CHAPTER 5

N-Methyl Carbamate Insecticides

HIGHLIGHTS

- Cause reversible carbamylation of AChE
- Muscarinic, nicotinic, CNS effects

Signs and Symptoms:

- Malaise, muscle weakness, dizziness, sweating
- Headache, salivation, nausea, vomiting, abdominal pain, diarrhea
- CNS depression, pulmonary edema in serious cases

Treatment:

- Clear airway, improve tissue oxygenation
- Administer atropine sulfate intravenously
- Proceed immediately with decontamination procedures

N-Methyl carbamate insecticides are widely used in homes, gardens, and agriculture. They share with organophosphates the capacity to inhibit cholinesterase enzymes and therefore share similar symptomatology during acute and chronic exposures. Likewise, exposure can occur by several routes in the same individual due to multiple uses, and there is likely to be additive toxicity with simultaneous exposure to organophosphates. However, due to the somewhat different affinity for cholinesterases, as compared to organophosphates, these poisonings are often somewhat easier to treat, as discussed later in this chapter.

Toxicology

The N-methyl carbamate esters cause reversible carbamylation of the acetylcholinesterase enzyme, allowing accumulation of acetylcholine, the neuromediator substance, at parasympathetic neuroeffector junctions (muscarinic effects), at skeletal muscle myoneural junctions and autonomic ganglia (nicotinic effects), and in the brain (CNS effects). The carbamyl-acetylcholinesterase combination dissociates more readily than the phosphoryl-acetylcholinesterase complex produced by organophosphate compounds. This lability has several important consequences: (1) it tends to limit the duration of N-methyl carbamate poisonings, (2) it accounts for the greater span between symptom-producing and lethal doses than in most organophosphate compounds, and (3) it frequently invalidates the measurement of blood cholinesterase activity as a diagnostic index of poisoning (see below).

N-methyl carbamates are absorbed by inhalation and ingestion and somewhat by skin penetration, although the latter tends to be the less toxic route. For example, carbofuran has a rat oral LD_{50} of 5 mg/kg, compared to a rat dermal LD_{50} of 120 mg/kg, which makes the oral route approximately 24 times more toxic when ingested.[1] N-methyl carbamates are hydrolyzed enzymatically by the liver; degradation products are excreted by the kidneys and the liver.

At cholinergic nerve junctions with smooth muscle and gland cells, high acetylcholine concentration causes muscle contraction and secretion, respectively. At skeletal muscle junctions, excess acetylcholine may be excitatory (cause muscle twitching), but may also weaken or paralyze the cell by depolarizing the end-plate. In the brain, elevated acetylcholine concentrations may cause sen-

sory and behavioral disturbances, incoordination, and depressed motor function (rarely seizures), even though the N-methyl carbamates do not penetrate the central nervous system very efficiently. Respiratory depression combined with pulmonary edema is the usual cause of death from poisoning by N-methyl carbamate compounds.

Signs and Symptoms of Poisoning

As with organophosphate poisoning, the signs and symptoms are based on excessive cholinergic stimulation. Unlike organophosphate poisoning, carbamate poisonings tend to be of shorter duration because the inhibition of nervous tissue AchE is reversible, and carbamates are more rapidly metabolized.[2] Bradycardia and seizures are less common than in organophosphate poisonings. However, **blood cholinesterase levels may be misleading due to in vitro reactivation of a carbamylated enzyme.**[3,4] A falsely "normal" level can make the diagnosis more difficult in the acute presentation in the absence of an exposure history.

The primary manifestations of serious toxicity are central nervous system depression, as manifested by coma, seizures, and hypotonicity, and nicotinic effects including hypertension and cardiorespiratory depression. Dyspnea, bronchospasm, and bronchorrhea with eventual pulmonary edema are other serious signs. Recent information indicates that children and adults differ in their clinical presentation. Children are more likely than adults to present with the CNS symptoms above. While children can still develop the classic muscarinic signs, the absence of them does not exclude the possibility of carbamate poisoning in the presence of CNS depression.[5]

Malaise, muscle weakness, dizziness, and sweating are commonly reported early symptoms. Headache, salivation, nausea, vomiting, abdominal pain, and diarrhea are often prominent. Miosis with blurred vision, incoordination, muscle twitching, and slurred speech are reported.

Confirmation of Poisoning

If there are strong clinical indications of acute N-methyl carbamate poisoning, and/or a history of carbamate exposure, treat the patient immediately. Do not wait for laboratory confirmation.

Blood for plasma pseudocholinesterase and RBC AChE should be obtained. Be advised that unless a substantial amount of N-methyl carbamate has been absorbed and a blood sample is taken within an hour or two, it is unlikely that blood cholinesterase activities will be found depressed. Even under the above circumstances, a rapid test for enzyme activity must be used to detect an effect, because enzyme reactivation occurs *in vitro* as well as *in vivo*. See the table on page 39 for methods of measurement of blood cholinesterase activities, if circumstances appear to warrant performance of the test.

Commercial Products

aldicarb+
- Temik

aminocarb+
- Matacil

bendiocarb+
- Dycarb
- Ficam
- Multamat
- Niomil
- Tattoo
- Turcam

bufencarb
- Bux
- metalkamate

carbaryl
- Dicarbam
- Sevin

carbofuran+
- Crisfuran
- Curaterr
- Furadan

cloethocarb+
- Lance

dimetan
- Dimethan

dioxacarb
- Elecron
- Famid

fenoxycarb
- Torus

formetanate hydrochloride+
- Carzol

isolan+
- Primin

isoprocarb
- Etrofolan
- MIPC

methiocarb+
- Draza
- Mesurol

methomyl+
- Lannate
- Lanox
- Nudrin

mexacarbate
- Zectran

oxamyl+
- DPX 1410
- Vydate L

pirimicarb
- Abol
- Aficida
- Aphox
- Fernos
- Pirimor
- Rapid

(Continued on the next page)

Commercial Products

(Continued)

promecarb
Carbamult
propoxur
aprocarb
Baygon
thiodicarb
Larvin
trimethacarb
Broot
Landrin

+ Indicates high toxicity. Highly toxic N-methyl carbamates have listed oral LD_{50} values (rat) less than or equal to 50 mg/kg body weight. Most other carbamates included in this table are considered moderately toxic, with LD_{50} values in excess of 50 mg/kg and less than 500 mg/kg.

Absorption of some N-methyl carbamates can be confirmed by analysis of urine for unique metabolites: alpha-naphthol from carbaryl, isopropoxyphenol from propoxur, carbofuran phenol from carbofuran, and aldicarb sulfone, sulfoxide, and nitrile from aldicarb. These complex analyses, when available, can be useful in identifying the responsible agent and following the course of carbamate disposition.

Treatment

Caution: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair. Vinyl gloves provide no protection.

1. Airway protection. Ensure that a clear airway exists. Intubate the patient and aspirate the secretions with a large-bore suction device if necessary. Administer oxygen by mechanically assisted pulmonary ventilation if respiration is depressed. **Improve tissue oxygenation as much as possible before administering atropine, to minimize the risk of ventricular fibrillation.** In severe poisonings, it may be necessary to support pulmonary ventilation mechanically for several days.

2. Atropine. Administer atropine sulfate intravenously, or intramuscularly if intravenous injection is not possible. Remember that atropine can be administered through an endotracheal tube if initial IV access is difficult to obtain. Carbamates usually reverse with much smaller dosages of atropine than those required to reverse organophosphates.[6] (See dosage on next page.)

The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of acetylcholine at end-organs having muscarinic receptors. Atropine does not reactivate the cholinesterase enzyme or accelerate excretion or breakdown of carbamate. Recrudescence of poisoning may occur if tissue concentrations of toxicant remain high when the effect of atropine wears off. Atropine is effective against muscarinic manifestations, but is ineffective against nicotinic actions, specifically, muscle weakness and twitching, and respiratory depression.

Despite these limitations, atropine is often a life-saving agent in N-methyl carbamate poisonings. Favorable response to a test dose of atropine (1 mg in adults, 0.01 mg/kg in children under 12 years) given intravenously can help differentiate poisoning by anticholinesterase agents from other conditions such as cardiogenic pulmonary edema and hydrocarbon ingestion. However, lack of response to the test dose, indicating no atropinization (atropine refractoriness), is characteristic of moderately severe to severe poisoning and indicates a need for further atropine. If the test dose does not result in mydriasis and drying of secretions, the patient can be considered atropine refractory.

Dosage of Atropine:

In *moderately severe poisoning* (hypersecretion and other end-organ manifestations without central nervous system depression), the following dosage schedules have proven effective:

- *Adults and children over 12 years:* 2.0-4.0 mg, repeated every 15 minutes until pulmonary secretions are controlled, which may be accompanied by other signs of atropinization, including flushing, dry mouth, dilated pupils, and tachycardia (pulse of 140 per minute). **Warning:** In cases of ingestion of liquid concentrates of carbamate pesticides, hydrocarbon aspiration may complicate these poisonings. Pulmonary edema and poor oxygenation in these cases will not respond to atropine and should be treated as a case of acute respiratory distress syndrome.
- *Children under 12 years:* 0.05-0.1 mg/kg body weight, repeated every 15 minutes until pulmonary secretions are controlled, which may be accompanied by other signs of atropinization as above (heart rates vary depending on age of child with young toddlers having a rate approaching 200). There is a minimum dose of 0.1 mg in children.

Maintain atropinization by repeated doses based on recurrence of symptoms for 2-12 hours or longer depending on severity of poisoning. Crackles in the lung bases nearly always indicate inadequate atropinization and pulmonary improvement may not parallel other signs. Continuation or return of cholinergic signs indicates the need for more atropine.

Severely poisoned individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be needed. Reversal of muscarinic manifestations, rather than a specific dosage, is the object of atropine therapy. However, prolonged intensive intravenous administration of atropine sometimes required in organophosphate poisonings is rarely needed in treating carbamate poisoning.

Note: Persons not poisoned or only slightly poisoned by N-methyl carbamates may develop signs of atropine toxicity from such large doses. Fever, muscle fibrillations, and delirium are the main signs of atropine toxicity. If these signs appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily, while the severity of poisoning is reevaluated.

3. Skin decontamination. In patients with contaminated skin, clothing, hair, and/or eyes, **decontamination must proceed concurrently with whatever resuscitative and antidotal measures are needed to preserve life.** Flush the chemical from eyes with copious amounts of clean water. For asymptomatic individuals who are alert and physically able, a prompt shower and shampoo may be appropriate for thorough skin decontamination, provided the patient is carefully observed to insure against sudden appearance of poisoning. If there are any indications of weakness ataxia or other neurologic impairment, clothing should be removed and a complete bath and shampoo given while the victim is recumbent, using copious amounts of soap and water. Attendants should wear rubber gloves as vinyl provides no protection against skin absorption. Wash the chemical from skin folds and from under fingernails.

Contaminated clothing should be promptly removed, bagged, and laundered before returning. Contaminated leather shoes should be discarded. Note that the pesticide can contaminate the inside surfaces of gloves, boots, and headgear.

4. Gastrointestinal decontamination. If N-methyl carbamate has been ingested in a quantity probably sufficient to cause poisoning, consideration should be given to gastrointestinal decontamination as outlined in Chapter 2. If the patient has presented with a recent ingestion and is still asymptomatic, adsorption of poison with activated charcoal may be beneficial. In significant ingestions, diarrhea and/or vomiting are so constant that charcoal adsorption and catharsis are not indicated. Attention should be given to oxygen, airway management, and atropine.

5. Urine sample. Save a urine sample for metabolite analysis if there is need to identify the agent responsible for the poisoning.

6. Pralidoxime is probably of little value in N-methyl carbamate poisonings, because atropine alone is effective. Although not indicated in isolated carbamate poisoning, pralidoxime appears to be useful in cases of mixed carbamate/organophosphate poisonings, and cases of an unknown pesticide with muscarinic symptoms on presentation.[7,8] See Chapter 4, Treatment section, p. 41.

7. Observation. Observe patient closely for at least 24 hours to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes pulmonary edema) do not recur as atropinization is withdrawn. The observation period should be longer in the case of a mixed pesticide ingestion, because of the prolonged and delayed symptoms associated with organophosphate poisoning. As the dosage of atropine is reduced over time, check the lung bases frequently for crackles. Atropinization must be re-established promptly, if crackles are heard, or if there is a return of miosis, sweating, or other signs of poisoning.

8. Furosemide may be considered for relief of pulmonary edema if crackles persist in the lungs even after full atropinization. It should not be considered

until the maximum effect of atropine has been achieved. Consult package insert for dosage and administration.

9. Pulmonary ventilation. Particularly in poisonings by large doses of N-methyl carbamates, monitor pulmonary ventilation carefully, even after recovery from muscarinic symptomatology, to forestall respiratory failure.

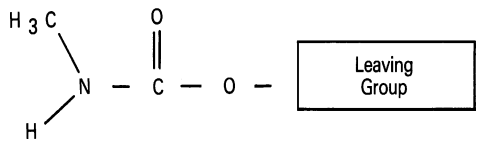
10. Cardiopulmonary monitoring. In severely poisoned patients, monitor cardiac status by continuous ECG recording.

11. Contraindications. The following drugs are probably contraindicated in nearly all N-methyl carbamate poisoning cases: morphine, succinlycholine, theophylline, phenothiazines, and reserpine. Adrenergic amines should be given only if there is a specific indication, such as marked hypotension.

12. Hydrocarbon aspiration may complicate poisonings that involve ingestion of liquid concentrates of some carbamates that are formulated in a petroleum product base. Pulmonary edema and poor oxygenation in these cases will not respond to atropine and should be treated as cases of acute respiratory distress syndrome.

13. Do not administer atropine prophylactically to workers exposed to N-methyl carbamate pesticides. Prophylactic dosage may mask early symptoms and signs of carbamate poisoning and thus allow the worker to continue exposure and possibly progress to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting: impaired heat loss due to reduced sweating and impaired ability to operate mechanical equipment due to blurred vision (mydriasis).

General Chemical Structure



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