Serotonin Syndrome After Methylene Blue Administration During Cardiac Surgery: A Case Report and Review

Timothy Wolvetang, Rineke Janse, MD, and Maarten ter Horst, MD, PhD

SEROTONIN SYNDROME, described for the first time by Rapport et al in 1948, is a syndrome that is caused by toxic levels of serotonin.[1] Selective serotonin reuptake inhibitors (SSRIs) and many other drugs can cause serotonin syndrome (SS), a rare but potentially lethal complication of these drugs.[2,3] The syndrome is well-described in psychiatric literature because SS occurs in approximately 14% to 16% of persons with an SSRI overdose, often intentional. Excess serotonin manifests itself through a spectrum of clinical features, ranging from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in severe cases. Later signs and symptoms include metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulation. Because there is no test available to confirm SS, criteria to diagnose the syndrome were derived by Sternbach in 1991.[3] Dunkley et al revised Sternbach's criteria, creating the Hunter criteria, which improved the sensitivity and specificity to 84% and 97%, respectively.[4] Many cases of SS occur in patients who use a combination of serotonergic agents.[4] This multi-drug scenario is very common during general anesthesia for cardiac surgery. Nearly 1 in 5 patients with ischemic heart disease are diagnosed with depression and treated with antidepressants such as SSRIs.[5]

Vasoplegic syndrome is a common reaction to cardiopulmonary bypass, occurring in 5% to 25% of patients.[6] Cardiopulmonary bypass initiates a proinflammatory state in which cytokines and endotoxins increase the expression of nitric oxide synthase, which ultimately leads to vasodilatation via an increase in cyclic guanosine monophosphate that blocks calcium from entering the smooth muscle cells.[7] Methylene blue blocks accumulation of cyclic guanosine monophosphate, leading to higher intracellular calcium concentrations, which increases vascular responsiveness.[6] Treating vasoplegia with methylene blue has become common because it improves outcome in vasoplegic patients.[8,9] Methylene blue and its metabolite azure B are noteworthy reversible inhibitors of monoamine oxidase A which, particularly in combination with SSRIs, have been linked to increased serotonin levels in the brain and serotonin toxicity.[10,11]

SS is one of the drug-induced hyperthermic syndromes, which also include malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), anticholinergic syndrome, and sympathomimetic syndrome. Management of SS includes benzodiazepines and supportive care. To the authors' knowledge, only 3 cases of SS after cardiac surgery have been reported.[12-14]

CASE PRESENTATION

A 64-year-old female was treated for severe mitral valve regurgitation with a mitral valve repair. Her prehospital medication included paroxetine (SSRI), quetiapine (atypical antipsychotic drug), and clonazepam. In addition to depression, this patient had a history of autoimmune hepatitis, stable multiple sclerosis, and a wedge excision of the upper lobe of the left lung as treatment for an adenocarcinoma 1 year before the mitral valve repair. Her history also included an estimated 50 pack-years of cigarette smoking, but no other substance abuse.

The surgical phase was unremarkable except for persistent low blood pressure unresponsive to norepinephrine infusion and intermittent boluses on institution of cardiopulmonary bypass. This suspected vasoplegia was treated with vasopressin and methylene blue, 2 mg/kg. Before the end of the procedure the patient was rewarmed gradually by cardiopulmonary bypass to 37°C, using central and nasal temperatures as control. To facilitate quick recovery, desflurane, granisetron, 1 mg, and s-ketamine, 25 mg, were administered.

The patient's airway was extubated in the operating room. On admission to the intensive care unit postoperatively, the patient was somnolent but responsive to verbal stimuli, and mydriasis was noted. However, over the next 8 hours her neurologic state deteriorated. Her temperature gradually rose to 40.5°C, her extremities became hypertonic without myoclonus, and nystagmus was observed. Blood tests revealed hyperkalemia of 6.5 mmol/L and creatinine of 1.69 mg/dL. The creatine kinase rose from 631 IU/L (normal range 0-144 IU/L) to 1,735 IU/L on the first postoperative day and gradually decreased to values less than 1,000 IU/L on the second postoperative day. High-sensitivity troponin T and creatine kinase MB remained relatively stable. On the third and fourth postoperative days the creatine kinase decreased to 618 IU/L and 463 IU/L, respectively. Liver function tests showed a mild elevation of aspartate amino transferase (72 U/L), with normal alanine amino transferase (24 U/L). Kidney function decreased with glomerular filtration rates dropping from 63 mL/min preoperatively to 31 mL/min. Because of her neurologic deterioration, computerized tomography of the brain was performed, which ruled out intracranial hemorrhage and ischemic stroke.

Because the patient had used 2 agents recognized as potentially causative of SS and NMS, paroxetine and quetiapine, both causative agents were stopped. The clinical signs

From the Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands.

T.W. and R.J. contributed equally to this article.

Address reprint requests to T. Wolvetang, MPA in training, Erasmus Medical Center, Department of Anesthesiology, H-1276, s-Gravendijkwal 230, 3000 CA Rotterdam, The Netherlands. E-mail: T.Wolvetang@aerasmusmc.nl

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developed very gradually, so malignant hyperthermia was clinically unlikely. The patient was sedated with midazolam and her airway was reintubated. With supportive care, including intravenous fluids, passive cooling, and sedation, her temperature dropped to normothermia within 6 hours. Infection parameters remained within the normal postoperative range, and blood cultures were negative for bacterial growth. Kidney function improved within 3 days and liver enzymes and creatine kinase values dropped to normal in 4 days.

The patient was weaned successfully from sedation and ventilation on the third postoperative day and transferred to the ward on the seventh day. The patient developed postoperative delirium for which, as standard care, haloperidol was started on the ward, without a relapse of symptoms. On the 12th postoperative day, the patient had recovered completely, and she was discharged to another hospital.

DISCUSSION

The Hunter criteria suggest serotonin toxicity in the presence of a serotonergic agent—paroxetine and quetiapine in this patient—and 1 of the 5 following clusters of symptoms: (1) spontaneous clonus, (2) inducible clonus and agitation or diaphoresis, (3) ocular clonus and agitation or diaphoresis, (4) tremor and hyperreflexia, and (5) hypertonia, hyperthermia ($>38^{\circ}C$), and ocular or inducible clonus.[4] Fig 1 depicts a flowchart of the Hunter criteria. The symptoms of this patient correlated with the fifth cluster, circled in Fig 1.

In addition to the preoperative serotonergic medication, several other agents that affect serotonin activity (Table 1) were administered during the surgical phase. Methylene blue was administered to treat vasoplegia, a common complication of cardiopulmonary bypass, with an incidence of 5% to 25%.[6]

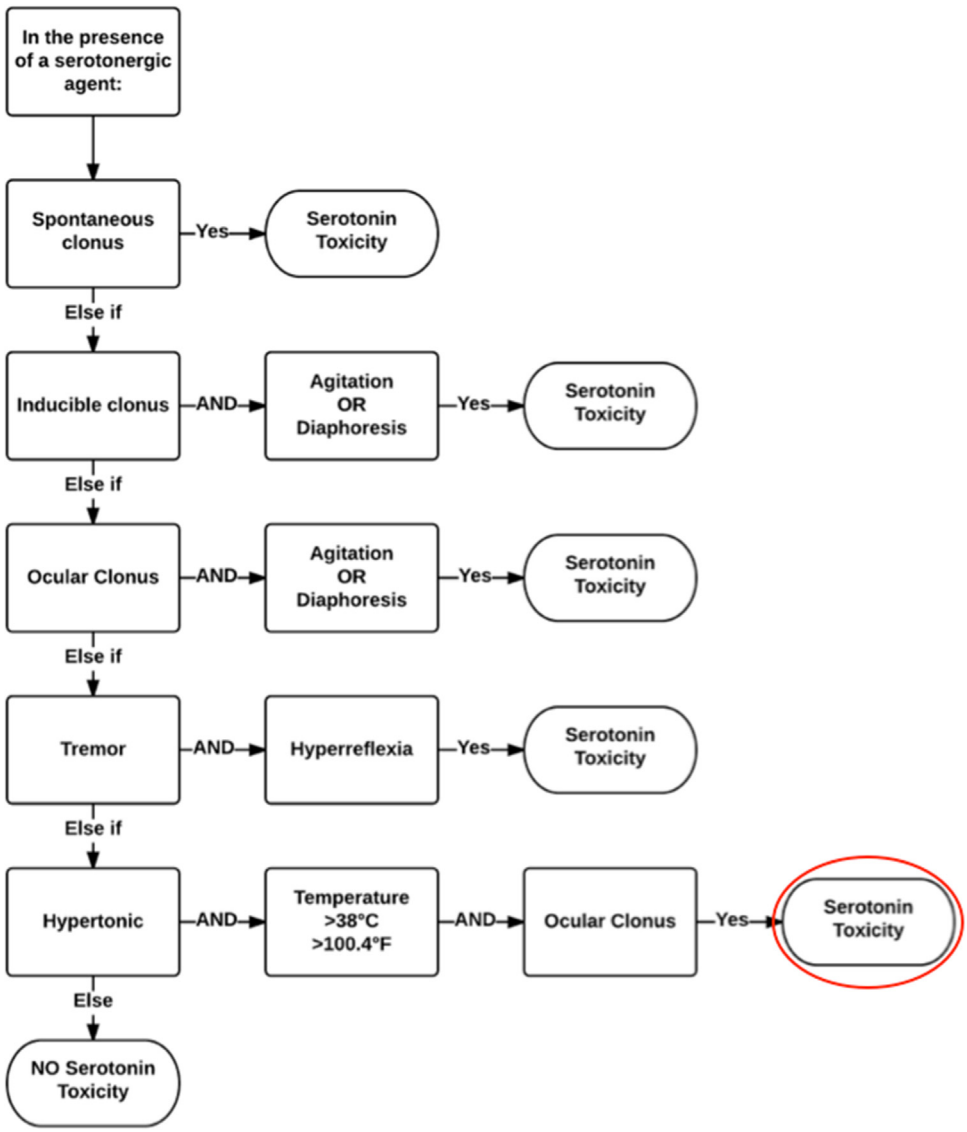

Fig 1. Flowchart of the Hunter criteria. The symptoms of the patient correlate with the fifth cluster, circled in the figure. Adapted from Dunkley EJ, Isbister GK, Sibbritt D, et al: The Hunter Serotonin Toxicity Criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. QJM 96:635-642, 2003.