Delayed Hypertensive Crisis Following Low-Dose Methylene Blue Administration During Pediatric Anesthesia

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Citation

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Abstract

Methylene blue possesses potent pharmacologic actions which may produce therapeutic benefits, but also harmful clinical conditions. Historically used to reduce methemoglobin levels, it has also been associated as a cause of hypertension. We describe a severe hypertensive crisis in a 6-yr-old girl undergoing bladder neck closure twenty minutes following low dose methylene blue administration.

INTRODUCTION

Methylene Blue has historically been used to reduce blood methemoglobin levels, as a diagnostic and antiseptic agent for the urinary tract, and in the treatment of malaria. More recently, it has been recognized that methylene blue is a guanylate cyclase inhibitor capable of limiting the cGMP-dependent smooth muscle vasodilatation effect of nitric oxide (NO). Thus it has been used therapeutically for refractory hypotensive states encountered in cardiopulmonary bypass, liver transplantation, and septicemia.

Methylene blue acts to accelerate methemoglobin conversion to hemoglobin in erythrocytes. It combines with nicotinamide adenine dinucleotide phosphate reduced (NADPH), in the presence of NADPH-methemoglobin reductase, to produce leukomethylene blue, and then reduces methemoglobin to hemoglobin. In higher concentrations, methylene blue oxidizes the ferrous iron of hemoglobin to the ferric state and converts hemoglobin to methemoglobin[1-4].

Methylene blue possesses potent pharmacologic actions which may produce therapeutic benefits, but also harmful clinical conditions. Hypertension has been known to occur, with mean arterial pressure elevations within 30-60 seconds following administration and normalizing within 90 seconds.[5] We describe a severe hypertensive crisis, blood pressure 242/174, in a 6-yr-old girl undergoing bladder neck closure twenty minutes following low dose methylene blue administration.

CASE REPORT

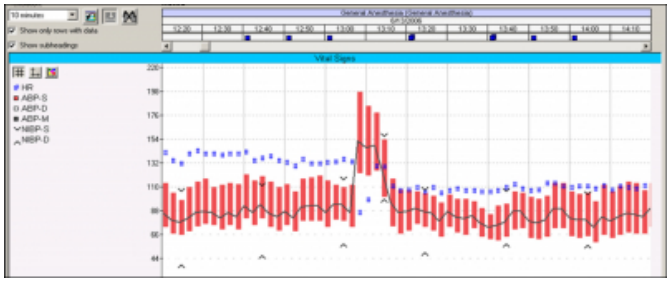
A 6 yr-old female with a history of cloacal exstrophy and Young-Dees bladder neck reconstruction was brought to the operating room for bladder augmentation and bladder neck closure to treat urinary incontinence. Prior surgical history consisted of surgical repair of imperforate anus with colostomy, release of tethered spinal cord, bilateral iliac osteotomies, and bladder neck reconstruction as above. Her previous anesthesia experiences were uneventful and without hemodynamic instability. Her physical examination revealed an otherwise healthy precocious six year-old, 108.5 cm in height, 17 kg weight, blood pressure 84/40, pulse 127. Preoperative medications included Furadantin 5 cc daily and Ditropan XL 10 mg daily. She had no known drug allergies. Intravenous induction of anesthesia consisted of midazolam 2 mg, fentanyl 20 mcg, lidocaine 20 mg, propofol 30 mg, and atracurium 8.4 mg. A 5.0 cuffed endotracheal tube was placed uneventfully. An arterial catheter and second 22 gauge IV were placed before the patient was prepped for surgery. Prior to administration of the methylene blue, this patient had received 0.5 mg (0.03mg/kg) of oxymorphone for intraoperative pain control. Anesthesia was maintained with isoflurane and oxygen. Nitrous oxide was not used.

After 90 minutes of surgery, and stable hemodynamic function, the surgeon requested methylene blue administration to allow visualization of ureteral orifices. Pediatric and adult intravenous dose recommendations of methylene blue are 1-2mg/kg, which for our patient, would be 17-34mg. She was given 10 mg, or 1 ml of 10mg/ml methylene blue which was then further diluted in 10 cc of

normal saline and infused intravenously over 10 minutes. Heart rate, blood pressure, and all respiratory parameters remained unchanged during and immediately following the infusion. By intraoperative records, 20 minutes later the surgeon requested and the patient received a fluid bolus to encourage urine output. Several minutes after this the arterial blood pressure rose acutely to 242/174, witnessed by two anesthesia providers. The computer, which records patient data every 2 minutes, captured the arterial systolic blood pressure of 198 mmHg as it was descending (Figure 1). The blood pressure spike was accompanied by a decrease in heart rate from 132 to 72. The patient was anesthetized at the time with 1.3 MAC of isoflurane, in addition to the oxymorphone, midazolam, and fentanyl she had received earlier. Isoflurane was increased to 2.2 MAC, and as the pressure began to decrease and heart rate increase, Labetalol 2.5 mg was given. No change in airway pressures occurred, and hemodynamic stability returned over the next several minutes. The procedure was completed without further complication. The patient manifested no untoward signs or symptoms on emergence from anesthesia, and the patient's mother was informed of the hypertensive episode and possible association with methylene blue. Her recovery from the operation was uneventful and positive results have been recorded at subsequent follow-up appointments.

Figure 1

Figure 1. Intraoperative record. Clearly seen is the brief but severe hypertensive response following Methylene Blue administration.



DISCUSSION

Untreated severe hypertensive crises in children have lead to hypertensive encephalopathy, end-organ ischemia, and death.[6-11] The anesthesia literature contains no published reports of severe, delayed hypertensive episodes following methylene blue administration, in either adult or pediatric patients. Nor has an adequate risk-benefit analysis or review of adverse events associated with methylene blue ever been published. In our patient, the hypertensive response to methylene blue is of interest for three reasons. The hypertensive event was: 1) delayed, 2) severe, 3) associated with low dosage.

First, hypertension is a known adverse effect of methylene blue but this reaction typically occurs immediately following large, rapidly administered doses. In one study of 12 patients who received 200 mg methylene blue intravenously (>2mg/kg), mean arterial blood pressure increased within 30 seconds. In all 12 patients, the blood pressure normalized within 3 minutes, the average being 177 seconds.[5] In our patient, the reaction occurred approximately 20 minutes after administration. This delay is curious and warrants further consideration. The possibility exists that the methylene blue remained in-line, hidden under drapes, resulting in a bolus just prior to the hypertensive crisis. The obvious coloration of this medication made this fact easily verifiable and the anesthesia provider is certain the entire infusion had been given. Moreover, IV fluids had continued to run slowly between the methylene blue infusion and the fluid bolus requested by the surgeon. Therefore, it is highly unlikely that a methylene blue bolus reached the patient immediately preceding the hypertensive episode. Another possible explanation for the delay is related to the fact that methylene blue is also known to inhibit hepatic degradation of catecholamines.[12] This patient, according to surgical team observation and documentation had an enlarged liver. Her hepatomegaly is of unknown significance and no preoperative liver function tests were indicated. It is interesting, though, that in an early study of methylene blue, it was shown to inhibit hepatic breakdown of adrenaline.[12] It is possible that the patient's hepatic function, following methylene blue administration, favored an excess of catecholamines due to delayed metabolism and lead to a vasoconstrictive crisis.

Another consideration involves the role of methylene blue and serotonin release. Schick and Yu found that methylene blue induces serotonin release from storage sites in human platelets.[13] Interestingly, they found that it often took up to 15 minutes before sizable amounts of serotonin, a known vasoconstrictor, is released. This physiologic phenomenon parallels more closely the time course of the hypertensive response in our patient.

Secondly, it is interesting that such a small dose of methylene blue produced such profound hemodynamic perturbations. Our patient received 0.58 mg/kg, a fraction of the 1-2 mg/kg recommended on the package insert and nearly 4-fold lower than the doses used in the study cited

above. Furthermore, the dose of 0.58 mg/kg was diluted in 10 cc of normal saline and administered slowly. The hypertensive responses in this study are from a far higher dose. It is thus unclear whether the magnitude of vasoconstriction can be correlated with dosage.

Thirdly, the severity of the hypertensive response merits explanation. The increase in systolic blood pressure, from 110 to 242, accompanied by decrease in heart rate from 132 to 72 clearly indicates a severe vasoconstrictive reaction with corresponding reflex bradycardia. The severity of this reaction, given the low dosage, is surprising and the patient was clearly at risk for cerebrovascular insult. It is has been shown in rat vas deferens studies that methylene blue enhances the sensitivity to noradrenaline through a pathway of neuronal uptake inhibition. Even though attempts are made to control sympathetic surges during surgical procedures by the anesthesiologist, it is not always possible to predict when the patient may manifest physiologic response to pain, especially when pre-emptive analgesia has been administered. Certainly in this case, surgical stimulation could cause sympathetic surges that were not adequately blunted pharmacologically leading to excessive adrenergic mediators. If the reuptake system of these mediators had been blocked by methylene blue, the excessive adrenergic stimulation could account for the observed hypertensive crisis, despite what would normally be considered adequate anesthesia.

Given the patient's history of tethered spinal cord and surgical release, an autonomic hypereflexic event was considered as a possible explanation for the hypertensive crisis. However, evaluation by pediatric neurologists, both before and after her surgery for urinary incontinence, demonstrated completely intact neurologic function. Documented sensory and motor examinations were completely normal and the patient was able to walk, run and perform complex gait maneuvers such as heel toe walk without difficulty. Therefore, an autonomic hypereflexic etiology for the hypertensive episode is an extremely remote possibility given her normal neurologic condition.

Methylene Blue remains an effective intraoperative medication with a long safety profile history. Like all medicines though, it may produce untoward effects in the right circumstances. In this case, it caused a hypertensive crisis in a young child. Though these reactions are rare, because of the potential problems they can lead to, it is important for the anesthesia provider to be aware of them.

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