Letters and Comments

Low dose methylene blue in the surgical management of hyperparathyroidism

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COMMENT ON

J Bewick, A Pfeleiderer. The value and role of low dose methylene blue in the surgical management of hyperparathyroidism. *Ann R Coll Surg Engl* 2014; **96**: 526–529

I am writing after reading the above paper and would like to point out several misleading statements.

Figure 1 illustrates the increase in the number of patients diagnosed in England and suggests that just over 3,000 patients were diagnosed between 1998 and 2012. This is in stark contrast with data published in a previous issue the *Annals* reporting that over 24,000 patients were operated on between 2000 and 2010.¹ The authors should revise their method of interrogating the Hospital Episode Statistics database and correct the data presented.

I work in a unit where methylene blue (MB) used to be administered routinely before all parathyroidectomies but we abandoned this practice after observing the first neurotoxic side effect in 2006.² The authors state that the lack of any observed side effects was related to using a low dose of MB (3.5mg/kg) and declare that other units might use much higher doses of 5–7.5mg/kg. This is factually wrong. The patient we reported in 2007 had only 1.75mg/kg and the meta-analysis quoted in the paper showed that most patients experienced side effects at low doses of MB.

Based on the 'rule of three', the lack of any observed neurotoxic incident in a (small) cohort of 104 patients leaves the statistical possibility of observing such an event in up to 3/104 patients. This could have significant implications if a 3% risk rate were to be applied to several thousand operations performed annually.

The authors could have reviewed the information published in the national audit maintained by the British Association of Endocrine and Thyroid Surgeons.³ In contrast to their statement that MB 'is used regularly in the identification of parathyroid adenomas', the 2012 report shows that MB was used in only 15% of targeted operations and 28% of non-targeted operations.³ The same source shows that MB staining was positive in 330 (87%) of 379 patients who had targeted parathyroidectomy and in 690 (83%) of 833 patients who had non-targeted parathyroidectomy (ie with negative or non-concordant imaging).

It is surprising how many intrathyroidal parathyroid adenomas were seen in this cohort of 104 patients as this is an exceedingly rare occurrence in most other series.

It would be interesting to know in how many patients it was necessary to stop selective serotonin reuptake inhibitor medication and whether this created additional difficulties with controlling their psychiatric symptoms.

I expect the paper will trigger many other questions from surgeons who have a large practice in parathyroid surgery and for whom some of the statements made throughout the paper might seem surprising.

References

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AUTHORS' RESPONSE

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Thank you for giving us the opportunity to respond to comments raised by Mr Mihai. Unfortunately, Figure 1 has been misinterpreted. First, the graph relates only to cases of primary hyperparathyroidism. Second, the three points on the graph show the correct Hospital Episode Statistics analysis, which highlights the steady increase in the number of cases diagnosed per year in three separate years during the study period quoted on the x-axis; they are not cumulative totals. The paper to which Mr Mihai refers looks at all cases of hyperparathyroidism¹ and is therefore not directly comparable with our data. On the contrary, Evans *et al* provide further evidence of the increasing burden of this disease, as discussed in our report.

Mr Mihai refers to a case report that he and his colleagues published in 2007,² which was not included in the systematic review that we quoted in our article. His case illustrates the dangers of giving methylene blue (MB) to patients who are on selective serotonin reuptake inhibitors (SSRIs) (his patient was taking paroxetine), which we made very clear in our paper. A number of case reports had been published prior to Mr Mihai's unfortunate case,

highlighting the association of neurotoxicity with MB in patients taking SSRIs, which were presumably overlooked.

In our series, a number of patients taking SSRIs (some of whom had been on them for some time) were asked to stop their medication when listed for surgery. None of them reported any adverse effects as a result, which suggests that some patients may be taking antidepressants unnecessarily. One or two did switch to a different family of antidepressant drugs that do not react with MB without any problems.

It was suggested that our cohort of patients was too small to observe potential rare complications, which is open to debate. Suffice it to say that our series shows that if simple guidelines in the use of MB are followed, it can be used in a safe and effective manner. However, we do accept Mr Mihai's point that the statement regarding MB use should have referred to 'some units'.

We felt the abundance of intrathyroidal parathyroid adenomas illustrated how useful MB is in these circumstances and

would argue that intrathyroidal adenomas are not 'exceedingly rare', with reported rates of 6%.⁵ Our case series demonstrates that the safe and controlled administration of MB is a helpful adjunct in locating intrathyroidal parathyroid adenomas as well as ectopic glands, particularly in fatty necks when the colour of the adenoma can 'shine through'. Our paper has indeed triggered much interest with personal correspondence from other surgeons who found the manuscript to be helpful to their practice.

References

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2. Mihai R, Mitchell EW, Warwick J. Dose-response and postoperative confusion following methylene blue infusion during parathyroidectomy. *Can J Anaesth* 2007; **54**: 79–81.
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