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# Fatal methylene blue associated serotonin toxicity

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## ABSTRACT

This is the first report of a fatal outcome from serotonin toxicity, precipitated by an interaction between methylene blue and venlafaxine. Methylene blue-associated serotonin toxicity has been described before but usually as mild toxicity. Its presentation after general anaesthesia may be atypical and therefore more difficult to diagnose. However, the syndrome is completely preventable if serotonin re-uptake inhibiting agents are stopped beforehand.

## KEYWORDS

Serotonin toxicity, serotonin syndrome, methylene blue, methylthioninium chloride, 5HT-2A antagonism, hyperthermia, fatal

## INTRODUCTION

Methylene blue (methylthioninium chloride) is, among other indications, used in parathyroid surgery to facilitate visualisation of the parathyroid glands.<sup>1</sup> It is administered intravenously shortly before surgery and is quickly absorbed into the pathological tissues with a resulting blue discoloration.

Methylene blue is commonly regarded as an inert dye, but has recently been shown to act as a potent reversible monoamine oxidase (MAO) inhibitor with a strong preference for MAO-A inhibition.<sup>2</sup> Because the inhibition constant is in the nanomolar range, even small doses of methylene blue (less than 1 mg/kg) may exert clinically relevant MAO inhibition.<sup>3</sup> This effect is enhanced because methylene blue is rapidly absorbed in nervous tissue

### What was known on this topic ?

Methylene blue has been associated with severe central nervous system toxicity and has subsequently been shown to act as a monoamine oxidase inhibitor and can give rise to serotonin toxicity.

### What does this add ?

Methylene blue-associated serotonin toxicity can be fatal and its presentation may be atypical after general anaesthesia.

where, in rat models, it reaches brain concentrations ten times higher than in serum.<sup>4</sup>

Therefore, methylene blue can lead to serious side effects. Because MAO inhibition increases the intrasynaptic levels of serotonin (5-HT), serotonin toxicity is to be expected, especially when methylene blue is combined with serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). This report is the first of a fatality precipitated by probable serotonin toxicity, involving methylene blue and a SNRI.

## CASE REPORT

A 70-year-old female was diagnosed with primary hyperparathyroidism and scheduled for surgery under general anaesthesia. Her past medical history was significant for diabetes, an ischaemic CVA and a mood disorder for which she used venlafaxine 75 mg twice daily. On the morning of her surgery, the patient took her last dose of venlafaxine and one hour before induction of

anaesthesia, 1 gram of methylene blue (9 mg/kg) was given intravenously. Anaesthesia was performed with propofol induction and sevoflurane maintenance and atracurium was used for muscle relaxation. After surgery, in the recovery room, the patient suddenly became agitated. Hypoglycaemia was ruled out and symptomatic treatment instituted with droperidol and midazolam. However, her mental status deteriorated for which the neurologist and internist were consulted. The neurological examination showed agitation, reduced consciousness, pupillary dilatation, ocular clonus, dysarthria, neuromuscular hyperactivity and hyperreflexia, predominantly in the lower limbs. The temperature was 36 °C. A relevant hypocalcaemia or hypercalcaemia and a haemorrhagic cerebrovascular accident (CT scan) could be excluded. Because of further neurological deterioration with profuse sweating, hypersalivation, opisthotonus and a bilateral pyramidal syndrome, the patient was transferred to the intensive care unit with a differential diagnosis of malignant neuroleptic syndrome, ischaemic brainstem infarction or epileptic insults with postictal status (for which valproic acid was started). On admission she had normal vital functions but after nine hours her temperature rose to 39 °C (figure 1). The patient became respiratory and haemodynamically unstable and she needed intubation and mechanical ventilation. Cooling was instituted with infusion of 2 litres of cold fluids and application of a fluid filled cooling blanket. Because of worsening hyperthermia, dantrolene (1.8 mg/kg) was given. Maximum temperature was 43.1°C. Although the temperature decreased after dantrolene administration, the patient died from circulatory collapse not responding to volume resuscitation, inotropes and vasopressors. Permission for autopsy was not granted.

## DISCUSSION

Methylene blue-associated neurotoxicity has been incidentally reported since 2003 and the association with serotonin toxicity was made in 2006. Ramsay showed that methylene blue is a potent MAO-A inhibitor.<sup>2</sup> Low doses of 0.7-1 mg/kg methylene blue intravenously may already give rise to clinically relevant MAO inhibition.<sup>3,5</sup>

Two retrospective surgical series describe postoperative encephalopathy in 17 of 325 patients (5%) after parathyroid surgery with the use of methylene blue.<sup>6,7</sup> All of them used SRI agents. Additionally, 15 cases have been reported with serotonin toxicity during the use of methylene blue.<sup>8,9</sup> Our patient, however, is the first fatality from probable serotonin toxicity described in the literature. We reported the case to the relevant authorities.

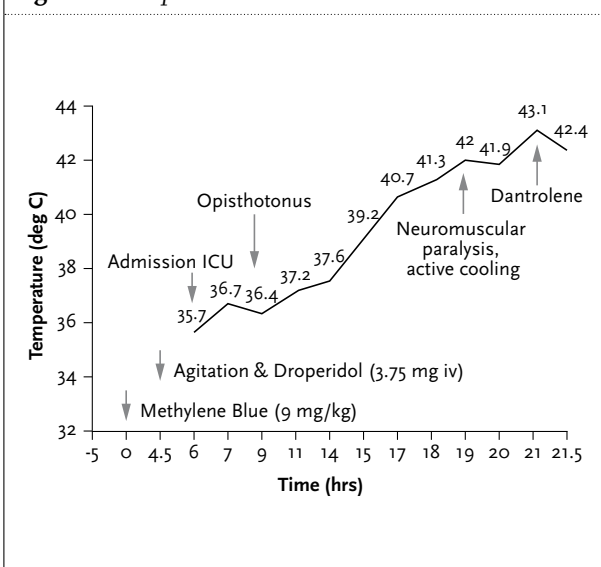
Serotonin toxicity or serotonin syndrome consists of a clinical trial of changed mental status, autonomic stimulation and neuromuscular excitation. Mono-intoxication with SRI agents only leads to moderate toxicity (without severe hyperthermia), for severe toxicity concurrent use of a MAO inhibitor is required.<sup>8</sup> Diagnostic criteria have been proposed and the Hunter criteria focus on specific neuromuscular signs in the context of SRI agents, such as a rapid onset, hyperreflexia, tremor and inducible or spontaneous (ocular) clonus, with symptoms often more pronounced in the lower limbs.<sup>10</sup>

Our patient showed most of these discriminating signs, except the rapid onset. This may be explained by her general anaesthesia which, in animals, induces preferential brain hypothermia and therefore may lead to a protracted course and atypical presentation of serotonin toxicity.<sup>11</sup> In our case, clinical symptoms arose 4.5 hours after administration of methylene blue, but hyperthermia was only observed after 15 hours.

Treatment is based on two key points: discontinuation of the implicated drugs and aggressive supportive therapy. Agitation can be controlled with benzodiazepines. Moderate and severe toxicity may benefit from serotonin receptor 2a (5-HT<sub>2A</sub>) blockade with cyproheptadine tablets or parenteral chlorpromazine most often cited. There are, however, also other potent 5-HT<sub>2A</sub> antagonists such as olanzapine and ketanserin.<sup>12,13</sup> Ketanserin does have the benefit of intravenous availability and a lack of effect on dopamine receptors which makes it a safer choice if neuroleptic malignant syndrome cannot be excluded.

Hyperthermia should be treated with cooling therapy including sedation and muscle relaxation. The use of dantrolene in hyperthermic syndromes apart from the classical malignant hyperthermia is not well defined. Dantrolene may be of additive value because it modulates not only peripheral muscle ryanodine receptors but also cerebral ryanodine receptors. This modulates the dopaminergic system which may be involved in the

Figure 1. Temperature course



pathogenesis of some centrally mediated hyperthermic syndromes.<sup>14</sup>

In conclusion, serotonin toxicity is a predictable and hence preventable side effect if methylene blue is combined with SRI agents. Routine use in parathyroid surgery is not advised and there are better alternatives available for intraoperative localisation. If methylene blue is applied, stopping SRI agents five half-lives before administration of methylene blue is sufficient to prevent serotonin toxicity. Therefore, a drug withdrawal of two weeks is needed for most SSRIs and of five weeks for fluoxetine.

Because of the wide use of SRI agents, the existence of other indications for methylene blue outside parathyroid surgery (*table 1*) and the unawareness of the diagnosis of serotonin toxicity in general, we think the real prevalence of methylene blue-induced serotonin toxicity is greater than reported and needs clinical attention.

**Table 1.** *Clinical indications or active recruiting studies with the use of methylene blue*

	Methylene blue dose	ST reported
Methemoglobinaemias	1-2 mg/kg IV	No
Ifosfamide-induced encephalopathy	50 mg IV every four hours till symptoms resolve	Yes <sup>5</sup>
Treatment of vasoplegic syndrome	2 mg/kg IV	No
Parathyroid imaging	3-7.5 mg/kg IV	Yes <sup>6,7</sup>
Treatment of malaria	10 mg/kg twice a day orally for three days	No
Colonic diagnostic staining	200mg orally single gift	No
PTSD treatment adjunct	260 mg orally for 6 days	No

PTSD = post-traumatic stress syndrome; ST = serotonin toxicity.

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