

TOXALERT

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Overdoses of Muscle Relaxants

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Overdoses with muscle relaxants occur frequently. In 2005, a total of 23,512 exposures to muscle relaxants were reported by poison centers to the American Association of Poison Control Centers. The majority of these exposures were to carisoprodol and cyclobenzaprine. The goal of this publication is to review the toxicity of the various muscle relaxants and discuss the management of overdoses.

Carisoprodol (Soma®)

Carisoprodol is a centrally acting muscle relaxant that is hepatically metabolized to its active metabolite, meprobamate. Both of these compounds are indirect GABA_A receptor agonists that open neuronal chloride channels and induce hyperpolarization, similar to benzodiazepines. The usual adult dose is 350 mg four times daily. Toxicity usually manifests as CNS depression which may progress to stupor, coma, shock, and respiratory depression. Agitation and delirium may occur as well. The onset of effects is 30 minutes with a duration of 4 to 6 hours.

Patients who are prescribed carisoprodol may become dependent on its metabolite meprobamate. Symptoms of withdrawal include anxiety, insomnia, irritability, headache, and muscle pain. It is important to be aware of this phenomenon in patients who have been chronically taking carisoprodol and the drug is discontinued or withheld.

Carisoprodol is often formulated with aspirin +/- codeine. Patients overdosing on this type of preparation need to be monitored for salicylate and opiate toxicity as well.

All skeletal muscle relaxants will cause some degree of central nervous impairment in overdoses, with some notable differences.

The most frequently reported muscle relaxant overdoses involve carisoprodol and cyclobenzaprine.

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Cyclobenzaprine (Flexeril®)

Cyclobenzaprine is a tricyclic amine, which is structurally similar to the tricyclic antidepressants (TCAs). In fact, cyclobenzaprine exposure can result in a false positive urine toxicology screen for TCAs. Its skeletal muscle relaxant effect is thought to be mediated through inhibition of brain stem somatic neuron activity. The typical adult dose is 10 mg three times daily. Clinical effects seen in overdose are related to cyclobenzaprine's anticholinergic (specifically, antimuscarinic), antihistaminic, and sedative properties. Despite the similarities to TCAs, one 5-year review of 402 cyclobenzaprine exposures found the major toxicity to be anticholinergic effects with less neurologic and cardiovascular effects. Patients may present with CNS depression or agitation, delirium, and hallucinations. Tachycardia may be noted in addition to hypertension, hyperthermia, flushed skin, dry mucous membranes, dilated pupils, urinary retention, and decreased bowel sounds.

Baclofen (Lioresal®)

Baclofen is a structural analogue of gamma-aminobutyric acid (GABA). It binds to presynaptic GABA_B receptors in the brain and spinal cord and decreases neurotransmitter (e.g., catecholamines, glutamate, substance P) release from excitatory pathways. Baclofen also binds to postsynaptic GABA_B receptors and similarly results in inhibition. These actions block the excitatory effects of the sensory input from limb muscles. Baclofen is used orally and intrathecally to control muscle spasticity, restless leg syndrome, hiccups, and pain. The normal oral adult dose is 40 to 80 mg/day. Intrathecal doses of 300 to 800 mcg/day are used for spasticity of spinal cord origin, and can be administered continuously by a pump. Because approximately 85% of an oral dose is excreted unchanged in the urine, dose adjustments must be made in patients with renal dysfunction. Common clinical effects seen after an acute baclofen overdose include lethargy and confusion. In severe oral or intrathecal overdose, coma, seizures, respiratory depression, bradycardia, hypotension, and rarely conduction disturbances and dysrhythmias may develop.

Abrupt discontinuation of intrathecal baclofen can result in withdrawal symptoms such as hyperthermia, tachycardia, altered mental status (i.e., hallucinations, delirium), and muscle rigidity. In rare cases symptoms may progress to rhabdomyolysis, multiple organ-system failure, and death. Withdrawal can be prevented by reintroducing the patient to baclofen.

Baclofen is abused, mainly by adolescents. Hypothermia, bradycardia, mild hypertension, seizures, and respiratory and CNS depression have been described following recreational use.

Methocarbamol (Robaxin®)

Methocarbamol is similar to carisoprodol and meprobamate. It is hepatically metabolized. It is believed that methocarbamol acts at the interneurons of the spinal cord where it blocks multisynaptic reflexes. The usual adult dose is 6 to 8 g/day in divided doses. The onset of effects is about 30 minutes and can last up to 24 hours. Although overdose data are limited, CNS depression is the most likely manifestation. Drowsiness and dizziness are common at therapeutic doses.

Tizanidine (Zanaflex®)

Tizanidine is an imidazole derivative similar to clonidine, which acts through central alpha-2 receptor agonism. The usual adult dose is 4 to 8 mg three times daily. At therapeutic doses, tizanidine has minimal antihypertensive effects compared to clonidine and is much less potent. It undergoes extensive first-pass metabolism, which contributes to its 40% bioavailability. Following overdoses, patients

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may present with hypotension and bradycardia, along with coma and respiratory depression. Miosis, agitation, and hyposalivation are also possible.

Orphenadrine (Norflex™)

Orphenadrine is an analogue of diphenhydramine (Benadryl®). Its pharmacologic action is similar to cyclobenzaprine (i.e. inhibition of brain stem somatic neuron activity). The normal adult dose is 100 mg twice daily. Oral bioavailability is nearly 100%; however, absorption may be delayed due to the drug's anticholinergic effects on gastric motility. Peak plasma levels usually occur within 2 to 4 hours after ingestion. Orphenadrine produces marked anticholinergic effects in overdose including mydriasis, tachycardia, agitation, CNS depression, hallucinations, hyperthermia, dry mouth, decreased gastrointestinal motility, urinary retention, and dry, flushed skin. Cardiac dysrhythmias have also been reported with orphenadrine overdoses and may be due to its sodium channel blocking effects, similar to the class 1A antiarrhythmics.

Metaxalone (Skelaxin®)

Metaxalone most likely exerts its muscle relaxant effects through CNS depression, rather than directly affecting skeletal muscles. The typical adult dose is 800 mg three to four times daily. Onset of effects is usually within 1 hour with a duration of 4 to 6 hours. Little information is available regarding poisonings with metaxalone. Sedation and CNS depression are the primary expected effects.

Chlorzoxazone (Parafon Forte® DSC)

Chlorzoxazone inhibits reflex pathways in the spinal cord that produce and maintain muscle tone. The usual adult dose is 250 to 750 mg three or four times daily. Chlorzoxazone is 100% bioavailable orally with an onset of action within one hour. It is metabolized by cytochrome P450 2E1. Overdose data are limited, but CNS and respiratory depression requiring intubation have been reported.

Management Options

The treatment of all muscle relaxant poisonings should begin with administration of activated charcoal to limit absorption if the patient's mental status can tolerate it and the ingestion is recent. Intubation and mechanical ventilation secondary to respiratory depression may be required with some agents. Patients with persistent neurologic symptoms need to be admitted to the hospital. Muscle relaxant-induced seizures or anticholinergic agitation and delirium usually respond to benzodiazepines and barbiturates. EKG monitoring is recommended for orphenadrine. If the QRS interval is prolonged beyond 100 msec, sodium bicarbonate should be administered. IV fluids should be used for hypotension, and for refractory hypotension, vasopressors such as dopamine and/or norepinephrine can be added. Symptomatic bradycardia can be reversed with atropine. Naloxone has been used with relative success to reverse the neurologic effects of clonidine, thus it may be of use in tizanidine overdoses. Hemodialysis can be considered in cases of life-threatening overdoses of baclofen, but its use is rarely reported.

In conclusion...

Skeletal muscle relaxant overdoses are commonly encountered, with carisoprodol and cyclobenzaprine being the most frequently reported. All overdoses to muscle relaxants will present with some degree of CNS impairment, but there are some notable differences. Cyclobenzaprine and orphenadrine can produce profound anticholinergic effects, while tizanidine can cause hypotension and bradycardia and baclofen can cause seizures.

References for this article are available on request.

Snakebite Season

The Maryland Poison Center (MPC) has been consulted on several poisonous snakebites already this Spring. The snakebite season is just beginning so we expect to hear about more “victims” as the warmer weather approaches.

There are two venomous snakes in Maryland: the Northern Copperhead (*Agkistrodon contortrix mokasen*) and the Timber Rattlesnake (*Crotalus horridus horridus*). Both are North American crotalid snakes, also known as pit vipers. Pit vipers are capable of producing local tissue injury, systemic effects and coagulopathies.

Poisonous snakebite patients are not commonly encountered by EMS providers or at Maryland hospitals, so it is important to consult with the experts at the Maryland Poison Center. The MPC Specialist in Poison Information will guide the clinician on the assessment and treatment of snakebites, including the use of CroFab™, the antivenin indicated for North American pit viper envenomations.



Northern Copperhead



Timber Rattlesnake

TOXNOTES

A 30 year old just arrived at our ED 30 minutes after taking an overdose of multiple medications. She underwent gastric bypass surgery a few months ago. Should my patient be treated differently than other overdose patients?

Overdoses in patients who have undergone bariatric surgery need to be evaluated carefully, especially when considering gastrointestinal decontamination. Important patient information that aids in developing a treatment plan includes what type and when the bariatric surgery was performed, and how much food and liquid they regularly ingest. The residual stomach volume is small; as low as 20 mL soon after the surgery. The dose of activated charcoal must be adjusted to an amount that the patient can tolerate. In many cases, only 15 mL of activated charcoal every 30 minutes can be given. In addition, activated charcoal products containing sorbitol should not be given. Patients may develop “dumping syndrome” following the administration of sugars, resulting in nausea, vomiting, diarrhea and lightheadedness. Other gastrointestinal decontamination methods such as gastric lavage and whole bowel irrigation are contraindicated.

Maryland Poison Center 2006 Annual Report

The Maryland Poison Center received 63,662 calls in 2006! While 33,006 of these calls involved a human exposure, the remaining 30,656 were requests for information or animal poisonings. More than 1,200 poisonings were assessed and/or transported by EMS and 24% of all cases were treated in a health care facility. Look for more of our 2006 Annual Report on our website soon: www.mdpoison.com .

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MPC Hits the Road for Poison Prevention Week

Poison Prevention Week (PPW) is always a busy time at the Maryland Poison Center and PPW 2007 was no different. Governor Martin O'Malley proclaimed March 18-24, 2007 as National Poison Prevention Week in Maryland. Throughout the week, Angel Bivens, Public Education Coordinator, teamed up with AMERIGROUP and traveled around Baltimore County and Baltimore City on their Community Outreach Vehicle. Programs were provided for parents that emphasized the importance of storing medicines and cleaning products safely out of sight and reach of children. Parents were also educated about the services of the Maryland Poison Center. Children learned the importance of "Always Ask First" as a means to stay poison-safe.

The poison center mailed poison prevention materials to all of the pharmacies and emergency departments in Maryland. These mailings resulted in additional requests for educational materials throughout the state. The week concluded by choosing the winner of the annual PPW Poster Contest. This year, the MPC teamed up with Safe Kids Baltimore and received posters from Baltimore City elementary schools. The winning poster (below) will become the official poster of the Maryland Poison Center for the next year. This poster will also be submitted to the National Poison Prevention Week Poster Contest.

Please remember to provide a poison-safe message all-year-round, and not simply during the third week in March. For more information about educational materials, contact Angel Bivens at abivens@rx.umaryland.edu, 410-563-5584, or go to <http://www.mdpoison.com/education/public.html>.



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