

The blue coma: the role of methylene blue in unexplained coma after cardiac surgery

More than 10% of U.S. citizens aged 12 and over take antidepressant medication, and this percentage is mirrored in many other countries. The most commonly prescribed antidepressant drugs are Selective Serotonin Reuptake Inhibitors (SSRIs), whose mechanism of action is the inhibition of the Serotonin Transporter with a consequent increase of Serotonin levels.

One of the most dangerous condition associated with increased serotonergic activity in the central nervous system is Serotonin Toxicity, also known as Serotonin Syndrome. Features of Serotonin Toxicity can be divided into three categories: altered mental status (agitation, excitement, confusion and coma), altered neuromuscular excitability (manifesting as clonus, hyperreflexia, myoclonus, tremor and pyramidal rigidity) and autonomic instability (hyperthermia, tachypnoea, tachycardia, diaphoresis and mydriasis). Serotonin Toxicity can lead to death or near death.

Methylene Blue (methylthioninium chloride, MB) is a redox dye with various clinical uses including the treatment of cyanide poisoning or methemoglobinemia and the staining of tissues. It is used off-label as a vasopressor to treat vasoplegic syndrome since it is able to reduce the dose of vasoconstrictors and possibly improve patients' outcome.

We describe three cases of severe Serotonin Toxicity in patients receiving Methylene Blue as a vasopressor after cardiac surgery who were later discovered to be on chronic SSRI therapy.

Three women on chronic SSRI therapy (paroxetine, citalopram and sertraline, respectively) underwent cardiac surgery with cardiopulmonary bypass. During surgeries, physicians used propofol, rocuronium, fentanyl and sevoflurane to induce and to maintain anaesthesia. All three patients developed vasoplegic syndrome while sedated with propofol in the intensive care unit (ICU) following surgery. After non responsive therapy with norepinephrine they received Methylene Blue as rescue therapy.

All three patients developed a coma, for which they underwent neurological investigation. Their brain computed tomography scans were negative, and all patients had pyramidal signs and lower limb hyperreflexia.

After the coma, ICU stay was uneventful in patients 1 and 2, who were discharged within 24 hours of awakening, while patient 3 had a complicated ICU stay caused by concomitant cardiogenic shock and sepsis.

The common features among patients were the regular use of SSRI medication, the administration of methylene blue because of a vasoplegic syndrome and the neurological signs and symptoms.

Management of serotonin toxicity is based on the discontinuation of all serotonergic agents, supportive care with oxygen (aiming at oxygen saturations? 94%), fluid therapy, continuous monitoring of vital functions, sedation with benzodiazepines (eg. lorazepam) and treatment of hyperthermia while avoiding antipyretics such as acetaminophen.

If serotonin toxicity is hypothesized, it must be distinguished from other syndromes that have similar clinical presentations: these include but are not limited to neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic toxicity, and infectious diseases such as meningitis and encephalitis.

The interaction with methylene blue holds true for other psychiatric medication with serotonergic effect: tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, other MAOIs, and other drugs such as bupropion, busiprone, trazodone, amoxapine, fentanyl and nefazodone. The complete list of drugs that can have a dangerous interaction with methylene blue is detailed in a Food and Drug Administration note from 2011.

In consideration of the widespread use of serotonergic drugs in the general population, and the increasing adoption of methylene blue to reduce the doses of standard vasoconstrictors in vasoplegic syndrome, the “blue coma” should be considered in the differential diagnosis of any postoperative coma with negative imaging and unspecific EEG, in fact in case methylene blue has been administered in a patient on chronic antidepressant therapy, the likelihood of this diagnosis is higher than microembolization or low cardiac output syndrome.

The off-label use of methylene blue in vasoplegic cardiac surgical patients chronically taking SSRIs, or other serotonergic drugs, must be avoided.

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