdotally, though, those patients without atherosclerosis appear to do well if they remain abstinent.

Given the widespread use of cocaine, routine queries as to drug use are in order in all patients who come in with chest pain, angina, and infarctions, and patients with known coronary disease should be cautioned against use.

Tokarski and colleagues (1990) looked further at cocaine-induced chest pain, evaluating 42 patients with ECG and cardiac enzymes. All had normal or nondiagnostic ECGs, but eight had elevated CK and cardiac isoenzyme on arrival; two were diagnosed as acute infarctions based on serial enzymes. Ten other patients had elevated total CK but no other evidence of cardiac source. Zimmerman and coworkers (1991) also described cocaine-related chest pain. Of 48 patients who were admitted to the hospital, 3 were confirmed as acute infarcts. In this series, ECG abnormalities were quite common, particularly significant repolarization abnormalities and T-wave inversions that persisted on serial tracings. The temporal relationship between drug use and onset of pain was variable.

**Myocardial Disease**

Cocaine acts acutely as a direct myocardial depressant, as shown in an animal model by Fraker and coworkers (1990). Acute, slowly reversible cardiomyopathy without infarction or myocarditis has been reported clinically (Chokshi et al. 1989), suggesting direct myocardial depression. Chronic use may lead to cardiomyopathy via recurrent infarctions, protracted vasospasm, or chronic sympathetic stimulation. Contraction band necrosis may be seen in some patients on postmortem histology; significance is unclear. Myocarditis with inflammatory myocardial infiltration is reported from autopsy (Virmani et al. 1988) and biopsy specimens from cocaine users.

**Acute Hypertension**

Sudden, severe elevations of blood pressure may rapidly follow cocaine taken via any route due primarily to the drug's systemic vasoconstriction. In most patients, pressure falls relatively rapidly to acceptable levels, and no intervention is needed. Most hypertensive patients also are agitated and thus respond well to benzodiazepine sedation. In very few cases the sudden hypertension is severe enough to produce catastrophic results, such as intracranial hemorrhage or thoracic aortic dissection/rupture. Severe hypertension with acute end-organ compromise is best treated with a short-acting vasodilator, such as nitroprusside or phentolamine. IV labetalol has been recommended because of its ß- and $\alpha$-receptor antagonism. It may be successful, but caution is advisable in that its $\alpha$-action may not be strong enough to overcome the $\alpha$-stimulation of cocaine; an even higher pressure may result, as with other ß-blockers.

### Shock

Rarely, cocaine use may be complicated by profound shock without an obvious direct cause such as arrhythmia, infarction, or hemorrhage. The mechanism is uncertain, and available information is anecdotal only. Cocaine “binges” lead to poor oral intake plus increased insensible fluid losses; severe volume depletion may result. Acute myocardial depression may contribute, but absence of pulmonary congestion speaks against this. Vasodilation may occur via atypical CNS effects of the drug. Management includes volume infusion followed if necessary by pressor support, plus aggressive evaluation for a cause (e.g., myocardial ischemia, unsuspected trauma, sepsis, aortic dissection, brain stem infarction, gastrointestinal bleeding, pulmonary embolism, other toxins) that may or may not be related to cocaine.

## GASTROINTESTINAL COMPLICATIONS

Abdominal pain due to cocaine use is increasingly being recognized by emergency physicians. Available literature is limited to case reports of the more serious complications. In the experience of the author and colleagues in Miami, however, most cases involve mild-to-moderate diffuse pain with vomiting, lasting a few hours followed by spontaneous resolution; physical signs and laboratory findings are generally nonspecific, and treatment is supportive. Return visits for recurrent symptoms are rare. Etiology is uncertain, though it likely represents mild intestinal ischemia. A minority of these patients present with persistent rigidity and diffuse rebound tenderness; although mandated by such findings, exploratory laparotomy may prove negative.

Cocaine clearly can precipitate severe mesenteric ischemia leading to bowel infarction manifested by elevated white blood cell count, metabolic acidosis, and shock. Presumably, cocaine acts as a potent vasoconstrictor in mesenteric vessels. Other possible mechanisms of ischemic insult to the bowel include focal vasospasm, intravascular thrombosis, or systemic hypotension due to cardiac complications of the drug (Freudenberger et al. 1990).

Gastric ulcers with perforation also have been reported in association with cocaine abuse. Here, too, the mechanism is uncertain but presumed to relate to vascular compromise (Abramson et al. 1989).

These ED patients also must be evaluated for other forms of drug abuse. In particular, alcohol use may precipitate abdominal problems such as gastritis or pancreatitis.

## COCAINE PACKET INGESTION

ingestion of large quantities of cocaine packaged in small packets is a smuggling technique of interest to medical personnel. These so-called “body packers” or “mules” attempt to pass through customs. They may be brought to the ED by customs agents because of suspected packet ingestion or may present on their own due to a complication. Many deaths have occurred due to massive cocaine poisoning from packet rupture, and standard recommendation a decade ago was surgical removal of all packets. However, improvements in the packaging materials and techniques, plus patients’ refusal of surgery, have led to the conservative approach of observation. The presence of packets can be confirmed by plain abdominal roentgenograms, contrast studies, ultrasonography, rectal exam, or by observation for spontaneous passage. Oral osmotic agents such as polyethylene glycol may safely be used to speed evacuation of the packets. The patient must be observed for evidence of packet leakage, often manifest initially by development of tachycardia. Also, evacuated packets may be assessed for evidence of breakdown. Cocaine intoxication may be seen even with intact packets, however, depending on permeability of the material. The surgical approach usually is reserved for patients who develop evidence of cocaine effect or who develop bowel obstruction from the packets (Caruana et al. 1984; McCarron and Wood 1983).

In the experience of the author and coworkers over the past 10 years, the approach of observing body packers has proven quite safe, with rare development of leakage, no ruptures, and one case of bowel obstruction. Most of the packets seen at the University of Miami/Jackson Memorial Medical Center were reportedly machine packaged.

These smugglers stand in contrast to the patient who swallows unpackaged or poorly packaged cocaine hydrochloride to avoid imminent police arrest. This latter type of patient is likely to develop symptoms of cocaine intoxication, though fortunately the dose is often small. Experience with swallowed crack cocaine is limited, but risk of symptoms appears to be much lower than with the hydrochloride compound, due to crack’s limited solubility in water.

## RESPIRATORY COMPLICATIONS

A variety of pulmonary complications have been described, primarily associated with nasal or inhaled routes of exposure. The role of adulterants in some of these conditions appears small but cannot be excluded.

Pulmonary barotrauma may result from maneuvers meant to enhance drug effect, such as Valsalva's maneuvers or mouth-to-mouth breathing with a partner. Paroxysmal coughing from smoke irritation also may produce barotrauma. The sudden increase in airway pressure leads to alveolar rupture, with free air then dissecting into the mediastinum, pleural cavity, or subcutaneous tissues. There are numerous case reports of pneumomediastinum, pneumothorax, and subcutaneous emphysema but no reports of arterial air embolism. These patients present with chest pain (typically pleuritic), dyspnea, and sometimes sore throat or hoarseness. Examination may find subcutaneous crepitus but rarely reveals a Hamman's sign. Chest x-ray is diagnostic. The quantity of free air is generally small, and spontaneous resolution during a short inpatient stay is the rule. The possibility of esophageal rupture must be considered in pneumomediastinum, particularly if the patient gives a history of vomiting.

Emergency visits for bronchospasm due to smoking crack cocaine are increasingly noted, perhaps in part due to increased frequency of questioning patients about recent cocaine use. Many but not all these patients have a prior history of asthma. Most respond to standard ED bronchodilator treatment, although a small percentage require intensive care with ventilatory support. The transient tachycardic effect of cocaine usually is gone by the time of presentation to the ED, so inhaled ß-agonists are quite safe. In most cases, the smoke appears to act as a nonspecific airway irritant. In some patients, bronchospasm occurs as part of an immunoglobulin-E-mediated hypersensitivity reaction, as reviewed by Ettinger and Albin (1989).

Lobar and nonlobar pneumonias also are seen in crack smokers. Most are not severely ill and are treated as outpatients with oral antibiotics for community-acquired organisms. Some of these cases may represent undiagnosed hypersensitivity reactions manifested by fever, transient infiltrates, and eosinophilia. Bronchiolitis obliterans also has been reported in association with crack use; mild cases may go undiagnosed.

Tracheobronchitis with severe cough is well recognized in crack smokers. Mild-to-moderate hemoptysis frequently accompanies the cough and is often the symptom that prompts the patient to seek medical attention. Symptoms resolve gradually with abstinence. Diffuse alveolar hemorrhage was reported by Murray and colleagues (1988).

A moderate degree of pulmonary edema is a frequent finding at autopsy in cocaine-related deaths but is an uncommon ED presentation. Although some cases may be cardiogenic in origin, others are clearly noncardiogenic, with lavage fluid consistent with increased pulmonary capillary permeability, The

mechanism may be mediated by central adrenergic outflow or may represent a direct effect on pulmonary vasculature (Ettinger and Albin 1989). Intravenously, massive doses of cocaine have produced pulmonary edema in mice (Robin et al. 1989); human cases of noncardiogenic pulmonary edema appear to be caused more often by smoking the drug. Treatment includes oxygen supplementation, assessment of cardiac function, and, if necessary, ventilatory support. Fortunately, most reported cases improve spontaneously.

## RENAL COMPLICATIONS

Acute rhabdomyolysis is a well-recognized consequence of cocaine use, particularly in patients who develop agitation with excessive motor activity, seizures, hyperthermia, coma (immobility), or hypotension. Since rhabdomyolysis also is seen in patients with none of these other conditions, this drug also may have a direct effect on myocytes or may cause ischemia to skeletal muscle via vasospasm. Muscle necrosis may occur following any route of exposure to cocaine. Myalgias or muscle tenderness are present in about half the patients; some complain of chest pain from damage to chest wall musculature.

The presence of rhabdomyolysis should be considered in cocaine-intoxicated patients. In one study (Welch et al. 1991), 24 percent of all patients presenting with a cocaine-related complaint were found to have rhabdomyolysis, defined as a CK level at least five times normal. Most of these cases were mild and asymptomatic. Myoglobinuria is another indicator of muscle necrosis, and patients may be rapidly screened for this with a urine dipstick for occult blood (detects hemoglobin or myoglobin); positive results necessitate assays for CK, renal function, and electrolyte disturbances.

Milder cases should not lead to any significant renal or electrolyte problems. Inpatient admission is unnecessary, but IV hydration in the ED over a few hours is appropriate to minimize renal insult. It is important for the clinician to consider the possibility of mild rhabdomyolysis as a confounding factor in the interpretation of cardiac enzyme results on patients with chest pain.

The cocaine-intoxicated patient with toxic delirium, hyperthermia, multiple seizures, coma, or shock must be considered a high risk for rhabdomyolysis complicated by myoglobinuric renal failure (Brody et al. 1990a). The hypotensive patient is also at risk for acute tubular necrosis. IV volume infusion with isotonic fluids is appropriate early in the course of treatment to maintain a urine output above 75 mL per hour; sodium bicarbonate infusion also may be considered if CK is dramatically elevated. The comatose patient should be turned periodically into different positions. Most of these patients

do well even if renal failure ensues, but the patient with failure of other organs (e.g., liver, heart) in addition to uremia carries a poor prognosis (Roth et al. 1988).

## NEUROLOGIC COMPLICATIONS

The various neurologic sequelae from cocaine use may be acutely dramatic and devastating or may develop much more chronically. Most do not appear to be dose dependent, although higher doses clearly and significantly increase the risk of seizures.

### Seizures

Generalized tonic-clonic seizures have been recognized as a consequence of cocaine intoxication for more than 70 years. These seizures usually occur within minutes after IV, nasal, or inhaled routes of use; time of onset after oral use is unpredictable. Although high doses of cocaine clearly increase the risk of seizure, many patients deny intake greater than "usual," and indeed a kindling effect has been reported in animal studies with repetitive use of smaller quantities of the drug.

Most seizures are single and short, without residual damage. However, repeated seizures signal high risk of death from respiratory arrest and warrant aggressive control. Airway maintenance and IV benzodiazepines are treatment priorities. Diazepam given before or after onset of seizures appears to protect against death from cocaine. In animal models, diazepam given prior to cocaine administration also decreases the risk of seizures. Phenobarbital or phenytoin may be tried if diazepam fails to control seizure activity. Neuromuscular blockade and general anesthesia occasionally may be required. Complicating factors such as hyperthermia, rhabdomyolysis, severe respiratory and lactic acidoses, hypoglycemia, electrolyte disturbances, and trauma must be looked for and treated in these patients. Once the patient has been stabilized, emergency evaluation by computerized tomography (CT) is in order to look for CNS hemorrhage, stroke, mass lesion, or trauma; selected situations (fever, meningeal signs, prolonged altered mental status) may warrant lumbar puncture or electroencephalogram. Toxicology screening for other drugs (e.g., amphetamine, phencyclidine) is especially indicated if seizure activity is prolonged. Cocaine use should be considered in the evaluation of ED patients (including pediatric ages) who present with new onset of seizures. The patient with an uncomplicated seizure who is found to have no underlying cause beyond cocaine intake may be discharged safely with education on risks and recommendation of abstinence, without long-term antiepileptic medication.

## Cerebrovascular Ischemia and Hemorrhage

Other potential neurologic catastrophes include subarachnoid hemorrhage, intracerebral bleeds, and ischemic strokes. Cocaine produces an intense, short-lived burst of systemic hypertension that may lead to hemorrhage. Subarachnoid hemorrhage (SAH) due to cocaine presents, as do non-drug-related SAHs, with severe headache, loss of consciousness, nausea/vomiting, and/or neck stiffness. Of 27 reported cases reviewed by Green and coworkers (1990), 78 percent were found to have an underlying predisposing condition such as an aneurysm or arteriovenous malformation. Other forms of intracranial hemorrhage due to cocaine present with headache, seizure, altered sensorium, and/or lateralizing findings. Approximately half the reported cases of intracerebral hemorrhage were found to have an underlying vascular lesion (Green et al. 1990). Cocaine may induce a bleed due to its transient hypertensive effect as in SAH or due to hemorrhage at a site of ischemia produced by vasospasm. lschmic cerebrovascular accidents may occur as often as hemorrhage in free base smokers (Levine et al. 1990), although both are fortunately rare events. Cocaine-induced hypertension and vasospasm appear to be the most likely mechanisms of ischemic stroke; thrombosis and embolic phenomena (seen with arrhythmias and cardiomyopathies) are also possible. Amphetamine-induced vasculopathy has been documented, but the association of cocaine with vasculitis remains debated.

Transient ischemic symptoms have been reported with cocaine, probably due to vasoconstriction. Management of these patients currently is identical to management of these same CNS events unrelated to cocaine. Transient syncope may be due to neurologic or cardiac effects of the drug; evaluation is typically unrewarding if physical examination and ECG are normal.

Evidence from single photon emission CT studies now suggests that many chronic cocaine users may have scattered deficits despite absence of symptoms (Tumeh et al. 1990). The incidence and long-term consequences of such damage are not yet known, although they may be found to contribute to significant neurologic impairment.

Headache following cocaine use is a relatively common ED presenting complaint among cocaine users. Most have no findings on exam but present a challenge to the ED physician because of the possibility of underlying hemorrhage. Thus, most are evaluated with at least an emergent CT scan.

## Toxic Delirium

Cocaine produces an array of neuropsychiatric states, and the violently agitated patient is perhaps the most dramatic ED presentation Caused by this drug. This person typically arrives with a multitude of personnel who are attempting physical control. There is an appearance of incredible strength, but this may reflect an indifference to pain; the risk of physical harm to both caregivers and the patient is significant. The patient is delusional, paranoid, and often overtly psychotic. This state does not clearly relate to cocaine dosage, blood level (Wetli and Fishbain 1985), route of administration, or frequency of use. It does not seem to be precipitated by adulterants or concomitant use of other drugs, with the possible exception of alcohol; the role of cocaethylene is under investigation. Untreated, this confusional, agitated state may last for several hours, far longer than cocaine's other effects. It often is followed by a period of complete exhaustion and obtundation.

In the ED, a rapid but systematic visual assessment should look for compromise of airway or ventilation, for obvious trauma, and for obvious neurologic deficit. Pulse rate and quality, pupillary reflexes, and skin temperature can be checked quickly; more thorough examination often has to wait for sedation but must not be neglected. ED personnel should be trained to act as a team to achieve adequate physical control of these patients with minimal risk of injury. Physical restraints may be required but must be checked often to minimize risk of extremity ischemia or respiratory compromise; they should not inhibit heat loss. More appropriately, parenteral pharmacologic sedation should be instituted promptly. Diazepam or other benzodiazepines are the agents of choice, with demonstrated efficacy, salutory effects on cardiovascular changes, and apparent lowering of seizure risk and lethality. Haloperidol has been used clinically with some success, but its use raises concerns in that it does not protect against seizures, may adversely affect thermoregulation, and is less well studied. A quiet environment and a calm approach are useful adjuncts.

As soon as possible, IV access should be established. Infusion of isotonic fluids is recommended to replete volume and limit myoglobinuric renal damage. Serial examinations are mandatory. A rather typical ED postsedation course includes several hours of deep sleep, then gradual awakening of a calm patient with little recollection of events.

Differential diagnoses of acute confusional states must be considered early. Glucose and electrolytes should be checked. Examination must search for evidence of head injury, intracranial hemorrhage, or thyrotoxicosis. Many other agents can produce similar behavior, although most are uncommon. Information from witnesses, friends, and family may be vital. In particular,

anticholinergic poisoning requires consideration; anticholinergic drugs also cause mydriasis but generally limit peristalsis, in contrast to the hyperactive bowel sounds from cocaine. Amphetamine effects are difficult to rule out clinically. Of course, toxicology testing is useful if diagnosis is unclear.

## HYPERTHERMIA

Contributory mechanisms of cocaine-induced hyperthermia include sympathetic discharge, excessive motor activity, seizures, increased metabolic rate, vasoconstriction, and loss of thermoregulatory control. Toxic delirium often is coupled with extreme hyperthermia, and these patients seem to be at high risk of cardiovascular collapse. Sequelae include neurologic damage, rhabdomyolysis, renal failure, coagulopathies, shock, and hepatic failure, with similarities to heat stroke.

Aggressive cooling, with controlled application of ice packs, cool baths, or cool water plus fans to increase evaporation, is vital. Core temperature should be brought down to 102 °F; further cooling risks hypothermia due to poor regulatory control. IV fluid support and, for the agitated patient, benzodiazepine sedation also are indicated. Dantrolene does not appear beneficial, since the underlying mechanism here is different from that of malignant hyperthermia.

## EMERGENCY DEPARTMENT DATA ON VISITS

Several authors have surveyed visits to busy, urban EDs for cocaine-related medical problems. These data provide an important perspective on cocaine's side effects and the need for intervention and also emphasize the rarity of catastrophic events.

Brody and colleagues (1990b) reviewed consecutive hospital visits by 233 patients over a 6-month period; 2 patients died (one death followed seizures, one followed chest pain). Half the patients used the drug intravenously; 18 percent smoked alkaloidal cocaine. The majority had multiple complaints. Fifty-six percent complained of cardiopulmonary symptoms; 36 percent had psychiatric symptoms; and 39 percent had neurologic symptoms. Pharmacologic intervention was deemed necessary in only 24 percent of patients, and most treatments were nonspecific (e.g., naloxone, thiamine, charcoal). Of admissions, 60 percent were related to direct drug effects, whereas others were necessitated by complications of IV injection practices. There were no documented myocardial infarctions on discharge diagnoses.

Derlet and Albertson (1989c) reviewed all cocaine intoxications seen over a 1-year period—137 patients, including one death. Thirty-four percent used an IV route, whereas 18 percent smoked the drug. Neurologic and psychiatric complaints accounted for the majority of visits (29 percent for altered mental status, 8.8 percent for seizures, 9.5 percent for suicide attempts, and 2.9 percent for transient ischemic symptoms). Chest pain prompted 15 percent of the visits; three patients were hospitalized for possible myocardial infarctions, but none were later confirmed. In this series, 19 percent required pharmacologic treatment, most frequently with diazepam, antipsychotic drugs, nitroglycerin, nifedipine, phenytoin, and naloxone.

Rich and Singer (1991) evaluated 144 consecutive visits due to cocaine effects seen over a 6-month period, including one death unrelated to the drug's presence. Routes of use were IV in 34 percent, nasal in 32 percent, and smoked in 24 percent. Psychiatric symptoms accounted for 31 percent of these visits, neurologic complaints for 17 percent, and chest pain/palpitations for 16 percent. Chest symptoms were more common with nasal use.

Experience in the ED at the University of Miami/Jackson Memorial Medical Center, a high-volume county hospital, parallels that of other metropolitan hospitals. A brief (1 month) review of all emergency medical complaints due to cocaine (41 patients; trauma and mild psychiatric complaints were excluded) found that 46 percent of visits were due to cardiovascular symptoms, primarily chest pain. There was one death in a cocaine user with known coronary disease who suffered prehospital arrest. Eight patients had abdominal complaints; seven were discharged; and one was admitted for pancreatitis due to ethanol. Three patients presented with toxic delirium, one with seizures. Significantly, the route of ingestion was by smoking in 83 percent of cases.

In all these series, the average patient age was about 30 years. A minority (10 to 20 percent) required inpatient admission. Acute myocardial infarction, intracranial hemorrhage, ischemic stroke, infarcted bowel, and pulmonary barotrauma were not seen in the 555 cases described in this section. Deaths were rare (four). The majority of patients (61 to 76 percent) were male. This gender difference may well represent community patterns of use and is unlikely to reflect any difference in risk of complications. In part, it also might reflect interviewer bias; a past review of ED chart documentation by house staff on all young adults with chest pain, palpitations, syncope, or new seizures documented information on cocaine use (positive or negative history) in most male patients but few females.

In these series, concurrent use of other drugs with the cocaine was commonly reported (34 to 50 percent of patients), most frequently alcohol and opiates.

Only a minority of patients required pharmacologic intervention for specific cocaine effects, primarily benzodiazepines for agitation or seizures. Other than the four cardiac arrests, no patients required treatment for arrhythmias.

In addition to the medical consequences of cocaine use, other ramifications, especially use in obstetrical patients and those with trauma, must be remembered. Although not discussed here, these do have an impact in the ED. Neonatal effects of maternal drug use present a national health problem now and for the foreseeable future. Cocaine is commonly present in patients who arrive at the ED due to traumatic injury. Marzuk and coworkers (1990) reported cocaine in 18.2 percent of autopsies on motor vehicle accident victims, with similar percentages in drivers and passengers. Rich and Singer (1991) found that 12 percent of cocaine-related ED visits were due to trauma. In our institution in Miami, a busy urban Level One Trauma Center, evidence of recent cocaine use is found in approximately 35 percent of major trauma victims (all causes). Causative relationships to motor vehicle accidents and effect on survivability from major trauma remain undefined.

## SUMMARY

Cocaine use is related to a vast array of emergency medical conditions, and emergency physicians throughout the United States are likely to be confronted with these patients. Although catastrophic complications are well recognized, they fortunately represent a very small fraction of cocaine sequelae. However, a high index of clinical suspicion should be maintained to avoid misdiagnosis of complications such as myocardial ischemia, significant rhabdomyolysis, or small subarachnoid hemorrhage. Rapid intervention is crucial in patients presenting with seizures, hyperthermia, lethal arrhythmias, or toxic delirium. Most patients do well with ED evaluation and nonspecific supportive care, but an understanding of this drug's mechanisms of action and its interactions with therapeutic interventions is vital in situations such as acute hypertension, cardiac arrhythmias, or agitated states. Reliable animal models that closely simulate human responses are not yet available. At this time, knowledge remains limited, particularly as to optimal pharmacologic management of specific cocaine effects. Further investigations into potentially adverse consequences of commonly used medical regimens, such as p-receptor antagonist, will be essential in guiding management of these cases.

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**AUTHOR**

Kathleen S. Schrank, M.D.
Associate Professor of Clinical Medicine
Section Chief, Emergency Medicine
Department of Medicine (R-60)
University of Miami School of Medicine
P.O. Box 016960
Miami, FL 33101

# Cerebrovascular Complications From Cocaine: Possible Long-Term Sequelae

***Bruce L. Miller, Frances Chiang, Lora McGill, Todd Sadow, Mark A. Goldberg, and Ismael Mena***

## INTRODUCTION

The first report of cerebrovascular complications from cocaine was written by Brust and Richter (1977). They described a man who developed aphasia and hemiparesis 2 hours following an intramuscular injection of cocaine. Because the subject was a polydrug abuser and because this complication had not previously been reported, the authors cautiously stated that ". . . cocaine may have contributed to the stroke." However, with great foresight they concluded: "If in fact cocaine played a causal role, we anticipate that more strokes will be seen among the many abusers of this agent in American cities."

Despite this prophecy there was scant literature on neurological sequelae from cocaine abuse prior to 1984, and until recently, most reports on cocaine toxicity focused on cardiac or respiratory symptoms. However, as predicted by Brust and Richter, beginning in 1984 several investigators began to report on an epidemic of cocaine-induced neurological problems. Mody and colleagues (1987) described a group of 11 patients with neurological complications from cocaine abuse, including transient ischemic attacks, ischemic spinal cord and brain infarction, brain hemorrhage, and focal and generalized seizures. They suggested that this epidemic of cocaine-induced stroke was due to the wide availability of crack cocaine. More recently, a large multicenter study (Levine et al. 1990) further delineated the extensive national presence of cocaine-induced stroke and confirmed that this epidemic was due to the use of crack cocaine.

With the widespread availability of crack, it has become clear that cocaine is a drug with serious and unpredictable effects on the brain. In fact, the authors' experience suggests that crack is the most toxic of the street drugs abused over the past three decades. One particularly disturbing feature of crack is that

permanent neurological injury can occur with first-time use. For example, Mody and coworkers (1988) reported on an 18-year-old man who developed a spinal cord stroke with subsequent irreversible quadriplegia after smoking crack for the first time. Of the 14 patients described in this study, 36 percent developed neurological symptoms the first time that they used the drug. This "side effect" of cocaine is not predictably dose related and occurs in patients without other symptoms of cocaine intoxication. Therefore, unlike most other illicitly used compounds, a single experimentation with cocaine can lead to irreversible brain injury. This potential toxicity has been underreported and underestimated.

Until recently the mechanisms for cocaine-induced strokes were poorly understood. For instance, some stroke patients in the authors' early studies had normal imaging studies of the brain, including computerized tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography. However, with the use of single photon emission computerized tomography (SPECT) and positron emission tomography (PET), the anatomical sites and physiological mechanisms associated with cocaine-induced neurological and psychiatric syndromes are becoming better understood.

This chapter briefly outlines the common neurological and neuropsychiatric syndromes associated with cocaine abuse and summarizes the findings via SPECT and PET in patients with acute and chronic cocaine intoxication. The long-term sequelae of chronic cocaine abuse also are discussed.

## COCAINE-INDUCED CEREBRAL HEMORRHAGE

Seven years after Brust and Richter (1977) predicted an epidemic of cocaine strokes, various authors began to describe patients with cocaine-induced cerebral hemorrhage. The first was a report on two patients who developed cerebral hemorrhage associated with intranasal cocaine (Lichtenfeld et al, 1984). One patient had an anterior communicating artery aneurysm, and the second had an arteriovenous malformation. Subsequently, Wojak and Flamm (1987) described six patients who had brain hemorrhage associated with cocaine abuse. Three of the six died; one was left in a vegetative state; one had a fair outcome; and only one had a good recovery. Most had an underlying vascular abnormality: Two demonstrated normal angiography; two had cerebral aneurysms; one had an arteriovenous malformation; and one had evidence for hemorrhage into a malignant brain tumor.

Jacobs and colleagues (1989) described 13 patients who developed neurological deficits attributable to cocaine. Of these, 23 percent had intracerebral hemorrhage; 23 percent had subarachnoid hemorrhage; and 54 percent showed evidence for ischemic brain infarction. Similarly, Mody

and coworkers (1988) described three patients who developed brain hemorrhage. Angiography was performed on each patient; in one an arteriovenous malformation was present; a second showed evidence for cerebral vasculitis; and the third had a normal angiogram. A typical hemorrhage case is described below:

> A 38-year-old man with a long history of cocaine abuse was brought to hospital with new onset of right-sided paralysis associated with loss of speech. The patient's friends stated that he had smoked crack shortly before developing his paralysis. In hospital he was mute and could not follow simple commands. He had a right homonymous hemianopsia and a dense right-sided hemiparesis and sensory disturbance. CT showed a large hyperdense hematoma in the left thalamus, which extended to basal ganglia. SPECT showed profound hypoperfusion in the left thalamus and basal ganglia with hypoperfusion in the overlying left temporal-parietal cortex. There was mild periventricular scalloping of perfusion. The patient's language and paralysis began to improve when he checked himself out against medical advice.

The studies on brain hemorrhage associated with cocaine have shown a remarkable consistency, with at least 50 percent of the patients demonstrating an underlying abnormality in cerebral blood vessels, with arteriovenous malformations and cerebral aneurysms accounting for most cases. Cocaine-induced hypertension leading to rupture of previously abnormal vessels is the most likely explanation for hemorrhage in most individuals. However, in others the angiogram is normal, or like the patient just described, the hemorrhage occurs in regions that are commonly associated with hypertensive hemorrhage. In these patients, the hypertension may cause the hemorrhage. Finally, it is possible that in some patients a cerebral vasculitis weakens and eventually leads to rupture of cerebral vessels. This issue is discussed in the section on vasculitis.

In any patient with brain hemorrhage associated with cocaine, it is mandatory that angiography be performed, as it often reveals an arteriovenous malformation or an aneurysm that will require neurosurgical intervention. Treatment for these patients is similar to the treatment of brain hemorrhage that is unrelated to cocaine.

## TRANSIENT ISCHEMIC ATTACKS AND ISCHEMIC BRAIN INFARCTION

Beginning with Brust and Richter's original report (1977), there has been increasing evidence that transient ischemic attacks (TIAs) and ischemic brain infarctions do occur in drug abusers, including those who abuse cocaine (Caplan et al. 1982). Although clinical stroke is not a common sequela of cocaine abuse, around 1987 numerous groups began to describe young individuals with TIA and ischemic brain infarction secondary to cocaine abuse. Golbe and Merkin (1986) described a single patient with a right middle cerebral artery infarct; following this study, several groups reported on larger series of patients with cocaine-induced stroke syndromes (Jacobs et al. 1989; Lowenstein et al. 1987; Levine et al. 1987). In the study by Jacobs and colleagues (1989) seven patients with ischemic stroke were reported. All were young (mean age of 34) and there was a surprising predilection for small-vessel occlusions: Four of their seven patients had lacunar strokes in a purely subcortical location; two patients had middle cerebral branch occlusions; and one had a mixture of cortical and subcortical stroke.

Similarly, Rowley and coworkers (1989) described three patients with a mean age of 33 in whom strokes occurred in the rostral midbrain and thalamus. These researchers noted that in a previous review of 25 subjects with thalamic stroke, none of whom had abused cocaine, only 3 were younger than 50. They concluded that the thalamic and midbrain strokes seen with cocaine abuse occurred in an unusual location and that strokes occurring in this region in non-cocaine abusers typically occurred in individuals age 50 and older. Also in the report by Mody and colleagues (1988), the patients tended to have branch occlusions, and none of the subjects had basilar or carotid artery occlusions. In a multicenter study, Levine and colleagues (1990) described 28 patients with cocaine-induced cerebrovascular complications; some had large-vessel occlusions, and others had small-vessel occlusions.

## WHY DOES ISCHEMIC STROKE OCCUR WITH COCAINE?

Often, individuals with cocaine-induced stroke are young without other known risk factors for stroke. The time interval between cocaine use and stroke has varied from minutes to many hours, but in some subjects it has been hard to extract a reliable history, making it difficult to define precisely a temporal relationship between abuse and stroke. The mechanism for these events remains uncertain, and due to the young age of the patients, atherosclerosis is not a likely explanation for most of the stroke syndromes. Cocaine and some of its metabolites are potent vasoconstrictors: Lange and coworkers (1989) have shown that intravenous (IV) cocaine produces intense spasm of coronary arteries. Myocardial infarction can occur with

excessive release of catecholamines, a major mechanism of action for cocaine. Evidence that similar changes occur in cerebral vessels leading to stroke is now beginning to emerge.

Some researchers suggest that the ischemic strokes seen with cocaine are due to cerebral vasospasm caused by catecholamine release (Mody et al. 1988). However, angiographic findings have been variable, with only a few cases demonstrating focal vasospasm. Similarly, Rowley and colleagues (1989) have reported that the arterial branches supplying the thalamus and midbrain, common locations for cocaine-stroke, are not heavily innervated with noradrenergic fibers, making catecholamine-induced stroke as a mechanism for cocaine far from certain. In these patients, angiography often shows either branch vessel occlusions or normal angiography; only a few subjects show "vasculitic" changes with angiography.

There are several explanations for the paucity of findings with angiography. Most stroke subjects are many hours out (up to 24 or more hours) from their dose of cocaine when they reach the hospital; by the time angiography is completed, it is usually days after the acute event. Therefore, even if spasm is the etiology for the stroke, the spasm might be gone by the time angiography is performed. Also, with cocaine there is selective involvement of small- and medium-size vessels, arteries that are not well resolved with angiography.

More research is needed to determine why some subjects develop ischemic stroke, whereas most do not. The role of cocaine metabolites in stroke has been incompletely investigated. Recent work shows that patients who simultaneously abuse alcohol and cocaine metabolize cocaine to cocaethylene, which is also centrally active (Hearn et al. 1991). It is possible that the combination of alcohol and cocaine is particularly toxic. Accelerated atherosclerosis is one possible explanation for ischemic stroke in chronic abusers, although there is a paucity of information to support this concept. Moreover, in Mody and colleagues' (1988) study, many of the stroke patients were first-time abusers, suggesting that certain individuals are particularly prone to stroke when using cocaine. In these cases the cocaine may be just one factor in the pathogenesis of the stroke syndrome. Two such patients with multiple risk factors for ischemic stroke are described below:

> A 17-year-old right-handed woman, $G^2P^0$Ab, was admitted to labor and delivery with a 25-week pregnancy. She had a past medical history significant for alcohol and polydrug abuse. She was admitted for pre-eclampsia with mild hypertension. Six days after admission, she had a generalized seizure, which was treated with phenytoin (Dilantin). Subsequently,

she delivered a small-for-gestational-age infant and her hypertension resolved with delivery. Postpartum the phenytoin was discontinued, but 3 days later a second generalized seizure occurred and phenytoin was restarted. Two days later she developed sudden onset right face and arm weakness with dysarthria. A CT scan was normal, but MRI demonstrated areas of hyperintensity in the left caudate and corona radiata and in the right centrum semiovale. An echocardiogram was normal, and serum studies revealed that antiphospholipid antibody was present. Two days after the stroke, she complained of acute onset of shortness of breath that was associated with hypoxemia, and a pulmonary embolus was diagnosed, for which she was started on heparin. She was switched to sodium warfarin (Coumadin) and gradually improved; after 2 weeks in hospital, she admitted to abusing cocaine throughout the pregnancy.

This patient had multiple risks for stroke, including the pregnant state and the presence of lupus anticoagulant (antiphospholipid antibody). Indeed, she developed both venous thrombosis and brain infarction, a characteristic of patients with this antibody. However, most pregnant women with lupus anticoagulant do not have strokes, and it is possible that the combination of all three risk factors-cocaine, antiphospholipid antibody, and pregnancy-led to her cerebrovascular complications.

Another cocaine abuser with multiple risk factors for stroke was a 56-year-old male admitted to hospital after developing left-sided weakness associated with dysarthria and dysphagia. Four days earlier he awakened unable to move his left arm or leg, and when this did not improve, he came to hospital. On examination, blood pressure was normal. He had mild bradycardia but the electrocardiogram did not show left ventricular hypertrophy. He was mentally slowed with slurred, hypophonic output and had mild word-finding difficulty, a memory disturbance, and a left hemiparesis. The clinical diagnoses were mild dementia, pseudobulbar syndrome, and left-sided hemiparesis due to multiple strokes, MRI showed multiple lacunar strokes in the deep white matter, basal ganglia, and internal capsule. SPECT showed bilateral temporal and frontal hypoperfusion. Although he initially denied cocaine abuse, urine toxicology was positive and he eventually admitted to chronic cocaine use for up to 3 days prior to his stroke. He left hospital after 4 days with little clinical improvement.

Despite the fact that this man had only mild hypertension and no history for previous stroke, his MRI showed multiple ischemic white matter infarctions, and clinically he had a dementia syndrome that was probably secondary to multiple strokes. It is possible that hypertension alone caused the strokes, although he was relatively young and blood pressure measured in the hospital was normal. More likely, the combination of mild hypertension and chronic cocaine abuse was responsible for the patient's vascular dementia.

This is one of several patients the authors have seen who developed a dementia syndrome associated with chronic cocaine abuse. One concern with the current epidemic of cocaine abuse is whether chronic abusers will develop a vascular dementia. Prospective neuropsychological and imaging studies that longitudinally assess chronic cocaine abusers will be important. Similarly, careful evaluation of other risk factors associated with stroke and cocaine needs to be performed. It seems unlikely that a single mechanism accounts for this phenomena and that the etiology for cocaine-induced ischemic stroke and cocaine-induced vascular dementia is multifactorial.

**VASCULITIS**

One unresolved issue related to cocaine-induced stroke is whether it is due to central nervous system (CNS) vasculitis. However, amphetamine, which also boosts brain catecholamines, can cause a CNS vasculitis. Citron and coworkers (1970) first described 14 polydrug abusers who developed catastrophic systemic or neurological complications from a necrotizing vasculitis. The common link among all was the use of amphetamine.

Subsequently, Rumbaugh and colleagues (1971a) showed that monkeys given a single IV injection of methamphetamine developed changes in the caliber of middle cerebral and lenticulostriate vessels. Although these changes disappeared within 24 hours angiographically, postmortem evidence for petechial hemorrhages and scattered areas of small infarction was found throughout the brain. This has disturbing implications for chronic abusers.

Kaye and Fainstat (1987) described a patient who abused cocaine in whom a diagnosis of vasculitis was made based on angiographic changes. However, as noted by Levine and coworkers (1988), this case is controversial, because the patient had a subarachnoid hemorrhage, which by itself could cause angiographic findings that mimic vasculitis.

The diagnosis of vasculitis often depends on interpretation of cerebral angiography, and the angiogram in patients with cocaine-associated stroke most often shows occlusions or segmental stenoses of the vessels of the circle

of Willis, the supraclinoid internal carotid artery, and horizontal segments of the anterior, middle, or posterior cerebral arteries. Areas of narrowing may be multiple, focal, or diffuse. If stenoses involve the vessel walls uniformly, the term “vasospasm” is used even though the findings may represent irreversible changes, Less commonly, the vessels show a beaded appearance or irregularly narrowed segments, which correlates with a vasculitis based on the appearance of necrotizing angiitis in connective tissue diseases (Ferris 1974).

With cocaine, vessel “spasm” may involve the major branches of the intracerebral arteries, particularly the sylvian branches of the middle cerebral artery (Jacobs et al. 1989). These lesions can cause either ischemic infarcts or intracranial hemorrhage (Klonoff et al. 1989). However, the numerous small artery occlusions seen on angiography in amphetamine-associated vasculitis (Rumbaugh et al. 1971b) are uncommon with cocaine abuse, and more typically, the cerebral angiogram is completely normal, despite an ischemic event. These patients most likely have true episodes of vasospasm that subsequently reversed after causing ischemic injury. Described below is one of the few cases that the authors have seen with a possible cocaine-induced vasculitis:

> A 36-year-old male was admitted to hospital with mental decline and a pseudobulbar palsy. He had developed trouble with speaking and swallowing over the previous 2 days. There was a history of hypertension, but blood pressure was normal on admission. On examination he had involuntary bursts of laughter, bilateral facial weakness, an absent gag reflex, and a spastic upper palate. Bilateral arm and leg weakness were present. CT and MRI showed multiple small infarcts in the corona radiata, basal ganglia thalamus, and pons (figure 1). Angiography showed multiple areas of irregular narrowing in branch vessels of the anterior, middle, and posterior cerebral arteries (figure 2). SPECT showed small areas of hypoperfusion in the frontal and temporal lobes.

This patient initially denied cocaine abuse but later admitted to episodic use. A broad screen for an etiology of the patient’s strokes was negative, including antinuclear and antiphospholipid antibody, hepatitis panel, human immunodeficiency virus, protein electrophoresis, cerebrospinal fluid examination, and erythrocyte sedimentation rate. A therapeutic trial with prednisone and cyclophosphamide (Cytoxan) was unsuccessful. It is possible that this man had multiple strokes on the basis of a primary CNS vasculitis unrelated to cocaine. However, the history was highly suggestive for a cocaine-induced syndrome, and primary CNS vasculitis is rare. Biopsy-proven cases of

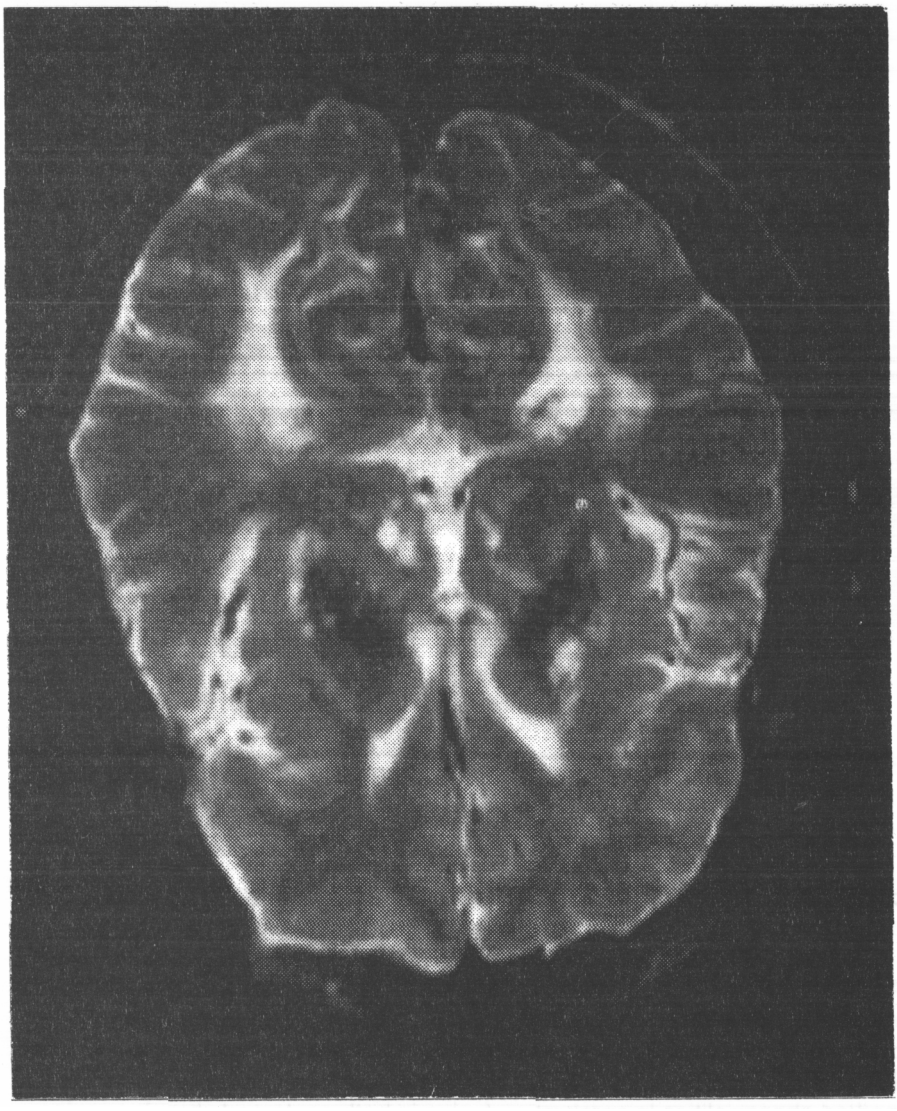

**FIGURE 1.** *This T2-weighted MRI scan demonstrates multiple ischemic infarctions in the corona radiata, thalamus, and basal ganglia.*

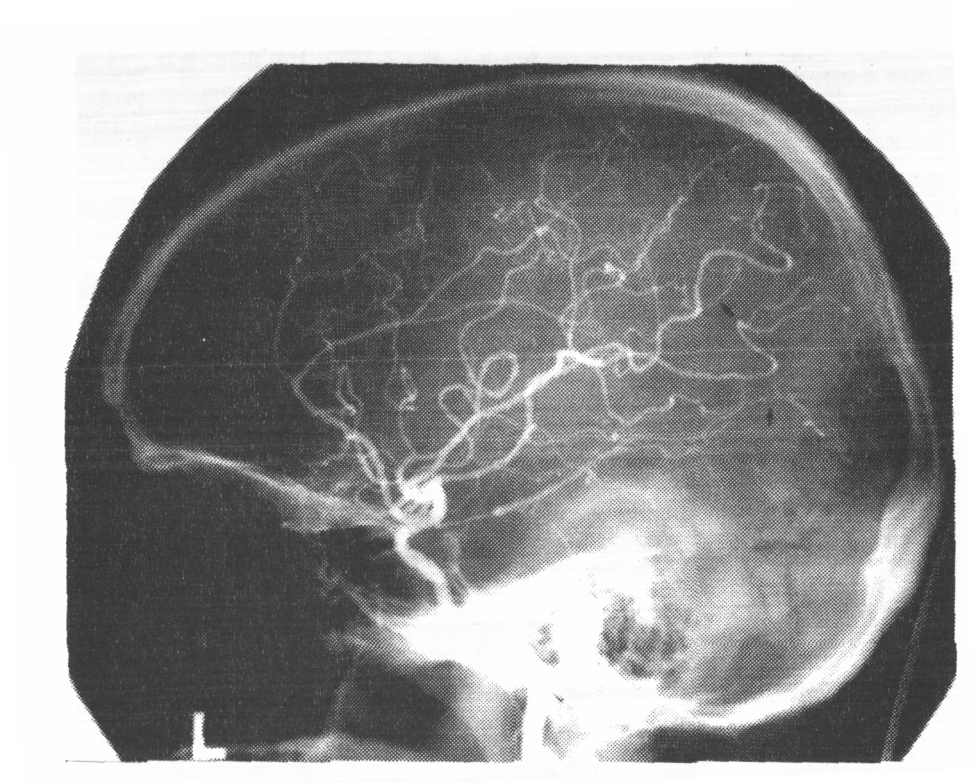

**FIGURE 2.** *This cerebral angiogram shows multifocal areas of cerebral spasm in the patient.*

cocaine vasculitis are rare, but Krendel and coworkers (1990) recently reported a biopsy-proven case of granulomatous vasculitis in a cocaine abuser.

Although cocaine-induced cerebral vasculitis appears to be unusual, better information should come from careful postmortem studies on the cerebral blood vessels of patients who had a history of cocaine abuse. As described in the next section, SPECT studies of cerebral blood flow appear to demonstrate marked abnormalities in cerebral perfusion in both acute and chronic cocaine abusers. Although in some cases this may be due to cerebral vasospasm, in a few there may be a vasculitis.

## NEUROIMAGING STUDIES OF COCAINE NEUROPSYCHIATRIC SYNDROMES

### Techniques

During the past decade there have been significant advances in radiological techniques that allow high-resolution imaging of both cerebral blood flow and metabolism. With PET, the subject is injected with a radiolabeled compound that emits positrons. These positrons are detected, and a three-dimensional image of their distribution can be produced. It is possible to measure different metabolic processes depending on the compound that is radiolabeled. For example, with fluorodeoxyglucose an image of the brain's glucose metabolism is obtained. Conversely, with radiolabeled haloperidol one can obtain an image that shows the distribution of the brain's dopamine receptors.

Simultaneously, there have been significant advances with SPECT. Currently, the lower resolution imaging agents such as $^{133}$Xenon are being augmented with higher resolution compounds such as $^{99m}$technetium-hexamethyl-propylene-amine-oxime (HMPAO) (Neirinckx et al. 1981; Sharp et al. 1986). HMPAO crosses the blood-brain barrier at a rate approximately equal to cerebral blood flow. After reaching the brain, HMPAO is enzymatically converted and trapped, allowing a high-resolution image of cerebral blood flow. Mena and coworkers (1990) have utilized both $^{133}$Xenon, which gives absolute numbers for cerebral perfusion, and HMPAO with its higher resolution capabilities to study cocaine abuse.

The advantage of SPECT and PET is that they give information about brain function independent of brain structure. For example, it is known that diffuse metabolic disturbances, even those that lead to coma and death, do not change the structural images of brain as shown by such techniques as MRI and CT. However, even subtle disturbances in metabolic function will alter functional brain images. Indeed, both PET and SPECT studies are beginning to demonstrate subtle changes in brain metabolism and perfusion in cocaine abusers with normal structural brain images. These studies are helping to elucidate pathogenetic mechanisms associated with cocaine abuse.

### SPECT Findings

For the past 2 years Miller and coworkers (1989) and Mena and coworkers (1990) have utilized SPECT to evaluate patients with a variety of cocaine-induced neurological and psychiatric problems. These studies have shown a sensitivity with SPECT that has exceeded that of CT and MRI. A recent study (R. Giombetti et al., personal communication, August 1991) evaluated 14

consecutive patients with acute cocaine intoxication and neurological symptoms with CT and SPECT. Symptoms included transient ischemic attacks, stroke, seizures, and confusional states. Cerebral blood flow was imaged with HMPAO and was measured using $^{133}$Xenon. Focal, multifocal, or diffuse areas of hypoperfusion were found in all 14 patients with either HMPAO SPECT or $^{133}$Xenon. Multiple small superficial and deep areas of hypoperfusion causing a "scalloped" appearance on SPECT were seen in 12 patients. This pattern appeared to be characteristic of cocaine abuse in this population. Mean cerebral blood flow measured with $^{133}$Xenon was slightly diminished at 43.6±3.4 mL/100 g/min compared with 55.1±1.4 mL/100 g/min in normals. SPECT was valuable in studying these patients, and cortical and subcortical vascular abnormalities, not seen on CT or MRI, were demonstrated with SPECT. A typical patient in whom SPECT was valuable is described below:

> A 25-year-old woman was admitted to hospital with a 3-day history of left-sided weakness and a generalized seizure. She had sudden onset of left arm and leg weakness that persisted for 3 days. On the day of admission she had a generalized seizure and was brought to the emergency room by friends. There she admitted to a history of occasional cocaine abuse but insisted that her last use had been more than 1 year ago. However, her urine toxicology screen was positive for cocaine. Neurologic exam showed mild left hemiparesis of arm and leg with mildly decreased left-sided sensation. CT, EEG, lumbar puncture, echocardiogram, and cerebral angiogram were normal. SPECT showed areas of hypoperfusion in right parietal, left temporal, and both frontal lobes. There was scalloping in the periventricular region (figure 3). She was admitted again 3 months later with increased left-sided weakness and dysarthria. Her urine screen was again positive for cocaine and this time she admitted to continued abuse. She left hospital with a persistent left-sided neurologic deficit.

This patient is fairly representative of the cocaine-stroke population at Harbor-UCLA Medical Center. She was young and initially denied the importance of her cocaine abuse as a factor in her stroke syndrome. Because cocaine strokes often involve small-size vessels, CT and MRI can be normal, as was the case in this patient. In contrast, SPECT often shows perfusion deficits in the brain area appropriate to the clinical syndrome. SPECT also can show other focal areas of hypoperfusion, which do not have clear clinical significance. The most consistent abnormality has been the scalloping of cerebral perfusion in the periventricular region, present in more than 80 percent of the acute cocaine-abuse population (Mena et al. 1990). This appears to represent an

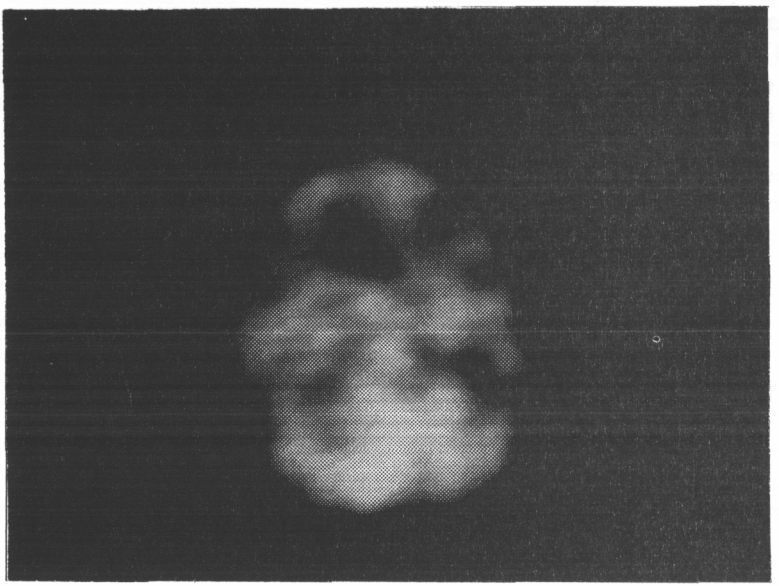

**FIGURE 3.** *This SPECT demonstrates large right parietal areas of hypoperfusion, diffuse small multifocal regions of cerebral hypoperfusion, and periventricular scalloping.*

area that is particularly vulnerable to the effects of cocaine, although the clinical significance of this hypoperfusion remains to be determined. Also, many cocaine abusers show multiple areas of cortical hypoperfusion, presumably representing areas of focal vascular spasm or possibly stroke.

One intriguing aspect of the SPECT studies in cocaine abusers has been the consistent demonstration that cerebral perfusion abnormalities may persist for many months after the cocaine abuse has stopped. Recently, in a population of chronic cocaine abusers, Holman and colleagues (1991) described focal or deep areas of diminished cerebral perfusion with SPECT in 16 of 18 subjects. Some of the subjects had abstained from cocaine for weeks prior to the study, and all 18 subjects had at least mild neuropsychological deficits (13 mild and 18 moderate). In another study that suggests that chronic cocaine abuse may cause permanent changes in brain structure and function, Pascual-Leone and coworkers (1991) found that CT atrophy strongly correlated with the duration of cocaine abuse.

Similarly, utilizing $^{133}$Xenon and HMPAO SPECT, Strickland and coworkers (1991) described periventricular scalloping and multifocal perfusion deficits in eight consecutive patients with a past history of cocaine abuse. All the subjects were participating in a drug rehabilitation program, and all tested negative for cocaine on repeated random screens. In addition to the SPECT findings, these subjects had neuropsychological deficits. In this study of chronic cocaine abusers, it appeared that chronic abuse led to longstanding (possibly permanent) changes in cerebral perfusion.

In total, SPECT studies to date suggest that this technique may be exquisitely sensitive to changes in cerebral perfusion associated with acute and chronic cocaine abuse. The mechanisms for these changes await pathological studies of cerebral blood vessels. Similarly, neuropsychological studies confirming the clinical significance of these SPECT perfusion deficits will be important. Finally, prospective studies on patients with cocaine-induced psychoses and confusional states may help to define the vascular contribution to these syndromes.

**PET Findings**

The most extensive PET studies of cocaine abusers have been done by Volkow and coworkers (1988, 1991). The first study measured $^{15}$Oxygen utilization in a group of chronic abusers and demonstrated modest decreases in oxygen utilization in the frontal regions. Patients for that study were recruited from a drug rehabilitation center, and unlike those that Mena and colleagues (1990) reported, these subjects had no major medical or neurological problems. In this study (Volkow et al. 1988), diffuse patchy areas of hypoperfusion were observed, $^{15}$Oxygen metabolism in the prefrontal cortex was markedly decreased, and repeat scans performed at 10 days revealed persistent deficits.

Volkow and colleagues (1991) also evaluated subjects during the first and second weeks following withdrawal from cocaine. This second study utilized fluorodeoxyglucose, and the researchers found increased metabolism of glucose in the orbital-frontal cortex and basal ganglia during the first week of cocaine withdrawal. In those subjects studied during the second week following cocaine withdrawal, the metabolism in the frontal regions had decreased. The researchers suggested that the findings might be related to the effects of cocaine on dopamine, a compound with extensive projections to the frontal lobes.

In contrast, London and coworkers (1990) found decreases in cerebral glucose utilization in 26 of 29 brain regions in patients acutely exposed to cocaine. Overall, these studies suggest that cerebral metabolism fluctuates

dramatically in cocaine abusers depending on whether the patient has acutely abused cocaine or is in a state of withdrawal.

Like Volkow and colleagues, with SPECT, Mena and coworkers (1990) also found a substantial group of patients with frontal hypoperfusion. It is hard to know whether the changes in frontal glucose utilization precede or follow the changes in blood flow shown with SPECT. They have seen some cocaine abusers with behavioral disinhibition in whom there is concomitant frontal hypoperfusion and have speculated that frontal ischemia induced by vasospasm from cocaine may be the primary event responsible for these patients' behavioral changes. Another possible consideration is that frontal hypoperfusion is a premorbid characteristic of the subjects who abuse cocaine. A third possibility is that the hypoperfusion is secondary to a cocaine-induced disturbance in neurotransmitters, which leads to hypometabolism and subsequent hypoperfusion.

## CONCLUSIONS

The recent epidemic of cocaine abuse has led to a variety of serious neurological complications. Of great concern is the growing number of cocaine-induced strokes in young healthy individuals. Many of these subjects initially deny that they abuse cocaine, which often confounds diagnosis. A particularly disturbing aspect of this epidemic is the SPECT finding of persistent changes in cerebral perfusion many months after the cocaine abuse has abated.

Some aspects of this epidemic have been incompletely studied and are poorly understood. One important goal for researchers should be to determine the neuropsychological and neuropathological substrate of these changes. Careful prospective studies that utilize SPECT, PET, MRI, and careful neuropsychological testing will help to determine the long-term toxicity of cocaine. However, the long-term complications associated with cocaine have been underestimated, and there is need for continued studies into the toxicity of this compound.

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**AUTHORS**

Bruce L. Miller, M.D.
Associate Professor
Department of Neurology, B-4

Frances Chiang, M.D.
Assistant Professor
Department of Radiology

Todd Sadow, M.D.
Assistant Professor
Department of Psychiatry

University of California, Los Angeles School of Medicine

Mark A. Goldberg, Ph.D., M.D.
Professor of Neurology and Pharmacology
UCLA School of Medicine
Chairman of Neurology

lsmael Mena, M.D.
Professor
Department of Radiology
UCLA School of Medicine
Chairman
Division of Nuclear Medicine

Lora McGill, M.D.
Neurology Fellow

Harbor-UCLA Medical Center
1000 West Carson Street
Torrance, CA 90509

# Cocaine Levels and Elimination in Inpatients and Outpatients: Implications for Emergency Treatment of Cocaine Complications

*Michael C. Rowbotham*

## INTRODUCTION

Despite the large volume of published medical literature on cocaine, knowledge of the pathophysiology of medical complications associated with its use remains incomplete. Treatment of cocaine-associated medical illness is still empirical; few emergency interventions have been tested prospectively in humans specifically for treatment of cocaine-related complications. Those that have been tested in animals may be ineffective, and some have been found harmful. Although a portion of the medical complications of cocaine use represents a sudden expression of previously silent anatomic abnormalities that put even a first-time user at risk, most are related to compulsive, high-dose cocaine abuse. Effective and well-tolerated pharmacological prevention of relapse in cocaine abusers still awaits demonstration.

The time course of the physiological and subjective effects of a single dose of cocaine is closely correlated with the route of administration and blood levels achieved. An oral dose of 2 mg/kg produces peak effects in about 45 minutes with easily demonstrable elevations in heart rate and systolic blood pressure, a decrease in skin temperature, and an increase in pupil size. Administered intravenously, intense effects can be achieved with doses one-fifth that administered orally. When smoked, an intense and relatively brief mental and physiologic state follows just one or two inhalations of cocaine, reflecting a concentrated bolus delivered efficiently to the brain with only 8 seconds of transit time. Intravenous (IV) infusion of lethal doses of cocaine in dogs produces a predictable sequence of events culminating in generalized convulsions and death (Catravas and Waters 1981). Heart rate, blood pressure, cardiac output, and body temperature all rise, with blood pH falling to near 7.0 as convulsions begin. Rapid administration of lethal doses can produce apnea and cardiac arrest without generalized convulsions.

Observation of cocaine “body packers” (persons who smuggle cocaine by ingesting many cocaine-filled balloons or condoms) in whom one or more packets ruptured while hospitalized has confirmed this same sequence of events in humans. Before the onset of generalized seizures, a toxic delirium was observed. Cocaine blood levels of 2,000 to 5,200 ng/mL have been reported in survivors.

The effects of repetitive administration of cocaine are more complex. In the acute situation, tolerance to both the subjective and the cardiovascular effects of cocaine occurs rapidly. Fischman and Schuster (1982) gave a group of experienced human cocaine users the opportunity to self-administer repeated bolus doses of cocaine, as often as every 10 minutes, in a tightly controlled experimental situation. Even though blood levels continued to rise throughout the experiment, the subjects could not discern any additional increase in effects after the first few doses. The same effect was observed for doses administered 60 minutes apart.

Access to the drug is a critically important factor in understanding complications of cocaine abuse. Under proper conditions, monkeys will self-administer the same drugs taken illicitly by humans, a laboratory model used extensively in research on psychoactive drugs. Animals will self-administer cocaine under a broad range of conditions and by all routes. Cocaine has been a potent reinforcer in all animal species tested so far, evidence that preexisting psychopathology is not a prerequisite for cocaine addiction in humans. Once self-administration has begun, the organism becomes totally preoccupied with drug acquisition to the exclusion of food and socialization. Given unlimited access, animals self-administer the drug in erratic bursts, similar to cocaine binging seen in humans, with seizures or exhaustion terminating each binge. In contrast, when access to cocaine is limited, animals self-administer cocaine in a relatively regular manner with greatly reduced morbidity and mortality. With the introduction of cheap cocaine in the smokable base form, extremely high blood levels can be achieved almost instantaneously and replenished frequently over longer periods, increasing the likelihood of behavioral and medical toxicity and establishing an addictive pattern of use much more rapidly, sometimes within weeks.

The role that drug metabolism and clearance play in the production of medical complications has been studied little in the clinical setting. The available data consist largely of single blood-level measurements in cocaine smugglers and postmortem samples. At least three blood samples drawn within a few hours time are needed to calculate an elimination drug half-life. In normal volunteers, the average plasma half-life of cocaine ranges from 40 to 90 minutes. Cocaine is metabolized primarily to ecgonine methyl ester (EME) and benzoylecgonine

(BE). EME is formed enzymatically via tissue and serum esterases, whereas BE is formed partially if not entirely by nonenzymatic hydrolysis. It has been hypothesized that low pseudocholinesterase activity may slow the metabolism and thereby increase the risk for cocaine toxicity.

## COCAINE ELIMINATION IN INPATIENTS WITH COCAINE-RELATED NEUROLOGICAL ILLNESS

As part of ongoing studies at San Francisco General Hospital (SFGH), a minimum of three blood samples were obtained for determination of cocaine and BE levels from a group of 14 patients hospitalized for evaluation and treatment of a cocaine-related neurological complication in 1989-90. In addition, a blood sample was obtained for measurement of plasma pseudocholinesterase activity. Three urine samples were collected within the first 12 hours of hospitalization and analyzed for cocaine and BE. In addition, a urine specimen was sent to the hospital toxicology laboratory for a comprehensive drug screen. Blood was collected in tubes containing sodium fluoride (to inhibit cocaine metabolism) and was immediately refrigerated. Afler centrifugation, the plasma was frozen. Blood for pseudocholinesterase measurement was collected in tubes containing ethylenediaminetetraacetic acid and was refrigerated. Urine was collected in containers adjusted to a pH of 3.0 to prevent hydrolytic degradation of cocaine and its metabolites and was frozen. Plasma and urine samples were analyzed for cocaine and BE by automated gas chromatography according to the method described by Jacob and colleagues (1987, 1990). The lower limit of quantitation for this assay is 5 ng/mL for cocaine, although sensitivity for cocaine detection is 1 ng/mL. For BE, the lower limit of quantitation is 10 ng/mL, with sensitivity for detection at 5 ng/mL. Plasma pseudocholinesterase activity was measured by a modification of the Ellman method (George and Abernathy 1983).

Data on the 14 hospitalized patients are summarized in table 1. Nine patients presented with seizures (one in status epilepticus), one with dystonic movements of the head and arms, three with stroke, and one with encephalopathy without focal neurologic deficits.

The route of cocaine administration was oral/nasal in three patients, combined oral/nasal and smoked in two, smoked in six, and IV in three. The latency between last cocaine use and the first blood sample (when known) ranged between 1 and 20 hours and was less than 3 hours in four patients. In these four patients, the maximum plasma cocaine level was 4,697 ng/mL, and the average initial plasma cocaine level was 1,597 ng/mL (range 275 to 4,697 ng/mL). The average of the highest measured urine cocaine level in each of these four patients was 28,995 ng/mL (range 13,879 to 61,656 ng/mL). In

**TABLE 1.** *Patient summaries, drug levels, and cocaine plasma half-life*

| Patient Age/Sex | Neurological Symptoms | Toxicology Screen[a] | Route[b] | Use to First Sample | Max Plasma [C] ng/mL | Max Plasma [BE][c] ng/mL | Max Urine [C][c] ng/mL | Max Urine [BE][c] ng/mL | Sampling Duration (Plasma) | Plasma C T1/2[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| DS/33/m | Seizure | C,BE,BZ | o/n | 1-2 hr | 4,697 | 41,694 | 61,656 | 54,323 | 1,850 min | 153 min |
| ED/18/m | Seizure | C,BE | o/n, sm | 10-14 hr | 1,358 | 4,836 | 2,845 | 143,599 | 720 min | 129 min |
| RG/31/m | Seizure | BE,O | sm | unknown | 7 | 690 | 157 | 9,087 | 240 min | BLQ |
| CE/21/m | Seizure | C,BE | sm | 1 hr | 1,127 | 3,886 | 24,024 | 114,697 | 295 min | 91 min |
| AM/29/f | Seizure | C,BE | sm | 9 hr | 465 | 3,063 | 101 | 64,297 | 313 min | 152 min |
| KD/21/m | Seizure | NA | sm | 3 hr | 275 | 1,721 | 16,421 | 103,336 | 480 min | 113 min |
| WA/24/f | Seizure | NA | sm | 9-12 hr | 297 | 1,820 | 764 | 119,328 | 360 min | 132 min |
| MM/20/m | Seizure | C,BE,A | IV | 5 hr | 580 | 2,492 | 14,922 | 148,177 | 120 min | 60 min |
| SW/38/m | Seizure | C,BE,O, CZ,OTC | IV | 4-6 hr | 206 | 3,167 | 49,992 | 338,519 | 390 min | 128 min |
| MQ/32/m | Dystonia | C,BE | o/n | unknown | 15 | 62 | 645 | 16,220 | 425 min | BLQ |
| SH/41/m | Stroke | BE,BZ, O | IV | unknown | 30 | 2,121 | 332 | 15,114 | 280 min | 158 min |
| JF/46/m | Stroke | C,BE,BZ, O,BT,OTC | o/n | 1.5 hr | 288 | 1,952 | 13,879 | 115,132 | 150 min | 197 min |
| AO/31/m | Stroke | BE,OTC | sm | 15-20 hr | 12 | 263 | 109 | 26,522 | 1,380 min | BLQ |
| RR/45/m | Coma | C,BE,O | o/n. sm | 4 hr | 201 | 2,255 | 14,945 | 102,313 | 265 min | 190 min |

KEY: [a]C=cocaine: BE=benzoylecgonine; BZ=benzodiazepines; O=opioids; A=amphetamine; CZ=carbamazepine; BT=benztropine; OTC-nonprescription analgesics. decongestants. or antihistamines; NA=no urine toxicology screen performed

[b]o/n=oral/nasal; sm=smoked

[c]Value listed is maximum measured value. independent of time of maximum plasma cocaine level.

[c]BLQ=plasma cocaine levels at times of quantitation, precluding calculation of plasma hail-life

contrast, in the 10 remaining subjects in whom the latency either was not known or was greater than 4 hours, the average initial plasma cocaine level was 317 ng/mL (range 7 to 1,358 ng/mL). The maximum urine cocaine levels in these patients averaged 8,481 ng/mL (range 101 to 49,992 ng/mL). Maximum plasma and urine BE levels are listed in table 1. Plasma pseudocholinesterase activity was measured in nine patients and ranged from 1.7 to 3.6 U/mL, all within the normal range for this assay.

Cocaine plasma half-lives could be calculated in 11 patients and averaged 137 minutes (median 132 minutes, range 60 to 197 minutes, range of sampling period 120 to 1,850 minutes). The calculated half-life was greater than 100 minutes in 12 of the 14 patients and did not have any obvious relationship to the highest measured cocaine level. Plasma cocaine half-life was not calculated in the remaining three patients because there were not three cocaine levels above 20 ng/mL. In comparison, the terminal phase half-life in 10 healthy volunteer subjects given 1.2 mg/kg cocaine by IV bolus followed by a 4-hour infusion of 1.2 mg/kg/hr was 95 minutes (median 86 minutes, range 62 to 176 minutes). The difference in cocaine plasma half-life between the two groups is significant ($p=0.02$, two-tailed unpaired t-test). The total dose of cocaine, the period over which it was used, and the true latency from last use to first blood sample cannot be known with any certainty. Therefore, it is not known what portion of the curve of declining blood levels is being sampled. With the possible exception of case DS and case CE, the peak blood level may have occurred many hours before the first sample. The calculated half-lives cannot be grouped together as representing a uniform portion of the elimination curve. The nature of these data does not allow differentiation between dose-dependent metabolism, an effect of chronicity of use, or a less specific effect of acute medical illness in explaining the prolonged elimination half-life observed.

## OUTPATIENTS WITH COCAINE-RELATED NEUROLOGICAL SYMPTOMS: COCAINE AND BE LEVELS

Another aspect of treatment of acute complications of cocaine abuse that has received relatively little attention are the implications of both the delay in seeking treatment and the magnitude of blood and urine levels of cocaine and metabolites on clinical presentation for emergency treatment. To gain perspective from the hospitalized group, a second group of 18 patients presenting for emergency treatment at SFGH in 1990-91 who did not require hospitalization was evaluated with three blood samples for cocaine and BE, a blood cholinesterase level, a comprehensive urine toxicology screen, and one urine sample for cocaine and BE level.

The ranges of values observed are shown in table 2. It is striking that 11 of the 16 patients who provided information regarding latency from last use to emergency room (ER) presentation had a latency of 4 hours or longer. Only five patients in the entire group had a blood cocaine concentration higher than 100 ng/mL, although 14 of the subjects were using smoked cocaine. However, the urine and plasma BE levels are probably the best index of total cocaine dose over the previous 24 hours and were typically very high. Six patients had urine BE levels exceeding 100,000 ng/mL, and only five patients had levels below 20,000 ng/mL. Five patients had plasma BE levels above 2,000 ng/mL, and only five had levels below 600 ng/mL.

By contrast, Jeffcoat and colleagues (1989) measured plasma BE levels of approximately 600 ng/mL after a 100-mg intranasal dose, and Ambre (1985) measured plasma BE levels of approximately 1,000 ng/mL afler 150 mg administered intravenously over a 3-hour period. Ambre has estimated that patients with urine BE levels of 100,000 to 200,000 ng/mL had consumed a total dose approaching 500 mg. Using Ambre's nomogram, which is based on very limited data, the subject with a urine BE level of 621,000 ng/mL probably used a total cocaine dose exceeding 1,000 mg (Ambre 1985).

## IMPLICATIONS FOR DEVELOPMENT OF A COCAINE ANTAGONIST FOR EMERGENCY USE

The experience at SFGH indicates that patients who present themselves for emergency treatment in most cases have not used the drug for several hours or more. On presentation, the peak plasma cocaine level almost certainly has passed, especially when drug use is by the IV or smoked route. The range of blood cocaine levels on presentation is quite broad, extending from near unmeasurable to levels well into those reported postmortem. Although the

**TABLE 2.** *Eighteen outpatients with cocaine-related neurological complications*

| Measure | Mean | Minimum | Maximum |
|---|---|---|---|
| Blood cocaine level | 136 ng/mL | 1 ng/mL | 1,700 ng/mL |
| Blood BE level | 2,209 ng/mL | 6 ng/mL | 15,149 ng/mL |
| Urine cocaine level | 7,704 ng/mL | 69 ng/mL | 56,546 ng/mL |
| Urine BE level | 118,591 ng/mL | 107 ng/mL | 621,251 ng/mL |
| Latency last use to ER visit | 312 min | 60 min | 760 min |

elimination half-life may be prolonged compared with healthy volunteers, plasma cholinesterase activity typically falls within the normal range.

The majority of acute complications of cocaine use can be tentatively categorized as (1) unmasking a previously unsuspected abnormality such as a cerebral arteriovenous malformation or aneurysm; (2) idiosyncratic complications not clearly related to magnitude of drug use at any particular time, such as headache, stroke, and myocardial infarction; (3) complex interactions of multiple drug use that span the spectrum of reported complications; and (4) complications that are dose related and mimic those observed in experimental animals given lethal doses of cocaine, such as multiple seizures, ventricular arrhythmias, agitated delirium, and hyperthermia.

This last category is potentially treatable by a medication that would antagonize the effects of cocaine. However, despite the lack of proven medication interventions, Brody and coworkers (1990) found an acute mortality rate of less than 1 percent, and only 24 percent required any type of short-term pharmacological intervention in a consecutive series of 233 hospital visits for cocaine-related medical problems. In addition, by the time a patient has survived long enough to present for treatment, the peak cocaine level has passed (cocaine body packers may be an exception because of prolonged absorption). The most difficult aspect of treatment of cocaine-related complications are the secondary effects set in motion by cocaine intoxication.

A good example of the complexity of treating cocaine complications are cocaine-induced seizures. Near total selective depletion of either brain dopamine or norepinephrine has no effect on cocaine-induced seizures. The convulsant effects of cocaine are most likely related to its local anesthetic effects. Comparison studies of amphetamine, cocaine, and lidocaine in kindling paradigms have shown that cocaine effects on brain electrical activity are similar to lidocaine (Russell and Stripling 1985). Lidocaine is an anticonvulsant at low doses but is a potent convulsant at doses similar to those required to produce convulsions with cocaine. Two factors greatly reduce the blood level of local anesthetic required for seizure production: elevated body temperature and decreased blood pH. Both are produced in the course of cocaine poisoning in dogs as observed by Catravas and Waters (1981). Merely placing the animals in a cold room at the time of cocaine administration prevented the hyperthermia, seizures, and death that otherwise would be produced by cocaine. Once elevated body temperature and lowered pH are established, seizure therapy must include correction of metabolic abnormalities and elevated temperature to be maximally effective.

Paradigms widely used in animal studies of antagonists of cocaine toxicity include pretreatment with the drug to be tested, coadministration of the antagonist and cocaine, and in a few studies, administration of the antagonist following a predetermined dose of cocaine but before the onset of toxicity. In only one study has the drug antagonist under study been administered after the onset of cocaine toxicity. Derlet and Albertson (1989) found diazepam to be highly effective in preventing cocaine seizures and death when given before or very shortly after cocaine. Once cocaine seizures began, efficacy in preventing death was reduced significantly.

Simple measures such as preventing or correcting elevated body temperature can be remarkably effective in preventing death from cocaine toxicity. In addition, on emergency presentation the diagnosis of a cocaine-related problem may be inferred based on history and examination, but nondrug causes also must be excluded. Until remedies become available that have been proven effective in animal studies that closely mimic the ER presentation of cocaine toxicity, treatment recommendations should follow currently accepted management guidelines based on presenting symptomatology.

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## AUTHOR

Michael C. Rowbotham, M.D.
Assistant Professor
Departments of Neurology and Anesthesia
University of California, San Francisco
M794, Box 0114
San Francisco, CA 94143

# Potential Adverse Interactions of Drugs With Cocaine

*Paul R. Pentel and Timothy N. Thompson*

## INTRODUCTION

The purpose of this chapter is to consider some potentially toxic interactions of cocaine with other drugs, focusing on drugs that are being evaluated as treatments for chronic cocaine abuse. Acute cocaine toxicity is an important clinical problem, but the opportunity to intervene medically is limited by the brief duration of signs and symptoms. Many patients die prior to receiving medical attention (see Wetli, this volume). In the emergency department, toxicity typically resolves rapidly with supportive care. In patients with sequelae such as myocardial infarction or stroke, these events usually have occurred prior to medical intervention. Therefore, new treatments for acute cocaine toxicity can be expected to have a limited impact on morbidity and mortality and must necessarily be supplemented with preventive measures. One area in which prevention could have an impact is the interaction of cocaine and other drugs that may be chronically administered to cocaine abusers to help maintain abstinence and prevent relapse. During inpatient studies, these drugs often are coadministered with cocaine to determine their effects. During outpatient studies or in clinical use, although abstinence is the goal, subjects undoubtedly use cocaine at times, making it important to identify, understand, and prevent any adverse interactions between cocaine and these drugs. This chapter describes selected examples of potential interactions.

## DRUGS THAT ACT ON DOPAMINERGIC NEUROTRANSMISSION

A variety of data suggest that dopamine is an important mediator of cocaine self-administration and of its discriminative stimulus properties (Witkin et al. 1991; Ritz et al. 1987). As a result, drugs that modify dopaminergic neurotransmission are of interest as potential treatments for cocaine abuse. Both agonists and antagonists have been studied in this regard-agonists because they might mimic the effects of cocaine and act as a cocaine substitute and antagonists because they might reduce cocaine's reinforcing effects. A few such drugs (bromocriptine, amantadine, flupenthixol) have been

studied in humans (Giannini and Billet 1987; Dackis et al. 1987; Gawin et al. 1989a). No important adverse effects have been noted; however, these studies were designed primarily to test efficacy rather than toxicity, and adverse interactions might not be detected for several reasons. First, the numbers of patients and duration of these initial studies have been limited. Second, in an outpatient setting it is not possible to monitor patients at the time they use cocaine or to know how much cocaine they are using. An exaggeration of cocaine's effects (such as increased hypertension or tachycardia) would be difficult or impossible to discern in this setting, and it is likely that only a markedly symptomatic interaction would be detected. An additional limitation of these trials is that any cocaine use that occurs typically involves recreational doses. A clinically important adverse interaction is presumably more likely if a large or toxic dose of cocaine is used. Because the use of such large cocaine doses is less common than the use of recreational doses, it is difficult to study the possibility of interactions involving high doses of cocaine. Therefore, the lack of reported adverse interactions in these studies is encouraging but should be considered preliminary.

Additional data from animal studies suggest that adverse interactions could occur. In studies of rodents, the toxic end points most often used are seizures and lethality; therefore, the doses of cocaine used are quite high. Whether the results of such studies also would apply to the use of recreational doses of cocaine as well is not clear. Nevertheless, these studies provide useful insights into the types of interactions that might be expected and their mechanisms. George and Ritz (in press) studied the lethality of cocaine and a variety of structurally and behaviorally similar compounds in mice, as well as their binding affinities for several neurotransmitters, receptors, and transporters. Lethality was correlated significantly with binding affinity for the dopamine transporter, suggesting that lethality in this paradigm is directly related to the synaptic dopamine concentration (figure 1). If increasing the synaptic dopamine concentration enhances the lethality of cocaine-like compounds, then dopamine receptor agonists or antagonists might be expected to increase or decrease (respectively) cocaine lethality. In support of this hypothesis, a protective effect of pretreatment with the $D_1$ antagonist SCH 23390 has been demonstrated for cocaine lethality in several studies of mice (George and Ritz, in press) and rats (Derlet et al. 1990a; Witkin et al. 1989) (figure 2). In each case the protective effect of SCH 23390 was modest, suggesting that mechanisms other than $D_1$ agonist activity also contribute to lethality. However, $D_2$ receptor antagonists such as haloperidol or spiperone have not reduced the lethality of cocaine in mice, rats, or dogs (Witkin et al. 1989; Derlet et al. 1989; Catravas and Waters 1981).

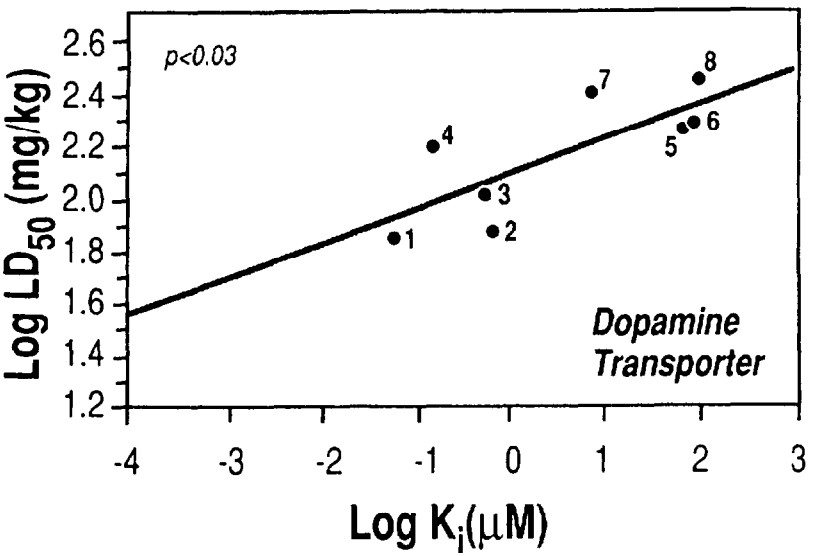


**FIGURE 1.** *Relationship between the lethal potencies in mice of cocaine-related compounds and their affinities for $^{3}$H-mazindol binding sites on dopamine transporters (p=0.03). The drugs represented are (1) WIN 35,428, (2) (-)norcocaine, (3) (-)cocaine, (4) WIN 35,062-2, (5) procaine, (6) (+)pseudococaine, (7) tropococaine, and (8) (-)pseudococaine.*

SOURCE: George, F.R., and Ritz, M.C. Cocaine-induced lethality is associated with interactions between dopamine transporters and muscarinic and sigma receptors. *J Pharmacol Exp Ther,* in press. Copyright 1992 by American Society for Pharmacology and Experimental Therapeutics (Baltimore).

In contrast to their relationship to lethality, dopamine receptors did not appear to be important mediators of cocaine-induced seizures. Ritz and George (in press) found no correlation between the seizure ED, and the dopamine transporter binding in mice of the same series of cocaine-like compounds studied by George and Ritz (in press). Derlet and colleagues (1990b) found a small protective effect of the $D_2$ antagonist haloperidol on cocaine-induced seizures in rats, but others have found no protective effect of either $D_1$ or $D_2$ blockers in mice (Ritz and George, in press), rats (Witkin et al. 1989), or dogs (Catravas and Waters 1981). Thus, $D_1$ or $D_2$ blockers do not appear to reduce cocaine-induced seizures in a variety of species, and the

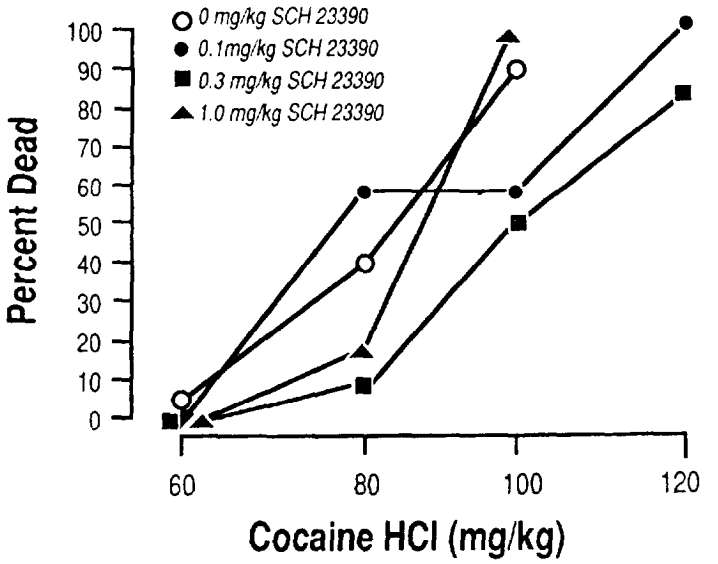


**FIGURE 2.** *The $D_1$ antagonist SCH 23390 prevented cocaine-induced lethality in rats. The $LD_{50}$ was increased from 79.7 to 100.1 mg/kg (95-percent) confidence interval 91.5-109.5 mg/kg) in the presence of 0.3 mg/kg SCH 23390.○: effects of cocaine alone.●: effects of cocaine in SCH 23390-treated rats. Each point represents effects in at least six animals.*

SOURCE: Witkin, J.M.; Goldberg, S.R.; and Katz, J.L. Lethal effects of cocaine are reduced by the dopamine-1 receptor antagonist SCH 23390 but not by haloperidol. *Life Sci* 44:1285-1291, 1989. Copyright 1989 by Pergamon Press plc. (Elmsford, NY).

beneficial effect of $D_1$ blockers on cocaine lethality cannot be attributed to a reduction in seizures.

The mechanism by which $D_1$ antagonists reduce cocaine lethality is unclear. In squirrel monkeys, SCH 23390 did not reduce cocaine-induced tachycardia or hypertension. Haloperidol produced a small reduction in tachycardia, but this did not appear to be mediated by dopaminergic blockade (Schindler et al. 1991). The $D_2$ antagonist pimozide did not reduce hypertension or tachycardia due to cocaine in dogs (Catravas and Waters 1981). Thus, there are no data to suggest a salutary cardiovascular effect of dopaminergic blockade as the mechanism by which these drugs reduce cocaine's lethality.

Also of interest are the potential interactions of cocaine with drugs that might cause its behavioral effects, such as agitation or delirium. In humans, behavioral toxicity is a major contributor to cocaine's morbidity and mortality. Drug interactions that increase the undesirable behavioral effects of cocaine therefore could increase its overall toxicity. Behavioral toxicity is difficult to study in animals because it is difficult to know whether an effect (such as a change in locomotor activity) represents a desirable pleasant effect or an undesirable toxic effect. It is reasonable to postulate, on the basis of clinical observations, that the behavioral effects most likely to be toxic are those associated with very high cocaine doses. Several animal studies are of interest in this regard, as they demonstrate different behavioral effects of cocaine at low and high doses. Katz and Witkin (1991) found that low cocaine doses increased fixed-interval (FI) responding maintained under schedules of electric shock presentation in squirrel monkeys, whereas high doses (1 to 3 mg/kg) decreased responding. The $D_1$ antagonist SCH 23390 attenuated both low- and high-dose responding, whereas the $D_2$ antagonist haloperidol reduced only the low-cocaine-dose response. Spealman (1990), using a similar paradigm, reported similar results with the D, antagonist SCH 39166 but found that the $D_2$ antagonist YM 09151-2 also decreased the high-dose cocaine response. Thus, $D_1$ and possibly $D_2$ antagonists may decrease some behaviors associated with high, potentially toxic doses of cocaine.

Taken together, these data generally support the hypothesis that dopaminergic neurotransmission modulates cocaine lethality and some of its high-dose behavioral effects and that decreasing dopaminergic stimulation is generally protective. These data also suggest that increasing dopaminergic stimulation might aggravate cocaine toxicity. This possibility is of concern because dopaminergic agonists have been proposed and studied as treatments for chronic cocaine abuse. Amantadine, bromocriptine, and flupenthixol have been administered to outpatients (Giannini and Billet 1987; Dackis et al. 1987; Gawin et al. 1989a). No adverse effects were reported, but as noted above, such events might not be detected in this type of outpatient study. Few animal data are available. Howell and Byrd (1991) studied the effects of the selective dopamine uptake inhibitor GBR 12909 in squirrel monkeys using a paradigm similar to the study of Katz and Witkin (1991) described above, which distinguishes low- and high-dose cocaine effects. GBR 12909 exaggerated the effects of high-dose cocaine on FI responding (figure 3). If this behavior represents a toxic effect of cocaine, these data are consistent with the hypothesis that dopamine uptake blockade aggravates cocaine's behavioral toxicity. In mice, the dopamine transporter inhibitor buproprion has been reported to increase cocaine lethality, but only modestly (Ritz and George 1992). These data are quite preliminary, but the possibility of a toxic interaction between cocaine and dopaminergic agonists or transporter inhibitors clearly warrants further study.

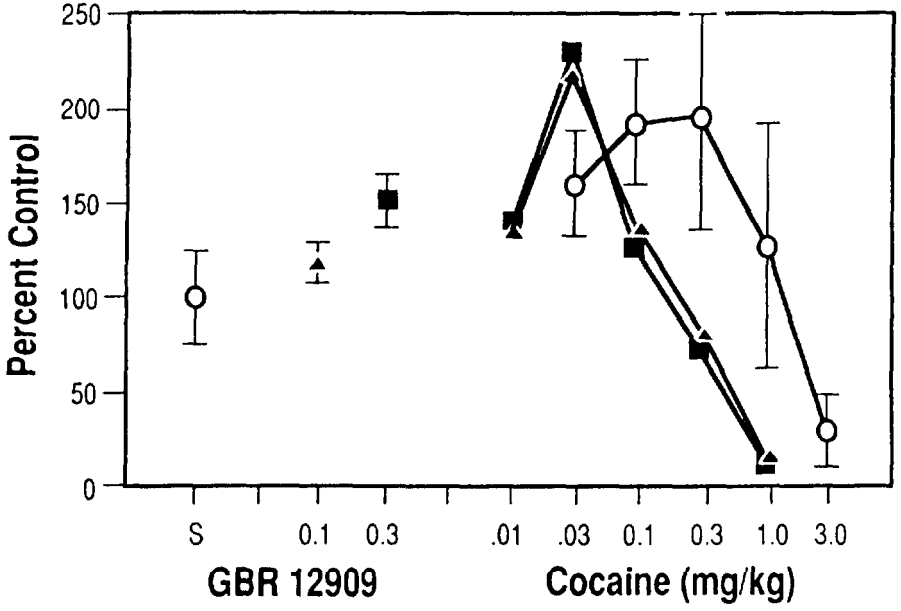


**FIGURE 3.** *Effects of cocaine administered a/one (o) or in combination with GBR 12909 (filled symbols) on mean (±SEM) rates of lever pressing maintained by an FI-300 schedule in a group of three monkeys. GBR 72909 exaggerated the effects of both low and high doses of cocaine. The effects of the pretreatment drug administered alone are shown with the filled symbols to the left of the dose-effect curves. S=saline.*

SOURCE: Howell, L.L., and Byrd, L.D. Characterization of the effects of cocaine and GBR 12909, a dopamine uptake inhibitor, on behavior in the squirrel monkey. *J Pharmacol Exp Ther* 258:178-185, 1991. Copyright 1991 by American Society for Pharmacology and Experimental Therapeutics (Baltimore).

## DRUGS THAT ACT ON SEROTONERGIC NEUROTRANSMISSION

Drugs that modify serotonergic neurotransmission may alter the behavioral effects of cocaine (Carroll et al. 1990a; Pollack and Rosenbaum 1991) and are of interest as potential therapies for cocaine abuse. With regard to toxicity, animal data suggest that serotonergic neurotransmission is related

to susceptibility to cocaine-induced seizures in mice. Ritz and George (in press) found that the seizure ED, for a variety of cocaine-like compounds was correlated significantly with their affinities for the serotonin transporter, suggesting that seizures may be related to the synaptic serotonin concentration. These data suggest that serotonergic antagonists might prevent seizures, whereas serotonergic agonists might aggravate seizures. In support of this hypothesis, administration of the serotonin transporter inhibitor fluoxetine enhanced cocaine-induced seizures in mice, whereas the serotonin 5-$HT_2$ receptor antagonist cinanserin reduced seizures (Ritz and George, in press). However, Tortella and colleagues (1992) using Swiss Webster mice, found no effect of cinanserin on cocaine-induced seizures, suggesting that strain differences in this response may exist. It is clear that strain differences exert a major influence on cocaine-kindled seizures and on seizures due to acute cocaine administration (Marley et al. 1991; George 1991). These data illustrate the problem of species or strain differences (see discussion of desipramine below) in response to cocaine or cocaine-drug interactions and underscore the importance of studying and comparing responses in different species or strains.

## DESIPRAMINE

The tricyclic antidepressant desipramine has been studied as an adjunct to reducing cocaine use in patients (Gawin et al. 1989b). Unlike many of the drugs discussed above, desipramine has been in clinical use for decades. A great deal is known about its pharmacology, some aspects of which suggest that it could interact adversely with cocaine. Desipramine is an inhibitor of the norepinephrine transporter. In humans, a therapeutic dose of desipramine prolongs the plasma half-life of norepinephrine (Esler et al. 1981) and a therapeutic dose of the closely related tricyclic antidepressant imipramine exaggerates the tachycardia and hypertension produced by norepinephrine or epinephrine (Boakes et al. 1973). Cocaine enhances sympathetic tone and inhibits the norepinephrine transporter. On the basis of these actions, even therapeutic doses of desipramine might be expected to exaggerate the sympathomimetic effects of cocaine. In addition, toxic doses of desipramine can cause seizures and tachycardia (Ellison and Pentel 1989), as can toxic doses of cocaine. An adverse interaction of high doses of desipramine and cocaine therefore might be expected as well.

A potentially adverse interaction between cocaine and desipramine in humans has been observed by Fischman and colleagues (1990). Desipramine was administered to cocaine abusers for 3 weeks at doses sufficient to maintain therapeutic serum concentrations. Subjects were allowed to self-administer intravenous (IV) cocaine before and after the 3 weeks of desipramine. Treatment with desipramine did not alter the amount

of cocaine self-administered but did exaggerate the maximum heart rate and diastolic blood pressure observed at any dose (figure 4). This was caused by both an increase in these parameters due to desipramine alone and an additional increase due to the cocaine. Although these data clearly demonstrate an interaction between cocaine and desipramine, its clinical importance is not known. No untoward clinical events were observed in this study despite the higher blood pressures and heart rates observed after desipramine, but the cumulative cocaine doses administered were lower than many cocaine abusers administer on their own. It would be of great interest to know whether desipramine also exaggerates the effects of larger or potentially toxic doses of cocaine, but this question is difficult to study in humans. Animal data are limited. Jackson and colleagues (1990) reported a protective effect of desipramine pretreatment on cocaine lethality in mice, whereas Ritz and George (in press) noted an increase in lethality from cocaine after desipramine pretreatment in C57BL mice. Blood pressure and heart rate were not monitored in either study. Because these protocols used similar doses of desipramine and cocaine, differing results could be due to the use of different strains of mice. Taken together with the data from humans, these studies suggest that caution should be observed with the concurrent use of desipramine and cocaine, but the data do not allow an estimate of the risk posed by desipramine used in an outpatient setting.

Desipramine also may exacerbate the behavioral toxicity of cocaine. In Fischman and colleagues' 1990 study (referred to above), ratings of cocaine's pleasant effects such as "positive mood" and "vigor" were decreased by desipramine, whereas unpleasant effects such as "anxiety" and "anger" were increased. Desipramine therefore shifted the profile of cocaine's subjective effects toward those that are less pleasant. The clinical consequences of this effect are not known, but these observations do raise the question of whether desipramine might increase undesirable or harmful behaviors due to cocaine.

## CARBAMAZEPINE

The anticonvulsant carbamazepine is being evaluated as a treatment for cocaine abuse. An adverse interaction with cocaine has not been noted in outpatient trials (Halikas et al. 1991), but inpatient and animal studies suggest that further study of this possibility is warranted. Like desipramine, carbamazepine can reduce norepinephrine turnover in vitro (Waldmeier et al. 1984), but it is probably less potent in this regard. Despite considerable experience with its clinical use, adverse interactions between carbamazepine and sympathomimetic amines have not been reported. Carbamazepine at toxic doses can cause seizures or tachycardia (Sullivan et al. 1981), as can

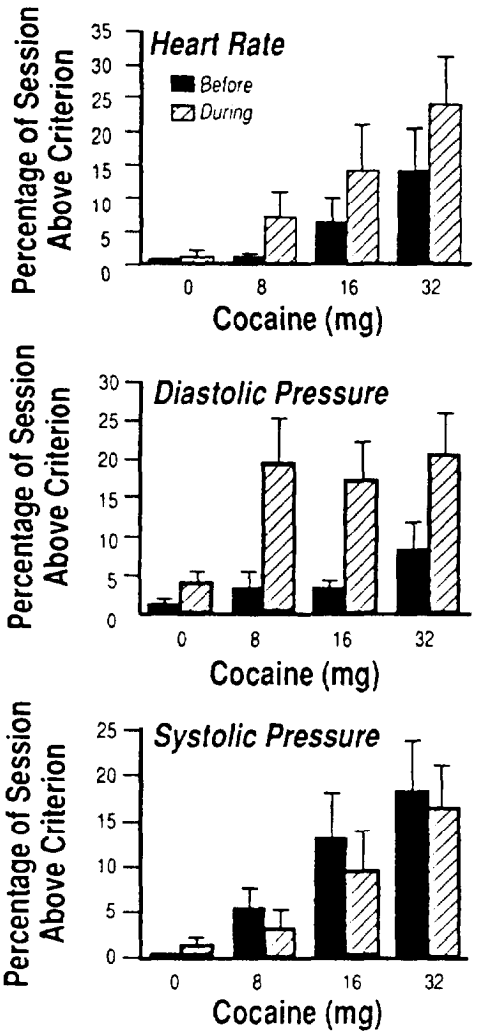


**FIGURE 4.** *Effects of desipramine pretreatment on responses to IV cocaine in human subjects. Closed bars: before desipramine. Hatched bars: during desipramine. Data are the mean percent of each session that heart rate was above 137 (top panel), diastolic blood pressure was above 100 mmHg (middle panel), and systolic blood pressure was above 170 mmHg (bottom panel). Cocaine doses represent the size of an individual dose for each multiple dose session. Desipramine did not alter the total dose of cocaine*

*administered at each session but did increase the percent of each session during which the heart rate and diastolic blood pressure exceeded the specified values.*

SOURCE: Fischman, M.W.; Foltin, R.W.; Nestadt, G.; and Pearlson, G.D. Effects of desipramine maintenance on cocaine self-administration by humans. *J Pharmacol Exp Ther* 253(2):760-770,1990. Copyright 1990 by American Society for Pharmacology and Experimental Therapeutics (Baltimore).

cocaine, so that an adverse interaction with excessive doses of both drugs might be expected. However, at therapeutic doses of carbamazepine (and recreational doses of cocaine), an adverse interaction would not be anticipated.

Nevertheless, one study of human subjects suggests that a therapeutic dose of carbamazepine could exaggerate the blood pressure and heart rate effects of cocaine. Hatsukami and coworkers (1991) administered carbamazepine 400 mg daily to subjects to achieve a therapeutic serum concentration of the drug, or placebo, for 5 days. Subjects then received a single dose of smoked cocaine (40 mg). Heart rate and diastolic blood pressure increased more after carbamazepine than after placebo (figure 5). Although this study examined only the short-term use of carbamazepine and a single dose of cocaine, it suggests that blood pressure and heart rate should be monitored carefully when carbamazepine and cocaine are coadministered. The potential use of carbamazepine in an outpatient setting presents the same problem discussed above regarding desipramine: Subjects might use much larger or toxic doses of cocaine, and the interaction of these high doses of cocaine with carbamazepine cannot be readily studied in humans.

In rats, both an increase and a decrease in cocaine-induced seizures have been reported with carbamazepine. Weiss and colleagues (1990) found that carbamazepine reduced kindled seizures produced by daily doses of cocaine (40 or 50 mg/kg) and its associated lethality. This effect was observed, however, only when carbamazepine was administered chronically prior to cocaine. Intermittent dosing of carbamazepine had the opposite effect, increasing seizures and lethality. An increase in cocaine toxicity during carbamazepine treatment also has been noted by Carroll and coworkers (1990b). In this study, rats were allowed to self-administer cocaine for 5 days and then were given carbamazepine. The introduction of carbamazepine resulted in seizures and lethality. The toxic interaction was confined to those groups of rats receiving the highest doses of cocaine and carbamazepine.

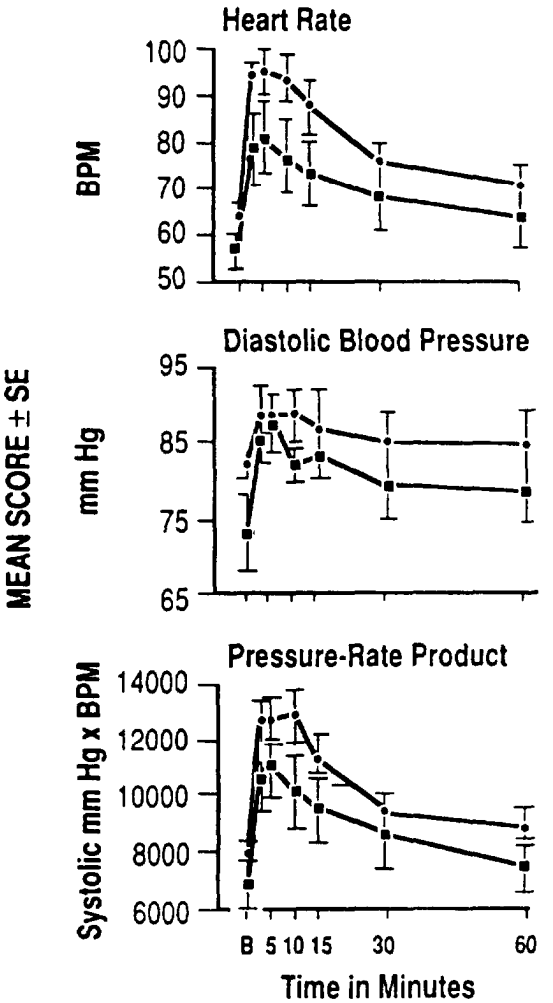


**FIGURE 5.** *Effects of carbamazepine pretreatment (circles) vs. placebo (squares) on responses to a single 40-mg dose of smoked cocaine in human subjects. Heart rate, diastolic blood pressure, and the rate-pressure product were significantly higher after carbamazepine pretreatment ($p<0.05$).*

SOURCE: Hatsukarni D.; Keenan, R.; Halikas, J.; Pentel, P.R.; and Brauer, L.H. Effects of carbamazepine on acute responses to smoked cocaine-base. Psychopharmacology 104:120-124, 1991. Copyright 1991 by Springer-Verlag (Heidelberg).

These data suggest that high doses of carbamazepine may increase the toxicity of high doses of cocaine in rats but that the occurrence of this interaction may depend on the manner and timing of carbamazepine administration. This complexity illustrates the difficulty of extrapolating the results of such animal studies to humans.

## CONCLUSIONS

Predicting *clinically important* interactions between cocaine and potential drug therapies for cocaine abuse is important but difficult for the following reasons.

1. Both animal and human data are limited. A few studies are available regarding potentially toxic drug-cocaine interactions. Many small animal studies use end points such as seizures or death that, although useful, may not comment on the proximate mechanisms of toxicity (e.g., hypotension, arrhythmia, respiratory depression). Many animal studies of cocaine toxicity involve short-term administration of very high doses of the interacting drug. Whether these results also would apply to the therapeutic use of the potentially interacting drug is not clear.

   Studies of potential interactions in humans have inherent limitations. The few inpatient studies available involved low doses of cocaine and only therapeutic doses of the potentially interacting drug. Interactions reported from such studies between cocaine and desipramine or carbamazepine have been small in magnitude, and it is not clear whether they are of clinical importance. The important question of whether larger doses of cocaine would produce a greater interaction is difficult to study safely in humans. The possibility of an adverse interaction due to an excessive dose of the interacting drug, which must also be considered in the setting of drug abuse, is likewise difficult to study.

   Outpatient trials of drug treatments for cocaine abuse generally have few subjects and have been of short duration, limiting their ability to detect adverse events. Equally important in the outpatient setting, subjects cannot be monitored at the time they are using cocaine.

2. Species or strain differences may exist. Contrasting reports of whether desipramine enhances or reduces cocaine lethality in rats or whether cinanserin inhibits cocaine-induced seizures in mice may be due in part to strain differences. If this is the case, the choice of appropriate animal models for such studies will be challenging.

3. Cocaine-drug interactions also may be dependent on the experimental paradigm. For example, the opposite effects of carbamazepine on cocaine-induced seizures observed by Carroll and coworkers (1990b) and Weiss and coworkers (1990) could be due to the order in which carbamazepine and cocaine were administered or the chronicity of carbamazepine administration.

Further study of potential drug-cocaine interactions is clearly needed, with particular focus on the selection of appropriate animal models, comparisons of different strains and species, attention to dose-response relationships for both cocaine and the interacting drug, and the use of inpatient studies with human subjects to supplement outpatient trials of drug treatment for cocaine abuse.

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**AUTHORS**

Paul R. Pentel, M.D.
Associate Professor of Medicine and Pharmacology
Department of Medicine
University of Minnesota Medical School
Hennepin County Medical Center
701 Park Avenue South
Minneapolis, MN 55415

Timothy N. Thompson, M.D.
Research Associate
Department of Psychiatry
University of Minnesota Medical School
Diehl 625
515 Essex Street Southeast
Minneapolis, MN 55455

# The Pathology of Cocaine: Perspectives From the Autopsy Table

*Charles V. Wetli*

## INTRODUCTION

As a local anesthetic, cocaine has three unique side effects that account for the majority of pathologic changes seen in individuals who have died from its toxic effects. The first reaction is that of vasoconstriction. Initially, it was thought that this phenomenon occurred only at the site of application of cocaine. However, more recent evidence indicates that the vasoconstrictive properties of cocaine are much more widespread: Coronary vasospasm has been demonstrated, and cocaine also may cause cerebrovasospasm and cutaneous vasoconstriction. The other two properties of cocaine that are responsible for fatal reactions and sudden death are the sometimes unpredictable stimulation of the central nervous system (CNS) and the cardiovascular system.

About 75 years ago, the adverse reactions attributed to cocaine included perforations of the nasal septum, unpredictable psychotic reactions (often violent), hyperthermia, convulsions, and sudden death by unknown mechanisms. However, these effects were anecdotal and derived from observations made at the turn of the century. Nonetheless, the overall impression in the earlier part of this century was that cocaine was a dangerous drug (McLaughlin 1973), which led to the passage of the Harrison Narcotics Act in 1914. However, the early empirical observations by no means met the scientific standards of the 1970s. Cocaine was presumed to be safe since there was no current scientific evidence to show that it was dangerous. Likewise, since cocaine use did not lead to "physical" dependency, it was presumed to be nonaddictive. Consequently, the recreational use of cocaine rapidly increased in the late 1970s and well into the 1980s. Therefore, knowledge of the pathologic consequences of virtually unrestricted cocaine use is derived from the relatively limited experience of the past 10 to 15 years.

The death rate in Dade County, FL, has increased steadily since the late 1970s (Mittleman and Wetli 1984). In 1980 the drug was relatively scarce and selling for $100 to $125 per gram; it was approximately 15 percent pure.

In summer 1983 the death rate increased as the result of increased cocaine production in South America. During that summer, the black market wholesale price of cocaine dropped from $50,000 to $22,000 per kilogram. This resulted in greater availability, lower price, and increased purity (approximately 35 percent), which in turn increased the death rate to approximately two per month. This rate persisted until 1986, when the availability and purity of street cocaine again increased and smokable "crack" cocaine became popular. The death rate in Dade County increased to about one per week and, with some fluctuation, has remained at about that level.

For the first half of the 1980s the vast majority of deaths due to cocaine toxicity were from ingesting the hydrochloride salt of cocaine. However, since 1986, increasing numbers of deaths have been associated with the use of free base cocaine, commonly known as crack or "rock" cocaine. Those who died from the use of cocaine hydrochloride often had blood levels of 3 to 5 mg/L at the time of autopsy; with crack cocaine, deaths are associated with much lower blood concentrations of cocaine, often less than 1 mg/L.

## SNORTING COCAINE

In the late 1970s and early 1980s it was commonly believed that one could not insufflate ("snort") enough cocaine to die unless a tremendous quantity was ingested. Indeed, there were occasions when individuals died with obvious cocaine particles in their nose or moustache, and a few had a nasal cavity completely packed with the drug. However, the more common scenario involved an individual who was snorting cocaine, often in a party atmosphere, who suddenly experienced a grand mal seizure that was followed rapidly by respiratory collapse and death (Wetli and Wright 1979). The reaction often occurred without warning about 25 to 30 minutes after the last line of cocaine was snorted. The convulsions often were associated with severe bite marks of the lower lip, the tongue, or the cheek. Prodromal symptoms sometimes appeared (e.g., light sensitivity due to mydriasis, agitation, tactile and/or visual hallucinations, hyperthermia). Cocaine-induced hyperthermia may be extreme (108 °F or more), and at the scene of death there is sometimes evidence that cold showers, wet towels, or ice were used in a frantic attempt to lower the body temperature.

Early observations of deaths from snorting cocaine suggested that these individuals did not necessarily die of a true overdose of the drug. When information could be obtained, they appeared to have been snorting the same amount of drug as they normally would. A possible explanation for the death is provided by the theory of reverse tolerance or "kindling": an accentuated response to the usual dose of a drug.

The time delay of 25 to 30 minutes between the last dose of the drug and the terminal seizure activity was thought to be related to the delayed absorption of cocaine from the nasal passages. The initial effect of cocaine, besides providing local anesthesia, is vasoconstriction, which limits the amount that is absorbed. It was thought that an unexpected, sudden vasodilatation led to a surge of cocaine into the blood and then into the CNS, initiating the convulsions.

Perforations of the nasal septum frequently are observed at the time of autopsy. Speculum examination of the nasal septum often discloses perforations that range from only a few millimeters in diameter to complete erosion of the nasal septum (figure 1). Three factors appear to be involved in these perforations of the nasal septum. One is the intermittent vasoconstrictive effect, which limits oxygen and nutrients to the area. Another contributory factor may be the dissociation of cocaine hydrochloride into a weak base and a strong acid. The third possibility (based on data from animal experiments), probably the most relevant, is that cocaine is directly toxic to capillary endothelial cells; destruction of the capillaries results in ischemia and tissue breakdown. Histologically, the

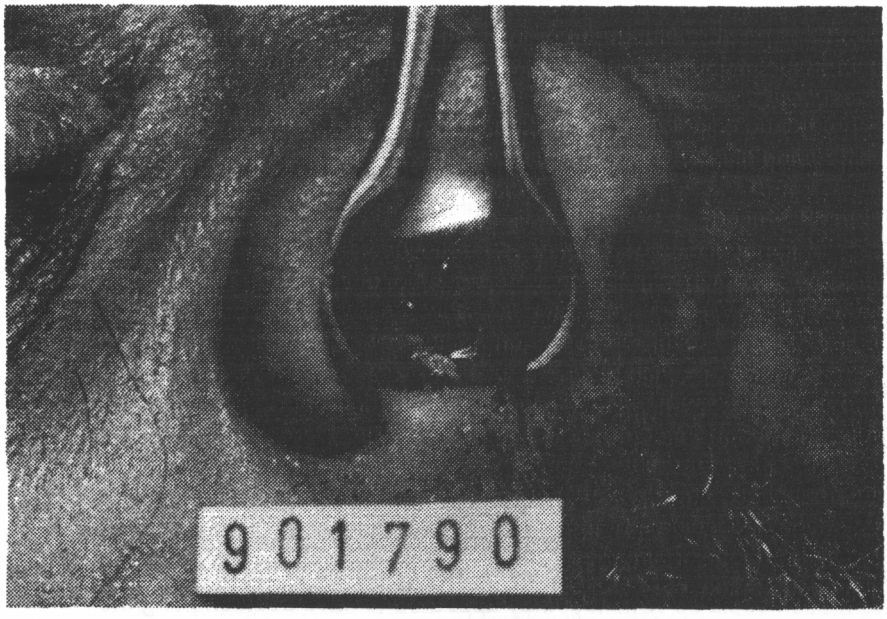


**FIGURE 1.** *Perforation of the nasal septum from chronic nasal insufflation of cocaine hydrochloride*

margins of these perforations have the usual characteristics of a coagulation or ischemic necrosis with a variable chronic inflammatory cell infiltrate.

## COMPLICATIONS OF THE INTRAVENOUS USE OF COCAINE

Any intravenous (IV) drug abuser has the potential of contracting a variety of diseases (e.g., local abscesses, bacterial endocarditis, malaria, acquired immunodeficiency syndrome). However, unlike the heroin addict who develops perivenous scars from the concomitant injection of excipients (starch or talc) from oral medication, the IV cocaine user paradoxically develops subcutaneous bleeding. The very fresh cocaine injection site appears as a needle puncture mark surrounded by a halo of normal skin, which in turn is surrounded by a very prominent ecchymosis. It is thought that this particular configuration is the result of the vasoconstrictive property of cocaine creating the halo of normal-appearing skin around the puncture mark with an acute backup of blood within the capillaries causing their rupture and subsequent ecchymoses. In time, the ecchymoses coalesce, and the blood pigment eventually breaks down and disappears (like any other bruise) and does not leave a scar. The only scars observed with chronic cocaine users are in individuals who never rotate injection sites and repeatedly traumatize one area over a period of years. Scars typical of those seen in heroin addicts have never been observed among those who restrict their IV drug abuse to cocaine.

A curious observation made of IV cocaine users is the appearance of numerous round and oval atrophic scars, often in sites of predilection for IV injection. These seem to be associated almost exclusively with IV cocaine users. They may be healed abscesses or healed areas of cutaneous gangrene (occurring for basically the same reasons that individuals may get perforations of the nasal septum from chronic nasal insufflation of cocaine). Cutaneous ulcers are seen occasionally with pearly gray epidermal margins, indicative of attempts at repair. This tends to support the theory of localized cutaneous gangrene. However, sometimes these round and oval scars are in areas that would be unlikely, or impossible, for a person to inject (such as the back). This suggests that another possibility for the etiology of these scars is the lack of adequate healing of unrelated local infections because of intermittent cocaine-induced peripheral vasoconstriction. That is, intermittent vasoconstriction would delay the healing of an infection by impeding the blood flow to the infected area. Prolonged chronic inflammation then could lead to formation of the scars.

Another cutaneous reaction associated predominantly with IV use of cocaine (and heroin users, if they also use cocaine) is the phenomenon of necrotizing fasciitis (Wetli 1987). In these individuals, large areas of skin slough from presumed injection sites. The area of skin slough may cover an

entire forearm or side of the lower extremity. The skin slough is usually full thickness, and erosions down to the muscle and tendons are not unusual. A cellulitis occasionally accompanies the process. For unknown reasons, the necrotizing fasciitis often is associated with a rather pronounced lymphedema of the affected extremity. Rarely, partial and complete autoamputations have resulted from extensive and untreated necrotizing fasciitis.

## ACUTE CARDIOVASCULAR EFFECTS OF COCAINE

It is now well recognized that cocaine, regardless of the route of administration, can exacerbate any underlying cardiovascular abnormality, including hypertension. The acute cardiovascular effects of cocaine are manifested as ischemic damage to the myocardium, aortic dissections, and the rupture of intracranial vascular malformations and saccular aneurysms. In cases of apparent natural death where a contributory role of cocaine can be demonstrated, cocaine is listed as a contributory cause of the death, and the manner of death then becomes listed as accidental (Mittleman and Wetli 1987).

The mechanism for the ischemic damage to the myocardium is based on an increased heart rate and, possibly, rhythm disturbances that could aggravate any underlying arteriosclerotic coronary artery disease. However, cocaine also has been demonstrated to directly constrict the coronary arteries and, thus, may precipitate ischemic myocardial damage even in the face of morphologically normal vessels (Lange et al. 1989).

Hypertensive crisis precipitated by cocaine may be quite dramatic and associated with the various complications of hypertension, such as ruptured vascular malformations. Should the individual survive for a period of time, he or she may encounter renal failure from rhabdomyolysis (Roth et al. 1988), most likely the result of increased muscular activity from convulsions and/or hyperthermia.

## CARDIOVASCULAR EFFECTS OF CHRONIC USE

Cumulative experience with the chronic, relatively unrestricted use of cocaine has spanned approximately a decade. During this time, the scientific community has had a growing suspicion that the chronic use of cocaine may result in irreversible cardiovascular damage. Proposed mechanisms include direct damage to the myocardial fibers by means of contraction-band necrosis (catecholamine effect) (Karch and Billingham 1988) intimal proliferation due to intermittent coronary vasospasm (Simpson and Edwards 1986), and

accelerated atherosclerosis (Langer et al. 1989). Reports also have linked the use of cocaine to dilated cardiomyopathies (Duell 1987).

## EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The most frequent manifestation of cocaine use in the CNS is subarachnoid hemorrhage (Nolte and Gelman 1989) due to ruptured vascular malformations or saccular aneurysms. Although intracranial vasospasm may result in ischemic changes (Rowbotham and Lowenstein 1990), these have not yet been documented at the time of autopsy.

A rare complication that has been reported among IV cocaine and amphetamine users is a very rapidly progressive, almost universally fatal, primary fungal cerebritis (Wetli et al. 1984; Micozzi and Wetli 1985). The organisms isolated from these individuals are generally opportunistic fungi (e.g., *Rhizopus* species). The syndrome generally begins with nonspecific but severe neurologic symptoms such as unsteady gait, double vision, or slurred speech. This rapidly progresses to coma within approximately 24 hours, and death generally ensues within 48 to 72 hours. The victims do not appear to have human immunodeficiency virus infection. Although the etiology is not certain, one possibility is that frequent intermittent constriction of the cerebral microvasculature may cause microscopic foci of necrosis of the CNS that would provide the “fertile soil” for these opportunistic fungi.

## PSYCHIATRIC COMPLICATIONS

It is well known that cocaine may exacerbate any underlying psychoneurotic abnormality (Post 1975). Generally, however, these abnormalities disappear as the blood level of cocaine diminishes. Morphologic expressions of these psychiatric abnormalities are obviously indirect for the most part. Occasionally, prominent scratches and abrasions from formication may be seen. Cocaine-induced paranoia has been known to include fatal, sometimes bizarre behavior: Some individuals have run from a domicile only to drown in a canal or other body of water; others have cringed in a closet while a small fire on the stove generated enough carbon monoxide to kill them; and others have been accidentally shot while fending off imaginary attackers.

The most serious psychiatric sequelae of cocaine abuse, however, is excited delirium, which may be associated with sudden death (Wetli and Fishbain 1985). Cocaine-induced excited delirium generally is manifested as the sudden onset of paranoia, followed shortly by violent activity generally directed toward objects, particularly glass (windows, mirrors). Typically, the individuals will strip off all their clothing and run through a neighborhood yelling, shouting, and

screaming. The bizarre and violent activity generally draws the attention of the police who encounter somebody who is not only frankly psychotic but also has a tremendous apparent increase in strength. After a fairly brief but extremely violent struggle, the individual is restrained, Sudden death may occur moments later or up to several minutes later. The mechanism of death is uncertain, but in some cases electrocardiograms have revealed persistant cardiac electrical activity but no pulse or blood pressure.

Sudden death from cocaine-induced excited deliruim presents problems from two main perspectives. One is the perception of onlookers, including news media, that the police are exerting unnecessary violence toward an individual. The second is that once these people enter the emergency room, they pose a threat of physical violence toward medical personnel. They must be restrained and their symptoms treated. Most individuals will respond to symptomatic treatment. However, hyperthermia appears to be a negative prognostic factor and frequently is associated with sudden unexpected death (K. Schrank, personal communication, July 1991).

In fatal cases, the autopsy findings are generally nonspecific and reveal only injuries sustained during the struggle with the police officers and from fighting against the restraints. Thus far, fatal injuries have not been reported with any of these cases, although careful interpretation of the autopsy findings is often necessary when extreme violence has been experienced (Mittleman and Davis 1991).

It is interesting to note that electrical stun gun devices and other injuries have no significant effect on people in the throes of cocaine-induced excited delirium. The presumption is that their sensation for pain is markedly diminished, a phenomenon that also may account for their apparent increase in physical strength.

**CRACK COCAINE**

Thus far, no physical abnormalities have been directly attributable to the use of crack cocaine. However, in an indirect sense, the most prominent manifestation of crack cocaine abuse is sudden death from violence, generally stemming from attempts on the part of the crack cocaine addict to obtain sufficient funds for the drug. Deaths include innocent victims, who are intentionally or unintentionally killed during robbery attempts, and the addicts themselves. For example, crack addicts have been electrocuted while stealing aluminum (to sell to recycling plants) from electrical power plant substations.

## EFFECTS ON THE FETUS AND NEWBORN

Although several anomalies have been associated with the maternal use of cocaine, these may be coincidental. In the author's experience at the Dade County Medical Examiner's office, the most common manifestation is spontaneous abortion due to placental insufficiency or abruptio placentae at approximately 28 weeks gestation. Autopsies of these fetuses thus far have not revealed any consistent congenital anomalies.

## THE BODY PACKERS

Ingesting packets filled with cocaine is a smuggling practice with intermittent popularity. These individuals pack cocaine into a variety of containers, including condoms or balloons. Each packet contains approximately 3 to 5 g of high-grade cocaine (figure 2). Up to .5 kg of cocaine has been transported by this method. The individuals swallow the cocaine in a South American country, generally Colombia, and board an airplane bound for the United States. Prior to boarding the airplane, they generally have ingested some sort of constipating agent, such as paregoric. The packets eventually may break open because of poor packaging or may leak through the ties. Also, the packaging material is often not waterproof, and consequently a dialysis membrane is established: Water leaks into the packets, and the cocaine dissolves and leaches out of the packet to be absorbed through the gastrointestinal tract. The intent of the individuals is to clear customs in the United States, find a hotel room, and pass the packets through the gastrointestinal tract with the aid of laxatives, enemas, and fast foods (usually hamburgers). However, cocaine toxicity may occur at any time, and the smugglers suddenly may go into convulsions aboard the airplane, in the customs area of the airport, or in the hotel room. After death, they frequently have signs of terminal seizure activity (e.g., bite marks of the lower lip) as well as hyperthermia (wet towels on their chest and postmortem temperatures of more than 102 °F). Recently, there have been cases where death resulted from the intestinal obstruction caused by these packets.

At autopsy, the packets may be retrieved from anywhere in the gastrointestinal tract, especially the stomach and the cecum (Wetli and Mittleman 1981). The mucosal lining of the gastrointestinal tract is frequently hemorrhagic where it has come in contact with the drug. Most packets retrieved from these individuals contain 3 to 5 g of cocaine compressed into a solid mass, wrapped in plastic, and wrapped several more times with the tips of surgical gloves. Some packets may be marked with "X's," possibly to denote various dealers to whom the cocaine is to be delivered. In one recent case from Georgia, the markings indicated which packets contained heroin and which contained only cocaine (J. Burton, personal communication, May 1991).

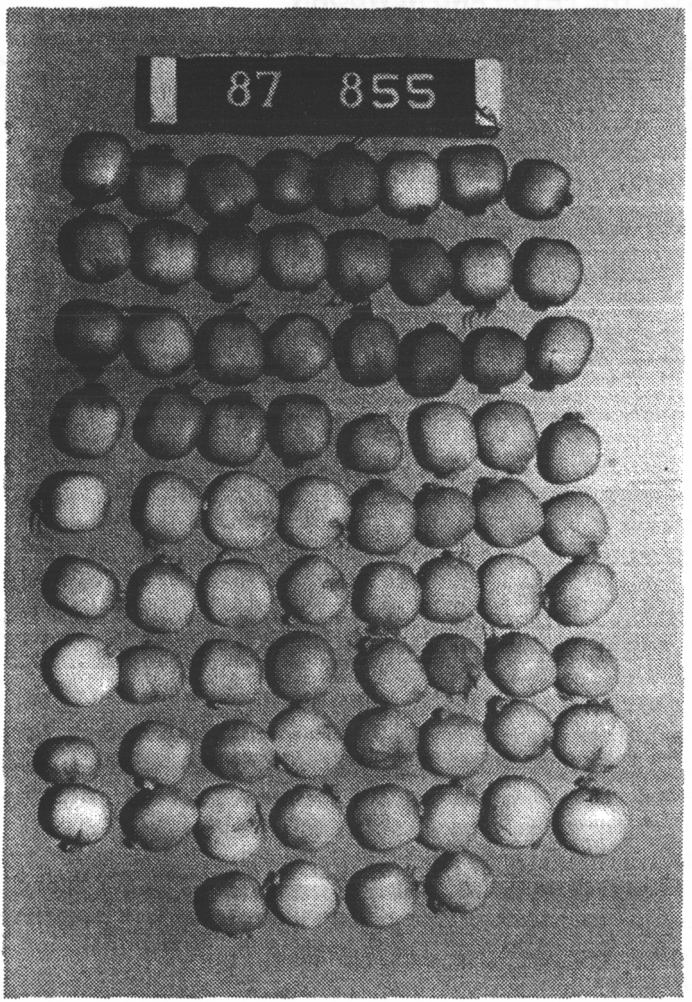


**FIGURE 2.** *These 76 packets of cocaine, totaling 429 g, were removed from the gastrointestinal tract of a body packer. Each packet was constructed with the tips of surgical gloves and tied with fishing line. Some packets are darker colored due to staining with bile.*

## EMERGING PATTERNS

In 1980 a typical victim of cocaine toxicity was a 26-year-old white male who died with grand mal seizure. At the autopsy table one might find a perforated nasal septum, a bite mark of the tongue, and nonspecific change of asphyxia (pulmonary edema, visceral petechiae) (Wetli and Wright 1979). Since then, the view from the autopsy table has changed considerably (Mittleman and Wetli 1991) as have the demographics of cocaine abuse (Escobeo et al. 1991).

More data are accumulating that strongly suggest the chronic use of cocaine may result in permanent cardiovascular damage and, possibly, permanent damage to the CNS. Whether this trend will manifest as premature, fatal, cardiovascular catastrophes in the 1990s remains to be seen. Certainly, the violent deaths related to cocaine addiction will be present for some time to come.

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**AUTHOR**

Charles V. Wetli, M.D.
Deputy Chief Medical Examiner
Dade County Medical Examiner Department
One Bob Hope Road
Miami, FL 33136-1133

# Summary Comments

***Marian W. Fischman, Reese T. Jones, and James W. Cornish***

A key question to be answered is whether there are sufficient untreated or unresponsive cases of acute cocaine toxicity to warrant a National Institute on Drug Abuse investment of funds and time. At present it appears that most cases of cocaine-related toxicity seen in emergency rooms are treated successfully. Only about one-quarter to one-third of the patients seen in emergency rooms for acute cocaine toxicity are subsequently hospitalized. For the most part these patients receive treatment directed at their presenting symptom complexes (e.g., seizure, myocardial infarction, hyperthermia) and not specific treatment for cocaine effects. In these cases, cocaine is the etiologic agent that sets into motion a cascade of pathologic events that causes the patient to seek medical care. Also, at times, it is very difficult to determine whether a patient has taken cocaine prior to the medical emergency.

Some questions related to which currently used medications are most efficacious remain to be studied, but overall, most acute cocaine toxicity patients are successfully treated. It would be useful to disseminate emergency medicine protocols that outline the current treatment approaches to patients with acute cocaine toxicity.

The following are potential research areas:

1. Effects of other drugs in combination with cocaine

    a. Other psychoactive substances
    b. Potential treatment medications
    c. Medications used to treat preexisting disorders
    d. Order of drug interactions (precocaine, postcocaine, or together)

2. Animal models for cocaine toxicity

    a. Determine which models are best to measure toxic effects
    b. Study toxicity vs. route of administration
    c. Evaluate genetic and strain differences for specific toxicities

d. Determine which models the Food and Drug Administration will need in evaluating data for new medications in combination with cocaine

3. Long-term effects of chronic cocaine use

   a. Cardiovascular
   b. Central nervous system
   c. Hormonal

4. Mechanisms of cocaine toxicity

   a. Which physiological systems are affected?
   b. Are there cocaine-specific symptom complexes?
   c. What sets off the cascade of pathophysiological events?

**AUTHORS**

Marian W. Fischman, Ph.D.
Professor
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, MD 21205

Reese T. Jones, M.D.
Professor of Psychiatry
University of California, San Francisco
Langley-Porter Psychiatric Institute
Box F 0984
401 Parnassus Avenue
San Francisco, CA 94143

James W. Cornish, M.D.
Research Assistant Professor
Department of Psychiatry
University of Pennsylvania
Director
Pharmacotherapy Division
Treatment Research Center
3900 Chestnut Street
Philadelphia, PA 19104-6178


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