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Clinical Record

Methylene blue toxicity following infusion to localize parathyroid adenoma

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Abstract

The parathyroid glands are small, inconspicuous, and variable in number, colour and position. Their identification is vital for excision of hyper-functioning glands and for preservation of normally functioning ones in patients undergoing thyroidectomy.

Intravenous infusion of methylene blue at a dose of 7.5 mg/kg is commonly used to aid visualization of the parathyroid glands intra-operatively. Methylene blue is generally considered benign, and there are only two cases published in the literature reporting toxicity following intravenous infusion – such toxicity is a diagnosis of exclusion.

We report a case of methylene blue toxicity resulting in expressive aphasia, confusion and disinhibition following infusion for parathyroid adenoma localization. The patient made a complete recovery over 48 hours. Methaemoglobinaemia was excluded as a cause. We suggest that the mechanism of toxicity was a direct effect of methylene blue, although an adverse interaction with serotonin re-uptake inhibitors could not be excluded.

In keeping with the UK National Poisons Information Service recommendations, we have altered our practice and now use methylene blue at a dose not exceeding 4 mg/kg. This has not affected our success rate for identification of parathyroid glands. We report this case to highlight the rare occurrence of methylene blue toxicity when used at a dose of 7.5 mg/kg.

Key words: Parathyroid Glands; Methylene Blue; Toxicity

Introduction

Several techniques have been used to identify overactive parathyroid glands pre-operatively, including ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), sestamibi scanning and selective venous sampling.[1,2] These are complemented by intra-operative techniques, including gamma-probing,[3] frozen section and methylene blue infusion.[4]

Methylene blue is most usually administered at a dose of 7.5 mg/kg as this is thought to provide optimum staining of the parathyroid glands.[5] We do not routinely use methylene blue for parathyroid preservation in thyroidectomy, but our practice for patients undergoing parathyroidectomy has been to infuse 7.5 mg/kg of 1 per cent methylene blue intravenously in 500 ml of 5 per cent dextrose. In cases of secondary hyperparathyroidism, due to the poor renal function, we use a reduced dose (5 mg/kg) in only 100 ml of 5 per cent dextrose. The infusion is commenced in the anaesthetic room following induction of general anaesthesia.

We report only the third case in the medical literature of methylene blue toxicity following infusion in a patient undergoing surgery for primary hyperparathyroidism.

Case report

A 52-year-old woman presented with weakness, fatigue, headaches and depression.

Her past medical history included iron deficiency anaemia and irritable bowel syndrome. A previous general anaesthetic for sterilization had passed without any adverse effects, and the patient had undergone an oesophagogastroduodenoscopy (OGD) and a colonoscopy without any ill effects. Her current medications were mebeverine, venlafaxine and ferrous sulphate. She had no allergies and was a non-smoker.

Biochemical tests revealed primary hyperparathyroidism, with a corrected serum calcium level of 2.76 mM and a parathyroid hormone (PTH) level of 8.3 pM. The patient had normal renal function and was euthyroid. A single adenoma at the right lower thyroid pole was confirmed with both an ultrasound and a sestamibi scan.

The patient underwent routine parathyroidectomy following infusion of 7.5 mg/kg of methylene blue in the anaesthetic room. Her weight was 86.9 kg and the total dose of methylene blue given was therefore 650 mg.

Post-operatively, the patient had a delayed recovery from the anaesthetic and was found in the recovery room to have nystagmus, expressive aphasia and confusion. The pupils were normal and there were no focal neurological signs. She had no respiratory or cardiovascular abnormalities and was apyrexial. Serology revealed a white cell count of 13.6, a C-Reactive Protein (CRP) of 27, a glucose concentration of 9.5 mM and a methaemoglobin level of only 3 per cent. Renal function was normal and the serum calcium concentration had decreased to

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2.32 mM. A neurology opinion was sought and a head CT scan was undertaken; this was normal. The patient improved spontaneously and made a complete recovery over the following 48 hours. A diagnosis of methylene blue toxicity was made. At her post-operative review, the patient was normocalcaemic and the histology report confirmed excision of a benign parathyroid adenoma.

Discussion

In 1966, while using toluidine blue dye to stain the gastric corpus in dogs, Klopper and Moe[6] incidentally discovered that the dye also stained the pancreas and the parathyroid glands. Although the mechanism of uptake in these glands was unknown, this finding was later utilized to successfully identify the parathyroid glands in patients undergoing thyroid surgery.[7] Unfortunately, toluidine blue dye had significant cardiac toxicity and its use had to be abandoned.

Methylene blue belongs to the same group of thiazide dyes and has replaced toluidine blue for the selective staining of parathyroid glands because of its lack of significant side effects. There have been several papers on its effectiveness, the first of which was published in 1971.[4] Methylene blue is generally considered benign; the only side effects reported have been pain at the infusion site, pseudocyanosis (leading to erroneously low readings on pulse oximetry) and intensely blue-stained urine.

There are only two previously reported cases of methylene blue toxicity in patients undergoing parathyroidectomy, and both of these have appeared in anaesthetic journals.[8,9] The first case was that of a 60-year-old woman with primary hyperparathyroidism and a history of depression who had received treatment with fluoxetine and coproxamol prior to surgery. She had undergone a previous general anaesthetic for tonsillectomy without any adverse effects. She was given 7.5 mg/kg of methylene blue pre-operatively, and in the recovery room was noted to be confused and to have nystagmus, myoclonic jerks, increased tone in all four limbs and bilateral up-going plantar responses. She was investigated with CT and MRI scans, arterial blood gas estimations and routine serology. The latter were normal, the methaemoglobin level was only 0.7 per cent and she made a complete recovery by the second post-operative day and was discharged home.

The second reported case was that of a 59-year-old man undergoing a parathyroidectomy for primary hyperparathyroidism. His medical history included depression, diabetes, hypertension, first-degree atrioventricular block, hyperlipidaemia and hiatus hernia, and he was taking paroxetine, glyburide, metformin, verapamil, furosemide, potassium supplements, simvastatin and rabeprazole (the metformin was stopped two days before surgery). This patient was also given methylene blue at a dose of 7.5 mg/kg prior to surgery. Post-operatively, he was awake and responsive but demonstrated marked aphasia with no other abnormalities. Again, methylene blue toxicity was diagnosed. This patient also made a complete recovery within 48 hours and was discharged home.

Nadler *et al.* showed that high doses of intravenous methylene blue can produce paraesthesia, restlessness and mental confusion in humans.[10] In that study, the symptoms completely resolved after 24–48 hours. In our case, as well as in the two cases reported in the literature, recovery was also complete by 48 hours.

Just as the mechanism of parathyroid staining by methylene blue is unknown, the mechanism of toxicity is unclear. The chemical structure of methylene blue (tetramethylthionine chloride) resembles that of the phenothiazines[11] and this, combined with the fact that the toxicity is mainly neurological, leads us to suggest that a direct central mechanism of methylene blue toxicity must be occurring.

One other potential mechanism of toxicity is the production of methaemoglobin (Fe^{3+}) – the oxidized version of haemoglobin (Fe^{2+}). Although methylene blue in small doses (1–2 mg/kg) is used for the treatment of methaemoglobinaemia, larger doses can have the reverse effect and induce the formation of methaemoglobin. Such altered haemoglobin is incapable of binding oxygen, but studies have shown that methaemoglobin levels of less than 20 per cent usually do not cause any signs or symptoms other than pseudocyanosis,[12] and toxicity normally manifests via a marked respiratory and cardiovascular response. Our patient had a methaemoglobin level of 3 per cent; methaemoglobinaemia was also excluded as the cause of toxicity in both the other reported cases.

Interestingly, all these three patients were taking antidepressants. Fluoxetine and paroxetine are selective serotonin re-uptake inhibitors and venlafaxine is a serotonin and noradrenaline re-uptake inhibitor. An adverse drug interaction between methylene blue and serotonin re-uptake inhibitors cannot therefore be excluded.

The UK National Poisons Information Service Centre recommend an intravenous dose of methylene blue not exceeding 4 mg/kg of a 1 per cent solution.[8] Following our case, we have altered our practice and now use this lower dose in all patients undergoing parathyroidectomy. This dose has proved perfectly adequate in staining the glands, and our results have therefore not been affected. We suggest that a dose of 7.5 mg/kg should not be routinely used in the future.

- **Intravenous infusion of methylene blue is commonly used to aid visualization of parathyroid glands intra-operatively**
- **This paper reports the third case of neurological toxicity following methylene blue infusion for excision of a parathyroid adenoma**
- **All three cases received 7.5 mg/kg methylene blue pre-operatively**
- **In keeping with the UK National Poisons Information Service recommendations, the authors have as a result of this case altered their practice and now use methylene blue at a dose not exceeding 4 mg/kg; they find this dose adequate**
- **This case highlights the rare occurrence of methylene blue toxicity when used at a higher dose**

References

1 Potchen JE. Parathyroid imaging: current status and future prospects. *J Nucl Med* 1992;**33**:1807–9
2 Casas AT, Burke GJ, Mansberger AR, Wei JP. Impact of technetium-99m-sestamibi localisation on operative time and success of operations for primary hyperparathyroidism. *Am Surg* 1994;**60**:12–17
3 Flynn MB, Bumpous JM, Schill K, McMasters KM. Minimally invasive radioguided parathyroidectomy. *J Am Coll Surg* 2000;**191**:24–31
4 Dudley NE. Methylene blue for rapid identification of the parathyroids. *Br Med J* 1971;**3**:680–1
5 Derom AF, Wallaert PC, Janzing HM, Derom FE. Intraoperative identification of parathyroid glands with methylene blue infusion. *Am J Surg* 1993;**165**:380–2
6 Klopper PJ, Moe RE. Demonstration of the parathyroids during surgery in dogs, with preliminary report of results in some clinical cases. *Surgery* 1966;**59**:1101–7
7 Hurvitz RJ, Perzik SL, Morgenstern L. In vivo staining of the parathyroid glands: a clinical study. *Arch Surg* 1968;**97**:722–6

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8 Martindale S, Stedeford JC. Neurological sequelae following methylene blue injection for parathyroidectomy. *Anaesthesia* 2003;**58**:1041–2
9 Bach KK, Lindsay FW, Berg LS, Howard RS. Prolonged postoperative disorientation after methylene blue infusion during parathyroidectomy. *Anesthesia & Analgesia* 2004;**99**:1573–4
10 Nadler JE, Green H, Rosenbaum A. Intravenous injection of methylene blue in man with reference to its toxic symptoms and effect on electrocardiogram. *Am J Med Sci* 1934;**188**:15–21
11 Shen WW. A history of antipsychotic drug development. *Compr Psychiatry* 1999;**40**:407–14
12 Wright RO, Lewander WJ, Woolf AD. Methemoglobin: aetiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;**34**:646–55

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