Short reports

Continuous infusion of methylene blue for septic shock

Glen Brown, David Frankl, Terry Phang

Summary

Nitric oxide has been determined to be a potential mediator of the haemodynamic changes associated with sepsis. The haemodynamic effects of nitric oxide can be partially antagonised by methylene blue, through inhibition of the enzyme, guanylate cyclase. The case report presented here demonstrates a beneficial haemodynamic effect of continuous infusion of methylene blue during sepsis. These findings could be extrapolated to other patients or prompt additional research.

Keywords: methylene blue, nitric oxide, septic shock

Nitric oxide has recently been implicated as a potential mediator of both the peripheral vascular and the cardiac response to endotoxin which results in the syndrome of septic shock.¹ Nitric oxide produces these effects by stimulating the soluble guanylate cyclase of vascular smooth muscle and cardiac cells, increasing cyclic GMP levels and producing vascular relaxation and impaired cardiac contraction.¹ Pharmacologic antagonism of nitric oxide production or receptor interaction has been shown to have beneficial effects on both the peripheral vascular and cardiac response to endotoxin.² Methylene blue has been demonstrated to inhibit guanylate cyclase² and anecdotal experience with methylene blue administration to patients with septic shock refractory to catecholamines has demonstrated short-term benefits of the drug.^{3,4} Improvements in mean arterial pressure and systemic vascular resistance have been demonstrated, although corresponding decreases in cardiac output have been noted.^{3,4} In an unblinded clinical trial of methylene blue administered to patients with septic shock requiring inotropic support, doses of 2 mg/kg over 15 minutes resulted in improved mean arterial pressure.⁵ However, in all of the above studies, the beneficial effects of methylene blue were transient, with return to pre-methylene blue haemodynamics within three hours.^{3–5} We now report a patient in whom the continuous infusion of methylene blue over 44 hours was associated with sustained haemodynamic benefit and lack of toxicity.

Case report

The patient was a previously well, non-immunocompromised, 61-year-old man who

presented to a community hospital with a 10-day history of left-sided chest pain causing shortness of breath. Chest X-ray on the day of presentation demonstrated a left lower lobe consolidation and a left pleural effusion. The provisional diagnosis was community-acquired pneumonia, and cefuroxime and erythromycin were initiated. The hypoxaemia worsened, necessitating intubation and mechanical ventilation on the following day. Sputum and blood samples grew no pathogens, and a ventilation-perfusion scan indicated no pulmonary embolism. To attempt to improve ventilation, a chest tube was placed which evacuated approximately 2.5 litres of a greenish-brown odourless liquid, which subsequently grew *Candida albicans* and an unidentified yeast. The patient was transferred to this institution after nine days of mechanical ventilation.

On presentation here, the patient was febrile, had a white cell count of $15.5 \times 10^9/l$ and chest X-ray demonstrated left lower lobe consolidation. A sample of pleural fluid was obtained the next day which grew *Candida parapsilosis*. A fiberoptic bronchoscopy performed on day 3 was unremarkable and protected brush specimens from the bronchoscopy grew *Candida*. Despite anti-fungal therapy, the patient deteriorated and developed adult respiratory distress syndrome. On day 33, the patient developed septic haemodynamics requiring vasopressors. Sputum and blood samples grew no pathogens; urine culture yielded *Enterococcus faecium* and vancomycin was begun. Over a 24 hour period, increasing vasopressor requirements resulted in treatment with dopamine at $10 \mu\text{g/kg/min}$ and norepinephrine at $15 \mu\text{g/min}$ to maintain tissue perfusion and end-organ function. A single dose of methylene blue 100 mg (approximately 1.5 mg/kg) was administered to antagonise the possible nitric oxide-mediated peripheral vasodilation of septic shock. This resulted in a transient improvement in blood pressure after 24 hours (figure 1) allowing a slight reduction in vasopressor support. Since the beneficial haemodynamic effects of methylene blue were transient following the initial five intermittent 100 mg doses (hours 24, 42, 48, 54, 60), a continuous infusion of methylene blue 17 mg/h was initiated. The infusion was administered continuously for 44 hours (hours 72–116), over which time the norepinephrine was tapered to nil, and the dopamine to $3 \mu\text{g/kg/min}$ (figure 1). Transient drops in the mean arterial blood pressure (hours 84 and 100) during the methylene blue infusion represent periods of

St Paul's Hospital,
1081 Burrard Street,
Vancouver, British
Columbia, Canada
V6Z 1Y6
Department of
Pharmacy
G Brown
Department of Critical
Care
D Frankl
Department of
Surgery
T Phang

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Figure 1 The mean arterial pressure (upper solid line) and corresponding vasopressor requirements (dopamine – dashed line, norepinephrine – dotted line) following methylene blue 100 mg doses (arrows) and infusion, 17 mg/h (thick solid line)

aggressive diuresis (urine output > 1200 ml in four hours). The patient demonstrated no significant toxicity during or following the infusion. The patient's urine turned a blue–green colour which persisted for three days after stopping the infusion, and he developed a noticeable blue–grey skin colouration that persisted for six days. No cardiac ischaemia or peripheral thrombosis were detected. The patient was sedated with continuous intravenous narcotics and benzodiazepines, preventing the assessment of the effects of methylene blue on central nervous system function. No assessment of methaemoglobinaemia was made.

Following recovery from the septic episode, the patient's adult respiratory distress syndrome, debilitation and weakness necessitated a slow wean from the ventilator. On day 87 of hospitalisation, the patient was transferred from the intensive care unit to the general medical ward, breathing room air via a tracheostomy.

Discussion

The beneficial haemodynamic effects of methylene blue on septic shock have until now only been demonstrated to be transient.^{3–5} The patient outcome of those individuals treated in the initial reports was frequently death, despite the apparent short-term haemodynamic benefits of the methylene blue. The mechanism for the attenuation of response to the intermittent administration of methylene blue is unknown, but a variety of pharmacodynamic and pharmacokinetic mechanisms are plausible. Decreased sensitivity of guanylate cyclase to methylene blue over time, or non-guanylate-cyclase-mediated haemodynamic effects are potential mechanisms. Similarly, metabolism, distribution through tissue binding, or excretion of methylene blue may explain the attenuated response. Continuous administration of methylene blue could potentially overcome the pharmacokinetic mechanisms accounting for the attenuation of

Methylene blue

- is a non-selective inhibitor of the enzyme guanylate cyclase, and thereby inhibits the effects of endogenous and exogenous nitric oxide
- antagonises the nitric oxide-mediated vasodilation seen with sepsis
- reduces sepsis-induced negative inotropism of the heart
- does not produce methaemoglobinaemia at doses successful in antagonising nitric oxide-induced haemodynamic changes
- single intravenous doses have only a transient (< 4 hours) effect on haemodynamics

response, although this administration schedule would not be expected to offset pharmacodynamic mechanisms. This case report demonstrates an ongoing beneficial response to methylene blue over 44 hours of continuous intravenous administration. The use of methylene blue may have restored vascular reactivity to endogenous catecholamines suggesting that its use results in more than antagonism of nitric oxide.³ Also, the methylene blue may have improved myocardial function⁶ which produced sustained benefits after withdrawal. It is possible that the patient's haemodynamics could have improved regardless of the methylene blue treatment. The underlying sepsis could have been resolving during the treatment period since antibiotic therapy was ongoing (vancomycin for *Enterococcus faecium* in the urine). We suspect that the underlying condition must have improved to some degree since discontinuation of the methylene blue did not result in a subsequent increase in vasopressor requirements. It is also possible that methylene blue 'bought time' until the underlying sepsis regressed.

The potential toxicity of continuous administration of methylene blue must be considered. In single doses of 1–2 mg/kg, methylene blue has been demonstrated to be safe in sepsis, and in the treatment of methaemoglobinaemia. Single doses of 2 mg/kg have not been associated with the development of methaemoglobinaemia,^{5,6} and the 50% lethal dose in sheep has been estimated at 40 mg/kg.⁷ Methylene blue has been reported to produce a blue–grey skin colouration which may be confused with cyanosis.⁸

The antagonism of nitric oxide-mediated peripheral vasodilation may counter the beneficial effects of nitrates on myocardial blood flow, resulting in cardiac ischaemia.⁹ Similarly, methylene blue may inhibit beneficial effects of nitroglycerin on platelet disposition on exposed aortic media.¹⁰ Methylene blue may inhibit platelet aggregation, which could affect haemostasis in thrombotic or haemorrhagic states.¹¹ Methylene blue has also been demonstrated to antagonise the anticoagulant effects of heparin.¹² The potential for methylene blue to cause haemolytic anaemia should be appreciated. The administration of larger doses (500 mg over 10 minutes) has caused restlessness, anxiety and reversible paresthesias.

The larger doses also produced dyspepsia and a sensation of burning in the mouth which persisted for 24 hours.¹³ Despite methylene blue's potential to cause diverse anti-inflammatory and physiologic effects,^{14,15} we were unable to detect any significant toxicity in our patient.

Based on the short-term haemodynamic benefits of methylene blue in septic shock, we would encourage investigators to consider more prolonged administration of the drug. Data on benefit and absence of toxicity can only be obtained through increased investigation.

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Cushing's syndrome due to autonomous macronodular adrenal hyperplasia: long-term follow-up after unilateral adrenalectomy

Mauro Boronat, Tomás Lucas, Balbino Barceló, Carmen Alameda, Hassan Hotait, Javier Estrada

Summary

This report describes a case of Cushing's syndrome due to autonomous macronodular adrenocortical hyperplasia in which unilateral resection of the right adrenal resolved the Cushing's syndrome.

Keywords: Cushing's syndrome, suprarrenal hyperplasia, adrenalectomy

Case report

In 1984, a 53-year-old man presented with weakness, weight gain, easy bruising and impotence, which had developed over a period of two years. He had a history of chronic obstructive pulmonary disease, heart failure and mixed angina, and was known to have been hypertensive for 10 years. On physical examination, the patient was found to have cushingoid appearance, with centripetal obesity, atrophic skin and ecchymoses on forearms.

Endocrine assessment is summarised in the table. Computed tomography (CT) of the turcica sella was normal. Abdominal CT revealed a tumour mass occupying the entire right adrenal gland. The contralateral gland was also enlarged and contained a focal nodule localised in its central portion (figure 1). Scanning with ¹³¹I-labelled cholesterol demonstrated bilateral but asymmetrical uptake of the tracer, indicating much greater activity on the right arm than on the left gland (figure 2).

Clinica Puerta de Hierro, C/San Martín de Porres 4, 28035 Madrid, Spain
Department of Endocrinology
M Boronat
T Lucas
B Barceló
C Alameda
J Estrada
Pathology Services
H Hotait

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Endogenous adrenocorticotropin (ACTH)-independent Cushing's syndrome is caused by an autonomous adrenal production of cortisol. In most cases, it is due to a primary adrenal neoplasm, adenoma or carcinoma, usually unilateral. Rare nontumorous primary adrenal processes that can also cause Cushing's syndrome are bilateral. They include pigmented micronodular adrenal dysplasia¹ and autonomous macronodular adrenocortical hyperplasia (AMAH).^{2–4} We describe a patient with AMAH who was treated successfully by unilateral adrenalectomy.