2002
VOLUME 4
ISSUE 4

UtoxUpdate

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

Serotonin Syndrome

Introduction

Serotonin syndrome was first described in 1959 in a patient with tuberculosis who received meperidine. His death was described as "fatal toxic encephalitis." The patient exhibited clonus, severe muscular hyperactivity, and rigidity. It was later discovered that patients on a monoamine oxidase inhibitor (MAOI) who took tryptophan developed an unsteady gait, clonus, tremor, incoordination, lightheadedness, paresthesias, CNS excitation, dilated pupils, and hyperactive reflexes.[1] In 1982, the term Serotonin Syndrome was used to describe the constellation of symptoms observed with administration of two or more medications that elevated serotonin concentrations.

Pharmacology and Physiology

Serotonin is formed in biologic systems from the amino acid L-tryptophan. Once formed, it is stored or rapidly inactivated by monoamine oxidase. Serotonin is one of three monoamine neurotransmitters most often associated with depression. Although serotonin is generally associated with clinical depression, there are over 10 known serotonin receptor subtypes found throughout the body in many organ systems other than the CNS. Over 90% of the serotonin in the body is found in enterochromaffin cells in the GI tract. It is also found in platelets. Serotonin is found in plant and animal tissues as well as in many venoms.[2] Vomiting, sleep, temperature regulation, appetite, mood, regulation of blood pressure, and the perception of pain are functions that involve brain serotonergic neurons. Serotonin may also be associated or involved in conditions such as migraine headaches and anxiety. While correct serotonin concentrations can greatly improve quality of life, too much serotonin can have deleterious effects manifested as Serotonin Syndrome.

Serotonin Syndrome results from an acute hyperserotonergic state. The patient does not develop serotonin syndrome by natural processes alone. Abnormally elevated concentrations of serotonin and clinical signs and symptoms of serotonin syndrome develop because of drug induced serotonin augmentation. Table 1 summarizes the most common cognitive-behavioral, neuromuscular and autonomic signs and symptoms associated with serotonin syndrome.[3] Ideally, the patient should have at least one or two manifestations from each category.

Table 1. Signs and symptoms associated with Serotonin Syndrome

Cognitive-Behavioral	Percent of total cases
confusion/disorientation	54%
agitation/irritability	35%
coma/unresponsive	28%
anxiety	16%
hypomania	15%
lethargy	15%
seizures	14%
insomnia	0%
hallucinations	6%
dizziness	6%
Neuromuscular	
myoclonus	57%
hyperreflexia	55%
muscle rigidity	49%
tremor	49%
ataxia/incoordination	38%
shivering/chills	25%
nystagmus	13%
Babinski's sign (bilateral)	14%
Autonomic Nervous System	
hyperthermia	46%
diaphoresis	46%
sinus tachycardia	41%
hypertension	33%
tachypnea	28%
dilated pupils	26%
non-reactive pupils	18%
flushed skin	14%
hypotension	14%
diarrhea	12%
abdominal cramps	5%
salivation	5%

Physiologic serotonin concentrations are altered by several mechanisms. The removal of serotonin from synapses is blocked by serotonin reuptake inhibitors or monoamine oxidase inhibitors (inhibits the metabolism of serotonin). Serotonin concentrations are increased by substances that release serotonin from the vesicles in the synapse or by serotonin agonists. Dopamine agonists may indirectly increase CNS serotonin activity. Table 2 provides a summary of drugs that may elicit serotonin syndrome.

Table 2. Drugs that increase serotonin.

Mechanism	Drug
Metabolic serotonin precursor	L-tryptophan
Inhibit serotonin metabolism	MAOIs
Increase serotonin release	amphetamines
	lithium
	MDMA (Ecstasy)
Inhibit serotonin reuptake	cocaine
	dextromethorphan
	merperidine
	SSRIs
	tricyclic antidepressants
	trazodone
	venlafaxine
serotonin receptor agonists	buspirone
	lysergic acid diethylamide(LSD)
dopamine agonists	l-dopa

Diagnosis

There is no laboratory test for the diagnosis of serotonin syndrome. The onset of clinical effects is relatively rapid and occurs within minutes to a few hours following a drug interaction that leads to an increase in serotonin concentration. Before a diagnosis of serotonin syndrome can be made, other toxidromes that may mimic serotonin syndrome must be excluded. Neuroleptic malignant syndrome (NMS) and stimulant toxicity share similar features to serotonin syndrome (Table 3). Once these diagnoses are excluded, patients that exhibit at least three clinical effects noted in Table 1 suggests the diagnosis of serotonin syndrome.

Meet the UPCC Staff

Francine Goitz

Francine joined the UPCC in February 1999. Prior to that, she worked in Neuro ICU at University of Utah Hospitals and Clinics. Francine received a bachelors degree in nursing from the University of Florida (Go Gators!) in 1991. Before coming to Utah, she worked as a travel nurse in various ICUs throughout the country. She came to Utah as a traveler and liked the snow and mountains so much that she decided to stay. Favorite Poisons: Recreational drugs and aspirin. Hobbies: mountain biking, skiing/snowboarding, cooking and hiking with her dog.

Table 3. Comparison of Serotonin Syndrome and NMS.

Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Mechanism	Serotonin excess	Dopamine antagonism
Onset of Symptoms	Minutes to hours	Days to weeks
Resolution of symptoms	Less than 24 hours	5-14 days
Neuromuscular	Myoclonus, hyperreflexia	"lead pipe" rigidity
Rhabdomyolysis	Rare	Common
Metabolic acidosis	Rare	Common
Elevated transaminases	Rare	Common

Treatment

Serotonin syndrome can be life threatening. The most important treatment is to discontinue the offending agent(s). The syndrome usually resolves within 24 hours after the withdrawal of the offending medication(s). If serotonin syndrome has occurred as a result of an acute overdose, activated charcoal may be beneficial soon after the ingestion. Supportive care is the mainstay of treatment. Hyperthermia should be treated with aggressive external cooling measures such as ice, mist, fans, and a cooling blanket. Rigidity, seizures, and agitation are treated with benzodiazepines. Severe symptoms have been successfully treated with cyproheptadine (a 5-HT2 antagonist) 4-8 mg PO every 1-4 hours (max 32mg/day) or 0.25mg/kg/day divided every 1-4 hours in children. It is available in 4-mg tablets and a syrup (2mg/5mL) . No parenteral product is available. Once the symptoms resolve there does not appear to be a need for continued medical monitoring.

Summary

Serotonin syndrome is a potentially life-threatening syndrome that usually occurs when more than one serotonergic medication has been ingested. Rapid onset of altered mental status, autonomic instability and myoclonus are hallmarks of the syndrome. Resolution of symptoms usually occurs within 24 hours after cessation of the offending agent(s) and the treatment is primarily supportive. The Utah Poison Control Center staff are available to assist you in evaluating the differential diagnosis of serotonin syndrome versus neuroleptic malignant syndrome or stimulant toxicity.

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References

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2 Burkhalter A, Julius DJ, Katzung BG. Histamine, Serotonin, & the Ergot Alkaloids. In: Katzung BG.Basic and Clinical Pharmacology,7th ed. Stamford, Connecticut. Appleton and Lange;1998:273-277.

3 Mills KC. Serotonin syndrome. A clinical update. Crit Care Clin 1997 Oct;13(4):763-83

POISON Help™
1-800-222-1222

Nationwide Toll-Free Number

The new national toll-free number is here! Calling this number anywhere in the US will connect you with the poison control center for that area. The UPCC hotline can be accessed by this number when calling from within the state. Our other number remains operational.

Update from the Utah Poison Control Center

Toxicology Clinic at University Hospital

Outpatient evaluations or follow-ups for patients with drug toxicity or poisoning, heavy metal, toxic gas or hazardous chemical exposures, and envenomations are available at University Hospitals and Clinics by physician referral. Referrals can be made by calling the Utah Poison Control Center at 800-222-1222 or 581-2151.

2002 Clinical Toxicology Meeting Highlights

The North American Congress of Clinical Toxicology (NACCT) met in Palm Springs on September 24-29, 2002. There were 234 abstract presentations that are published in J Toxicol Clin Toxicol 2002;40:599-698.

Droperidol (abstracts 4,167)

Data from 270 MedWatch reports between November 1997 and January 2002 was reviewed and found a total of 99 deaths associated with droperidol use. Only 3 deaths (5%) were associated with doses < 2.5 mg. Most of the deaths were from foreign cases (83%), often involving doses more that ten times that used in the US. (Mullins M, et al. Unexpected cardiovascular deaths with droperiol: A smoking gun or just smoke and mirrors? Pg 600-601) Only 19 cases (7%) had documented prolongation of the QT interval or torsades de pointes (Mieckowski A, Burns M. Droperidol and the black box. Pg 669-670).

Tramadol (abstract 24)

Over 600 cases of tramadol overdose reported to the California Poison Control System were reviewed. The most frequent clinical effects were CNS depression, nausea/vomiting, tachycardia and seizures. Naloxone was administered to 11 patients and seven "responded" with improved mental status. The smallest dose associated with seizures was 200 mg and 15% of seizures occurs more than 6 hours post-ingestion. (Marquardt K, et al. Retrospective Review of tramadol cases reported over 2.5 years. Pg 609)

Activated Charcoal (abstract 31)

A prospective study was conducted to 1) determine the incidence of vomiting after administration of activated charcoal to overdose patients and 2) assess the efficacy of using accupressure to prevent AC-induced emesis. The incidence of vomiting after AC (1 gm/kg) was 26% in the control group (n=81). The treatment group had accupressure bands placed at the Nei-Guan P6 point of both wrists prior to AC and vomiting occurred in only 14% (n=106). The rate of emesis was 46% lower in the accupressure group (p=0.04). (Eizember F, et al. Accupressure to prevent emesis due to activated charcoal. Pg 612)

Physostigmine (abstract 202)

All cases of physostigmine administration at a poison treatment center over a 28-month period were reviewed. Patient ages ranged from 2-86 years (n=255) and 66% involved single substance ingestions. One patient (0.5%) with co-ingestants of sertraline and valproic acid had a single seizure five minutes after physostigmine was administered. It was concluded that physostigmine was safe and rarely associated with adverse effects. (O'Donnell SJ, et al. Safety of physostigmine use for anticholinergic toxicity. Pg 684)

Drug Interactions-Elderly (abstract 6)

A case –control study of patients over 65 years old treated with digoxin, an ACE inhibitor, or glyburide and admitted for hypoglycemia (n-909), hyperkalemia (n=523), or digoxin toxicity (n=1051) were evaluated. Patients on glyburide given co-trimozaxole and patients on digoxin given clarithromycin in the preceding week had a tenfold risk of hypoglycemia and digoxin toxicity respectively. Patients receiving ACE inhibitors admitted for hyperkalemia were approximately twenty times more likely to have recently received a potassium sparing diuretic. Predictable and avoidable drug-drug interactions still commonly cause morbidity in the elderly. (Juurlink DN. Adverse events following drug interactions in the elderly. Pg. 601)

"Chasing the Dragon" (abstract 131)

An increasingly popular method among heroin abusers is to heat heroin on aluminum foil and inhale the vapor (pyrolysate) and thus avoid the use of needles. A 43-year-old woman developed bizarre behavior, choreoathetoid movements, restless legs and pseudobulbar speech after "chasing the dragon". She was diagnosed with heroin pyrolystae-induced leukoencephalopathy and treated with coenzyme Q. Similar cases have been reported in the literature and it may be fatal. (Long H, et al. Heroin-induced leukoencephalopathy due to chasing the dragon. Pg. 654)

Digital Epinephrine Injection (abstract 38)

Treatment recommendations for unintentional injection of digits by epinephrine auto-injectors vary widely. Supportive therapy (warmth and range of motion) was compared to more aggressive therapies of phentolamine, digital blocks, or vasodilators (nitroglycerine paste). Forty-four cases were evaluated, 37 received supportive care only and 7 received more aggressive care. No tissue necrosis occurred in either group. Only one patient (phentolamine treatment) had prolonged morbidity of pain for seven days. Most patients suffering intra digital injections of epinephrine appear to do well with supportive care only. (Von Derau K, Martin TG. Supportive treatment for intra digital epinephrine injections. Pg. 614-615.)

HOLIDAY SAFETY TIPS – REMIND YOUR PATIENTS!

Toxic Decorations:

- Mistletoe and holly berries may be poisonous if swallowed.
- Old tinsel may contain lead, discard if composition is unknown.
- Lamp oils are colorful and attractive to children and extremely toxic. Keep holiday lamps out of reach.

Coughs & Colds:

The onset of winter brings the cough and cold seasons. There may be more medicines in the home than at other times of the year.

Remember:
- Keep all medicines in a locked cupboard, out of reach of children.
- There is no such thing as childproof! Child-resistant lids delay access to medicines, but children can often open the lids.
- Always keep medicine in the original container. Don't transfer to a food container or plastic bag.

Holiday Visitors:

- Children are home from school, relatives are visiting and daily routines are disrupted. Greater parental supervision is necessary to prevent poisonings.
- Remind visitors to keep pills in a secure location, away from children.

Food, Drink & Parties:

- Improper handling, preparation, cooking or storage of food can result in food poisoning. Keep hot foods hot and cold foods cold!
- Clean up immediately after parties. Leftover alcohol or cigarette butts sitting on tables are toxic to children and pets.

For more information call the specialists at Utah Poison Control Center at 1-800-222-1222 or visit our new website at www.uuhsc.utah.edu/poison.

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*CSPI denotes Certified Specialist in Poison Information.

We need your feedback!

The UPCC would like your help in ensuring that we are meeting your education needs. A Needs Assessment Survey was developed by a group of University of Utah MBA Students and is now posted on our website at (http://uuhsc.utah.edu/poison). Follow the link for Health Professionals and select Needs Assessment Survey. We are interested in your feedback about Utox Update and would like to hear from you about other education needs you might have related to toxicology. Please take a moment and fill out the survey. You may return the survey by facsimile (801-581-4199) or by mail. We are close to having a version that you can submit electronically, so stay tuned for more details. Thank you in advance for your help in providing high quality clinical toxicology education to health professionals in Utah.

And speaking of feedback...

Thank you very much for the tremendous response to our customer satisfaction surveys. Surveys are sent to clinicians for each case that we have contact information. Some of you have probably received several of these surveys. We do appreciate your feedback related to each case. If you have not received a survey but would like to provide us with feedback on a particular case or in general, please contact Barbara Insley Crouch (barbara.crouch@hsc.utah.edu) or Martin Caravati (martin.caravati@hsc.utah.edu). Thank you again for your feedback!

The Utah Poison Control Center expresses its sincere thanks to

MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

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

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