Can J Anesth/J Can Anesth (2016) 63:896–897
DOI 10.1007/s12630-016-0622-1

CORRESPONDENCE

Methylene blue-induced serotonin syndrome presenting with ocular clonus and failure of emergence from general anesthesia

George Nicolaou, MBBCh · Dennis Lee, MBBS

Received: 17 December 2015 / Revised: 10 February 2016 / Accepted: 23 February 2016 / Published online: 4 March 2016
© Canadian Anesthesiologists' Society 2016

To the Editor,

We wish to report an interesting case of perioperative methylene blue-induced serotonin syndrome in a 50-yr-old woman (83 kg) who presented for hysterectomy. In addition to menorrhagia and anemia, her medical history included depression, for which she took the selective serotonin reuptake inhibitor paroxetine (40 mg *po* daily).

On the day of surgery, anesthesia was induced with sufentanil 15 μg *iv*, propofol 200 mg *iv*, and rocuronium 50 mg *iv*. Anesthesia was maintained with desflurane. Intraoperatively, she was given hydromorphone 0.8 mg *iv* and ketorolac 15 mg *iv* for analgesia and ondansetron 4 mg *iv* for antiemesis. Surgery and anesthesia proceeded without complications. Toward the end of the surgery, methylene blue 50 mg ($\sim$ 0.6 mg·kg^{-1}) was administered to aid in confirming patent ureteric orifices via cystoscopy. At the end of the operation, muscle relaxation was reversed with neostigmine 2.5 mg and glycopyrrolate 0.4 mg *iv*. Despite an unmeasurable end-tidal desflurane concentration, the patient did not awaken. She was maintained on spontaneous ventilation via the endotracheal tube. Arterial blood gas analysis and all other bloodwork was unremarkable.

After an additional 45 min of observation, the patient remained hemodynamically stable but still unresponsive. Physical examination revealed an absent gag reflex, hyperreflexia, no response to pain, and diaphoresis. The corneal reflexes were intact, with normal-sized reactive pupils and ocular clonus. A computed tomography scan excluded an intracerebral event, and the patient was transferred to the intensive care unit (ICU) for continued ventilator and other supportive management with a presumptive diagnosis of serotonin syndrome. Continuous electroencephalographic monitoring in the ICU excluded any seizure activity. Given that she did not exhibit evidence of clinical deterioration, a decision was made not to administer an antiserotonergic agent such as cyproheptadine.[1] She was kept sedated overnight with a propofol infusion. After her propofol sedation was stopped in the morning, the patient began responding appropriately to commands, and she was successfully extubated. Her ocular clonus had self-resolved, and she had no recollection of the events during this episode.

Because of shortages of indigo carmine and indocyanine green, intravenous methylene blue is now commonly used at our institution to identify the ureteric openings during gynecological and urological surgery. Our practice has been to administer methylene blue 50 mg *iv* approximately ten minutes prior to cystoscopy. It is known to be a monoamine oxidase inhibitor and therefore may interact with serotonin and norepinephrine reuptake inhibitors and with tricyclic antidepressants.[2]

Compared to previous reports, our patient received a relatively small dose ($\sim$ 0.6 mg·kg^{-1} *iv*) of methylene blue. In other cases of methylene blue-induced serotonin syndrome, the doses ranged from 1.0-7.5 mg·kg *iv*.[3]

Serotonin syndrome classically consists of a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.[2] Tools available for diagnosing clinically significant serotonin syndrome include Sternbach's criteria[4] and Hunter's serotonin toxicity criteria[5], which are summarized in the Table. Hunter's criteria have greater sensitivity and specificity than Sternbach's criteria (84% and 97% *vs* 75% and 96%,

G. Nicolaou, MBBCh (✉) · D. Lee, MBBS
Department of Anesthesia and Perioperative Medicine, Schulich Medicine and Dentistry, Western University, London, ON, Canada
e-mail: george.nicolaou@lhsc.on.ca

Table Hunter's serotonin toxicity criteria

In the presence of a serotonergic agent:
Spontaneous clonus;
Inducible clonus OR ocular clonus AND agitation OR diaphoresis;
Inducible clonus OR ocular clonus AND hypertonicity AND temperature > 38°C;
Tremor AND hyperreflexia.

respectively) when compared with a "gold standard" diagnosis by a clinical toxicologist.[5] Our patient exhibited a decreased conscious state, ocular clonus, hyperreflexia, and diaphoresis despite normothermia, thereby meeting Hunter's criteria for serotonin syndrome.

In patients at risk of developing this syndrome, there should be a discussion between the anesthesiologist and the surgeon regarding dose reduction and whether an intravenous dye is absolutely required or an alternative could be employed. Alternatives to methylene blue - other than indigo carmine and indocyanine green - include the azo dye phenazopyridine and oral vitamin B complex. Ultimately, it behoves the anesthesiologist to remain knowledgeable and vigilant for any potential drug interactions and to respond rapidly to prevent serious morbidity or mortality.

Acknowledgement We would like to acknowledge Dr. Davy Cheng for reviewing and providing feedback on this case report.

Conflicts of interest None declared.

References

1. *Gillman PK*. The serotonin syndrome and its treatment. J Psychopharmacol 1999; 13: 100-9.
2. *Gillman PK*. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth 2005; 95: 434-41.
3. *Schwiebert C*, *Irving C*, *Gillman PK*. Small doses of methylene blue, previously considered safe, can precipitate serotonin toxicity. Anaesthesia 2009; 64: 924.
4. *Sternbach H*. The serotonin syndrome. Am J Psychiatry 1991; 148: 705-13.
5. *Dunkley EJ*, *Isbister GK*, *Sibbritt D*, *Dawson AH*, *White IM*. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003; 96: 635-42.