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Serotonin Syndrome: Pediatric and Neonatal Considerations

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Toxicity resulting from excessive serotonin activity, referred to as serotonin syndrome, was first described by Oates and Sjoerdsma in 1960. Since that time, over 100 cases have been reported.¹ Over the past decade, the diagnosis of serotonin syndrome has become more frequent, as the use of drugs which raise serum serotonin concentrations has increased.^{1,2} The syndrome may result from normal therapeutic use of drugs which increase serotonin concentrations, but is more commonly associated with drug overdose or interactions between two drug therapies. This issue of *Pediatric Pharmacotherapy* will provide a brief review of serotonin syndrome, as well as some examples from the pediatric literature.

Mechanism

Serotonin (5-hydroxytryptamine or 5-HT) is produced in presynaptic neurons from L-tryptophan. The concentration of serotonin available at postsynaptic receptors is regulated through feedback loops which govern reuptake and metabolism. Serotonin receptors are divided into seven types, 5-HT₁ through 5-HT₇, each of which contains several subtypes. Serotonergic receptors are found throughout the central nervous system where they are involved in regulation of the sleep-wake cycle, behavior, appetite, temperature, and muscle tone. In the periphery, serotonin neurotransmission is involved with the regulation of gastrointestinal motility and vascular tone.¹⁻³

Serotonin syndrome results from excessive stimulation or agonism at postsynaptic serotonin receptors. While the specific receptor subtypes associated with serotonin syndrome have not been determined, it has been suggested that excessive serotonin binding at 5-HT_{2A} receptors may be the predominant cause of symptoms.¹⁻³

Clinical Presentation

Serotonin syndrome is characterized by a wide range of clinical symptoms related to the triad of autonomic hyperactivity, neuromuscular hyperactivity, and altered mental status.¹⁻³ Onset

is typically rapid. In a recent review of 41 cases documented since 1995, 61.5% of patients presented within 6 hours of drug initiation, dosage change, or overdose.¹

Mild cases may present with mydriasis, diaphoresis, tachycardia, shivering, clonus, hyperreflexia, and tremor. A fever may or may not be present. Clonus, hyperreflexia, and tremor are typically more prominent in the lower extremities. Moderate cases may present with the symptoms previously described, as well as hypertension, hyperthermia (a core temperature up to 40° C), horizontal ocular clonus, nausea, vomiting, hyperactive bowel sounds, and diarrhea. Patients often have changes in mental status, including agitation, hypervigilance, and pressured speech.¹⁻³

Severe cases may present with profound hypertension and tachycardia, and proceed rapidly to shock. Patients may exhibit severe agitation or delirium, seizures, muscular rigidity, and hypertonicity. Core temperatures may exceed 40° C, and may be accompanied by metabolic acidosis, rhabdomyolysis, elevated aminotransferases and creatinine, renal failure, and disseminated intravascular coagulation.¹⁻³

At this time, serotonin syndrome remains a clinical diagnosis. There are no confirmatory laboratory tests. A careful medication history, as well as the exclusion of other potential causes, such as anticholinergic poisoning, malignant hyperthermia, and neuroleptic malignant syndrome, is necessary to establish the diagnosis.¹⁻⁶ The diagnostic criteria suggested by Sternbach may be useful in establishing the diagnosis:

1. The patient has had recent exposure to or a change in a serotonergic agent.
2. At least three symptoms consistent with serotonergic excess are present.
3. Other causes have been ruled out.⁷

A wide array of drugs (Table 1) can increase serum serotonin concentrations, through both direct and indirect mechanisms, such as inhibition of metabolism through monoamine oxidase or cytochrome P450 (CYP) 3A4.¹⁻⁶

Table 1. Drugs Associated with Serotonin Syndrome

Drugs that increase serotonin synthesis

L-tryptophan

Dopamine/serotonin receptor agonists

Buspirone

Lithium

Sumatriptan

Dopamine agonists

Amantadine

Bromocriptine

Bupropion

Levodopa

Increase serotonin release

Amphetamines

Lithium

Reserpine

Drugs that decrease serotonin metabolism

Monoamine oxidase (MAO) inhibitors

Clorgiline

Isocarboxazid

Linezolid

Moclobemide

Phenelzine

Selegiline

Tranlycypromine

Inhibition of CYP3A4

Ritonavir

Inhibit serotonin reuptake

Tricyclic antidepressants

Amitriptyline

Clomipramine*

Desipramine

Doxepin

Duloxetine

Imipramine*

Nortriptyline

Protriptyline

Trazodone

*Selective serotonin reuptake inhibitors (SSRI)**

Citalopram

Escitalopram

Fluvoxamine

Fluoxetine

Paroxetine

Sertraline

Other antidepressants

Nefazodone

St. John's wort

Venlafaxine*

Opioids/opiates

Dextromethorphan*

Fentanyl

Meperidine*

Methadone

Pentazocine

Tramadol*

Others

Brompheniramine

Chlorpheniramine

Sibutramine

* definite association between drug and development of serotonin syndrome as demonstrated by case reports

The potential for serotonin syndrome is increased when a new drug from the list is introduced, the dose is increased (intentionally or inadvertently), or an interacting or potentiating drug is added. In a review of 469 patients admitted after SSRI overdose, 14% developed serotonin syndrome.⁸

Drug interactions are another frequent underlying source of serotonin excess. A retrospective study of patients receiving meperidine in an emergency department over a 2 month period revealed that 26 out of 262 patients (10%) were taking one or more serotonergic drugs at the time, placing them at risk for serotonin syndrome.⁴ The majority were receiving antidepressants. While no patients experienced serotonin syndrome in the period evaluated, the authors highlighted the importance of a careful medication history and questioned the routine use of meperidine in the emergency setting.

Management

Management of patients with serotonin syndrome is primarily supportive. Muscular rigidity is often treated with benzodiazepines, although severe cases may require mechanical ventilation and neuromuscular paralysis to control hyperthermia and excessive clonus. Nondepolarizing neuromuscular blocking agents are recommended. Depolarizing neuromuscular blockers, such as succinylcholine, may increase the risk of arrhythmia from the hyperkalemia associated with rhabdomyolysis. Antipyretics are not useful in the management of hyperthermia associated with serotonin syndrome.¹⁻⁵

Removal of the causative agent is generally recommended, unless the case is mild and further treatment outweighs potential risks. Administration of a 5-HT_{2A} antagonist, such as cyproheptadine, is often recommended for moderate to severe cases.¹⁻⁴ In their 2005

review, Mason and colleagues found that 22% of serotonin syndrome cases reported since 1995 were treated with cyproheptadine.² An initial dose of 12 mg (given orally or through a nasogastric tube) has been recommended for adults, followed by additional doses of 2 mg at 2 hour intervals until symptom resolution. This may be followed by a maintenance dose of 4 to 8 mg every 6 hours until the potential cause is believed to have been eliminated. The dosing of cyproheptadine in children is less well established, but a dose of 0.25 mg/kg/day up to a maximum of 12 mg/day has been successful in reversing symptoms.^{5,9}

In addition, antipsychotic agents with 5-HT_{2a} antagonist activity, such as chlorpromazine, may be used. In adults, doses of 50 to 100 mg may be given intramuscularly every 6 to 8 hours as needed. More recently, olanzapine, an atypical antipsychotic, has been used in this setting. In most cases, symptoms resolve within 24 hours after initiation of supportive care. Patients receiving serotonergic drugs with longer half-lives or active metabolites may exhibit symptoms for a longer period of time.¹⁻³

Pediatric Case Examples

Several pediatric cases of serotonin syndrome have been reported in the medical literature. The majority have involved the use of SSRIs. In 1994, Kaminski and colleagues reported serotonin syndrome after an accidental sertraline overdose by a 9 year old boy.¹⁰ Upon arrival to the Emergency Department, he exhibited tachycardia, hypertension, hyperthermia, hallucinations, and tremors. Symptoms persisted upon transfer to the intensive care unit, with a heart rate over 200 beats/min and a temperature of 42.2° C rectally. He was given activated charcoal and treated with physostigmine, lorazepam, acetaminophen, and chloral hydrate. The serum sertraline concentration approximately 9 hours after ingestion was 68 ng/mL (in adults, normal therapeutic doses of 50 to 100 mg/day produce maximum concentrations of 30 to 55 ng/mL). The patient's symptoms progressed, and he eventually developed rhabdomyolysis with elevated renal and liver transaminases. With continued supportive care, he returned to baseline status within 4 days, and was discharged with a mild tremor.

Pao and Tipnis reported a similar case of sertraline-induced serotonin syndrome in a 5 year old girl in 1997.¹¹ The patient ingested at least eight 50 mg tablets. Shortly after ingestion, she complained of feeling "jittery" and having a fast heartbeat. On admission to the hospital, she was afebrile, diaphoretic, tachycardic, hypertensive,

and tachypneic. Her pupils were dilated. Symptoms began to resolve over the next day, and she was discharged after 48 hours. The next day, however, she began to experience increased irritability, agitation, and tachycardia, and she was readmitted. A serum sertraline concentration obtained at that time (72 hours after ingestion) was 99 ng/mL. She was discharged 7 days later with resolution of most of her symptoms, but she did not experience a full recovery until approximately one month after the ingestion.

Three additional cases were reported in 1999. The first of these involved an 11 year old boy who was being treated for attention-deficit disorder.¹² After failing traditional therapies, he had been placed on fluvoxamine 50 mg once daily. Within an hour of taking the first dose, the patient experienced agitation and tremors. On arrival to the Emergency Department, he was hyperthermic, with jaw myoclonus, dilated pupils, and markedly fluctuating heart rate and blood pressures. He was initially treated with benzodiazepines, but eventually required intubation and mechanical ventilation in order to allow for pharmacologic neuromuscular blockade with rocuronium. He remained paralyzed for 24 hours, but then made a rapid recovery. Within 48 hours, his examination was normal.

Another case involved a 12 year old boy receiving sertraline who developed serotonin syndrome after being given erythromycin for an infection.¹³ Within 4 days of starting erythromycin, he developed agitation and anxiety. Over the next 10 days, he progressed to paresthesias, tremulousness, and confusion. Once the diagnosis was made, both sertraline and erythromycin were discontinued. The patient recovered over the next 72 hours.

The third report in 1999 described another accidental ingestion of sertraline.⁹ The patient, a 24 month old girl, ingested ten 50 mg tablets. She was taken to the hospital within an hour of the ingestion, where she was asymptomatic. She was given activated charcoal, which produced numerous pill fragments, and was discharged when stable. Twelve hours after the ingestion, she was taken back to the Emergency Department with agitation and tremors. The temperature on arrival was 38.4° C. She had dilated pupils, was hyperactive, hyperreflexic, and ataxic. She was treated with 1 mg cyproheptadine (0.08 mg/kg) orally. Within 40 minutes, symptoms resolved. She was given a prescription for 1 mg cyproheptadine every 8 hours (0.23 mg/kg/day) for 48 hours, and she remained asymptomatic.

In 2004, Thomas and colleagues reported a case of serotonin syndrome in a 4 year old girl receiving fluoxetine who was subsequently started on linezolid.¹⁴ She had been receiving fluoxetine at a dose of 5 mg daily for a week for acute stress disorder following a burn injury. After 11 days of fluoxetine therapy, linezolid (140 mg orally every 12 hours) was added to her treatment for presumed infection. Two days later, she was given fentanyl (200 mcg orally) as a pre-medication for wound debridement. She was noted to be agitated and have mydriasis, with eye deviation, after the procedure. She also developed myoclonic movement in the arms and legs. The diagnosis of serotonin syndrome was made at that time, but the role of the potential drug interaction was not recognized. Fluoxetine was discontinued and diphenhydramine (25 mg) was given. Symptoms began to resolve until another dose of linezolid was administered. The interaction was identified, and the linezolid discontinued. Symptoms resolved over the next 2 days.

Summary

Serotonin syndrome has become more prevalent as the use of drugs affecting serotonin concentrations has increased. As in adults, the increased use of SSRIs and other newer antidepressants in pediatric patients places them at risk for this adverse drug effect. While most cases of serotonin syndrome are mild and require minimal supportive care, some patients may develop severe cardiovascular compromise. Prompt recognition of symptoms, along with a complete drug history, can aid in a more rapid response and reduce the likelihood of serious complications.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/24/06:

1. A combination of ipratropium and albuterol for nebulization (Duoneb[®]) was added to both the Inpatient and Outpatient Formularies.
2. Liposomal lidocaine 4% topical cream (LMX-4[®]) was also added to the Inpatient and Outpatient Formularies. It has the advantage of a faster onset of action than EMLA (30 minutes versus 60 minutes). This product is available in a kit with five 5 gram tubes and 10 Tegaderm[™] dressings. This product will replace EMLA after a 3 to 6 month conversion period.
3. Daptomycin (Cubicin[®]) was added to the Inpatient Formulary with restriction to Antimicrobial Category A. It is a cyclic lipopeptide antibacterial agent with activity against gram positive organisms.
4. The restriction on the use of dexmedetomidine (Precedex[®]) was amended to include use in the PICU. Previous restrictions to patients in the NNICU and patients undergoing awake craniotomy or complex spinal procedures were retained.
5. The 2005 annual report on the Adverse Drug Reaction Reporting System was presented. For more information on the results, contact the Drug Information Center at 4-8084.

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