The Blue Coma: The Role of Methylene Blue in Unexplained Coma After Cardiac Surgery

Enrico Antonio Martino, MD,* Dario Winterton, MD,* Pasquale Nardelli, MD,* Laura Pasin, MD,* Maria Grazia Calabrò, MD,* Tiziana Bove, MD,* Giovanna Fanelli, MD,† Alberto Zangrillo, MD,*‡ and Giovanni Landoni, MD*‡

Objectives: **Methylene blue commonly is used as a dye or an antidote, but also can be used off label as a vasopressor. Serotonin toxicity is a potentially lethal and often misdiagnosed condition that can result from drug interaction. Mild serotonin toxicity previously was reported in settings in which methylene blue was used as a dye. The authors report 3 cases of life-threatening serotonin toxicity in patients undergoing chronic selective serotonin reuptake inhibitor (SSRI) therapy who also underwent cardiac surgery and received methylene blue to treat vasoplegic syndrome.**

Design: **An observational study.**

Setting: **A cardiothoracic intensive care unit (ICU) in a teaching hospital.**

Participants: **Three patients who received methylene blue after cardiac surgery, later discovered to be undergoing chronic SSRI therapy.**

Interventions: **None.**

Measurements and Main Results: **All 3 patients received high doses of fentanyl during general anesthesia. They all developed vasoplegic syndrome and consequently were given methylene blue in the ICU. All 3 patients developed serotonin toxicity, including coma, after this administration and diagnostic tests were negative for acute intracranial pathology. Coma lasted between 1 and 5 days. Two patients were discharged from the ICU shortly after awakening, whereas the third patient experienced a complicated postoperative course for concomitant refractory low-cardiac-output syndrome.**

Conclusions: **Patients undergoing chronic SSRI therapy should not be administered methylene blue to treat vasoplegic syndrome.**

KEY WORDS: methylene blue, coma, vasoplegic syndrome, selective serotonin reuptake inhibitors, serotonin syndrome, thoracic surgery, anesthesia, intensive care

SEROTONIN TOXICITY is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system. There are reports of serotonin toxicity in intentional self poisoning and inadvertent interactions between drugs and therapeutic medication use.[1] Serotonin toxicity often is not recognized immediately,[2] and can manifest with findings that range from benign to lethal. Features of serotonin toxicity can be divided into the following 3 categories: altered mental status (agitation, excitement, confusion, and coma); altered neuromuscular excitability (clonus, hyperreflexia, myoclonus, tremor, and pyramidal rigidity); and autonomic instability (hyperthermia, tachypnea, tachycardia, diaphoresis, and mydriasis).[3] Serotonin toxicity can lead to death or near-death conditions.[4–6] It is important to note that serotonin toxicity is a predictable consequence of excess serotonergic agonism of the central receptors, 5-HT1A and 5-HT2 in particular, and thus can be prevented.[2]

More than 10% of U.S. citizens ages 12 and older take antidepressant medications,[7] and this percentage is mirrored in many other countries.[8] 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 5-HT levels.[9] SSRIs are unlikely to cause severe serotonin toxicity on their own, even when taken in overdose, but combination with monoamine oxidase inhibitors (MAOIs) is a known trigger for this life-threatening condition.[10]

Methylene blue (methylthioninium chloride) is a redox dye with various clinical uses, including the treatment of cyanide poisoning or methemoglobinemia and the staining of tissues. It exhibits powerful reversible MAOI activity, in particular as an MAO-A inhibitor.[3] It also is used off label as a vasopressor to treat vasoplegic syndrome and has been found to be safe and effective in a recent meta-analysis of randomized trials by Pasin et al;[11] although Weiner et al have challenged this evidence, identifying methylene blue as an independent predictor of poor outcome in cardiac surgery patients who are vasoplegic.[12]

The authors describe 3 cases of severe serotonin toxicity with otherwise unexplained coma in patients who received methylene blue as a vasopressor after cardiac surgery who were later discovered to be undergoing chronic SSRI therapy.

MATERIALS AND METHODS

Three women undergoing chronic SSRI therapy with paroxetine, citalopram, and sertraline, respectively, underwent cardiac surgery with cardiopulmonary bypass. Anesthesia was induced with propofol, rocuronium, and fentanyl. Anesthesia was maintained with a combination of propofol, rocuronium, sevoflurane, and high doses of fentanyl. Details on the patients are reported in Table 1.

Serotonin toxicity was diagnosed retrospectively in all 3 patients using the Hunter criteria (reported in Table 2).[13]

Patients signed a written consent for the scientific use of their data. Ethics committee approval was waived according to Italian law.

*From the *Department of Anesthesia and Intensive Care; †Department of Neurology, IRCCS San Raffaele Scientific Institute; and ‡Vita-Salute San Raffaele University Milano, Italy.*

E.A.M and D.W. contributed equally to this work.

Address reprint requests to Giovanni Landoni, MD, Department of Cardiothoracic Anesthesia and Intensive Care, San Raffaele Scientific Institute, Via Olgettina 60, Milano, 20132 Italy. E-mail: landoni.giovanni@hsr.it

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2015.09.011

Table 1. Clinical Preoperative and Intraoperative Details of the 3 Patients Who Experienced Serotonin Toxicity Coma After Methylene Blue Administration

Patient	Surgery	Medical History	SSRI	Other Chronic Medications	Anesthesia
Patient 1: 65-year-old woman (160 cm, 65 kg)	Aortic valve replacement	COPD	Paroxetine* (20 mg/day)	Lansoprazole	Induction:
	Ostium secundum atrial septal defect repair	Pulmonary embolism		Valsartan	Propofol (50 mg)
	Surgical time: 250 minutes	Atrial fibrillation		OAC therapy	Midazolam (5 mg)
	CPB length: 112 minutes	RV dilation		Lormetrazepam	Fentanyl* (250 μg)
		Aortic valve disease		Furosemide	Rocuronium (50 mg)
		Panic disorder			Maintenance:
					Propofol (1,354 mg)
					Fentanyl* (700 μg)
					Rocuronium (80 mg)
					Sevoflurane (0.5-1 MAC/hr)
Patient 2: 82-year-old woman (158 cm, 70 kg)	Aortic valve replacement	Hypertension	Citalopram* (20 mg/day)	Losartan	Induction:
	Surgical time: 110 minutes	Atrial fibrillation		Levothyroxine	Propofol (100 mg)
	CPB length: 57 minutes	Aortic valve disease		Pantoprazole	Fentanyl* (300 μg)
		Hypothyroidism		Bisoprolol	Rocuronium (50 mg)
		Osteoporosis		Furosemide	
				Canrenone	Maintenance:
				Warfarin	Propofol (513 mg)
				Nitroglycerin plaster	Fentanyl* (400 μg)
				Acetylcysteine	Rocuronium (90 mg)
					Sevoflurane (0.3-0.8 MAC/hr)
Patient 3:	Aortic valve replacement	Aortic valve disease	Sertraline* (25 mg/day)	Amisulpride*	Induction:
74-year-old woman (165 cm, 78 kg)	Mitral valve replacement	Mitral valve disease		Trazodone*	Propofol (100 mg)
	Tricuspid valve repair	Rheumatoid arthritis		Levothyroxine	Fentanyl* (250 μg)
	Radiofrequency	Depressive syndrome		Lansoprazole	Rocuronium (50 mg)
	Surgical time: 255 minutes	Atrial fibrillation		Gabapentin	
	CPB length: 149 minutes	Recurrent cardiac failure		Vitamin D	Maintenance:
		Hypothyroidism		Furosemide	Propofol (962 mg)
				Simvastatin	Fentanyl* (750 μg)
				Canrenone	Rocuronium (170 mg)
				Foline	Sevoflurane (0.5-1 MAC/hr)
				Acetaminophen	
				Allopurinol	
				Prednisone	
				Methotrexate	
				Nitroglycerin	

Abbreviations; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; OAC, oral anticoagulant; SSRI, selective serotonin reuptake inhibitor; RV, right ventricular.

*Drugs with a serotonergic effect.

RESULTS

All 3 patients (described in Table 3) developed vasoplegic syndrome while sedated with propofol in the intensive care unit (ICU) after surgery and received a continuous infusion of norepinephrine and/or epinephrine. Methylene blue (100 mg over 20 minutes) was administered to reduce the dose of vasoconstrictors and was repeated after a few hours in all patients.

All 3 patients developed coma, for which they underwent neurologic investigation. Their brain computed tomography scans were negative for acute intracranial pathology, and all patients experienced pyramidal signs and lower limb