2003
VOLUME 5
ISSUE 3

UtoxUpdate

UPCC A PUBLICATION OF THE UTAH POISON CONTROL CENTER FOR HEALTH PROFESSIONALS

Physostigmine for Anticholinergic Toxicity

Anticholinergic Toxicity

Anticholinergic drugs were involved in 5,650 exposures reported to the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) in 2001.[1] Life-threatening symptoms were present in 186 cases and eight resulted in a fatal outcome. However, this only includes pure anticholinergic drugs (hyoscyamine, dicyclomine, scopolamine, atropine, etc). Numerous prescription and over-the-counter medications have anticholinergic properties which are not their primary pharmacologic activity. Anticholinergic toxicity can occur with these medications as well as the pure anticholinergic drugs. Table 1 is a list of medications and plants that have anticholinergic properties.

Anticholinergic agents competitively inhibit acetylcholine by blocking the action of acetylcholine at muscarinic and central cholinergic receptors. Central cholinergic pathways are important for memory, wake-sleep cycle, alertness, orientation and fine motor movements. Nicotinic receptors at the skeletal muscle and ganglion are unaffected by anticholinergic agents.

Both central and peripheral anticholinergic effects may be seen following an overdose. The following mnemonic has been used to describe adverse and toxic effects associated with anticholinergic agents: "Mad as a hatter, red as a beet, dry as a bone, blind as a bat, and hot as a hare." A comprehensive list of anticholinergic adverse and toxic effects can be found in Table 2. The most common peripheral anticholinergic effects are mydriasis, dry mucous membranes, flushed skin, tachycardia, urinary retention and hypoactive bowel sounds. Common central effects include confusion, disorientation, ataxia and hallucinations.

Supportive care is the primary treatment for anticholinergic toxicity. Activated charcoal may be useful to prevent absorption if the ingestion was recent. Because anticholinergic drugs can decrease GI motility, activated charcoal may be of benefit more than one-hour post ingestion. Activated charcoal should not be used in patients with an ileus. Benzodiazepines can be used to treat delirium and agitation. Physostigmine can also be used to reverse anticholinergic toxicity.

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Physostigmine (Antilirium®)

Physostigmine, also known as eserine, is an alkaloid obtained from the dried ripe seed of Physostigma venenosum, a perennial plant found in West Africa. It was first used therapeutically in 1877 to treat glaucoma. In addition to being used as a treatment for anticholinergic poisoning, it has also been used as a non-specific treatment for coma and for tricyclic antidepressant poisoning.

Pharmacology

Physostigmine is a short-acting, reversible cholinesterase inhibitor that binds to acetylcholinesterase and prevents it from hydrolyzing acetylcholine. It increases concentrations of acetylcholine at both muscarinic and nicotinic receptor sites. Unlike other drugs that inhibit acetylcholinesterase, physostigmine has a tertiary ammonium structure that allows it to pass the blood-brain barrier and exert its effects centrally as well as peripherally. Physostigmine does not shorten the duration of action of anticholinergic agents, but temporarily reverses the effects.

Pharmacokinetics

Physostigmine is readily absorbed following intramuscular or subcutaneous injection and following ophthalmologic administration. Its onset of action following parenteral administration is usually within 3-8 minutes and the duration of action is 0.5-5 hours. The half-life of physostigmine is 15-40 minutes. Physostigmine is metabolized in the liver by plasma esterases. Only a small amount is excreted unchanged.

Dosing and administration

The dose of physostigmine to treat anticholinergic toxicity is 0.5 to 2 mg in an adult and 0.01-0.03 mg/kg in children. It can be administered intramuscularly, subcutaneously or intravenously. The usual route of administration is intravenously at a rate not to exceed 1 mg/minute. The dose can be repeated, as needed every 20 to 30 minutes. It is recommended to start with the lowest dose possible for older adults. Repeat administration of physostigmine may be necessary due to its short duration of action. Signs of relapse may occur as soon as 30 minutes or as long as three hours following physostigmine administration. Patients should be monitored closely for 4 hours after the last dose of physostigmine. A flow chart may be helpful to monitor the dose of physostigmine administered and any changes in pulse, temperature, bowel motility and urine output.

Physostigmine should be used cautiously in patients with asthma, peptic ulcer disease, colitis, chronic obstructive pulmonary disease, gangrene, cardiovascular disease, and

diabetes mellitus. Comatose patients should be intubated prior to receiving physostigmine to avoid possible aspiration of emesis. Patients with mechanical obstruction of the intestine or urogenital tract or any vagotonic state should not receive physostigmine.

Adverse effects

Adverse effects reported following administration of physostigmine include bradycardia, nausea, vomiting, diarrhea, and other signs of cholinergic excess. Seizures have also been reported and may be associated with rapid administration or high doses. Asystole has been reported when physostigmine has been used to treat tricyclic anticholinergic toxicity. In a recent study evaluating complications of diagnostic physostigmine administration in an emergency department no patient had an arrhythmia or signs of cholinergic excess.[2] One patient, who had 1-2 seizures prior to arrival at the emergency department, experienced another seizure approximately 12 minutes after the administration of physostigmine.

Atropine can be used to reverse the effects of excessive physostigmine. Atropine can cross the blood-brain barrier and add to the delirium of anticholinergic toxicity. It should be reserved for patients with central cholinergic symptoms. Glycopyrrolate (Robinul®) and methscopolamine bromide (Pamine®) are the drugs of choice for reversing physostigmine overdose because both agents are quaternary amines and are not able to cross the blood-brain barrier. Each 1 mg of physostigmine can be counteracted with either 0.4 mg of glycopyrrolate, 0.5 mg of methscopolamine bromide, or 0.5 mg of atropine sulfate.

Management of Anticholinergic Delirium

Benzodiazepines are often used as sedatives to manage the central toxic effects of anticholinergic agents. Large doses may be required to treat the anticholinergic delirium leading to oversedation, need for intensive care monitoring, respiratory support, and potentially an increased length of stay in the hospital.

Physostigmine has shown clinical success in reversing anticholinergic toxicity, but it has not been used routinely for the treatment of severe anticholinergic delirium. Some hesitation to use physostigmine has occurred due to the reports of seizures and arrhythmias. The majority of these problems occurred when physostigmine was used in the treatment of tricyclic antidepressants or non-specific coma. In 2001, physostigmine was used in the management of poisoning exposures reported to U. S. poison centers only 302 times.[1] Many treatment protocols consider physostigmine a last resort.

Several recent reports highlight the benefits of physostigmine in the treatment of anticholinergic agitation and delirium. In one case series, five patients who presented to an inner-city emergency department with anticholinergic agitation and delirium were successfully treated with physostigmine.[3] All five patients had used heroin that was mixed with scopolamine, thiamine, dextromethorphan and small amounts of cocaine. Physical restraints were required and benzodiazepines were not effective in calming the patients. Treatment with physostigmine resulted in decreased agitation within 15 to 20 minutes.

A recent retrospective study was conducted at a University teaching hospital with a medical toxicology service to compare the safety and efficacy of physostigmine and benzodiazepines for the treatment of anticholinergic agitation or delirium.[4] Medical records for 52 patients treated with physostigmine, benzodiazepines or both for anticholinergic toxicity were reviewed for the specifics of drug therapy and side effects of treatment. Physostigmine was used in 86%, benzodiazepines in 50% and 4% received additional sedating agents such as haloperidol to control agitation. Physostigmine controlled agitation in 96% and reversed delirium in 87%. Relapse occurred in 78% of patients who initially responded with a mean relapse time of 100 minutes. Multiple doses were given in 58% of patients. The mean number of doses of physostigmine was 2.5. The mean total dose of physostigmine given was 3.9 mg with a range of 0.5 to 13.5 mg. Benzodiazepines controlled agitation in 24% and did not reverse delirium in any patient. Initial treatment with physostigmine had a significantly lower incidence of complications and shorter time to recovery than those treated initially with benzodiazepines (Table 3).

Summary

Physostigmine is a short-acting drug that requires close patient monitoring and frequent dosing. It is an effective agent to reverse severe anticholinergic toxicity. Benzodiazepines may not control agitation and delirium associated with anticholinergic toxicity in all patients. Physostigmine, when used appropriately, may control agitation and delirium with minimal side effects. However, it should not be used to treat tricyclic antidepressant overdose or non-specific coma. It should be reserved for patients that present with moderate to severe anticholinergic effects with agitation and delirium. Atropine should be readily available to reverse cholinergic toxicity associated with physostigmine. Any treatment for anticholinergic toxicity should be based on symptoms and not only on history of ingestion.

Sophea Koy, PharmD Student

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3. Beaver KM and Gavin TJ. Treatment of acute anticholinergic poisoning with physostigmine. Am J Emerg Med. 1998 Sept; 16(5):505-507.
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The Utah Poison Control Center expresses its sincere thanks to

MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

for their generous contribution that allows us to produce and distribute this newsletter.

Table 1

Drugs and Chemicals That May Produce the Central Anticholinergic Syndrome			
Antidepressants	**Antipsychotic drugs**	**Antihistamines**	**Plants**
Amitriptyline	Chlorpromazine	Brompheniramine	Bittersweet
Amoxapine	Prochlorperazine	Chlorpheniramine	Black henbane
Clomipramine	Thiothixene	Cyclizine	Black night shade
Desipramine	Thioridazine	Dimenhydrinate	Deadly night shade
Doxepin		Diphenhydramine	Fly agaric
Imipramine	**Local Mydriatics**	Hydroxyzine	Jerusalem cherry
Nortriptyline	Atropine	Meclizine	Jimson weed
Protriptyline	Cyclopentolate	Orphenadrine	Lantana
	Homatropine	Promethazine	Loco seed or weed
Antispasmodics	Tropicamide	Cyproheptadine	Mandrake
Clidinium			Matrimony vine
Methantheline			Night blooming
Propantheline	**Others**	**Antiparkinsonian**	Jessamine
	Asthma-Dor	Benztropine	Panther
	Compoz		
	Ipratropium	Biperiden and lactate	Potato leaves
Belladonna Alkaloids	Excedrin-PM	Ethopropazine	Red sage
Atropine	Sleep-Eze	Procyclidine	Stinkweed
Scopolamine	Sominex	Trihexyphenidyl	Sprouts
Glycopyrrolate	Doxylamine		Tubers
	Amantadine		Wild sage

Table 2

Anticholinergic Clinical Presentation			
Central*		**Peripheral**	
Short-term memory loss	Psychomotor agitation	Dilated pupils unreactive to light	Dry, mucous membranes
Confusion	Delirium	Dry, flushed skin	Tachycardia
Ataxia	Seizures+	Hyperpyrexia	Urinary retention
Visual/auditory hallucinations	Extrapyramidal reactions	Rhabdomyolysis	Decreased bowel sounds
Disorientation	Psychosis	Hypertension	Hypotension (late finding)

*The degree of central toxicity depends on the drug's ability to cross the blood-brain barrier.
+may be related to other properties of drug as opposed to pure anticholinergic effect

Table 3[4]

Intergroup Comparisons After Physostigmine and Benzodiazepine Therapy			
Characteristics	**Physostigmine (n=30)**	**Benzodiazepine (n=22)**	**P value**
Incidence of agitation	1/28 (4%)	16/22 (73%)	*P<0.001*
Level of CNS stimulation	0.1	3	*P<0.001*
Incidence of complications	2 (6.7%)	3 (45.5%)	*P<0.002*
Recovery time (median)	12 hours	24 hours	*P=0.004*
Length of stay (median)	32 hours	39 hours	P=0.15
Side effects	7%	14%	P=0.6

Meet the UPCC Staff

John Johnson

John started working for the Utah Poison Control Center after graduating from The University of Utah with a bachelor's degree in Pharmacy in 1996. He left the Poison Center for a year and a half to try his luck in retail and long-term care pharmacy practice. He has now been back with the center for over a year. His favorite part of working at the Poison Center is the fact that he can say that he saves lives by being a poison specialist. He is the father of 3 boys and 1 girl, ages 4 to 12 years old, and recently adopted a cat. His hobbies include: golfing, skiing (water and snow), biking, camping and reading.

New Employees

The Utah Poison Control Center is pleased to welcome Scott Marshall, PharmD as a poison information specialist-pharmacist and Erlynn Wallace, RN as a poison information specialist. Scott graduated from the University of Utah in 2000 and now joins us from within the University of Utah Hospitals and Clinics network. Erlynn has been working for IHC in a variety of capacities for many years and is new to the University of Utah.

Employment Opportunities

The UPCC has one position available. The UPCC is looking for a Specialist in Poison Information to work days and evenings. You can find out more about this position on our website at http://uuhsc.utah.edu/poison/employment.

Utah Poison Control Center Staff

Please send comments and suggestions for future articles to the editor of UTOX Update at:
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*CSPI denotes Certified Specialist in Poison Information.

Education Update

Mrs. Alyson O'Steen appeared on Oprah on July 15th to tell the story of her young son's iron ingestion. Upon discovery of an empty bottle, Mrs. O'Steen of Salt Lake City, quickly called the Utah Poison Control Center and received instructions that saved her child's life. Both the Oprah show and Lifetime T.V. devoted a segment to the incident and highlighted the importance of the services of poison control centers.

Mercury Thermometer Exchange Program
The Mercury Thermometer Exchange Program conducted between June 9th and June 21st was a great success. The project was sponsored by Smith's Pharmacies, Household Hazardous Waste Division of the Salt Lake Valley Health Department, Department of Environmental Quality, and Utah Poison Control Center. The exchange program was held in every Smith's pharmacy across the state of Utah. Residents who took a mercury thermometer into the store received a coupon for a digital thermometer at half price. 2,116 mercury thermometers were collected in a two week period and were sent to Household Hazardous Waste for disposal.

Journal Donation Request!

The UPCC would like your help in completing our resource library. We are missing assorted issues between the years 1983 and 2000 of **THE AMERICAN JOURNAL OF EMERGENCY MEDICINE**. We are also in need of various issues between the years 1982 and 2002 of the **ANNALS OF EMERGENCY MEDICINE Journal**. Please contact Renate at 801-581-7504 to make arrangements for pickup or delivery.

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