SSRI Toxicity

SSRIs – treatment for depression
-high toxic to therapeutic ratio

Serotonin is a neurotransmitter synthesized from the amino acid L-tryptophan and is stored in neuronal vesicles or metabolized by monamine oxidase (MAO) to 5-hydroxyindoleacetic acid.

Serotonin binds one of seven postsynaptic 5-hydroxytryptophan (5-HT) receptors. A variety of mechanisms exist that can potentially increase the quantity or activity of serotonin. These mechanisms and corresponding agents include the following:

- Increasing production of serotonin by providing increased amount of precursors - L-tryptophan–containing substances
- Prevention of metabolism of stored serotonin - MAOIs
- Increased release of stored serotonin - Amphetamine, cocaine, MDMA (ecstasy)
- Prevention of reuptake of serotonin released into the synapse - SSRIs, TCAs, MDMA, St. John's Wort
- Direct stimulation of serotonin receptors - Buspirone, lysergic acid diethylamide (LSD)
- Unknown mechanism - Lithium

Pharmacokinetics

All SSRIs are metabolized by cytochrome P450 microsomal enzymes. SSRIs undergo extensive metabolism. They possess a large volume of distribution and circulate highly bound to plasma proteins. Peak plasma levels are reached in about 5 hours. Half-lives are variable depending upon the specific drug but tend to be prolonged. For example, fluoxetine and its active metabolite, norfluoxetine, have half-lives that average 19 days

Because the enteric nervous system is richly innervated by serotonin, acute toxicity is frequently manifested by altered gastrointestinal motility and nausea. The most serious drug-related adverse effect of SSRI is the potential to produce SS.

SS typically develops within hours or days of the addition of a new serotonergic agent to a medication regimen that already includes serotonin-enhancing drugs. SS may also develop when a new serotonergic agent is started following the recent discontinuation of another serotonergic drug without allowing an adequate washout period. Isolated overdoses of SSRIs can also cause the syndrome.

Serotonin Syndrome

Symptoms attributed to serotonin excess may include the following:Restlessness, hallucinations, shivering, sweating, nausea, diarrhoea, headache.

Signs of serotonin excess are variable and can be subdivided into the following 3 categories:

- Mental status changes - Confusion, agitation, coma. In 40%
- Neuromuscular findings - Myoclonus, rigidity, tremors, hyperreflexia (tends to be more prominent in the lower than the upper extremities), clonus, ataxia, teeth grinding. In 50%
- Autonomic instability - Hyperthermia (excessive heat generation may develop secondary to prolonged seizure activity, rigidity, or muscular hyperactivity), mydriasis, tachycardia, blood pressure alterations (hypertension, hypotension) and flushing. In 50%

- In 1991, following an extensive review of the literature, Sternbach defined the following criteria for the diagnosis of SS:
  - Symptoms must coincide with the initiation or increase in dose of a known serotonergic agent.
  - At least 3 of the following symptoms and signs should be present: altered mental status, agitation, tremor, shivering, diarrhoea, hyperreflexia, myoclonus, ataxia, or hyperthermia.
  - Other aetiologies (infections, metabolic disturbances, substance abuse, withdrawal) must be excluded.
  - A neuroleptic agent should not have been initiated or increased in dose prior to the onset of the symptoms and signs.
- Symptoms may also be attributed to toxicity from drug interactions.
  - SS can ensue after the addition of a second serotonergic drug to an existing drug regimen or with administration of a serotonergic drug before allowing an inadequate washout period after discontinuation of a serotonergic drug.
  - Overdosage of SSRIs can lead to inhibition of the cytochrome P450 enzyme system. If an SSRI overdose occurs in a patient on medication that relies on that system for its metabolism, toxicity from the concomitant medicine may occur. Examples include warfarin, digitalis, and carbamazepine.
- SS produces a clinical picture that is very similar to neuroleptic malignant syndrome (NMS). Both syndromes are associated with autonomic dysfunction, alteration of mental status, rigidity, and hyperthermia. Clinical differentiation between these syndromes is very important because management may differ. For example, chlorpromazine may be of some benefit in SS, whereas it may cause further deterioration in NMS. Distinctions between the two syndromes include the following:
  - NMS develops in association with neuroleptics, whereas SS develops in association with serotonergic agents.
  - NMS has a slow onset (days to weeks) and a slow progression of 24-72 hours, whereas SS has a more rapid onset and progression.

- NMS is associated with bradykinesia and lead pipe rigidity, whereas SS is associated with hyperkinesia and less rigidity.
- NMS is an idiosyncratic reaction to therapeutic doses, whereas SS is a manifestation of toxicity, frequently generated from the combination of two drugs with serotonergic activity.

Management

- Rapid bedside glucose determination
- Serum pH
- Electrolytes, including calcium, magnesium, and phosphorus: Check for anion gap acidosis that may be present in co-ingestions.
- Serum salicylate and paracetamol levels
- Creatine kinase (CK)
- Urinalysis and urine toxicological screen. Myoglobin
- Urine pregnancy test when indicated
- Electrocardiography is helpful to screen for any arrhythmia or conduction disturbances (ie, prolongation of the QRS or QTc interval) that may be due to co-ingestions.
- Pay careful attention to the airway, breathing, circulatory, and neurological parameters. Anticipate airway compromise due to deterioration of mental status, autonomic instability, and neuromuscular dysfunction. Secure the airway if gastric lavage and/or charcoal administration are to be performed in the setting of a decreasing level of consciousness.
- Gastric lavage is generally not indicated but may be performed within 60 minutes of suspected ingestion provided the airway is secure.
- Gastrointestinal decontamination with activated charcoal should be performed with careful attention to the possibility of impending airway compromise.
- Two large-bore intravenous catheters should be placed in anticipation of volume and medication administration. Central venous access is necessary in the patient with progressive cardiovascular dysfunction. Hydration is of utmost importance because of the risks of rhabdomyolysis and possible dehydration from increased insensible water losses due to hyperthermia.
    - Rhabdomyolysis should be dealt with quickly, with emphasis on maintaining a high urine output combined with alkalinization using sodium bicarbonate with a target urine pH of 6.
    - Aggressive cooling may be achieved by removal of clothing, fanning, cooling blankets, spraying with cool water, and IV fluids.
    - Mechanical ventilation with proper sedation and paralysis with a nondepolarizing muscle relaxant may be necessary in the setting of life-threatening hyperthermia or rhabdomyolysis.

    - Continuous monitoring of urine output is indicated if the patient requires vigorous fluid resuscitation, especially in the presence of rhabdomyolysis.
- Seizures and muscular rigidity are managed best by the use of a benzodiazepine, such as clonazepam if myoclonic jerks (0.5 mg PO tds) or lorazepam.
- Consider dantrolene 1mg/Kg IV over 10 minutes repeated every 10 minutes up to 10 mg/Kg.
- Most cases resolve within 24-36 hours with supportive care; however, serotonin receptor antagonists may be considered in selected cases (eg, cyproheptadine, chlorpromazine, methysergide, propranolol).
- Antihypertensives often are unnecessary unless the hypertension is persistent and clinically significant. If needed, the agent should have a short half-life.
- Arterial catheter placement is necessary in the patient with progressive cardiovascular dysfunction. An arterial catheter provides continuous arterial pressure monitoring and waveform analysis.
- Both hemodialysis and hemoperfusion generally are ineffective in enhancing elimination because of the large volume of distribution of SSRIs and should not routinely be employed

Prognosis:

- Most cases resolve without sequelae within 24-36 hours with adequate supportive measures.
- The patient who remains asymptomatic for several hours following an SSRI overdose is unlikely to need further medical evaluation and treatment.