CASE REPORT

Vasoplegic Shock Treated with Methylene Blue Complicated by Severe Serotonin Syndrome

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Abstract

Introduction Management of severe vasoplegic shock in overdose can be very challenging. We describe a case of severe refractory vasodilatory shock in poisoning where methylene blue (MB) was used with success. However, the patient subsequently developed severe Serotonin Syndrome (SS) as a result of an interaction between serotonergic drugs and MB. **Case Report** A 15-year-old male developed severe vasoplegic shock 1.5 hours after overdosing on several different medications including quetiapine slow release, quetiapine immediate release, desvenlafaxine slow release, venlafaxine, amlodipine, ramipril, fluoxetine, promethazine and lithium. His vasoplegic shock was resistant to high doses of noradrenaline and vasopressin. MB was administered 6.5 hours post ingestion and within 1 hour there was an improvement in his hemodynamic status and reduction of catecholamine requirements. Twelve hours post ingestion, he developed severe Serotonin

Syndrome that lasted 5 days as a result of interaction between MB, a reversible monoamine oxidase inhibitor (MAO-I), and the antidepressants taken in overdose. MB had a calculated half-life of 38 hours.

Conclusion MB is a useful additional strategy for severe drug induced vasodilatory shock and may be potentially life-saving. Clinicians should be aware that it can interact with other drugs and cause life-threatening Serotonin Syndrome. Lower doses or shorter durations may be wise in patients at risk of this interaction.

Keywords Methylene blue · Vasoplegic shock · Overdose · Serotonin syndrome

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Introduction

Poisoning-induced vasoplegic shock caused by the loss of vascular smooth muscle tone and severe vasodilatation can progress to multi-organ failure and mortality in up to 25% of patients, especially if it is resistant to catecholamine treatment and lasts longer than 48 h. [1] Methylene blue (MB) has been used for the management of distributive shock such as sepsis and toxic vasoplegic shock. [1] While MB has been reported to cause serotonin syndrome (SS) in cases where it was used as a surgical dye, there have been no reported cases of SS in association with its use in poisoning related vasoplegic shock. We report a case of severe SS in an overdosed patient treated with MB to manage catecholamine-resistant vasoplegic shock and calculated MB pharmacokinetic data.

Fig. 1 This figure demonstrated the temporal relationship of the vital signs and the administration of vasopressors and methylene blue

Case Report

A 70-kg 15-year-old male with a background history of essential hypertension and major depression presented to the Emergency Department 1.5-h post ingestion of a large mixed overdose of his own medications. Empty packets suggested ingestion of quetiapine slow release 1.5 g, quetiapine immediate release 12 g, desvenlafaxine moderate release 5.6 g, venlafaxine 1050 mg, amlodipine 290 mg, ramipril 100 mg, fluoxetine 560 mg, promethazine 500 mg and an unknown amount of lithium.

On arrival at the Emergency Department, he had a systolic blood pressure of 80 mmHg, pulse of 130 bpm and Glasgow Coma Score of 8 (Fig. 1). He was resuscitated with 3.5 L of crystalloid fluid, 10 ml 10% calcium gluconate and intubated. A dose of activated charcoal (50 g) was administered. Over the next hour, he required rapidly escalating boluses of metaraminol (total dose 1.5 mg) to maintain a mean arterial pressure (MAP) of 50 mmHg (normal dose for metaraminol, 0.5 mg slow intravenous bolus, repeated as needed to achieve blood pressure target). He was then commenced on noradrenaline, followed by vasopressin. Doses quickly escalated to 2 mcg/kg/min noradrenaline and 7 μ /h of vasopressin, with no improvement. Bedside transthoracic echocardiogram showed a hyperdynamic heart with good global contractility. Lithium concentration was 0.8 mmol/L (N 0.6–1.2 mmol/L) 5-h post overdose and subsequent concentrations were also within normal limits.

Due to persistent hypotension with MAP of 48 mmHg, a bolus of MB 1.5 mg/kg was given at 6.5-h post overdose, followed by an infusion of 1.5 mg/kg/h for 12 h and then 1 mg/kg/h for a further 12 h. The MAP improved in less than 30 min to 70 mmHg. Within 60 min of MB infusion, his BP increased from 65/40 to 120/45 mmHg. A PiCCO (pulse index contour continuous cardiac output) catheter was inserted post commencement of MB infusion. This showed a cardiac output of 8 L/min and systemic vascular resistance (SVR) of 300 dyn s cm⁻⁵ (N 700–1600). His hemodynamic status stabilised and vasopressin was weaned to 2.4 μ /h within 3 h and noradrenaline to 0.6 mcg/kg/min within 1 h. He developed transient oliguria for about 4 h and urine output was

otherwise maintained around 0.5 ml/kg/h. His creatinine rose to 130 μ mol/L (N: 60–100 μ mol/L) but it subsequently improved and returned to normal 60-h post overdose.

Twelve-hour post overdose, the patient developed fixed dilated pupils measuring 6 mm and an increasing temperature to over 38.5 °C. A CT brain showed no acute abnormality. He was sedated and paralysed with fentanyl, midazolam and rocuronium infusion, given levetiracetam (1 g) for seizure prophylaxis, and actively cooled. He developed progressive hyperthermia and increasing tone and rigidity in the lower limbs with sustained ankle clonus. The tone and reflexes in the upper limbs were increased but there was no rigidity. This progressed to chest and abdominal wall rigidity making ventilation difficult. Electroencephalography confirmed there was no seizure activity. He met the Hunter Criteria for SS with fever, autonomic instability, severe rigidity and sustained ankle clonus. [2] He was diagnosed with severe serotonin syndrome (SS) and was managed with active cooling and ongoing paralysis with rocuronium infusion for 5-day post overdose. He developed ventilator-acquired pneumonia, was extubated on day 7 and made a complete recovery.

Fig. 2 Methylene blue concentration (natural log) versus time since ingestion. The patient was given a bolus dose of methylene blue 100 mg followed by 100 mg/h for 12 h and then 75 mg/h for 12 h. The data was fitted into a one compartment model

Table 1 Constructed pharmacokinetic data of methylene blue from the patient based on a one compartment model. *CL* clearance, *V* volume of distribution, *K_{el}* elimination rate constant, *t*_{1/2} half-life, *SE* (CV%) standard error (coefficient of variation%)

Parameter	Final estimate (SE – CV%)	Confidence interval (95%)
CL (L/h)	76.44 (3.94)	68.7–84.18
V (L)	4152 (5.983)	3513–4791
<i>k_{el}</i> (h ^{−1})	0.01841(5.194)	0.001595–0.02087
<i>t</i> _{1/2} (h)	37.65(5.194)	32.62–42.68

Plasma quetiapine, amlodipine and MB concentrations were measured using liquid chromatography mass spectrophotometry (LCMS). Plasma quetiapine concentrations were 7.1 and 3 mg/L (therapeutic range 0.1–1 mg/L) at 2 and 5-h post ingestion, respectively. Amlodipine concentrations peaked at 84.5 µg/L (N 5–18 µg/L) 22-h post ingestion, with a calculated half-life of 80 h. This is longer than the reported half-life of 35–65 h in therapeutic doses. This could be partly explained by erratic gut absorption as a result of the anti-muscarinic effect of quetiapine. Methylene blue concentrations peaked at 218 µg/L. The MB plasma concentration time profiles, fitted to a one compartment pharmacokinetic model by nonlinear regression (Scientist: Micromath, Missouri), were well described (Fig. 2) and had a calculated elimination half-life of 37.6 h (Table 1). This half-life falls within the range of half-lives of 7.7 to 48.3 h for an intravenous MB dose of 50 mg in 16 healthy volunteers (Fig. 2). [3]

Consent was obtained to publish this case report from the patient and his parents.

Discussion

We present a case of massive overdose of multiple vasodilating agents including amlodipine, ramipril and quetiapine resulting in profound vasoplegia. Vasoplegia is generally defined by hemodynamic criteria which include mean arterial pressure < 50 mmHg, systemic vascular resistance < 800 dynes s cm^{−5} and cardiac index > 2.5 L/in/m². There are case reports of severe hypotension following overdoses of amlodipine and angiotensin antagonists. [4] This increased toxicity is reported to be the result of the synergistic vasodilator effect of calcium channel antagonist [5], nitric oxide production and inhibition of angiotensin-converting enzymes. [6] Quetiapine causes vasodilation mediated by alpha-1-adrenoreceptor and has H₁-histamine receptor antagonist effect. Our patient has a peak serum concentration of 7.1 mg/L, comparable with other severely poisoned quetiapine patients. [7] High-dose insulin euglycaemic therapy was not considered in this patient as it is useful primarily as an inotropic agent in

cardiogenic shock but our patient has a high cardiac output of 8 L/min and low systemic vascular resistance.

Methylene blue (MB) has been used for the management of methaemoglobinaemia and as a second-line agent for the management of septic, anaphylactic and toxic or post cardiac surgery vasoplegic shock. [1] Side effects associated with its use include dyspnoea, tremors, vomiting, blue discoloration of skin and acute haemolytic anaemia. MB causes an increase in SVR and reduces catecholamine requirements, [8] by inhibiting guanylate cyclase, resulting in less cGMP production and reduced endothelial smooth muscle relaxation. MB has been successfully used in vasoplegic shock caused by quetiapine [9] and amlodipine poisoning. [10] The dose used varied from 1 to 2 mg/kg bolus followed by an infusion 1–2 mg/kg/h. In a recent systematic review of drug-induced vasoplegic shock treated with MB, there were just 17 reported cases. [11] Twelve patients survived and nine had hemodynamic improvement following MB administration. Of the 17 cases, 6 had taken amlodipine and 3 patients had improvement in hemodynamic status. In our case, there was a convincing temporal relationship with improvement in blood pressure and reduction in catecholamine infusion within an hour of MB administration.

An alternative diagnosis for the late deterioration is neuroleptic malignant syndrome (NMS) caused by quetiapine, an atypical neuroleptic. Neuroleptic malignant syndrome is characterised by hyperpyrexia, cogwheel rigidity, confusion and autonomic dysfunction but the symptoms have been reported to be less severe with second-generation or atypical neuroleptics. [12] Quetiapine has affinity for 5-hydroxytryptamine and dopamine receptors. There have been case reports of quetiapine-induced neuroleptic malignant syndrome, but they were usually from therapeutic doses of quetiapine and associated with the concurrent use of other neuroleptic drugs. [13] NMS has not been reported after an acute overdose of quetiapine. In addition, this patient had severe lower limb muscle rigidity and sustained ankle clonus which are characteristic features of severe SS and not NMS.

MB is a reversible monoamine oxidase inhibitor and its use in cardiac surgery and peri-operatively for diagnostic purposes has been associated with SS. [14, 15] This happened in normal patients taking therapeutic doses of either a selective serotonin reuptake inhibitor (SSRI) or selective noradrenaline reuptake inhibitors (SNRI) who received 1–2 mg/kg intravenous MB prior to surgery and developed mild to moderate SS. [15] Moreover, this reaction can be fatal, with one case report of a 75-year-old patient on therapeutic doses of venlafaxine, given 1 g (9 mg/kg) intravenous MB prior to surgery, who developed severe SS and died. [14] MB is a potent, concentration-dependent, reversible monoamine oxidase (MAO-A) inhibitor and has an active metabolite (azure B) which is thought to be

at least 6 times more potent as an MAO-A inhibitor and readily penetrate into the brain tissue. [16] In vitro, MB is a potent inhibitor of MAO-A with an inhibition constant (K_i) of 27 nM. [17] Our patient's peak MB concentration was 25-fold greater than this ($218 \mu\text{g/L} = 680 \text{ nM}$) indicating a high degree of MAO-A inhibition would have been present. Bolus doses as low as 0.75 mg/kg methylene blue can produce plasma concentrations that inhibit MAO-A in the brain. [18] In general, overdoses of combinations of SSRI and/or SNRI drugs produce mild to moderate serotonin toxicity, but the addition of a MAOI causes much more severe effects [2].

In our case, it is likely that severe SS was precipitated by high doses of MB in conjunction with an overdose of venlafaxine, desvenlafaxine and fluoxetine. The delayed onset of severe toxicity maybe the time required for enzyme inhibition and subsequent built-up of neurotransmitters or reflect delayed central nervous system penetration or that the metabolite concentrations peaked later. [19] The prolonged effect is easily explained by the long half-lives observed for MB and expected for the SSRIs. Fluoxetine and its active metabolite norfluoxetine are known to have half-lives of 4–6 and 16 days, respectively.

Our patient had a half-life of MB (37.6 h) that is consistent with the literature (8–48 h) and developed prolonged severe SS that required paralysis for 5 days. Due to the long half-life of MB seen in this patient, perhaps bolus doses of MB (1 mg/kg) given as clinically required would have been sufficient and potentially reduced the severity of SS.

One limitation of this case is that the findings may not necessarily be generalised to other overdoses due to the unusual massive poisoning with multiples drugs including vasodilators, neuroleptics and antidepressants. However, the temporal relationship and known pharmacology of drug interactions and SS in this case are convincing. We were also unable to confirm all drug levels in this case of polypharmacy overdose.

In conclusion, this patient developed vasoplegic shock from a massive overdose of quetiapine, amlodipine and ramipril that was resistant to high doses of vasopressors. He was successfully managed with MB but this was complicated by severe SS due to monoamine oxidase inhibition from MB and resulting interaction with SSRI (fluoxetine) and SNRI (venlafaxine and desvenlafaxine) agents. Hence, MB should be considered as a second- or third-line treatment for severe vasodilatory shock. Lower doses or shorter infusions of MB should be considered in patients who are at risk of developing SS. Further research is needed to work out the optimal dosing protocol for MB in poisoning.

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Compliance with Ethical Standards

Informed Consent Consent for publication of this case was obtained from the family and provided to the journal in accordance with JMT policy.

Conflict of Interest There is no conflict of interest to report.

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