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# PROLONGED ANESTHETIC EMERGENCE AFTER LOW DOSE METHYLENE BLUE FOR PARATHYROID GLAND VISUALIZATION

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## OBJECTIVE

The monoamine oxidase (MAO) inhibitor properties of methylene blue can lead to a serotonin syndrome in patients on serotonergic drugs. We report a case of prolonged anesthetic emergence diagnosed as a serotonin syndrome after the use of 1.5mg/kg methylene blue in a patient on paroxetine.

**CASE HISTORY** - A 52-year old overweight female patient (BMI 42) with primary hyperparathyroidism was scheduled for right inferior parathyroidectomy and adenoma removal.

The patients medical history was significant for hypertension, hyperlipidemia, depression, vascular thrombosis-related pulmonary embolism and rheumatoid arthritis. She underwent several previous general anesthesia without notable adverse events. Her medications included bisoprolol, atorvastatine, paroxetine, alprazolam, methylprednisolone, ledertrexate, etanercept, rivaroxaban and zolendronate. Rivaroxaban was stopped 2 days before surgery without bridging. The patient underwent general anesthesia with administration of droperidol, fentanyl, xylocaine, propofol, suxamethonium, and sevoflurane maintenance. After induction, 150 mg (1.5 mg/kg) methylene blue was administered by intravenous injection over 20 minutes. After an uneventful 60 minute surgical procedure, a bilateral horizontal nystagmus was noticed on extubation. In the recovery room, the patient was slightly agitated and remained aphasic. She presented uncoordinated limb movements. The patient developed slight hyperthermia (38.2°C) and was transferred to the intensive care unit. She was unreactive to verbal or pain stimulation (Glasgow Coma Score 6) with motoric agitation and bilateral reactive mydriasis. Ocular clonus and bilateral Babinski sign were noted. Her body temperature remained between 38°C and 38.5°C.

**EXAMINATION** - Her serum routine biochemistry was unremarkable. A computed tomography (CT) of the brain showed no evidence of stroke, mass or hemorrhage; a lumbar puncture was performed with normal cerebrospinal fluid examination. All catheter cultures remained negative.

**OUTCOME** - Six hours after admission in the ICU her consciousness gradually improved. She began to answer on simple orders and was mentally confused (Glasgow Coma Score 9). Twenty-four hours after the procedure, the patient totally recovered, became fully awake and responsive and was discharged to the floor. Review of the patients medication lead to suspicion of a serotonin syndrome due to a drug interaction between methylene blue and the selective serotonin reuptake inhibitor paroxetine.

## DISCUSSION

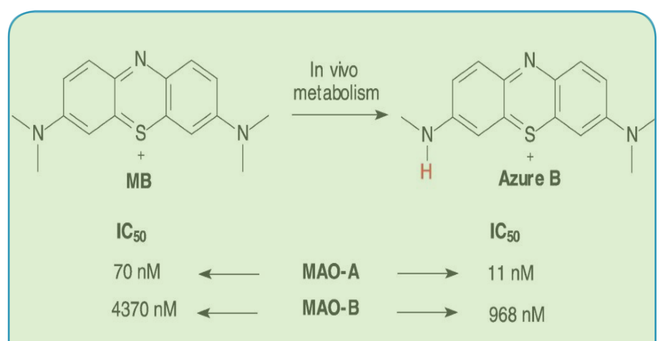
Methylene blue is used in medicine for more than 40 years. Its principal indication is the treatment of methemoglobinemia at a dose of 1-2 mg/kg intravenous. It is also used in the treatment of refractory distributive shock. At higher dose, up to 10 mg/kg, methylene blue is used for perioperative organ staining, particularly in parathyroid and urological surgery.

Methylene blue and its metabolite, azure B, have Monoamine oxidase A (MAO A) inhibiting properties that can cause a serotonin syndrome at high dose or by drug interactions with serotonin drugs. (Fig.) A dose of 0.75 mg/kg is sufficient to inhibit the monoamine oxidase in the CNS.

Between 2003 and 2012 several reports of neurotoxicity related to the use of high dose methylene blue as a staining agent in surgery or as a vasopressor in intensive care were published. Medical professionals were informed by the U.K. Medicines and Health care products regulatory Agency on the CNS toxicity of methylene blue in April 2009.

Patients with hyperparathyroidism surgery are at high risk for depressive syndrome and are more susceptible to be prescribed antidepressants, SSRIs and SNRIs being the most widely prescribed. The serotonin syndrome presents a clinical triade which involves autonomic, neuromuscular and mental status changes. The diagnosis may be challenging as symptoms can vary in nature and intensity. Hunter's criteria (see table) may be used to diagnose this condition with a sensitivity of 84% and a specificity of 97%. (ref. 1)

At the time of surgery, our patient was taking paroxetine 40 mg/day. The time course of her neurological disorders and the presence of ocular clonus, agitation and a body temperature >38 C° lead to the diagnosis of serotonin syndrome. The dose of methylene blue used by the surgeon was quite low (1.5 mg/kg in comparison with the 7-8 mg/kg dose commonly used in perioperative staining) and lead to a moderate and self-limiting symptomatology.




(Fig.) (ref. 2) Methylene blue and its metabolite, azure B have Monoamine oxidase A (MAO A) inhibiting properties that can cause a serotonin syndrome.

### Hunter serotonin toxicity criteria

In the presence of a serotonic agent ANY of

- Spontaneous clonus
- Inducible clonus AND agitation OR diaphoresis
- Ocular clonus AND agitation OR diaphoresis
- Tremor AND hyperreflexia
- Hypertonia AND Temperature >38°C AND ocular OR inducible clonus

## CONCLUSION

Diagnosis of a serotonin syndrome is a diagnosis of exclusion. In our patient, the symptoms of agitation, ocular clonus, impaired consciousness with moderate elevation of body temperature with no evidence of infection or neurological lesion lead to the diagnosis of a serotonin syndrome due to interaction between paroxetine and methylene blue.

Surgery is usually planned a long time in advance. Serotonin syndrome due to drug interaction is a preventable event. Tapering of serotonin reuptake inhibitor antidepressants several weeks before surgery should be considered when the use of methylene blue is planned. Good communication between caregivers who usually have little interactions like anesthesiologists and psychiatrists is advisable.

### References

(1) Dunkley (E.J.), Isbister (G.K.), Sibbritt (D.), Dawson (A.H.) and Whyte (I.M.). The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM (2003), vol. 96, iss. 9, p. 635-642.
(2) Petzer (A.), Harvey (B.H.), et al. Azure B, a metabolite of methylene blue, is a high-potency, reversible inhibitor of monoamine oxidase. Toxicology and Applied Pharmacology (2012), p. 403-409.