



Serotonin Syndrome After Methylene Blue Administration: A Case Report

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DEFINITION

- Toxidrome due to excessive serotonin receptor activities in central nervous system
- Normally due to medications and drug interactions
- Several drug classes have serotonergic effects
- Wide range of clinical presentation
- Life-threatening
 - Mortality around 11%

EPIDEMIOLOGY

- First noted in 1960s in studies of single and combination antidepressants usage
- All age groups involved
- Incidence of syndrome parallels with increased use of serotonergic agents
- Most likely drug class associated with syndrome: serotonin reuptake inhibitors
- Might be more common among chronically and/or critically ill patients due to multiple drug use and decreased drug metabolism
- Incidence difficult to assess due to misdiagnosis and dismissal of mild symptoms

COMMON CAUSES

Mechanisms	Examples
Decrease serotonin reuptake	SSRI, tricyclic antidepressants, tramadol, buprenorphine, carbamazepine, valproate, ondansetron, metoclopramide, St. John's wort
Decrease serotonin breakdown	MAOI, linezolid, methylene blue
Increase serotonin precursors/ formation	Tryptophan
Increase serotonin release	Cocaine, fentanyl, amphetamines, methylenedioxymethamphetamine
CYP2D6 and CYP2A4 inhibitors	Erythromycin, ciprofloxacin, fluconazole, grapefruit juice

CLINICAL PRESENTATION

- Neuromuscular excitation: myoclonus, hyperreflexia, akathisia, muscle rigidity, Babinski
- Autonomic dysfunction: diaphoresis, hypertension/hypotension, hyperthermia, mydriasis, diarrhea, nausea and vomiting, flushing, tachycardia
- Altered mental status

CASE PRESENTATION

62-year-old male with history of ischemic cardiomyopathy status post left ventricular assist device (LVAD), prostate cancer, transient ischemic attack, type 2 diabetes mellitus, hypertension, obesity, obstructive sleep apnea, chronic obstructive pulmonary disease, chronic kidney disease, general anxiety disorder and depression

- Presented to emergency department for low flow alarms from LVAD
- Admitted to advanced heart failure service

Approved for heart transplant and removal of LVAD

Vasoplegia during surgery requiring **methylene blue for vasopressor**

After surgery, worsening kidney function with **creatinine level to 2.1 mg/dL** from baseline of 1.6-1.8 mg/dL

- On post-op day 1, patient have difficulty following commands
 - Shaking or dorsiflexion of ankles and feet
 - Fever at max temperature of 38.7 degree Celsius
 - Tachycardic at 100 bpm

Differential diagnoses for symptoms include infection, seizure, anticholinergic toxicity, neuroleptic malignant syndrome, serotonin syndrome

- **Neurology** consultation: determined likely serotonin syndrome
 - Patient had mildly dilated pupils, severe hypertonia of all extremities, lower extremity clonus, increased patellar reflex, rigid dorsiflexion of calcaneal tendon, Babinski's sign, roving extraocular movements
 - Patient takes bupropion XL 150 mg and sertraline 50 mg daily
 - Recommended midazolam with bolus of 2 mg IV then infusion

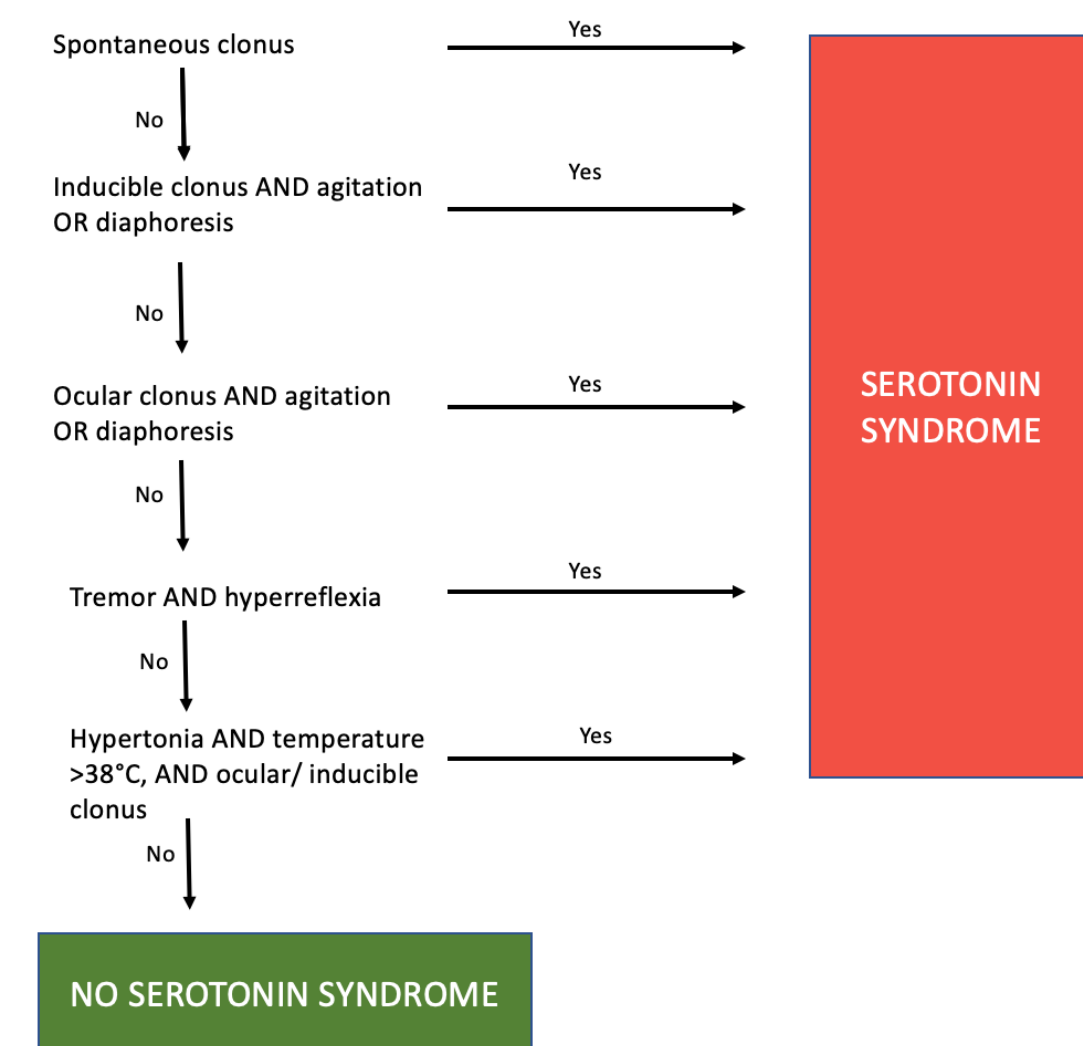
Toxicology consultation: agreed with likely serotonin syndrome

- Midazolam titrated up to 8 mg/hr for symptom control
- Cooling blanket for elevated temperatures

- Symptom resolution on post-op day 2
 - Improved creatinine level and urine output

DIAGNOSIS

- Physical and neurological exam
- Patient's medication history
- Hunter Serotonin Toxicity Criteria considered as gold standard
 - Improved sensitivity and specificity to 84% and 97%, respectively
 - Systematic review of 412 cases showed that Hunter criteria miss 37% of cases while other criteria miss only 10 or 24% of cases



TREATMENT

- Symptomatic treatment
- Discontinue all serotonergic agents
- Cooling methods for hyperthermia and IV fluids for tachycardia and hypertension/hypotension
- No use for antipyretic medications
- Benzodiazepines for agitation
- Medications preferred over physical restraints to avoid risk of rhabdomyolysis and worsening hyperthermia
- Hyperthermia above 41°C should be intubated and paralyzed to address muscle rigidity
- Mild cases may just need close observation
- Can consider cyproheptadine if refractory

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