



Toxicology Letter

SCHEDULED EVENTS:

Date and times for Grand Rounds
July 10, 2002 11AM
August 14, 2002, 11 AM
September 11, 2002, 11 AM

Toxicology Case Conference
CNYPCC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 1:30 PM – 2:30 PM

PROGRAM ANNOUNCEMENT:

Mark your calendars for the Sixth Annual Toxicology Teaching Day, to be held on October 30, 2002 at the University Sheraton. Please watch for our brochure to be sent in early September and save the date now !! (Please call 315-464-7078 with any questions)

CNYPCC TIDBITS:

Gastrointestinal Decontamination – Match the treatment with the reported ingestion

- | | |
|-------------------------------------|---|
| A. Syrup of Ipecac | 1. 10 times too much aminophylline intravenously |
| B. Orogastric lavage | 2. 100 Lithium carbonate 450 mg tablets (5 min ago at home) |
| C. Single dose activated charcoal | 3. 100 diltiazem 360 mg tablets |
| D. Multiple dose activated charcoal | 4. 100 digoxin 0.25mg tablets |
| E. Whole Bowel Irrigation | 5. 100 amitriptyline 50 mg tablets |

TOX TRIVIA: HISTORY

1. This was the common ingredient in many universal antidotes of antiquity?
2. Cocaine use dates back at least to:
a. 300 BC, b. 1870 AD, c. 1200 AD
3. What poison may have contributed to the fall of the Roman empire?

Case History

Contributed by: Deborah Drumm, Pharm.D. Candidate and Christine M. Stork, Pharm.D., DABAT

DISCONTINUATION REACTIONS ASSOCIATED WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS

Case:

A 54 year old female presents to the emergency department with new onset vertigo which caused her to fall several times in the past 24 hours. Her past medical history is significant for one episode of depression a year ago. She is maintained on no medications and has no significant social history. Upon questioning, the patient also describes difficulty sleeping and nausea in addition to vertigo for the past 48 hours. Physical examination including vital signs are non-contributory. A full medical work-up is performed with no significant findings noted. Upon further questions the patient reveals that she discontinued her antidepressant medications, paroxetine 10 mg daily and amitriptyline 25 mg at bedtime daily 3 days prior to presentation.

Can SSRIs or TCAs cause discontinuation reactions?

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are commonly prescribed medications used in a variety of disorders including depression and panic. Upon discontinuation of therapy, both are associated with withdrawal symptoms. Awareness and recognition of the signs and symptoms of withdrawal is important for proper patient management.

How can you identify which SSRIs or TCAs cause the greatest risk for drug discontinuation reactions?

SSRIs and TCAs vary in their ability to cause discontinuation syndromes. Increased risk of SSRI withdrawal occurs with those drugs having shorter duration of activity and higher potency (e.g. paroxetine, sertraline). In fact, paroxetine is reported to cause discontinuation reactions in as many as 1 out of every 3 patients. Also, patients withdrawn from shorter acting drugs typically exhibit more severe withdrawal symptoms than those that occur in drugs with longer durations of activity. (e.g. citalopram, fluoxetine)

The onset of SSRI withdrawal symptoms occur as soon as after the second missed dose. Commonly reported symptoms include; disequilibrium (dizziness, lightheadedness, vertigo, ataxia), nausea, lethargy and headache. These symptoms are usually mild to moderate and self-limiting, resolving within 1 to 3 weeks or more immediately upon reinstatement of the SSRI.

TCA discontinuation symptoms can persist for as long as 4 to 5 weeks. Rates of discontinuation symptom are reported to be 100% after imipramine, 80% after amitriptyline, and 33% after clomipramine discontinuation. As with SSRIs, the shorter the duration of drug effect,

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DISCONTINUATION REACTIONS...

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the more rapid and more severe the discontinuation symptoms. Common discontinuation symptoms associated with TCAs include lethargy, headache, tremor, insomnia, vivid dreams and nausea.

Why do SSRI and TCS discontinuation reactions occur?

Discontinuation reactions can occur for several reasons; noncompliance, changing from one SSRI or TCA to another, discontinuation of therapy deemed no longer medically necessary or by accidentally missing doses. In the case of discontinuation of therapy, tapering doses too quickly or not at all can lead to withdrawal symptoms. Gradual tapering over at least a four-week period when discontinuing a SSRI or TCA that has been administered for 8 weeks or more should decrease the incidence of discontinuation symptoms. Many experts recommend reducing the dose by 25% every 4 to 6 weeks. It is important to note that even with gradual tapering, symptoms can occur, especially when the drug has a short duration of activity, is a TCA or has been administered for a long period of time.

What causes SSRI and TCA discontinuation reactions?

The physiologic mechanism by which SSRIs and TCAs cause withdrawal symptoms is largely unknown, although most proposed mechanisms are related to drug pharmacokinetics and pharmacodynamics. SSRIs act to inhibit the reuptake of serotonin causing high levels of serotonin at autoreceptors and post-synaptic receptor sites. Long-term treatment with SSRIs and TCAs can lead to desensitization of these receptors. Upon discontinuation of the antidepressant there is a decreased level of available serotonin, which provides insufficient receptor agonist stimulus. Serotonin 5HT-1A receptors have been linked to motion sickness symptoms. A decreased level of serotonin at these receptors upon discontinuation is postulated to cause symptoms such as dizziness, lightheadedness, lethargy, nausea and ataxia. TCAs and to a lesser extent, paroxetine, also act to block muscarinic receptors. Upon their discontinuation, cholinergic rebound may occur, which explains symptoms such as sleep disturbances, akathisia, gastrointestinal symptoms, and anxiety. Direct or secondary effects on other neurotransmitters, such as serotonin-mediated inhibition of dopaminergic neurons, GABA, and norepinephrine may also be responsible for some of the discontinuation phenomenon.

How can SSRI and TCA discontinuation reactions be recognized?

Recognition of the key clinical features of these syndromes is important in order to prevent unnecessary medical interventions. Discontinuation reactions can be misdiagnosed as reoccurrence of depressive symptoms, ineffective or inadequate drug therapy, or adverse effects of the medication. It is important to recognize the symp-

toms and correlate their onset, severity, and duration. Discontinuation reactions are rare in patient treated for less than 5 weeks and symptoms are short in duration and are transient, lasting only a few days to a few weeks if left untreated.

How can discontinuation symptoms be prevented?

Patient education is extremely important in maintaining awareness of the consequences of noncompliance. Before discontinuing or tapering the dose of the medication, it is important to educate the patient on the symptoms which may develop.

How should SSRI and TCA discontinuation reactions be treated?

The best approach to treatment of the symptoms is to prevent them before they occur. Gradual tapering of the SSRI or TCA should be done over at least a 4-6 week period. The severity of symptoms should determine if treatment is necessary. Continued depression coupled with discontinuation symptoms should be treated by reinstatement of the antidepressant with a more gradual tapering schedule. Insomnia associated with discontinuation syndromes can be treated with short-term use of benzodiazepines or agents such as zolpidem (Ambien®) or xaleplone (Sonata®). Headaches and nausea can be symptomatically treated with pharmacological agents as well. Simple reassurance is also helpful in easing the concern of a worried patient.



CNYPCC Tidbits answers:

- A. 2
- B. 5
- C. 4
- D. 1
- E. 3

Tox Trivia answers:

- 1. Opium
- 2. a
- 3. Lead

SPI CORNER TOPIC: DRUG-INDUCED HYPERTHERMIA

Contributed by: Laurie Piwinski, R.N., SPI

Serotonin Syndrome

Serotonin syndrome typically occurs in susceptible individuals 1-2 hours after exposure to concomitant serotonergic drugs. Common interactions include SSRIs, MAOIs, TCAs, meperidine, lithium, dextromethorphan, atypical antidepressants with serotonergic properties, and some drugs of abuse such as LSD, MDMA, and Ecstasy. Symptoms include mental status changes, restlessness, muscular rigidity, myoclonus, hyperreflexia, diaphoresis, shivering, fever and tachycardia. Treatment includes aggressive supportive care, sedation and cooling 24-48 hours after discontinuation of the offending agent. In severe cases, neuromuscular blockage may be required. Serotonergic antagonists, such as cyproheptadine can be used but are not critical in reducing life-threatening hyperthermia.

Neuroleptic Malignant Syndrome (NMS)

NMS is characterized by fever, muscle rigidity, extrapyramidal effects, and mental status changes. It is the result of central dopamine blockade and is typically precipitated by medications including phenothiazines, butyrophenones, thioxanthenes and loxapine.

Treatment includes discontinuation of the causative drug, supportive care, cooling, and sedation. As with serotonin syndrome, paralysis may be indicated in severe cases, in which hyperthermia caused by muscular rigidity cannot be otherwise controlled.

Malignant Hyperthermia (MH)

MH is a genetic disease that involves muscle hypermetabolism triggered by exposure to certain anesthetic agents and succinylcholine. Symptoms include muscular rigidity, excess oxygen consumption and carbon dioxide production, continuous calcium reuptake leading to depletion of cellular ATP, and potentially life threatening hyperkalemia. Hyperthermia is one of the later findings.

Treatment consists of immediate discontinuation of the offending agent and giving dantrolene, which blocks the reuptake of calcium, reversing the muscular contractions. Good supportive care is essential. Follow up should always include referral to a malignant hyperthermia biopsy center for genetic counseling and definitive diagnosis.

FDA SAFETY SUMMARIES 4/02-6/02

Seroquel (quetiapine fumarate) - medication errors involving confusion with Serzone (nefazodone hydrochloride)

Procrit (epoetin alfa) - lot number P002641, P002384, P002970 found to contain active ingredient that is approximately 20 times lower in potency

Lioresal Intrathecal (baclofen injection) - cases of intrathecal baclofen withdrawal that can lead to life threatening sequelae

Serostim [somatropin (rDNA origin) for injection] - counterfeit lot of Serostim [somatropin (rDNA origin) for injection]. S810-1A1.

Combivir (lamivudine plus zidovudine) - bottles containing 60 tablets of Combivir (lamivudine plus zidovudine) that actually contained another medicine

PLAS+SD (Pooled Plasma, (Human) Solvent Detergent Treated) - contraindicates the use of PLAS+SD in patients undergoing liver transplant, patients with severe liver disease and known coagulopathies

Zyprexa (olanzapine) - product tampering of 10 and 15 mg bottles

Vioxx (rofecoxib) - strengthened the WARNINGS, PRECAUTIONS, and CLINICAL STUDIES sections of Vioxx to describe new cardiovascular & GI information

Heparin Sodium Injection, USP - voluntarily recalling ALL lots of Heparin Sodium Injection, due to the presence of clear crystals

Thiazolidinediones [Actos (pioglitazone HCl), Avandia (rosiglitazone maleate)] - more clearly describe the cardiovascular risks

Rapamune (sirolimus) - risk of hepatic artery thrombosis, graft loss, and death

Albuterol Sulfate - Solution for Inhalation (0.5%) recent hospital outbreaks of lower respiratory tract colonization and infection with Burkholderia cepacia attributed to contamination.

Milk Based Powdered Infant Formulas Used in Neonatal Intensive Care Units - Enterobacter sakazakii infections in neonates

Lovenox (enoxaparin sodium) - not recommended for thromboprophylaxis in patients with prosthetic heart valves.

Zerit (stavudine) - potential for lactic acidosis as a complication of therapy with Zerit (stavudine), d4T.

Kava-containing Dietary Supplements (Piper methysticum) - severe liver injury

Alpha Interferons - Intron A (Interferon alfa 2b, recombinant) Rebetron Combination Therapy (Rebetrol (Ribavirin, USP) Capsules and Intron A) Roferon-A (Interferon alfa-2a, recombinant) -

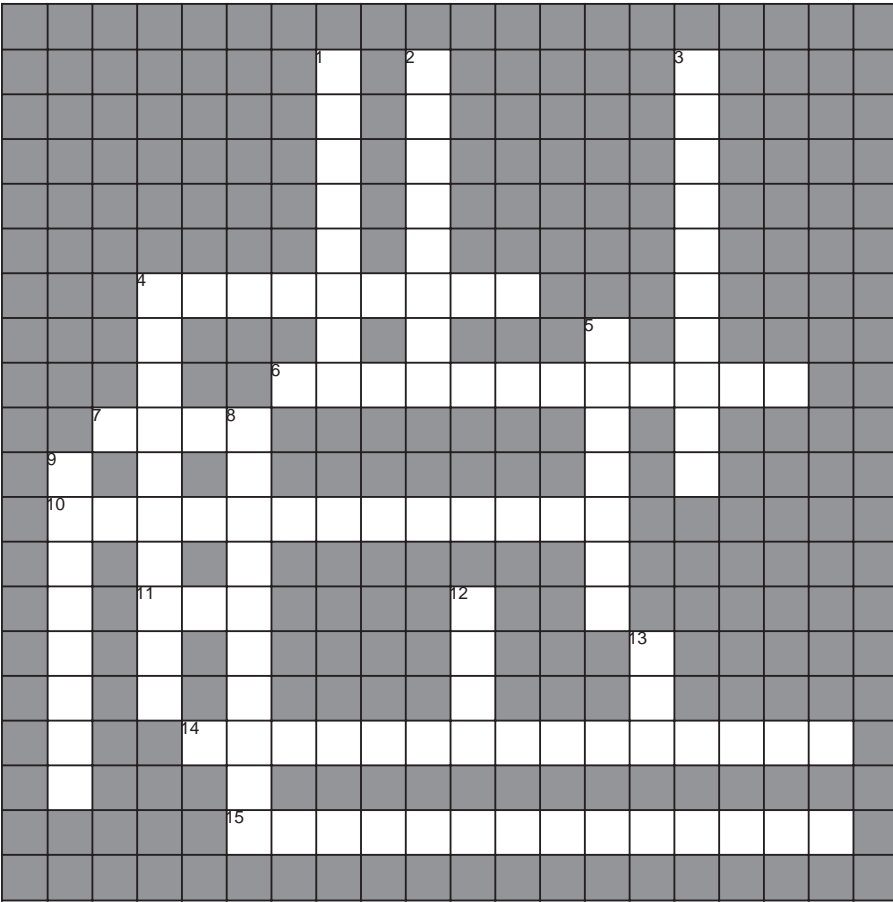
occurrence of neuropsychiatric, autoimmune, ischemic, and infectious disorders

Versed Syrup (midazolam HCl) CIV - potential presence of a crystalline precipitate

PC SPES, SPES (BotanicLab) - warned to stop using the dietary supplement / herbal products PC SPES and SPES capsules because they contain undeclared prescription drug ingredients

Serzone (nefazodone HCL) - Black Box Warning. Rare cases of liver failure

CROSSWORD PUZZLE



DOWN

1. SERIOUS SUNBURNS, ESPECIALLY IN CHILDHOOD CAN INCREASE THE CHANCES OF DEVELOPING THIS CANCER.
2. THIS TOXIN IS FOUND IN TOMATOES AND NIGHTSHADE BERRIES; HAS RELATIVELY LITTLE TOXICITY IN ADULTS, BUT FATAL INTOXICATIONS HAVE OCCURRED IN CHILDREN
3. THIS UNCOMMON FORM OF HEAT ILLNESS CONSTITUTES A TRUE MEDICAL EMERGENCY
4. THESE MUSHROOMS HAVE A LSD-LIKE EFFECT
5. THIS MUSHROOM ACCOUNTS FOR 95% OF MUSHROOM-RELATED FATALITIES.
8. MOST VENOMOUS FISH OF THE TEMPERATE ZONE FOUND ON THE BOTTOM IN SHALLOW WATER
9. CARRIER OF THE LYME DISEASE
12. ACUTE POISONING IN CHILDREN FROM USE OF THIS SPRAY MAY BE MISTAKEN FOR VIRAL INFECTION
13. THESE TYPE OF RAYS CAN BE HARMFUL TO THE SKIN

ACROSS

4. THIS PLANT;OFTEN REFERRED TO “LEAVES OF THREE LET THEM BE”, CAN CAUSE EDEMA, ERYTHEMA,BLISTERS AND IS OFTEN SPREAD WITH SCRATCHING OF CONTAMINATED AREAS
6. SOME CONSIDER THIS PLANT THE MOST VIOLENTLY POISONOUS OF THE NORTH TEMPERATURE ZONE.
7. THIS STICK WHICH IS OFTEN SOLD AT COUNTY FAIRS MAY CAUSE ORAL IRRITATION WHEN BITTEN INTO
10. MAY GET THIS ORGANISM FROM EATING UNDERCOOKED HAMBURGER FROM THE GRILL
11. MORE DEATHS IN THE U.S. ANNUALLY FROM THIS INSECT STING THAN FROM SNAKE BITES
14. THESE DAINTY, FRAGRANT, BELL-LIKE, WHITE FLOWERS HAVE DIGITALIS-LIKE SXS
15. THIS ILLNESS OFTEN OCCURRING IN ATHLETES IN WARM TEMPERATURES IS CHARACTERIZED BY WEKNESS, H/A, N/V, DIARRHEA, AND MUSCLE CRAMPS

ANSWERS
 DOWN 1. melanoma, 2. solanine, 3. heatstroke, 4. psilocybin, 5. amanita, 8. weeverfish, 9. deer tick, 12. DEET, 13. UVA
 ACROSS 4. poison ivy, 6. water hemlock, 7. glow, 10. escherichia coli, 11. bee, 14. lily of the valley, 15. heat exhaustion