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.

Case Report.

A 70kg 15-year-old male presented 1.5 hours post ingestion of a large polypharmacy overdose of quetiapine slow release 1.5g, quetiapine immediate release 12g, desvenlafaxine slow release 5.6g, venlafaxine 1050mg, amlodipine 290mg, ramipril 100mg, fluoxetine 560mg, promethazine 500mg and an unknown amount of lithium. He developed severe vasoplegic shock that was resistant to maximal doses of noradrenaline and vasopressin. MB was administered 6.5 hour post ingestion. Within 1 hour there was an improvement in his haemodynamic 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, and the antidepressants taken in overdose. MB had a calculated half-life of 38 hours.

Conclusion

MB is a useful second or third line strategy for severe drug induced vasodilatory shock, and may be potentially life-saving. Conversely, physicians 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.

Introduction:

Methylene blue has been used for the treatment of vasoplegic shock. Case Report: We report a 15-year-old male with a massive overdose of quetiapine, amlodipine, ramipril, venlafaxine, desvenlafaxine and fluoxetine, resulting in vasopressor resistant vasoplegic shock, successfully managed with methylene blue(MB) but was complicated by severe prolonged serotonin syndrome(SS). MB was administered 6.5 hour post ingestion. Within 1 hour there was an improvement in his haemodynamic status and reduction of catecholamine requirements. Twelve hours post ingestion, he developed severe SS that lasted 5 days as a result of interaction between MB, a reversible monoamine oxidase inhibitor and his antidepressants overdose. We report MB pharmacokinetic data with a calculated half-life of 38 hours.

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 up to 25%, especially if it is resistant to catecholamine treatment and lasts longer than 48 hours.(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 SS in surgical 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.

Case details

A 70 kg 15-year-old male with a background history of essential hypertension and major depression presented to the Emergency Department 1.5 hours 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 and promethazine 500 mg.

On arrival at the Emergency Department, he had a systolic blood pressure of 80mmHg, pulse of 130 bpm and Glasgow Coma Score of 8 (Figure 1). He was resuscitated with 3.5 L of crystalloid fluid, 10 ml 10% calcium gluconate and intubated. A dose of activated charcoal (50g) 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. He was then commenced on noradrenaline, followed by vasopressin. Doses quickly escalated to 2 mcg/kg/min noradrenaline and 7 u/h of vasopressin, with no improvement. Bedside transthoracic echocardiogram showed a hyperdynamic heart with good global contractility.

Due to persistent hypotension with MAP of 48 mm Hg, a bolus of MB 1.5 mg/kg was given at 6.5h post overdose, followed by an infusion of 1.5mg/kg/h for 12 h and then 1 mg/kg/h for a further 12 h. The MAP improved in less than 30 minutes to 70 mmHg. Within 60 minutes of MB infusion, his BP increased from 65/40 mm Hg to 120/45 mm Hg. A PiCCO (Pulse index Contour Continuous Cardiac Output) catheter was inserted post commencement of MB infusion. This showed a cardiac output of 8L/min and systemic vascular resistance (SVR) of 300 dyn.s.cm^{-5} (N:700-1600). His haemodynamic status stabilised and vasopressin was weaned to 2.4 u/h within 3 hours and noradrenaline to 0.6 mcg/kg/min within 1 hour. He developed transient oliguria and creatinine rose to 130 µmol/L (N: 60-100µmol/L) but subsequently improved.

Twelve hours 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 paralysed, given levetiracetam (1g) and actively cooled. He developed progressive hyperthermia and increasing rigidity in the lower limbs with sustained ankle clonus. This progressed to chest and abdominal wall rigidity making ventilation difficult. Electroencephalography confirmed there was no seizure activity. He was diagnosed with severe serotonin syndrome(SS) and required active cooling and ongoing paralysis with rocuronium infusion for five days post overdose. He met the Hunter Criteria for SS with

fever, autonomic instability, severe rigidity and sustained ankle clonus.(2) He developed ventilator acquired pneumonia, was extubated on day 7 and made a complete recovery.
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 (Figure 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 48.3h for an intravenous MB dose of 50 mg in 16 healthy volunteers (Figure 2).(3)

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 haemodynamic criteria which include mean arterial pressure < 50 mm Hg, systemic vascular resistance < 800 dynes.s.cm^{-5} and cardiac index > 2.5 L/in/m^2. 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 H_1-histamine receptor antagonist effect. Our patient has a peak serum concentration of 7.1 mg/l, is comparable with other severely poisoned quetiapine patients.(7)

Methylene blue (MB) has been used for the management of methaemoglobinaemia, a second line agent for the management of septic, anaphylactic and toxic vasoplegic shock(1) or post cardiac surgery. 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 reduce 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 1-2 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 haemodynamic improvement following MB administration. Of the 17 cases, 6 had taken amlodipine and 3 patients had improvement in haemodynamic 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 feature 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, 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 (9mg/kg) intravenous MB prior to surgery, developed severe SS and died.(14) MB is a potent, reversible monoamine oxidase (MAO-A) inhibitor and has an active metabolite (azure B) which is thought to be 10 times more potent as an MAO-A inhibitor. 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 may reflect delayed central nervous system penetration or that the metabolite concentrations peaked later.
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 days 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.

In conclusion, this patient developed vasoplegic shock from a massive overdose of quetiapine, amlodipine and ramipril that was resistant to maximal dose of vasopressors. He was successfully managed with MB but this was complicated by delayed onset of persistent severe SS due to the interaction with SSRI (fluoxetine) and SNRI (venlafaxine and desvenlafaxine) agents.

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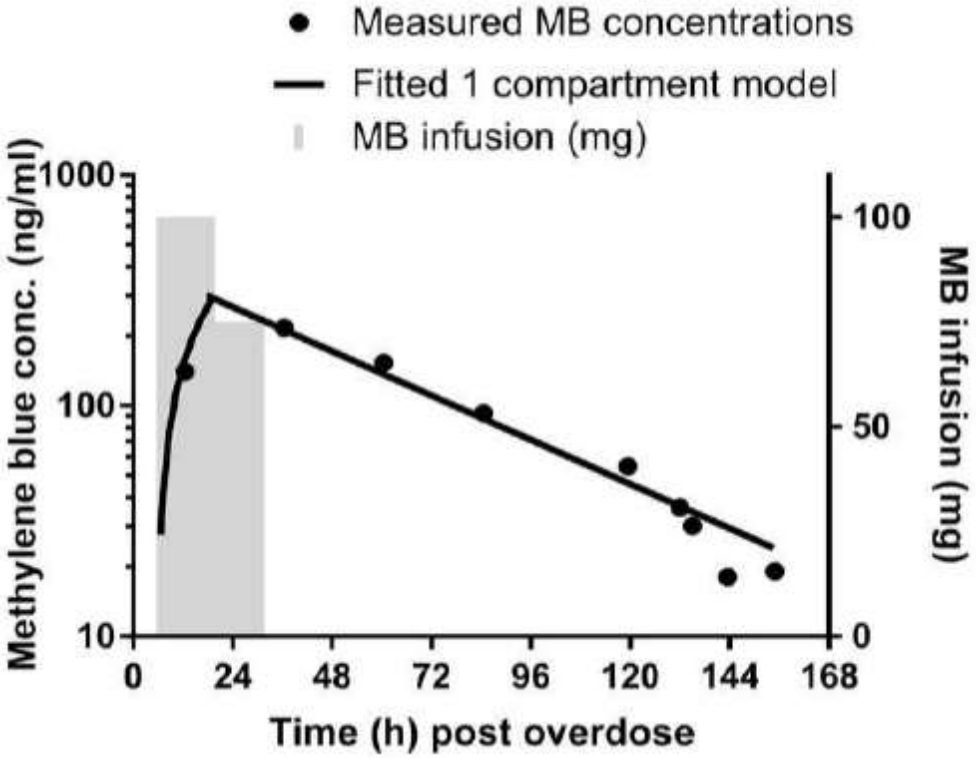
Table 1. Constructed pharmacokinetic data of Methylene Blue from the patient based on a one compartment model. CL: clearance; V: volume of distribution; K_{el}: elimination rate constant; $t_{1/2}$: Half-life; SE (CV%): standard error (coefficient of variation%).

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
k_{el} (h^{-1})	0.01841	5.194	0.001595 – 0.02087
$t_{1/2}$ (h)	37.65	5.194	32.62 – 42.68


Measured MB concentrations
Fitted 1 compartment model
MB infusion (mg)
Methylene blue conc. (ng/ml)
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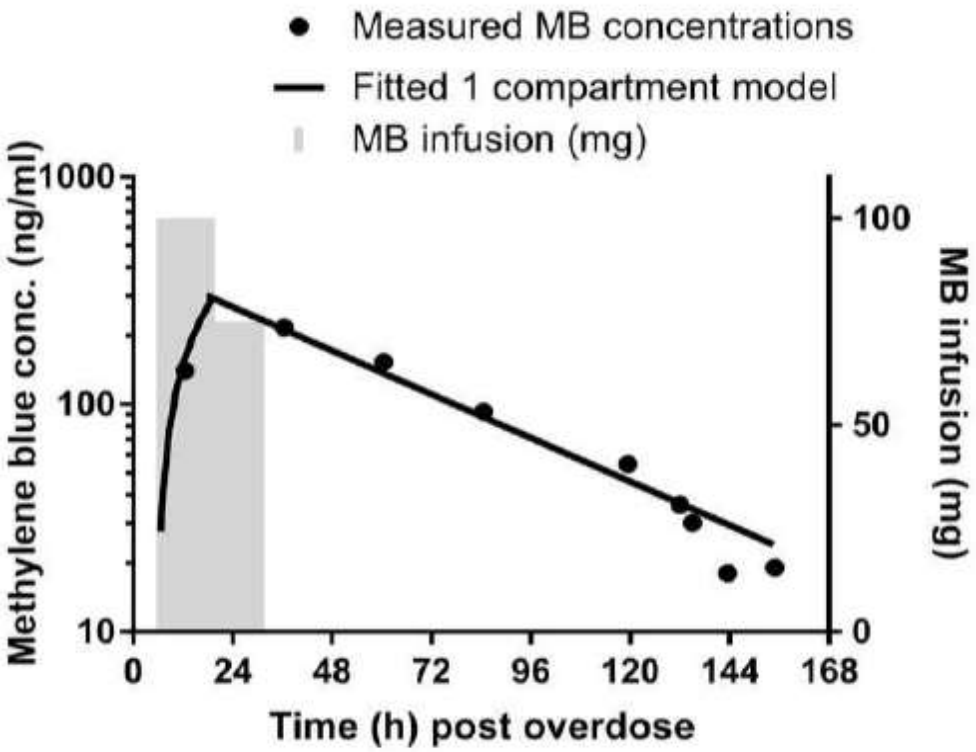
100
10
MB infusion (mg)
100
50
0
0
24
48
72
96
120
144
168
Time (h) post overdose


Measured MB concentrations
Fitted 1 compartment model
MB infusion (mg)
Methylene blue conc. (ng/ml)
1000
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MB infusion (mg)
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0
24
48
72
96
120
144
168
Time (h) post overdose