



## Functional Medicine

## Methylene Blue Causing Serotonin Syndrome Following Cystocele Repair

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## ABSTRACT

Methylene blue is an intravenously administered agent that may potentiate serotonin syndrome. The usage of methylene blue to evaluate ureters for injuries and patency during urological surgeries is recognized as common practice. However, there is no mention of serotonin syndrome caused by methylene blue in urological literature or for urological surgery. We report the first urological case in order to raise awareness of the risk for serotonin toxicity with utilizing methylene blue.

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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).<sup>1</sup> The three hallmark signs of SS include altered mental status, hyperactive automaticity, and abnormal neuromuscular function.<sup>1</sup> 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<sup>®</sup> 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/ $\mu$ L). 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

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**Table 1**  
Diagnostic criteria for serotonin syndrome<sup>1</sup>

Sternbach's criteria	Hunter's criteria
<ol style="list-style-type: none"> <li>1. Patient on serotonergic agent</li> <li>2. Absence of other causes or etiologies</li> <li>3. No current use of neuroleptic agent</li> <li>4. Presence of three of the following: <ul style="list-style-type: none"> <li>• Mental status change (confusion, hypomania, restlessness, ataxia)</li> <li>• Agitation</li> <li>• Myoclonus</li> <li>• Hyperreflexia</li> <li>• Diaphoresis</li> <li>• Shivering</li> <li>• Tremor</li> <li>• Diarrhea</li> <li>• Incoordination</li> <li>• Fever</li> </ul> </li> </ol>	<ol style="list-style-type: none"> <li>1. Patient on serotonergic agent</li> <li>2. Presence of any of the following: <ul style="list-style-type: none"> <li>• Spontaneous clonus</li> <li>• Inducible clonus AND agitation OR diaphoresis</li> <li>• Ocular clonus AND agitation OR diaphoresis</li> <li>• Tremor AND hyperreflexia</li> <li>• Hypertonic AND hyperthermia (&gt;38 °C) AND ocular clonus OR inducible clonus</li> </ul> </li> </ol>

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 hypertonia. 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

**Table 2**  
Patient history

Past medical history	Past surgical history	Home medications
<ul style="list-style-type: none"> <li>• Anxiety</li> <li>• Asthma</li> <li>• Cystocele</li> <li>• Depression</li> <li>• Gastroesophageal Reflux Disease (GERD)</li> <li>• Gout</li> <li>• Hypothyroidism</li> <li>• Hypertension</li> <li>• Hyperlipidemia</li> <li>• Incontinence (urinary, stress, urge)</li> <li>• Nocturia</li> <li>• Obesity</li> <li>• Osteoporosis</li> <li>• Parkinson's</li> <li>• Obstructive sleep apnea</li> <li>• Uterovaginal prolapse</li> </ul>	<ul style="list-style-type: none"> <li>• Cystocele repair</li> <li>• Cystoscopy</li> <li>• Interstim</li> <li>• Hip replacement</li> <li>• Hiatal hernia repair</li> <li>• Abdominoplasty</li> <li>• Knee replacement</li> <li>• Total abdominal hysterectomy</li> <li>• Tonsillectomy/adenoidectomy</li> </ul>	<ul style="list-style-type: none"> <li>• Allopurinol 100 mg</li> <li>• Ascorbic acid 500 mg Q24H</li> <li>• Aspirin 81 mg Q24H</li> <li>• Carbidopa/entacapone/levodopa QID (Stalevo)</li> <li>• Diclofenac topical BID, PRN for pain</li> <li>• Duloxetine 60 mg Q24H<sup>a</sup></li> <li>• Ergocalciferol</li> <li>• Estradiol 1 mg Q24H</li> <li>• Fluoxetine 10 mg Q24H<sup>a</sup></li> <li>• Furosemide</li> <li>• Levocetirizine 5 mg</li> <li>• Levothyroxine 75 mcg Q24H</li> <li>• Lisinopril 20 mg Q24H</li> <li>• Multivitamin Q24H</li> <li>• Olopatadine nasal BID</li> <li>• Omeprazole 40 mg Q24H</li> <li>• Potassium chloride 10 mEq BID</li> <li>• Ropinirole TID</li> <li>• Rosuvastatin Q48H</li> <li>• Ubiquinone 300 mg Q24H</li> </ul>

<sup>a</sup> Warning for serotonin syndrome.

**Table 3**  
General anesthesia course during cystocele repair

Midazolam 1 mg/mL INJ IV Push	1 mg
Fentanyl 50 mcg/mL IV Push <sup>a</sup>	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

<sup>a</sup> Warning for serotonin syndrome.

hospital course was uneventful. The patient was discharged on hospital day 7 to a rehabilitation facility.

## 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 antidepressant medications.<sup>2</sup> There are 31 cases of SS reported in literature following MB administration during parathyroidectomies used for visualization of parathyroid tissue.<sup>3</sup> There are also cases reported after cardiac surgery where MB is used to treat vasoplegic syndrome.<sup>4</sup> While most cases resolve, Top et al reports a fatal case of SS.<sup>5</sup> 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.<sup>6,7</sup> MB is also used during pelvic and abdominal surgeries to identify potential injury to the ureters or bladder.<sup>8</sup> However, only two of these cases were reported and there was no case specific to urology.<sup>9,10</sup>

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.<sup>1</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup>

## 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.

## References

1. Dunkley EJ, Isbister GK, Sibbrit D, et al. The hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635–642.
2. Varma S, Sareen H, Trivedi JK. The geriatric population and psychiatric medication. *Mens Sana Monogr*. 2010;8(1):30–51.
3. Shopes E, Gerard W, Baughman J. Methylene blue encephalopathy: a case report and review of published cases. *AANA J*. 2013;81(3):215–221.
4. Wolvetang T, Janse R, Ter Horst M. Serotonin syndrome after methylene blue administration during cardiac surgery: a case report and review. *J Cardiothorac Vasc Anesth*. 2015.
5. Top WM, Gilliman PK, de Langen CJ, Kooy A. Fatal methylene blue associated serotonin toxicity. *Neth J Med*. 2014;72(3):179–181.
6. FDA Drug Safety Communication: Updated Information about the Drug Interaction between Methylene Blue (Methylthionium Chloride) and Serotonergic Psychiatric Medications. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm276119.htm>; 2011. Accessed 11.07.16.
7. Martino EA, Winterton D, Nardelli P, et al. The blue coma: the role of methylene blue in unexplained coma after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2016;30(2):423–427.
8. Hudak S, Coburn M. *Renal, Ureter – AUA Core Curriculum*. American Urological Association; 2016. Available from: [https://www.auanet.org/university/core\\_topic.cfm?coreid=87](https://www.auanet.org/university/core_topic.cfm?coreid=87). Accessed 11.07.16.
9. Francescangeli J, Vaida S, Bonavia AS. Perioperative diagnosis and treatment of serotonin syndrome following administration of methylene blue. *Am J Case Rep*. 2016;17:347–351.
10. Nicolaou G, Lee D. Methylene blue-induced serotonin syndrome presenting with ocular clonus and failure of emergence from general anesthesia. *Can J Anaesth*. 2016;63(7):896–897.
11. Morey AF, Brandes S, Dugi DD, et al. Urotrauma: AUA guideline. *J Urol*. 2014;192(2):327–335.
12. *Indigo Carmine Injection*. American Society of Health-System Pharmacists website; 2015. Available from: <http://www.ashp.org/menu/DrugShortages/CurrentShortages/Bulletin.aspx?id=861>. Accessed 28.06.16.
13. Doyle PJ, Lipetskaia L, Duecy E, et al. Sodium fluorescein use during intraoperative cystoscopy. *Obstet Gynecol*. 2015;125(3):548–550.