

HIGHLIGHTS

Muscarinic, nicotinic, CNS effects

Absorbed by inhalation, ingestion, skin

Lipophilic

Poisonings tend to be of shorter duration than OPs

SIGNS & SYMPTOMS

Malaise, muscle weakness, dizziness, sweating

May include blurred vision, incoordination, muscle twitching, slurred speech

May include headache, salivation, nausea, vomiting, abdominal pain, diarrhea

Blood cholinesterase levels not reliable indication

Severe symptoms may include coma, seizures, hypotonicity, hypertension, cardio/respiratory depression

TREATMENT

Ensure clear airway

Administer atropine

Decontaminate concurrently

Consider pralidoxime in mixed poisonings

Consider GI decontamination

CONTRAINDICATED

Adrenergic amines without specific indication (e.g., hypotension)

CHAPTER 6

N-Methyl Carbamate Insecticides

Toxicology

The **N-methyl carbamate** esters cause reversible carbamylation of acetylcholinesterase (AChE) 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 difference between symptom-producing and lethal doses than exists in the case of most organophosphate compounds and (3) it frequently invalidates the measurement of blood cholinesterase activity as a diagnostic index of poisoning (see below).

Carbamates are absorbed by inhalation, ingestion and through the skin, although the last tends to be the less-toxic route. For example, carbofuran has a rat oral LD₅₀ of 5 mg/kg, compared to a rat dermal LD₅₀ of 120 mg/kg, which makes the oral route approximately 24 times more toxic when ingested.¹ The LD₅₀ is only one measure of pesticide toxicity. The dose must also be considered since a compound with a high LD₅₀ can produce life-threatening symptoms if a large enough dose is ingested. N-methyl carbamates are hydrolyzed enzymatically by the liver, and the 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 sensory and behavioral disturbances, incoordination, seizures and depressed motor function including lethargy and coma.^{2,3,4} The N-methyl carbamates are lipophilic and penetrate the central nervous system as evidenced by distribution throughout all tissues including the brain on post mortem.^{5,6} 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. Carbamate poisonings tend to be of shorter duration than organophosphate poisonings because of the reversibility of the AChE binding and the more rapid metabolism of carbamates.⁷ However, as mentioned in the next section of this chapter, blood cholinesterase levels may be misleading because of *in vitro* reactivation of a carbamylated enzyme.^{8,9} This falsely normal or near-normal level can make the diagnosis more difficult in the acute presentation in the absence of an exposure history.

Malaise, muscle weakness, dizziness and sweating are commonly reported early symptoms. Miosis with blurred vision, incoordination, muscle twitching and slurred speech are reported. Headache, salivation, nausea, vomiting, abdominal pain and diarrhea are often prominent. Transient hyperbilirubinemia may occur.¹⁰ Acute pancreatitis has also been reported in some of the cases of **aldicarb** and **methomyl** poisoning. Some cases of pancreatitis have required surgical drainage of a pancreatic pseudocyst.^{3,11,12,13}

The most severe manifestations of carbamate poisoning occur in the respiratory and central nervous (CNS) systems. CNS findings include coma, seizures and hypotonicity, and nicotinic effects including hypertension and cardiorespiratory depression. The respiratory depression also results from skeletal muscle impairment in which the chest wall cannot expand for adequate respiration. Dyspnea, bronchospasm and bronchorrhea with eventual pulmonary edema are other serious signs.^{3,14} Data indicate 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 develop the classic muscarinic signs, the absence of them does not exclude the possibility of carbamate poisoning in the presence of CNS depression.^{2,4,15,16}

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. 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*.

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 of N-methyl Carbamate Insecticide Toxicosis

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. 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, so as to minimize the risk of ventricular fibrillation. In severe poisonings, it may be necessary to support pulmonary ventilation mechanically for several days.
2. Administer atropine sulfate intravenously or intramuscularly if intravenous injection is not possible. Atropine can be administered in small volume doses through an endotracheal tube if initial IV access is difficult to obtain. Carba-

COMMERCIAL PRODUCTS

Highly Toxic¹

aldicarb (Temik)
aminocarb² (Matacil)
bendiocarb² (Ficam, Dycarb, Multamat, Niomil, Tattoo, Turcam)
carbofuran (Furadan)
cloethocarb² (Lance)
formetanate (Carzol)
isolan² (Primin)
methiocarb (Mesurol)
methomyl (Lannate, Nudrin)
oxamyl (Vydate L, DPX 1410)

Moderately Toxic¹

bufencarb² (Metalkamate, Bux)
carbaryl (Sevin, Dicarbam)
dimetan² (Dimethan)
dioxacarb² (Elecron, Famid)
isoprocarb² (Etrofolan, MIPC)
pirimicarb² (Pirimor, Abol, Aficida, Aphox, Fernos, Rapid)
promecarb² (Carbamult)
propoxur (Aprocarb, Baygon, various flea/tick products)
trimethacarb² (Landrin, Broot)

¹ "Highly toxic" N-methyl carbamates have listed oral LD₅₀ values (rat) less than or equal to 50 mg/kg body weight; "moderately toxic" agents have LD₅₀ values in excess of 50 mg/kg and less than 500 mg/kg.

² Products no longer registered in the United States.

mates may reverse with smaller dosages of atropine than those required to reverse organophosphates, though the required dosage is still considerably larger than that required to atropinize a non-poisoned patient.^{17,18} A common dosing pitfall is giving too little atropine initially to achieve timely atropinization. Severely poisoned individuals may exhibit remarkable tolerance to atropine and require large doses.¹⁴ (See dosage below.)

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 AChE or accelerate excretion or breakdown of carbamate. Multiple doses of atropine may be necessary, as recrudescence of poisoning can occur if tissue concentrations of toxicant remain high when the antidotal effect 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 lifesaving agent in N-methyl carbamate poisonings.

Reassess the clinical situation after an adequate loading dose has been given. If symptoms persist, but the history is consistent with carbamate poisoning, then continue atropine therapy. However, if the clinical picture is unclear, clinicians should reassess and consider alternative causes of poisoning, such as pyrethroid insecticide poisoning, which may present a similar clinical picture.

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

Dosage of Atropine

Adults and Children Over 12 Years

- **Initial Dose: 1-3 mg IV. Repeat in 3-5 minutes if no change in clinical symptoms. Dose may be doubled with each administration until the patient is atropinized. Once adequate atropinization has been achieved, the patient can be maintained on an atropine continuous infusion at about 10%-20% of the loading dose and titrated to effect.^{18,19,20,21} Clear breath sounds and absent pulmonary secretions are the primary end point. Other signs of atropinization including flushing, dry mouth and dilated pupils; tachycardia (pulse of 140 per minute) may occur. Early in therapy, monitor for improving blood pressure and heart rate (above 80 beats/minute), normal pupil size and drying of the skin and axillae.^{20,21} Autoinjectors containing 2.0 mg atropine for IM injection are also available.**

WARNING: *Poisonings in which liquid carbamate pesticide concentrates have been ingested may be complicated by hydrocarbon aspiration. 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.*

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Dosage of Atropine, continued

Children Under 12 Years

• **Initial Dose: 0.02 mg/kg body weight IV. As with adults, double the dose every 5 minutes until pulmonary secretions are controlled. Consider continuous infusion at 10%-20% of the required loading dose and titrate. Signs of atropinization, including: flushing, dry mouth, dilated pupils and heart rates vary depending on age of child, with young toddlers having a rate approaching 200. Crackles in the lung bases nearly always indicate inadequate atropinization, and pulmonary improvement may not parallel other signs. Continuation of, or return of, cholinergic signs indicate the need for more atropine.**

Reversal of muscarinic manifestations, rather than a specific dosage, is the object of atropine therapy.

NOTE: Persons not poisoned or only slightly poisoned by N-methyl carbamates may develop signs of atropine toxicity from large doses, such as fever, muscle fibrillations and delirium. If these signs appear and become the predominant clinical effects, atropine administration should be discontinued, at least temporarily, while the severity of poisoning is reevaluated.

3. Save a urine sample for metabolite analysis if there is need to identify the agent responsible for the poisoning.
4. Consider pralidoxime in cases of mixed carbamate/organophosphate poisoning and cases of an unknown pesticide with muscarinic symptoms on presentation (see **Chapter 5, Organophosphate Insecticides**, subsection *Treatment*, item 5, page 49.^{22,23} Pralidoxime has been used in some cases of carbamate poisoning, although other cases have resolved from supportive care alone.^{24,25} Pralidoxime is probably of little value in N-methyl carbamate poisonings and is not indicated in isolated carbamate poisonings. Atropine alone usually is effective.
5. Decontaminate concurrently with whatever resuscitative and antidotal measures are needed to preserve life. Contamination of the eyes should be removed by flushing with copious amounts of clean water. For asymptomatic individuals who are alert and physically able, skin decontamination should occur as previously outlined in **Chapter 3, General Principles**. Specifically, skin and hair should be washed with soap and water. Attending personnel must take precautions including rubber gloves to avoid contamination. Contaminated clothing should be promptly removed, bagged and laundered before returning, and items such as shoes, boots and headgear should be discarded.
6. Consider gastrointestinal decontamination if N-methyl carbamate has been ingested in a quantity sufficient to cause probable poisoning. If the patient has presented with a recent ingestion and still asymptomatic, adsorption of poison with activated charcoal may be beneficial. If the patient has already vomited or

is symptomatic, which is highly likely in significant poisonings, attention should be placed on oxygen, airway management and atropine. In significant ingestions, diarrhea and/or vomiting are so constant that charcoal adsorption and catharsis are not included.

7. Observe patient closely for at least 24-48 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 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 reestablished promptly if crackles are heard or if there is a return of miosis, sweating or other signs of poisoning.
8. Monitor pulmonary ventilation carefully, particularly in poisonings by large doses of N-methyl carbamates, even after recovery from muscarinic symptomatology, to forestall respiratory failure.
9. Monitor cardiac status in severely poisoned patients by continuous ECG recording.
10. Give adrenergic amines (n-morphine, succinylcholine, theophylline, phenothiazines and reserpine) only if there is a specific indication, such as marked hypotension. Otherwise, they are probably contraindicated in N-methyl carbamate poisoning cases.
11. Treat cases in which liquid concentrates of some carbamates formulated in a petroleum product base have been ingested as acute respiratory distress syndrome. Hydrocarbon aspiration may complicate these poisonings. Pulmonary edema and poor oxygenation in these cases will not respond to atropine.
12. 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 possible progression to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting, impairing heat loss (due to reduced sweating) and impairing the ability to operate mechanical equipment due to blurred vision caused by mydriasis.

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