Methylene Blue Causing Serotonin Syndrome Following Cystocele Repair

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Introduction

Serotonin syndrome (SS) results from high levels of serotonin within the nervous system causing a range of symptoms from mild to life-threatening. Most commonly seen medications that may induce SS include selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) in combination with monoamine oxidase inhibitors (MAOIs).1 The three hallmark signs of SS include altered mental status, hyperactive automaticity, and abnormal neuromuscular function.1 Two common criteria used in literature are the Sternbach’s criteria and the Hunter’s Serotonin Toxicity criteria (Table 1).

Case presentation

A 74-year-old woman with past medical history notable for Parkinson’s disease, depression, anxiety, and pelvic organ prolapse presented with cystocele (Table 2). She was scheduled for repeat cystocele repair, due to worsening of incontinence and pelvic organ prolapse. Her current medications consisted of Ropinirole for her restless leg syndrome, as well as Fluoxetine (SSRI) and Duloxetine (SNRI) for depression and anxiety. At baseline, the patient was alert and oriented with normal mental status.

The patient underwent general anesthesia (Table 3). There was successful reduction of a large cystocele with cadaveric fascia without any surgical complications. 100 mg of 1% MB was administered at the beginning of the procedure to rule out potential vesical–ureteral injury. Cystoscopy did not demonstrate any injuries and blue-tinged ureteral jets were visualized from both ureteral orifices.

Approximately 1 h post-operatively the patient became agitated and tachycardic to 108 bpm. She was unable to express herself and had uncontrollable movements of all four limbs. She was given her Parkinson’s medications, Stalevo® and Ropinirole. Bladder scan demonstrated 450 cc residual urine and a foley catheter was placed. Urinalysis and urine culture were obtained. The patient was transferred to the main hospital emergency room and neurology was consulted.

Five hours post-operatively the patient’s heart rate remained elevated along with a mild elevation in temperature (37.6 °C). She was nonverbal with hyperactive delirium. Labs demonstrated elevated AST (44 IU/L) and CPK levels (556 IU/L); critically low lactic acid (4.7 mmol/L); and leukocytosis (17.8 K/mL). She was started on empiric antibiotics, IV fluids, and benzodiazepines for agitation. Head CAT scan and chest X-ray were normal. On neurologic exam, the patient was obtunded and dysarthric with restlessness in all extremities. Reflexes were normal and coordination was unable to be assessed.

The patient was transferred to the medical intensive care unit. She gradually improved with supportive care over the course of the
Table 1
Diagnostic criteria for serotonin syndrome

| Sternbach’s criteria | Hunter’s criteria |
|----------------------|------------------|
| 1. Patient on serotonergic agent | 1. Patient on serotonergic agent |
| 2. Absence of other causes or etiologies | 2. Presence of any of the following: |
| 3. No current use of neuroleptic agent | • Spontaneous clonus |
| 4. Presence of three of the following: | • Inducible clonus AND agitation OR diaphoresis |
| • Mental status change (confusion, hypomania, restlessness, ataxia) | • Ocular clonus AND agitation OR diaphoresis |
| • Agitation | • Tremor AND hyperreflexia |
| • Myoclonus | • Hypertonic AND hyperthermia (>38 °C) AND ocular clonus OR inducible clonus |
| • Hyperreflexia | |
| | |

next 2 days with normalization of her AST and CPK. CPK elevation was presumed to be elevated from agitation. Suspicion for SS was based on the patient being on a serotonergic agent and presentation of altered mental status, agitation, diaphoresis, hyperthermia, and hyperreflexia. This met Sternbach’s criteria for SS (Table 1). Benzodiazepines were discontinued and all anti-psychotic medications were held.

The following day her mental status improved. Her fever and leukocytosis resolved. Urine culture was negative. Foley catheter was removed and the patient was able to void without difficulty. She was downgraded to regular floor bed and the remainder of the hospital course was uneventful. The patient was discharged on hospital day 7 to a rehabilitation facility.

Table 2
Patient history

| Past medical history | Past surgical history | Home medications |
|----------------------|----------------------|------------------|
| • Anxiety             | • Cystocele repair   | • Allopurinol 100 mg |
| • Asthma              | • Cystoscopy         | • Ascorbic acid 500 mg |
| • Cystocele           | • Interstim          | • Aspirin 81 mg Q24H |
| • Depression          | • Hip replacement    | • Carbidopa/entacapone/levodopa QID |
| • Gastroesophageal    | • Hiatal hernia repair | (Stalevo) |
| Reflux Disease (GERD) | • Abdominoplasty     | • Diclofenac topical BID, PRN for pain |
| | • Knee replacement    | • Diltiazem 60 mg Q24H |
| | • Total abdominal hysterectomy | • Ergocalciferol |
| | • Tonsillectomy/adenoidectomy | • Estradiol 1 mg Q24H |
| | | • Fluoxetine 10 mg Q24H |
| | | • Furosemide |
| | | • Levocetirizine 5 mg |
| | | • Levotyroxine |
| | | • Multivitamin Q24H |
| | | • Olopatadine nasal BID |
| | | • Omeprazole 40 mg Q24H |
| | | • Potassium chloride 10 mEq BID |
| | | • Ropinirole TID |
| | | • Rosuvastatin Q48H |
| | | • Ubiquinone 300 mg Q24H |

4 Warning for serotonin syndrome.

Table 3
General anesthesia course during cystocele repair

| Medication                | Dose |
|---------------------------|------|
| Midazolam 1 mg/ml INJ IV Push | 1 mg |
| Fentanyl 50 mcg/ml IV Push | 25 mcg |
| Propofol 10 mg/ml INJ IV Push | 150 mg |
| Propofol 20 mg/ml INJ Continuous IV | 252 mg |
| Rocuronium 50 mg/5 mL INJ IV Push | 20 mg |
| Dexamethasone 4 mg/ml INJ IV Push | 4 mg |
| ePHEDrine 5 mg/1 mL NS OR SYRINGE IV Push | 10 mg |
| Ondansetron 2 mg/ml 2 mL INJ IV Push | 4 mg |
| Acetaminophen (OFIRMEV) 10 mg/ml INJ IVPB | 1 g |
| Methylene blue 1% 10 mL INJ IV Push | 10 mL |
| Neostigmine 1:1000 INJ IV Push | 2 mg |
| Glycopyrrolate 0.2 mg/ml INJ IV Push | 0.4 mg |

4 Warning for serotonin syndrome.

Discussion

Methylene blue (MB) is a MAOI utilized during surgical procedures as a dye or vasopressor demonstrated in the literature to cause SS in high risk patients. The primary risk factor is present use of serotonergic medications. Age is an independent risk factor as elderly patients are more likely to be on anti-depressant medications. There are 31 cases of SS reported in literature following MB administration during parathyroidectomies used for visualization of parathyroid tissue. There are also cases reported after cardiac surgery where MB is used to treat vasoplegic syndrome. While most cases resolve, Top et al reports a fatal case of SS. In 2011 the FDA issued a warning regarding the use of MB in patients on psychiatric medications, however incidences of SS continue to appear in literature. MB is also used during pelvic and abdominal surgeries to identify potential injury to the ureters or bladder. However, only two of these cases were reported and there was no case specific to urology.

The diagnosis of SS was evaluated with Sternbach’s and Hunter’s criteria (Table 1). Our patient was at risk due to her serotonergic medications: fluoxetine and duloxetine. She presented with four clinical features of serotonin toxicity: mental status change (restlessness and confusion), agitation, diaphoresis, and fever. This met Sternbach’s criteria, which only required three. Other etiologies such as malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), and infection were ruled out. She did not meet Hunter’s criteria though, which emphasized the presence of clonus. Whereas Hunter’s criteria had better sensitivity than Sternbach’s criteria (84% vs 75%), they have similar specificity (97% and 96% respectively). The high specificity of both criteria yields a high positive predictive value, hence a low false positive rate.

Evaluation of ureteral patency, injury, or identifying the ureteral orifices is common practice during urological surgeries according to the American Urological Association guidelines. Urologists often times use marker dyes to identify ureteral injuries, and MB should be used with caution. Other options include indocyanine green and indigo carmine. However, indocyanine green has not been studied for cystoscopy and indigo carmine is no longer readily available due to national supply shortages. There have been recent studies looking at alternatives for intraoperative cystoscopy. Phenazopyridine (given orally preoperatively) and sodium fluorescein are other agents used to visualize bilateral ureteral jets.
Conclusion

The shortage of indigo carmine has increased the usage of alternatives including MB in urology, which in tandem with the increase in patients on psychiatric medications, heightens the risk of SS. It is therefore important to raise awareness about this drug interaction within the urological field. It is strongly recommended that physicians take the necessary precautions before utilizing MB on patients on serotonergic medications.

Conflict of interest

The authors of this case report declare that they have nothing to disclose and no conflict of interests. No outside financial support was received for the preparation of this case report.

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