

**Methylene blue toxicity following infusion to localize parathyroid adenoma** *J Laryngol Otol* 2006;**120**:138–40

Dear Sirs

I was very interested to read the recent article 'Methylene blue toxicity following infusion to localize parathyroid adenoma' by A Majithia and M P Stearns.<sup>1</sup>

The authors state that the only reported side effects of methylene blue are pain at the infusion site, pseudocyanosis and intensely blue-stained urine and that the agent is generally considered benign. Although not in the context of parathyroid surgery, I would like to draw attention to the existence of reports of anaphylactic reactions,<sup>2</sup> blue urticaria<sup>3</sup> and pulmonary oedema<sup>4</sup> following the use of methylene blue in gynaecological surgery to assess tubal patency.

The use of methylene blue as an adjunct to parathyroidectomy was discussed at the recent British Association of Endocrine Surgeons annual meeting held at Newcastle upon Tyne, UK, in October 2005. Cardiac effects, including chest pain and bradycardia, and a case of status epilepticus were reported following its peri-operative use (A S Patel, personal communication). Nevertheless, it was concluded that serious reactions to methylene blue were very rare.

The authors quote that 'the UK National Poisons Information Service (NPIS) Centre recommend an intravenous dose of methylene blue not exceeding 4 mg/kg of a 1 per cent solution'. I would be interested to know where this figure is cited. The current NPIS guidelines, as detailed on the TOXBASE database, advise an intravenous dose of 1–2 mg/kg of a 1 per cent solution infused over a 5 minute period for the treatment of methaemoglobinaemia, repeated after an interval of 30–60 minutes in the absence of response. Doses exceeding 15 mg/kg are not advised due to the associated risk of haemolysis. However, there is no mention of a threshold of 4 mg/kg or of any recommendations relating to its use in parathyroid surgery.<sup>5</sup>

In parathyroid exploration surgery, doses of methylene blue ranging between 1 mg/kg (A S Patel, personal communication) and 10 mg/kg<sup>6</sup> have been used. Firm evidence in support of the optimum dose for use in this setting is lacking. Doubtless, thousands of patients worldwide have received methylene blue at doses exceeding 4 mg/kg without ill effect, including, I suspect, a sizeable cohort who have received the agent at a dose of 7.5 mg/kg. Serious adverse reactions to methylene blue are exceedingly rare events and, given the number recorded to date, those reported in the literature may represent idiosyncratic responses. Certainly, there is insufficient evidence to suggest they are dose-related. I therefore would not entirely agree with the authors' final statement advocating that a dose of 7.5 mg/kg should not routinely be used in parathyroid surgery, and I would be very keen to hear their further comments regarding this.

T S Ahmed,  
Department of Ear, Nose and Throat Surgery,  
Southampton General Hospital,  
Southampton, UK.

**References**

- 1 Majithia A, Stearns MP. Methylene blue toxicity following infusion to localize parathyroid adenoma. *J Laryngol Otol* 2006;**120**:138–40
- 2 Dewachter P, Mouton-Faivre C, Tréchet P, Lléu J-C, Mertes PM. Severe anaphylactic shock with methylene blue instillation. *Anesth Analg* 2005;**101**:149–50
- 3 Rzymiski P, Wozniak J, Opala T, Wilczak M, Sajdak S. Anaphylactic reaction to methylene blue dye after laparoscopic chromopertubation. *Int J Gynaecol Obstet* 2003;**81**:71–2
- 4 Trikha A, Mohan V, Kashyap L, Saxena A. Pulmonary edema following intrauterine methylene blue injection. *Acta Anaesthesiol Scand* 1996;**40**:382–4
- 5 TOXBASE. <http://www.spib.axl.co.uk> [5 February 2006]
- 6 Rowntree T. Parathyroids – a personal series. *J R Soc Med* 1980;**73**:14–18

*Author's reply*

Dear Sirs

We would like to thank Mr Ahmed for his comments and for highlighting some other side effects of methylene blue (MB). As he mentions, these are rare and not linked to its use in parathyroid surgery.

Mr Ahmed suggests that thousands of patients have received MB at doses exceeding 4 mg/kg without any ill effect. We entirely agree with this, as we used MB at doses of 7.5 mg/kg in our own department prior to our only case of MB toxicity.

Advice that MB should not be used at a dose exceeding 4 mg/kg originates from the UK Poisons Information Database. This was forwarded to S J Martindale<sup>1</sup> from the Cardiff Centre of the UK National Poisons Information Service. The TOXBASE database recommendations regarding MB are only in the context of treating methaemoglobinaemia. I have contacted the TOXBASE reviewers and they have agreed to add a reference to our paper to their database, with an additional caution regarding doses of 7.5 mg/kg of MB.

The American hospital formulary service reports adverse effects of MB if dosage exceeds 7 mg/kg.<sup>2</sup> Manufacturers of MB advise against its use at doses exceeding 7 mg/kg.<sup>3</sup> The British National Formulary refers to MB only in the context of treating methaemoglobinaemia, recommending a dose of 1 mg/kg.

The point is that all three cases<sup>1,4,5</sup> of MB toxicity in parathyroid localization occurred at doses of 7.5 mg/kg. As 4 mg/kg of MB is adequate for staining the parathyroid glands, we can no longer justify the higher dose.

A Majithia  
Amersham, UK.

**References**

- 1 Martindale SJ, Stedeford JC. Neurological sequelae following methylene blue injection for parathyroidectomy. *Anaesthesia* 2003;**58**:1041–2
- 2 Anon. *AHFS Drug Information*. Bathesda, Maryland, USA: AHFS, 2002

- 3 Methylene Blue datasheet-information for Health Professionals, <http://www.medsafe.govt.nz/Profs/Datasheet/m/MethyleneBlueinj.htm> [12 July 2006]
- 4 Bach KK, Lindsay FW, Berg LS, Howard RS. Prolonged postoperative disorientation after methylene blue

- infusion during parathyroidectomy. *Anesth Analg* 2004;**99**:1573–4
- 5 Majithia A, Stearns MP. Methylene blue toxicity following infusion to localize parathyroid adenoma. *J Laryngol Otol* 2006;**120**:138–40