Physostigmine is an effective antidote that can reverse the effects of anticholinergic poisoning. In the 1970's it was considered the first-line treatment for all anticholinergic overdoses, but subsequent reports of adverse effects greatly decreased its use. In 2007, physostigmine use was reported in only 209 poison exposures reported to US poison centers. (Bronstein)

Mechanism of Action
Anticholinergic substances competitively inhibit acetylcholine at muscarinic receptors in the central and peripheral nervous system. Physostigmine is a short-acting, reversible inhibitor of acetylcholinesterase, the enzyme responsible for breaking down acetylcholine. Inhibition of acetylcholinesterase increases acetylcholine at the synapse, overwhelming the inhibition of muscarinic receptors by anticholinergic agents.

Dosing
Physostigmine should be infused slowly (< 1 mg/min) because adverse effects may be related to rapid infusion. The recommended adult dose is 0.5 to 2 mg slow IV push. In children administer 0.02 mg/kg at less than 0.5 mg/min. Doses may be repeated after 10-20 minutes to a usual total dose of 4 mg in adults and 2 mg in children. Reversal of anticholinergic-induced agitation and delirium lasts from 30 to 120 minutes and repeat dosing may be needed.

Indications
Physostigmine is indicated for the management of severe anticholinergic syndrome. Clinical effects include agitated delirium, mydriasis, sinus tachycardia, dry skin and mucous membranes, diminished or absent bowel sounds, and hyperthermia. Physostigmine can also be used diagnostically to confirm that anticholinergic agents are the cause of agitation and delirium. (Manning)

Agitation may impede provision of care, as well as put the patient in danger of injuring herself. Parenteral benzodiazepines are frequently recommended for controlling agitation. (Burns) Antipsychotic agents with anticholinergic properties (e.g., haloperidol, olanzepine) should be avoided because they can increase anticholinergic effects. Judicious use of physostigmine may prevent administration of large doses of benzodiazepines that result in over sedation. Physostigmine can also be used diagnostically, to show that a toxic agent is the cause of mental status changes and avoid the need to do other expensive diagnostic tests such as CT of the head.

Contraindications
Physostigmine should not be used as an antidote for tricyclic antidepressants (TCA). It has been associated with seizures, worsening cardiac conduction disturbances and asystole in the setting of a TCA overdose. (Pentel) However, there is some debate concerning the role physostigmine played in the development of these adverse outcomes. (Suchard) In general, anticholinergic toxicity plays a minor role in the clinical presentation of a severe tricyclic antidepressant overdose. Physostigmine should be used with caution in patients with a prolonged QRS interval, even without a known TCA ingestion. Physostigmine should not be used with depolarizing paralytics such as succinylcholine because it can prolong the duration of neuromuscular blockade by inhibiting enzymatic breakdown by plasma cholinesterases. It is also contraindicated in patients with hypersensitivity to components of the IV preparation: benzyl alcohol and bisulfite. Relative contraindications to use of physostigmine include asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the gastrointestinal tract.

Mnemonic for Anticholinergic Symptoms
*Blind as a bat, dry as a bone, red as a beet, mad as a hatter, & hot as a hare*
WHAT YOU SHOULD KNOW ABOUT MERCURY AND CFLs

Mercury Light Bulbs
Compact florescent lights (CFLs) are being used by consumers more and more because they are more energy efficient, however, they contain mercury. Mercury is a heavy metal that can cause adverse health affects in humans. Mercury in CFLs is only released if the bulb is broken. To avoid breakage use care when removing bulbs from the package or when installing or replacing bulbs. Used CFLs should be recycled instead of tossed in the trash, because they can break after disposal causing mercury to leak into the environment. Check your local health department for locations in your community to dispose of used unbroken bulbs. It is important to safely cleanup any spill and properly dispose of CFLs if breakage occurs. If a bulb does break there are very specific steps to follow in order to protect against mercury poisoning.

Phosphostigmine Adverse Effects
If given in a dose in excess of what is required to counteract anticholinergic effects, phosphostigmine can cause cholinergic adverse effects. Bradycardia can result from increased parasympathetic depression of heart rate. Bronchorrhea and bronchospasm may result because of increased respiratory secretions due to muscarinic stimulation. Diarrhea, vomiting, and fecal or urinary incontinence can also occur due to stimulation of smooth muscle activity in the gastrointestinal tract. (Howland)

In 2003 Schneir and colleagues conducted a retrospective chart review to evaluate complications associated with use of phosphostigmine diagnostically in the ED. (Schneir) A total of 39 adult patients received phosphostigmine. In 35 patients a cause of altered mental status was determined, of which 19 were identified as purely anticholinergic, 10 not anticholinergic, 2 mixed anticholinergic and non-anticholinergic and 4 psychiatric in nature. One patient had a seizure after receiving phosphostigmine, but he also had one seizure before phosphostigmine was given. Another patient developed hypoxia after receiving 2 mg lorazepam followed by 2 mg phosphostigmine. During the next hour, the patient’s oxygen saturation decreased and he was treated with oxygen therapy with no long-term effects.

Phosphostigmine was also given to three patients who were later found to have TCAs present on urine drug screens. One of these patients had a prolonged QRS interval of 138 ms before phosphostigmine was given. There were no complications in these patients. In 33 patients heart rates were recorded after phosphostigmine administration and none were less than 60 bpm. None of the patients experienced dysrhythmia, bronchospasm, vomiting, diarrhea, or had to be administered atropine.

Burns and colleagues compared phosphostigmine and benzodiazepines in the treatment of anticholinergic poisoning. (Burns) The incidence of adverse effects was lower in patients treated with physostigmine (n=30) than for those treated with benzodiazepines (11% vs. 15%). There were no reports of seizures associated with physostigmine in this study. In a series of five cases of anticholinergic poisoning, physostigmine was used successfully to treat agitation and delirium. (Beaver) All patients presented to the same ED within two days of using a drug concoction composed of heroin, scopolamine, thiamine, dextromethorphan, and cocaine. After unsuccessful use of benzodiazepines, all patients were treated with physostigmine with a decrease in agitation within 15 to 20 minutes. One patient experienced fecal incontinence two hours after the last dose of physostigmine. There were no other signs or symptoms of physostigmine toxicity.

Use in Pediatrics
Phosphostigmine has not been well studied in children. In a three-year-old child who presented with agitation and hallucinations with no known ingestion, use of physostigmine calmed the patient within two minutes. (Shannon) The child admitted to ingesting liquid diphenhydramine, which avoided the need for further evaluation.

The Do’s & Don’ts of Mercury Clean-up:
DO open the windows and leave the room where the debris is for at least 15 minutes.
DO shut-off the central air system if you have one.
DO call the Utah Poison Control Center (UPCC) for help 1-800-222-1222.
DO clean up the mercury as instructed by the UPCC or the Environmental Protection Agency (EPA) www.epa.gov/mercury/spills/index.htm. Clean-up steps are different based on the type of surface the spill is on.
DON’T vacuum up the debris. This spreads the mercury and contaminates the vacuum.
DON’T use a broom to sweep up the debris.
DON’T put mercury down the drain. This contaminates the sewer.
DON’T put items that have come into direct contact with mercury into the washing machine. It can contaminate the machine and the sewer. Discard the clothing.
DON’T walk around if your shoes are contaminated with mercury. Clothing can also spread the toxin.

Note: These same procedures apply to other types of florescent lights as well as thermometers containing mercury.

References EPA and Utah DEQ

Check out our website for more poison prevention information at www.utahpoisoncontrol.org
Conclusion

Physostigmine can reverse the agitation and delirium associated with anticholinergic toxicity. Bradycardia and asystole has been associated with the use of physostigmine in patients with severe TCA overdose. However, the relationship between these factors and risk of adverse effects is not well understood. Physostigmine is not a benign antidote, however; it can be used safely in patients with anticholinergic toxicity. It can be especially useful in treating severe agitation resistant to benzodiazepines and as a diagnostic tool in select cases to avoid the need to perform expensive and invasive tests. Clinicians are welcome to consult the Utah Poison Control Center when considering the use of physostigmine for anticholinergic toxicity.

References


POISON PEARLS

CITALOPRAM TOXICITY

Andre Crouch, MD
Emergency Medicine Resident

Citalopram is a racemic compound with the highest selectivity for the 5-HT receptors amongst the selective serotonin reuptake inhibitors (SSRIs). When taken as prescribed it helps to regulate mood, personality, appetite, wakefulness, and sexual behavior. Like other SSRIs, overdose can cause nausea, drowsiness, tremor, diaphoresis, tachycardia, hypokalemia, serotoninergic syndrome, rhabdomyolysis, coma, seizures, and QTc prolongation. Citalopram, however, has a higher incidence of QTc prolongation and proconvulsant effect than other SSRIs. (Kelly)

Decontamination with single dose activated charcoal decreased the incidence of prolonged QT segments in a retrospective study of 254 citalopram overdose patients. (Isbister) If a patient develops severe effects consistent with serotonin syndrome (e.g., clonus, agitation, delirium, hyperreflexia, muscle rigidity, hypertension, hyperthermia) intubation with chemical paralysis and sedation along with administration of cyproheptadine, a serotonin receptor antagonist, should be considered.

References


TOXINS IN THE NEWS


1. Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
2. Ask patients about history of structural heart disease, arrhythmia, and syncope.
3. Obtain pretreatment ECG for all patients to measure the QTc interval and a follow-up ECG within 30 days and annually. Additional ECG is recommended if methadone dosage > 100 mg/d or if patients have unexplained syncope or seizures.
4. If the QTc interval is > 450 ms but < 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If QTc interval > 500 ms, consider discontinuing/reducing methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
5. Clinicians should be aware of interactions between methadone and other drugs that prolong the QT interval or slow the elimination of methadone.

For more information: http://www.annals.org/cgi/content/full/150/6/387
Thank you

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.

Toxicology Today

Meet the UPCC Staff

Poison Information Providers (PIPs)

Monique Hall remembers graduating from high school with dreams of being either a chemical engineer or a pharmacist - soon she'll be able to say she is both. In 2005, after a 15+ year career in engineering, Monique was accepted to the Doctor of Pharmacy program at the University of Utah. Since May 2006, she has worked at UPCC as a Pharmacy Intern, Poison Information Provider. Monique has been active in student leadership and community volunteer efforts at various health fairs and immunization clinics. She will graduate in 2010 with her Doctor of Pharmacy degree and plans to pursue residency opportunities while staying on at UPCC. Monique and her husband Christopher live in Sandy. They will celebrate their 10th wedding anniversary in September.

Ryan Farrington grew up in Sandy, UT. He graduated from BYU with a BA in Media Arts Studies (aka FILM) in 2003 and then went back to school for a pharmacy degree. He has really enjoyed his experiences at the University of Utah, College of Pharmacy and continues to have a great time learning here at the UPCC as a Poison Information Provider. When he’s not here or at school, he enjoys playing with his family, hiking, camping, watching movies, listening to music, and eating delicious foods and treats.

Megan Glanville is a student in her final year of the Doctor of Pharmacy program at the University of Utah. At school she is heavily involved with the Health Science Student Council working to increase the interactions of all health care students through social events and community service projects. The majority of her undergrad work was complete in North Carolina at a small community college. She has been married for 6 years and has 3 beautiful dogs- two Great Danes and a Yorkshire terrier. Megan has been with the Poison Control Center as a Poison Information Provider for 2 years and also works part-time at Intermountain Medical Center in the pharmacy department. She hopes to slow down a little after graduation, but it's pretty unlikely.