Serotonin Syndrome

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Shwetha Simhan

Introduction

With a rise in the number of patients dependent on multiple pharmaceutical products, we are bound to encounter adverse drug reactions including serotonergic toxicity. Unfortunately, we do not have enough data to report the incidence of serotonin syndrome. However, it was found in 2005 by U.S. Poison Control Center that 48,279 cases of adverse reactions were reported for Selective Serotonin Reuptake Inhibitors (SSRI), with moderate to severe reactions occurring in 18% and death in 0.2% [1, 2].

Clinical Findings and Diagnosis

Serotonin syndrome is essentially a clinical diagnosis. The classical presentation of serotonin syndrome involves cognitive behavioral changes, neuromuscular abnormalities and autonomic hyperactivity. In practice, the above symptoms are not simultaneously present and are often missed in its milder forms which includes tremors, tachycardia, hypertension, mydriasis, myoclonus, hyperreflexia and agitation. Intermediate and severe symptoms of serotonin syndrome would present with hyperthermia, diarrhea, agitation, confusion, incoordination, muscle rigidity and even coma and death. Although serotonin syndrome tends to occur in an overdose or as a multiple serotonergic drug interaction, it is not unusual for the syndrome to present in milder forms at therapeutic doses of single serotonergic drug [1, 2]. Hunter's Toxic Criteria for diagnosis of serotonin syndrome is 84% sensitive and 97% specific in comparison to the gold standard, medical toxicology report [2]. When entertaining a diagnosis of serotonin syndrome, we need to rule out various conditions including neuroleptic malignant syndrome, anticholinergic syndrome, malignant hyperthermia, sympathomimetic drugs, meningitis, encephalitis, thyroid storm, heat stroke, sepsis, delirium tremens, opioid withdrawal and illicit drug consumption [1, 2]. The following lab tests and imaging studies may help rule out other etiologies. The tests include complete blood count, basic metabolic panels including electrolytes, renal and liver function tests, creatinine phosphokinase, coagulation studies, urine drug screen, blood, urine and cerebrospinal fluid cultures, urine and Cerebrospinal fluid analysis, Imaging studies such as chest x-ray and head computed tomography [3].

S. Simhan (✉)
Pain Health and Wellness Institute, S.C., Milwaukee, Wisconsin, USA
e-mail: ssimhan@painhealth.org

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Classes of Drugs That Increases the Risk of Serotonin Syndrome Are as Follows [1]

Antidepressants
- Selective serotonin reuptake inhibitors.
- Serotonin and norepinephrine reuptake inhibitors.
- Tricyclic Antidepressants.
- Monoamine Oxidase Inhibitors.

Pain medications
- Headache medications: like triptans, ergot alkaloids and tegretol.
- Opioids which are morphine analogues (codeine and oxycodone) and phenylpiperidine analogues (meperidine, methadone, fentanyl, tramadol),

Antiemetics: like Ondansetron,
Illicit drugs: like Amphetamine
Herbal medications like St. John's wort's, Ginseng and nutmeg.

Pharmacology

Serotonin (5HT) is a neurotransmitter formed from hydroxylation and decarboxylation of L-tryptophan [2]. Serotonin, when released, binds to 5HT family of receptors and acts on both the central and peripheral nervous system [l]. It is involved in mood regulation, pain perception, gastrointestinal function, vasoconstriction, uterine contraction, bronchoconstriction and more [4]. Overstimulation of 5HT family of receptors, especially 5HT-1A and 5HT-2A receptors, leads to serotonin syndrome [1, 4]. Other mechanisms may also be involved in the manifestation of serotonin syndrome including genetic predisposition involving variation of serotonin transporter gene or polymorphism of 5HT receptors [5]. When serotonergic drug is taken in combination with cytochrome P450 enzyme inhibitor, especially CYP3D6 or CYP3A4 enzymes, this can lead to increased accumulation of serotonin neurotransmitters leading to over stimulation of 5HT receptors [2, 4]. Intimate knowledge of such interactions would allow a clinician to preemptively identify potential risks and make an informed clinical decision.

Management

Once a patient has been diagnosed with symptoms of serotonin syndrome, consider contacting a medical toxicologist or poison control center for assistance [2]. If a patient were to present to the Emergency department with mild symptoms of serotonin syndrome, they should be observed for at least 4–6 h to ensure stable vital signs, and normal physical exam including normal mental status, deep tendon reflexes and negative clonus [4]. If patient presents with moderate symptoms, they may need to be admitted for 24-h observation for cardiac monitoring and symptom resolution after discontinuation of the serotonergic medications [4]. If symptoms do not resolve within 24 h, it is likely that the triggering drug(s) has long half-life and possibly even longer duration of active metabolites, as seen with SSRI such as fluoxetine [2]. Treatment with serotonin antagonist called cyproheptadine, a 5HT1A and 5HT2A blocker, may help manage mild to moderate symptoms but may be counterproductive if heat dissipation is hindered by reduced sweating due to its mild anticholinergic activity [1, 2, 4]. A Patient presenting with severe symptoms of autonomic instability or mental status changes with erratic vital signs would need very close monitoring in an intensive care unit where muscular paralysis and intubation may be needed [1, 4]. Supportive care with intravenous fluids, oxygen, sedatives and cardiac monitoring would be essential. High blood pressure and heart rate should be managed with short acting drugs such as esmolol so that tachycardia may be a useful measure of severity of serotonin syndrome [4]. Sedation with benzodiazepines such as lorazepam may be titrated to effect when treating agitation [1]. It has been reported that an agitated patient should be managed pharmacologically with neuromuscular paralysis and intubation rather than physical restraint [4] which may promote muscular contractions which in turn may exacerbate lactic acidosis and hyperthermia. It is important to realize

that antipyretic agents are not effective in serotonin syndrome because hyperthermia is due to over active muscles and not due to increase in hypothalamic temperature set point [4].

High Yield Points

- When a clinician starts a patient on serotonergic agent, potential adverse reactions need to be discussed with the patients.
- Many of the mild to moderate signs and symptoms such as inducible clonus, ocular clonus, hypertonia, hyperreflexia need to be assessed.
- Ideally, it is important to provide refill scripts for serotonergic drugs during an office visit, after a history and exam, however practicality of this recommendation is up for debate.

Questions

1. Risk of serotonin syndrome increases not only with increasing dose but with combination of serotonergic drugs. In a patient already on SSRI antidepressant, which of the following drugs likely to increase the risk of serotonin syndrome?
   A. Diltiazem
   B. Erythromycin
   C. Phenelzine
   D. All of the above
   Answer: D
2. An antidote for serotonin syndrome especially mild to moderate cases are
   A. Benzodiazepine
   B. Muscle relaxant such as cyclobenzaprine
   C. Baclofen
   D. Cyproheptadine
   Answer: D
3. Serotonin syndrome can present as:
   A. Tachycardia
   B. Hyperension
   C. Agitation
   D. All of the above
   Answer: D

References

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