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BRIEF COMMUNICATION

Methylene blue used in the treatment of refractory shock resulting from drug poisoning

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Background. Methylene blue inhibits the nitric oxide–cyclic guanosine monophosphate (NO–cGMP) pathway, decreasing vasodilation and increasing responsiveness to vasopressors. It is reported to improve haemodynamics in distributive shock from various causes including septicaemia and post-cardiac surgery. Reports of use in overdose are limited. We describe the use of methylene blue to treat a case of refractory distributive shock following a mixed drug poisoning. *Case details.* A 41-year-old male presented following reported ingestion of 18 g extended-release quetiapine, 10 g controlled-release carbamazepine, 240 mg fluoxetine, 35 g enteric-coated sodium valproate and 375 mg oxazepam. He was comatose and intubated on presentation. Progressive hypotension developed. Echocardiogram revealed a hyperdynamic left ventricle, suggesting distributive shock. The patient remained hypotensive despite intravenous fluid boluses, escalating vasopressor infusions. Arterial blood gas revealed metabolic acidaemia and high lactate. Methylene blue was administered as loading-dose of 1.5 mg/kg and continuous infusion (1.5 mg/kg/h for 12 h, then 0.75 mg/kg/h for 12 h) resulting in rapid improvement in haemodynamic parameters and weaning of vasopressors. Serum quetiapine concentration was 18600 ng/mL (30–160 ng/mL), collected at the time of peak toxicity. *Conclusion.* Severe quetiapine poisoning produces hypotension primarily from alpha-adrenoreceptor antagonism. Methylene blue may have utility in the treatment of distributive shock resulting from poisoning refractory to standard vasopressor therapy.

Keywords Quetiapine; Overdose; Poisoning; Methylene blue; Vasoplegia; Shock

Background

Methylene blue is commonly recognised as a treatment for methaemoglobinaemia. It is also reported to improve blood pressure in cases of distributive shock from various causes including septicaemia[1] and post-cardiac bypass surgery.[2] The effect of methylene blue in this scenario is thought to result from inhibition of the nitric oxide–cyclic guanosine monophosphate (NO–cGMP) pathway, resulting in reduced vasodilation and an increased responsiveness to vasopressors.[3–5] Reports of its use in drug-induced distributive shock are limited. We describe the use of methylene blue to treat a case of refractory shock following a mixed drug poisoning.

Case details

A 41-year-old male with a history of epilepsy and bipolar disorder presented to the emergency department 2 h following reported ingestion of 18 g extended-release quetiapine, 10 g controlled-release carbamazepine, 240 mg fluoxetine, 35 g enteric-coated sodium valproate and 375 mg oxazepam. The dose and timing of the ingestion was confirmed by a family member. Clinical data were obtained from an electronic medical record. On arrival he had a heart rate of 85 bpm, systolic blood pressure of 90 mmHg, respiratory rate of 17 breaths/min, temperature 34.6°C and Glasgow Coma Scale of 3. General physical examination was otherwise normal. ECG revealed sinus rhythm, rate 82 bpm, QRS 120 ms, and QT-interval (uncorrected) 536 ms. He was intubated on presentation, administered intravenous crystalloids, and given 50 g activated charcoal via nasogastric tube.

Progressive hypotension developed and 4.5 h following ingestion, despite 4000 mL intravenous fluid infusion and repeated doses of metaraminol (total 5 mg), his blood pressure was 70/40 mmHg. Noradrenaline and metaraminol infusions were commenced and doses were rapidly escalated (Fig. 1) with little improvement in haemodynamics. Six hours post-ingestion the patient was transferred to the Intensive Care Unit. His blood pressure at this time was 68/35 mmHg. A vasopressin infusion was added to his treatment regimen. Transthoracic echocardiogram revealed a hyperdynamic left ventricle with normal contractile function (ejection fraction 70%), without pericardial effusion, suggesting distributive shock. Hypotension was made worse after a single-dose of intravenous adrenaline (200mcg) with systolic blood pressure falling to 50 mmHg.

Twelve hours post-ingestion the patient's blood pressure was 88/40 mmHg despite infusions of noradrenaline

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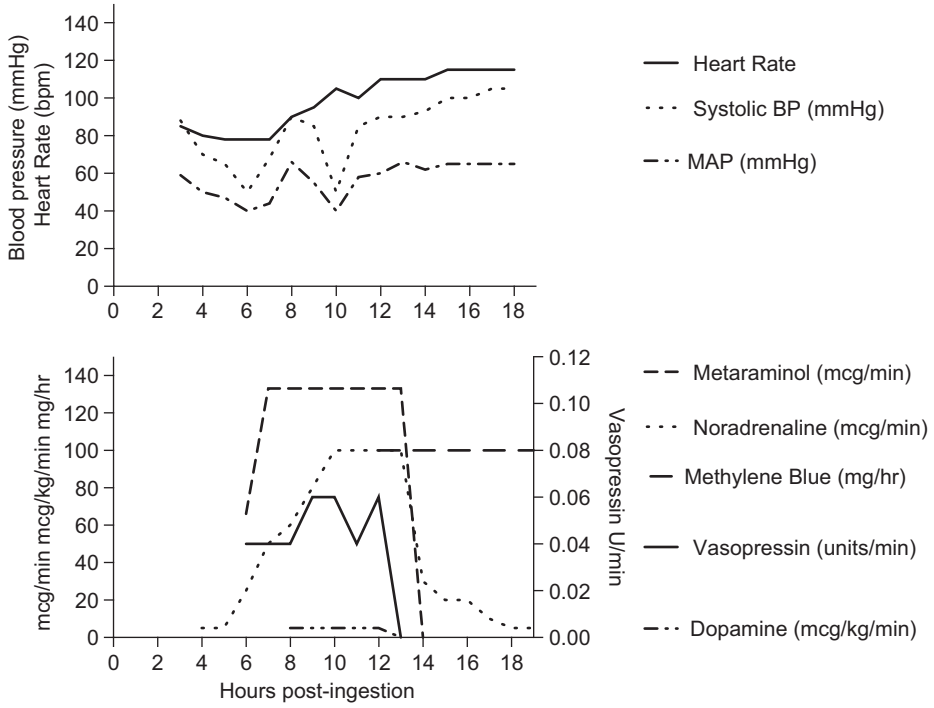

Fig. 1. Summary of haemodynamic data and vasopressor infusion doses before and after methylene blue infusion. There was a significant fall in systolic blood pressure at 10 h when a single dose of intravenous adrenaline (200 μg) was administered. Methylene blue was commenced at 12 h. This was associated with a rapid weaning of vasopressors.

100mcg/min, vasopressin 0.06 units/min, metaraminol 133 mcg/min and dopamine 5 mcg/kg/min. Arterial blood gas revealed metabolic acidaemia (pH 7.33, pCO_2 31 mmHg and HCO_3^- 16 mmol/L) with a high lactate (peak 13 mmol/L). At this point, methylene blue was administered intravenously as a loading-dose of 1.5 mg/kg and continuous infusion (1.5 mg/kg/h for 12 h, then 0.75 mg/kg/h for 12 h). Rapid improvement in haemodynamic parameters and weaning of vasopressors resulted in the hour following the loading-dose (Fig. 1). One hour following commencement of methylene blue, his blood pressure was 90/40 mmHg. The vasopressin, metaraminol and dopamine infusions were ceased. The noradrenaline infusion was decreased to 30 mcg/min within the hour and to 5 mcg/min within 5 h, and was subsequently ceased on Day 4 post-ingestion.

Serum quetiapine concentration measured 7 h post-ingestion, by high-performance liquid chromatography, was 18600 ng/mL (therapeutic range: 30–160 ng/mL). This was collected at the time of peak toxicity. Serum valproate and carbamazepine concentrations were measured using particle-enhanced turbidimetric inhibition immunoassay. Serum valproate concentration peaked at the same time and was 1221 micromol/L (300–700 micromol/L). Serum carbamazepine concentration at that time was 44 micromol/L (20–50 micromol/L). Screening for paracetamol, ethanol and salicylates was negative. Screening for benzodiazepines is not routinely performed, therefore oxazepam concentration was not measured.

His admission was complicated by aspiration pneumonia before he was discharged home without permanent sequelae on Day 13.

Discussion

Quetiapine is an atypical antipsychotic agent used frequently in the treatment of schizophrenia and bipolar disorder. Symptoms of quetiapine overdose include drowsiness, tachycardia and hypotension. Hypotension is mediated by alpha-1-adrenoreceptor and H1-histamine receptor antagonism.[6] It may be severe requiring vasopressor support. In this patient, the vasodilatory shock was confirmed by echocardiographic evidence of good left ventricular function. Hypotension was severe and resistant to treatment with multiple vasopressor agents. Hypotension was most likely due to quetiapine given the relatively low blood concentrations of valproate and carbamazepine. Oxazepam may have contributed but the degree of vasodilatory shock was more consistent with quetiapine ingestion in the setting of markedly elevated concentration (more than 100 times the normal therapeutic level).

Nitric oxide (NO) is produced in vascular endothelium and is integral to the regulation of blood flow. It activates guanylate cyclase, increasing production of cGMP, inducing vascular smooth muscle relaxation. Regardless of the initial aetiology, distributive shock is likely due to dysregulation of this NO–cGMP pathway, with overproduction of NO.[4] A number of mechanisms by which methylene blue inhibits this pathway have been proposed including NO synthase inhibition[3,4] and guanylate cyclase inhibition.[5] Whilst there is no clear mechanism linking quetiapine to the NO–cGMP pathway, the administration of methylene blue, in this case, was associated with an improvement in haemodynamics suggesting potential benefit in distributive shock regardless of the cause.

Methylene blue has been used in distributive shock from various causes including septicaemia[1] and post-cardiac bypass surgery.[2] While there are reports of benefit, its use is still controversial.[7] Reports of use in overdose are limited. Rapid improvement in haemodynamics has been described following the administration of methylene blue (loading dose and continuous iv infusion) in shock due to overdoses of amlodipine and amlodipine/atenolol in combination, resistant to standard treatment including calcium, insulin-glucose and vasopressors.[8–10] It has also been used in the treatment of refractory vasodilatory shock due to chronic metformin overdose.[11]

Methylene blue cannot definitively be proven to be the cause of recovery in this patient's blood pressure. However, the rise in blood pressure was rapid and reduction in vasopressors occurred in a short time frame following administration. The rapid response is less likely to be explained by falling blood quetiapine concentration related to either redistribution or metabolism of quetiapine.

A decrease in blood pressure was noted in our patient following administration of intravenous adrenaline. Worsening hypotension in quetiapine overdose has been reported previously following adrenaline administration.[12] This is likely due to beta-2 adrenoreceptor mediated vascular smooth muscle relaxation in skeletal muscle beds resulting in an overall decrease systemic vascular resistance in the setting of quetiapine-induced alpha-receptor blockade. Noradrenaline is therefore recommended as the initial vasopressor of choice for hypotension in quetiapine poisoning.

Adverse effects of methylene blue include nausea, vomiting, chest pain, confusion, sweating and hypertension.[4] Most importantly, methylene blue is a potent monoamine oxidase-A inhibitor and carries a risk of inducing serotonin syndrome.[13] No adverse effects of methylene blue were observed in this patient, including serotonin syndrome, despite the co-ingestion of a selective serotonin reuptake inhibitor (240 mg fluoxetine).

Conclusion

Severe quetiapine poisoning may produce hypotension that is most likely primarily mediated by alpha-adrenoreceptor antagonism. In this case, methylene blue administration was associated with an increase in blood pressure. Methylene blue may have utility in the treatment of distributive shock resulting from mixed drug poisoning refractory to standard vasopressor therapy.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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