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Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

guidelines for the clinical evaluation of General Anesthetics

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

HHS (FDA) 82-3052

GUIDELINES FOR THE CLINICAL EVALUATION OF GENERAL ANESTHETICS

PRINTED SEPTEMBER 1977
REVISED MAY 1982

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Dockets Management Branch (HFA - 305)
Docket Number - 82D-0115
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ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics' Committee on Drugs, and consultants to the Pharmaceutical Manufacturers' Association has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in man, and pertain to Phases I through III of the investigation. They represent generally acceptable principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two-year intervals.

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be acceptable by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

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GUIDELINES FOR THE CLINICAL EVALUATION OF GENERAL ANESTHETICS

"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines.

I. INTRODUCTION

A. Nature of the Recommendations

The nature of general anesthetic drugs precludes the use of traditional controlled studies comparing the agent to placebo. Comparison with well-accepted agents is not required because published experience with these compounds is extensive and well documented. Furthermore, the patient's welfare dictates that the anesthesiologist be aware of the identity of the agent which he or she is administering.

Those items designated as required may be construed as minimal acceptable standards. Those designated optional represent maximal achievable goals. The category of recommended falls between these extremes and should be interpreted by the individual investigator. Even those items labeled required may be complied with by other tests or techniques which provide equivalent information.

B. Guide to symbols

** - Required
* - Required -- except as noted
+ - Recommended
x - Optional

II. PRECLINICAL STUDIES

A. Physical and Chemical Properties

1.** Purity (toxicological studies of impurities with significant biological activity resulting from synthesis, storage, or use)

2.** Shelf life

a. Preservatives, if used

b. Stability and interactions - light, heat, alkali, metals, rubber and plastics

c. Solubility in conductive rubber tubing and plastics

3.** Vapor pressure curve

4.** Flammability

5.** Vapor density, liquid density, molecular weight

6.** Partition coefficient (blood-air)

7.** Oil/Water solubility, or Oil/Plasma solubility, or Fat/Blood solubility, or solubility in Plasma and Water

B. Animal Pharmacology

** Normal range of values for the reporting laboratory must be included to provide baseline for comparison.

1.** Standardization of the protocol for animal care and environmental conditions

2.** Acute multiple species testing

a. Four species (three if one is a primate)

3.** Comparison of the investigational agent with known tested agents with comprehensive monitoring and biochemical studies

4.** Dose response

a. Induction and emergence times

b. Anesthesia requirements (Example: MAC)

c. Reflex activity

d. The mechanism of death should be sought in experimental animals, with and without respiratory support, to determine whether overdosage produces death by circulatory alterations, central nervous system alterations (including EEG evaluation) and/or respiratory alterations.

5.* System studies (host response, time and dose to be investigated whenever possible)

a. Cardiovascular

(1) Blood pressure

(2) Heart rate

(3) Electrocardiogram

(4)+ Cardiac dynamics (output)

(5)+ Peripheral resistance, organ and limb bloodflow

(6)+ Autonomic activity

(7)x Catecholamine titers (urine and blood)

(8)* Myocardial sensitization

(a) Epinephrine challenge

(b) CO_2 response

(c)x Cardiac accelerator nerve stimulation

b. Respiratory (spontaneous and controlled respiration)

(1)** Tidal volume

(2)** Rate

(3)** CO_2 response

(4)** Acid base and blood gas studies

c. Central nervous system

(1)** Electroencephalogram

(2) Tonic and clonic movements not related to depth of anesthesia

(3)** Convulsions

d.** Reproductive system - If the pharmacological profile of the product is such that modification of reproduction guidelines is indicated, individualization is permitted after consultation.

(1) Male

(2) Female

(3)x In vitro studies of myometrial contractility. Response to oxytocics.

e.** Liver (liver function studies should be performed prior to and after the animal has been exposed to surgical levels of anesthesia at least twice; and evaluated, if possible, with regard to time-dose relationship).

(1)** Prothrombin time

(2)x Cholesterol

(3)** BSP

(4)** Enzymes

(a) SGOT

(b) SGPT

(c) LDH

(d) Alkaline phosphatase

(5)** Serum bilirubin (direct and indirect)

(6)** Albumin

(7)** Globulin

f.** Kidney : renal function studies should be performed prior to and after multiple (at least two) exposures to surgical levels of anesthesia. Results should be evaluated, if possible, with regard to time-dose relationship.

(1) Urine

a. Urinary output

b. Microscopic examination

c. Specific gravity

d. pH

e. Albumin

f. Sugar

g. Blood

(2) Blood

(a) Creatinine

(b) BUN

(3) Glomerular filtration rate

(4) Renal bloodflow

g.** Endocrine

(1)** Blood glucose

(2)x Blood corticoids

6.** Drug Interactions (representative members of the following groups) should be studied.

a. Narcotic

b. Sedative

c. Anticholinergic

d. Tranquilizer (major and minor)

e. Local Anesthetics

7.** Metabolic

a. Biotransformation

b. Methods of excretion

8.** Chronic toxicity - use 2 species (to include time-dose relationship)

a. Administer anesthetic for 3 hours a day three times per week (e.g., Mon. Wed. Fri.) for 8 weeks.

b. If the pharmacologic profile of the agent make this impractical, this can be modified.

c. Body weight

d. Gross observations

e. Hematology - Pretest - weeks, 1, 2, 4, 6, and termination

f. Clinical chemistry - Pretest - weeks 1, 2, 4, 6, and termination

g. Urinalysis - Pretest - weeks 1, 2, 4, 6, and termination

h. Gross and histopathology

(Object here is to determine what repeated administration of the agent does. Dose-effect data would by this time have been generated.)

9.** Carcinogenicity and teratogenicity

10.** Animal screening in susceptible swine for malignant hyperthermia

III. CLINICAL STUDIES

A. Phase I

** Phase I protocols should be designed to establish the safety and effectiveness of the new drug in man. The preclinical studies will determine which parts of the following protocols should be studied first and most intensively.

1.** Subject selection

The use of healthy volunteers may be desirable in Phase I studies in order to separate the effects of anesthesia from those of surgery. Under certain circumstances healthy adult patients of either sex (women of childbearing potential should be excluded) undergoing superficial surgical operations may also be employed. The following should be completed prior to administration:

a.** A complete history with particular reference to drug usage, including prior anesthesias

b.** A complete physical examination

c.** Baseline laboratory studies as defined in the protocol, with an absolute minimum of urinalysis, CBC, BUN, liver enzymes, and recent ECG and chest x-ray

2. Drug administration

*General anesthetics should ideally be studied alone initially and later in combination with other drugs that are commonly used to extend the performance of general anesthetic agents.

a.** Preanesthetic medication - Eventually required. Compatibility is being looked for here. Depending on the knowledge gained from the animal studies, one may wish to use one or more of these.

(1)** Anticholinergics

(2)** Narcotics

(3)** Hypnotics

(4)** Tranquilizers (major and minor)

b.** Neuromuscular blocking agents - Eventually required

c.** Inhalation agents, such as nitrous oxide - Eventually required

d.** Parenteral induction agents - Eventually required

Early studies should ordinarily be limited to short procedures.

3. Clinical observations and measures. (These observations and measurements should be recorded on appropriate forms and accompanied by a standard anesthesia record used by all investigators.) All of them need not be in the same protocol.

   a.** Hypnosis or sleep

   b.** Analgesia

   c.** Patient acceptability (odor, irritation, etc.)

   d.** Reflex response (tendon, pharyngeal, laryngeal, and eye signs)

   e.** Muscle tone

   f.** Salivation and other respiratory secretions

   g.** Resistance to passive ventilation

   h.** Response to tracheal intubation

   i.** Cyanosis (skin, mucous membrane and nailbed color)

   j.** Abnormal muscular activity

   k.** Recovery period

      (1)** Duration and nature of emergence

      (2)** Recovery of consciousness

      (3)** Nausea, retching, and vomiting

      (4)** Psychological reactions, including delirium, hallucinations, etc.

      (5)** Headache

4. Physiologic measurements

   a.** Blood pressure

   b.** Heart rate

   c.** Respiratory rate

   d.** Depth of respiration, minute volume

   e.** Electrocardiogram

   f.+ Electroencephalogram

   g.** Body temperature

h.** End expiratory PCO_2 or arterial blood gases and pH

i.+ Intraocular pressure

j.+ Appropriate blood or alveolar concentration of anesthetic agent

k.** Hepatic function studies

l.** Renal function studies

m.** CBC and platelet count

n.+ Hematopoietic function studies

5.** Measurements and observations above should be correlated as closely as possible with inspired anesthetic concentration and estimations of depth of anesthesia.

6.** All unusual or unanticipated phenomena or physiologic responses should be reported.

B. Phase II

1.** Subject selection

Those individuals outlined in Phase I and ASA Class I or 2 patients (no systemic disease or mild systemic disease) for surgical or diagnositic procedures. Patients with greater disability or requiring more extensive procedures may be accepted in graded fashion as experience with the agent warrants such progression. Women of childbearing potential should be excluded in this phase.

2. Drug administration

** It is in this phase that overall efficacy and safety and optimal dosage range is established.

* Comparison studies may be made with established agents in current usage.

3.** Observations and measurements

Protocols should be designed based upon results of Phase I studies. Further studies of pertinent facets should be carried out independently by more than one group of investigators.

4. Additional measurements

a.+ Venous pressure

b.** Electroencephalogram

c.** Pulmonary mechanics

d.+ Cardiac output and contractility

e.+ Blood or alveolar levels of agent

f.+ Limb and organ bloodflow

g.+ Cardiac sensitization to catecholamines. If animal studies show limited dose related sensitization, and potential benefits such as hemostasis exist, protocols must be approved in advance during Phase III.

h.** Carbon dioxide response curve and indices of myocardial function (do with spontaneous ventilation)

i.** End expiratory PCO_2 or arterial blood gases and pH

j.** Cerebrospinal fluid pressure under normocapneic conditions

k.x Intraocular pressure

C. Phase III

** Phase III is directed toward the assessment of the drug under investigation under operating room conditions. At this time the effects of a multiplicity of variables such as different types of surgery, nueormuscular blockade, and other anesthetic adjuncts must be evaluated and studied. Special attention should be focused on the effect of other drugs and upon adverse reactions.

1.** Experimental design considerations for protocol development. In designing the study, consideration should be given to the following:

a. Specification of patient population with respect to identifiable subgroups of homogeneous subjects.

b. Specification of important stratifications of subjects

c. Specification of hypotheses to be tested and variables to be compared.

d. Specification of statistical risks one will allow in the study comparisons (e.g., Type 1 and Type 2 errors) or the precision in estimates of anesthetic effects one will expect. In this regard, consultation with a statistician is recommended.

e. Specification and justification for study sample sizes.

2.** Subject selection

Patient population and variety of surgical procedures may be expanded as dictated by the properties of the drug. Women of childbearing potential may be included if animal reproduction studies have been complete. Studies may be extended to the younger age groups as experience warrants. In this phase, studies may be extended to include the drugs used in obstetrical anesthesia.

3. Clinical observations and measurements

The clinical observations should be selected from those employed in Phase I and II. In addition, advantage may be taken of special circumstances to utilize information obtained with special patient populations.

a. ** In obstetrical patients measurements should be made of placental transfer, effect on the newborn (such as 1 and 5 minute Apgar scoring and time to sustained respiration), degree of postpartum bleeding, effect of oxytocics. (Required for recommendation in obstetrics.)

   ** Short term neonatal neurobehavioral studies

b. ** Effect of repeated administration to be obtained in patient undergoing frequent procedures such as burn therapy, plastic surgery, radiation therapy, etc.

c. + Patients with recognized hepatic, renal or cardiac disease may be studied as indicated to determine the effects of the agent on the abnormal system. (Recommended if this constitutes no significant patient hazard.)

d. ** Data should be gathered on cerebrospinal fluid pressure in neurosurgical procedures, intraocular pressure in ophthalmologic procedures, cardiovascular hemodynamics in patients undergoing cardiac surgery.

4.** Plan for reporting of data and findings from completed studies

In designing the plan for analysis and reporting of the data and findings from completed studies, consideration should be given to the following:

a. Data and findings should be reported separately for each protocol, investigator, clinic, etc.

b. Summary tables of selected parameters should be presented for all relevant subgroups of subjects studied so that appropriate comparisons can be made. For example, time to recovery, incidence of nausea or vomiting, blood pressure, respiratory rate, body temperature, etc., should be displayed by factors such as age, sex, severity of surgery, duration of anesthesia, etc.

c. For all safety parameters, a display of appropriate pre and post treatment parameters measured and an appropriate statistical evaluation of the changes in pre-to-post-measurements.

d. A detailed documentation of the statistical methods employed along with the conclusions based on the analysis

e. A well organized and documented data base (including data on all subjects entered into the study and on all measurements taken)

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HHS Publication No. (FDA) 82-3052