*Brief Report*

Cancer Control
2017, Vol. 24(5) 1–4

DOI: 10.1177/1073274817729070
journals.sagepub.com/home/ccx
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# Serotonin Syndrome Complicating Treatment of Ifosfamide Neurotoxicity With Methylene Blue

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**Abstract**

Methylene blue is a widely used treatment for ifosfamide neurotoxicity. We present a case of severe encephalopathy complicating ifosfamide-based therapy for recurrent retroperitoneal leiomyosarcoma. After treatment with methylene blue, the patient experienced clinical decompensation and was diagnosed with serotonin syndrome based on a constellation of clinical findings. Withdrawal of methylene blue and other serotonergic medications led to clinical stabilization and ultimately neurological recovery. Our case highlights the challenge of diagnosing serotonin syndrome in the face of preexisting ifosfamide neurotoxicity, as there is significant clinical overlap between these 2 syndromes. Practitioners must remain vigilant of this potential life-threatening complication in this vulnerable population.

**Keywords**

serotonin syndrome, ifosfamide neurotoxicity, methylene blue

Received August 17, 2016. Accepted for publication May 22, 2017.

## Introduction

Methylene blue is a phenothiazine derivative that is used in a variety of roles in clinical practice that range from a dye used in diagnostic applications to a therapeutic utilized for the treatment of methemoglobinemia. An off-label but common use of methylene blue in the oncology population is for the treatment of ifosfamide neurotoxicity.[1] Approximately, 10% to 40% of patients treated with ifosfamide develop encephalopathy.[2] Although most cases are self-limited and do not require treatment, the condition can be severe or even fatal.[3] Methylene blue is thought to help in cases of ifosfamide neurotoxicity due to its inhibition of monoamine oxidase (MAO). This enzyme is responsible for producing chloroacetaldehyde, the neurotoxic metabolite of ifosfamide.[4] Similar to other MAO inhibitors, a well-known potential toxicity of methylene blue is serotonin syndrome, particularly with concomitant use of other serotonergic drugs.[5] Based on this risk, the US Food and Drug Administration has issued a black box warning for the concomitant use of methylene blue with such agents. Serotonin syndrome is a potentially life-threatening condition. Early recognition and discontinuation of offending agents is essential in its management. We present a unique case of severe serotonin syndrome in a patient receiving methylene blue for the treatment of ifosfamide neurotoxicity. This case highlights the diagnostic challenge of identifying serotonin syndrome in a patient with preexisting encephalopathy. Serotonin syndrome should

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be suspected in patients with worsening mental status after methylene blue treatment for ifosfamide neurotoxicity, particularly if autonomic dysfunction is present.

## Case Report

A 58-year-old woman with a history of hypertension, generalized anxiety disorder, depression, and hepatitis C was diagnosed with retroperitoneal leiomyosarcoma. She underwent radical resection of the tumor with negative margins and subsequent segmental duodenectomy and inferior vena cava closure. Two years later, she presented with nausea, vomiting, and right upper quadrant abdominal pain secondary to 2 new retroperitoneal masses. Biopsy confirmed recurrent disease. The patient was started on chemotherapy with AIM75/10 (doxorubicin 25 mg/m$^2$/d intravenous [IV] over 24 hours on days 1 to 3, ifosfamide 2500 mg/m$^2$/d IV over 24 hours on days 1 through 4, mesna 2500 mg/m$^2$ IV concurrently with ifosfamide over 24 hours on days 1 through 4, then 2500 mg/m$^2$ IV over 12 hours on day 5).[6] The first cycle of Mesna, Adriamycin, and Ifosfamide (chemotherapy regimen) was complicated by neutropenic fever. The second cycle was also complicated by neutropenic fever, despite a reduction in ifosfamide dose to 2000 mg/m$^2$/d for 4 days. During the third cycle, the patient developed acute altered mental status shortly after receiving her second dose of ifosfamide despite being on thiamine 100 mg Oral /peroral (PO) daily as prophylaxis. Other concurrent scheduled medications at the time included bisacodyl 5 mg PO daily and docusate-senna 50 to 8.6 mg PO daily for constipation; clonidine 0.2 mg PO twice daily, losartan 50 mg PO daily, and nifedipine extended release (ER) 60 mg PO every morning and 90 mg every evening for hypertension; ondansetron 8 mg IV every 8 hours, dexamethasone 18 mg PO daily, and metoclopramide 10 mg PO at meals and at bedtime for chemotherapy-induced nausea and vomiting; oxycodone ER 15 mg PO twice daily for pain; fluconazole 200 mg PO daily for thrush; and paroxetine 20 mg PO daily for generalized anxiety disorder and depression. She displayed confusion, memory impairment, and an inability to follow commands or form coherent speech. Her total delirium observation score was 10. The thiamine dose was increased to 100 mg IV every 4 hours for presumed ifosfamide neurotoxicity. After 2 doses of IV thiamine and continued neurological decline, methylene blue 50 mg IV was added every 6 hours. As a precaution, the patient's paroxetine, which she had been taking daily for at least the past 3 years, was discontinued. Over the next 6 to 12 hours and after 2 additional doses of methylene blue, her status deteriorated further. In addition to worsening confusion (total delirium observation score of 13), she developed severe sinus tachycardia (185-210 beats/min), hypertension (increase from 120/77 to 150/87 mm Hg), diaphoresis, fever (peak temperature 38°C), and combativeness. On physical examination, she demonstrated hyperreflexia, ocular clonus, spontaneous muscular clonus, and facial tremors. These symptoms and physical examination findings led to concern for serotonin syndrome, and as a result, methylene blue was discontinued. Her ondansetron was stopped for the same reason. She received IV lorazepam, metoprolol, acetaminophen, and hydromorphone for symptomatic management. During the course of her clinical decline, she was transferred to the critical care unit to provide elevated measures of care and intubation for airway protection. Initial laboratory tests, which included blood cell counts, electrolytes, renal function panel, and liver function tests, were within normal limits. A workup for sepsis consisting of blood and urine cultures in addition to chest imaging was unremarkable. Computed tomography and magnetic resonance imaging of the head revealed no acute vascular events or other abnormalities. Intravenous thiamine was continued in combination with general supportive care measures, and the patient was monitored closely. Her mentation slowly improved over the next 6 days in the critical care unit, and she was extubated. She demonstrated normal memory and fluent speech without the presence of any uncontrolled movements. After 15 total days of hospitalization, including 8 in the critical care unit, she was discharged from the hospital without residual encephalopathic or neurological symptoms. Subsequently, the patient was seen for a follow-up appointment in the sarcoma ambulatory care clinic to assess her response to therapy and discuss further disease management. Given the severe toxicities the patient had experienced with ifosfamide, it was determined that it would not be safe to rechallenge with the agent. Alternative options included further systemic therapy with single-agent doxorubicin or different agents altogether or surgical management. Given that her disease recurrence continued to be oligometastatic and that more systemic therapy would not be likely to provide any significant benefit, her oncologist elected to attempt surgical resection with the goal of leaving the patient with no evidence of disease. Two months later, the patient underwent resection of regional recurrence of 2 sites of disease. At last clinic follow-up prior to publication, imaging displayed no evidence of disease.

## Discussion

Serotonin syndrome is a disorder arising from increased serotonergic activity in the central nervous system that is precipitated by medications, drug–drug interactions, or drug overdose via accidental or purposeful intentions.[7] Patients presenting with this potentially life-threatening condition classically display the triad of autonomic hyperactivity, neuromuscular abnormalities, and mental status changes. Autonomic overactivation can present as a variety of symptoms ranging from hypertension, tachypnea, and tachycardia to diaphoresis and hyperthermia. Mental status changes often include disorientation, delirium, anxiety, or severe agitation.[8,9] Potential neuromuscular abnormalities include akathisia, tremor, myoclonus, or hyperreflexia, with the latter 2 more commonly displayed in the lower extremities.[9]

Initial treatment of the disorder is relatively straightforward, as discontinuing all offending serotonergic agents and managing associated symptoms are primary steps of care. However, accurately recognizing the disorder is more complex. Serotonin

**Table 1.** Commonly Used Agents in the Oncology Population Associated With Increased Risk of Serotonin Syndrome.[a]

| Indication | Class or Specific Agent |
|---|---|
| Depression | Selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, serotonin modulators, dopamine–norepinephrine reuptake inhibitors, monoamine-oxidase inhibitors |
| Pain management | Tramadol, methadone, fentanyl |
| Migraine | 5-hydroxytryptamine-1B/1D receptor agonists (triptan class) |
| Nausea | 5-hydroxytryptamine-3 antagonists, metoclopramide |
| Anxiety | Buspirone |
| Infection | Linezolid, tedizolid |

[a]Potential agents in the oncology population associated with the increased risk of serotonin syndrome.

syndrome is a diagnosis of exclusion after other metabolic, infectious, ischemic, and toxic etiologies are ruled out. Timely diagnosis is of utmost importance, as the differential is wide and includes neuroleptic malignant syndrome, anticholinergic toxicity, sympathomimetic drug intoxication, meningitis, encephalitis, or withdrawal from sedative-hypnotic agents.[10] Physical examination is pivotal to this process, and there are several tools available to aid practitioners in utilizing the information gathered. Of these, the Hunter Serotonin Toxicity Criteria (HSTC), found to be more sensitive and specific than Sternbach criteria, appear to be the most useful.[11] To meet the HSTC, a patient must be on a serotonergic agent in addition to 1 of the 5 following criteria: ocular clonus plus agitation or diaphoresis, inducible clonus plus agitation or diaphoresis, tremor and hyperreflexia, spontaneous clonus, and hypertonia and a temperature above 38°C plus ocular or inducible clonus.[10,11] Despite the potential utility of the HSTC, appropriate diagnosis is often delayed or missed altogether. An essential workup component involves obtaining an extensive, detailed patient medication history. Doses, dosing schedules, and formulations for every medication or substance a patient takes prior to onset of symptoms should be assessed for serotonergic potential. It is especially imperative to look for any recent changes to a patient's regimen, as serotonin syndrome commonly presents within 24 hours of initiating a new agent or changing the dose of a current medication.[9]

Several pharmaceutical agents commonly used in the management of patients with cancer are serotonergic and therefore can contribute to the risk of serotonin overdose (Table 1).[10] Monoamine oxidase inhibitors, while less common in clinical practice than some of the other agents listed, can be contributory to serotonin syndrome as they effectively inhibit serotonin metabolism. Methylene blue falls into this category as an inhibitor of both MAO A and MAO B.[12] Compounds that are strong inhibitors of select cytochrome P450 (CYP450) enzymes can also increase the risk of serotonin overdose via drug−drug interactions. Several of the listed agents are CYP2C19, CYP2D6, and CYP3A4 substrates and will have their serotonergic properties greatly increased with concomitant administration of such an inhibitor.[10]

Encephalopathy is a well-described potential neurologic complication of treatment with ifosfamide. Neurotoxicity typically occurs hours or days after drug administration. Initial management includes supportive care, close monitoring, and slowing the rate of or discontinuing the ifosfamide infusion. Most patients with mild symptoms do not require additional treatment, and the disorder resolves spontaneously. Methylene blue has been explored as a treatment of ifosfamide neurotoxicity to shorten the duration of severe symptoms and as a prophylactic measure to stop the disorder from occurring altogether.[12] However, evidence demonstrating benefit for the practice is sparse and is limited to retrospective reports with no controlled trials. A literature review by Patel[1] found that while the agent appeared to work rapidly in select cases, in most instances, the efficacy of methylene blue was not well established. This review also made the astute recognition that the potential of ifosfamide neurotoxicity to spontaneously improve complicates any assessment of true treatment efficacy.[1] Still, these shortcomings are not enough to deter use of the agent in severe cases. Even if uncertain, the chance for potential benefit that methylene blue offers in these instances can outweigh the risks of associated adverse events, including serotonin syndrome.

Methylene blue is known to cause serotonin syndrome, most commonly with nononcologic uses.[13] However, to our knowledge, only 1 previous case of serotonin syndrome has been reported in association with methylene blue treatment for ifosfamide neurotoxicity.[13] Factors that may contribute to the rarity of this event include relative uncommonness of the treatment indication, a lower dose of methylene blue than used for other indications (eg, this report: 50 mg in a 68-kg patient, approximately 0.74 mg/kg), and challenges in establishing the diagnosis of serotonin syndrome in the face of a preexisting neurological condition. Our case highlights the difficulty in diagnosis of serotonin syndrome in patients with ifosfamide neurotoxicity because of symptom overlap between these 2 conditions, including confusion, disorientation, and movement disorders such as generalized myoclonus.[14] In the case reported here, a diagnosis of serotonin syndrome was strongly suspected given the correlation between methylene blue initiation and worsening of symptoms just 5 to 8 hours later as well as the new development of autonomic dysregulation and classic physical examination findings. Utilizing the HSTC, our case had a high probability of serotonin syndrome. The resolution of serotonergic symptoms after discontinuation of the agent validated this diagnosis. Of note, the patient was also on several additional medications that increase the risk of serotonin syndrome, which is common in the oncology population.

Given the unproven benefit of methylene blue in the treatment of ifosfamide neurotoxicity, potential toxicities of this medication should carry weight in the treatment decision. For this reason, in our opinion, methylene blue should only be used in severe cases. In situations where methylene blue is utilized,

clinicians must consider the diagnosis of serotonin syndrome in patients with further encephalopathic decline, particularly if new autonomic dysfunction is present. Rapid recognition of serotonin syndrome and discontinuation of the offending agent or agents are essential to proper management.

## Conclusions

Methylene blue is a commonly used agent for the treatment of severe cases of ifosfamide neurotoxicity. However, the administration of methylene blue can precipitate serotonin syndrome. This risk is increased if other serotonergic medications are administered concurrently, which is common in the oncology population. Practitioners should be vigilant to make an early diagnosis and remove the offending agents to treat this potentially fatal disorder.

### Authors' Note

No significant relationships exist between the authors and the companies/organizations whose products or services may be referenced in this article.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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