

Delayed Recovery from General Anaesthesia: A Post-operative Diagnostic Dilemma and Implications of ICU Management of Serotonin Toxicity. Case report: Comment

PK Gillman

PsychoTropical Research, Bucasia, Queensland, Australia

Keywords

methylthionimium, methylene blue; serotonin uptake inhibitors; drug combinations; drug–drug interactions, serotonin toxicity, serotonin syndrome, neurotoxicity, general anaesthesia, Information Storage and Retrieval, Libraries Medical.

Comment

This case report by Naik et al. of probable serotonin toxicity in a patient previously taking venlafaxine, who was then given intravenous methylthionimium (aka methylene blue) during a parathyroid surgical procedure (1), is a typical example of a perennial problem in medical publishing. The case is unremarkable, except for the fact that it is of concern that methylene blue was given at all, bearing in mind that such interactions have been well documented for nearly a decade. Neither was it, nor should it have been, a ‘diagnostic dilemma’. Therefore it is also of concern that methylene blue was not recognized as the culprit in the interaction until after a significant (life endangering) delay.

The first major point readers will benefit from being aware of is that an authoritative and comprehensive review of the subject was published some time ago (2), which these authors were clearly not aware of and did not cite. Indeed, they have failed to cite various important papers, but have cited a number of poor or barely relevant papers. There are many similar previous case reports (most equally poorly referenced), which they did not recognize or reference. It is difficult to see why the editor or referees would have regarded this offering as worthy of publication, had there been a proper awareness of the previous literature. Their paper is poorly argued, it is poorly referenced, and it is uninteresting and unoriginal.

This lack of awareness of the previous literature illustrates the next major point, which is that doctors, despite the availability of powerful computers and databases, still repeatedly fail to find most of the relevant references when they attempt these kinds of reports (3-5). They presumably failed to enlist the assistance of a librarian, the result being a poor literature review. Appropriately knowledgeable referees should be picking up these kinds of omissions and either rejecting such papers, or

guiding the authors to an appropriate coverage of the literature with pertinent citations.

This failure by authors and referees to ensure that previous quality literature is appropriately cited is a major problem in modern medical publishing. It dilutes and degrades the whole corpus of literature and muddies the water for all subsequent researchers. That this is a consequential problem is attested to by the continuing stream of seriously misinformed and misreferenced reports on serotonin toxicity.

Another contributing factor is the excessive proliferation of a huge number of mediocre journals, many publishing poor quality and mostly drug company sponsored material, which saturates the medical literature with substandard material. Even librarians experienced in search techniques have trouble wading through this mass of misinformation. The average junior doctor trying to get ‘runs on the board’, by publishing a nice easy case report, hardly stands a chance.

The competitiveness of academic medicine (H-indexes, number of citations etc.), which emulates the excessive commercialization of research and publishing, is producing a strong tendency for anyone who wants to succeed to concentrate on their own publications, and not on refereeing those of others. The unfortunate consequence of this is that many referees who are not experts in the field are flattered into offering their services to editors, and those editors are neither willing nor able to take responsibility for the quality or scholarly credibility of what they publish. And so we descend further into a world of mediocrity where an even greater percentage of case reports are pointless, misleading and counter-productive (6).

An exhaustive critique of the mediocrity of the report of Naik et al., and the clinical management of the case is not the point of this communication. However, it is worth noting that had these authors intubated and paralysed the patient (with a non-depolarizing paralytic), which would have been an appropriate course of action, that would have revealed that it was not malignant hyperthermia, because the rigidity would have disappeared. If it was malignant hyperthermia rigidity would remain. Whether or not the authors appreciated this important point is unexplained, but discussing it would have been an important learning point for readers. Thyroid storm does not cause rigidity. Therefore, their listed differential diagnosis is confidently and quickly resolved.

Despite the fact that their report concerns a hyper-thermic syndrome, and that their patient was ‘sweaty, pyrexial*’, and that the patient was in ICU, they do not give one single measurement of body temperature, let alone information about where, by what method, how frequently and over what period of time it was elevated (7, 8). That the referees of a journal of critical care medicine failed to comment on this must be regarded as an unfortunate omission, which is a charitable way of putting it.

*NB Pyrexia is an incorrect term in this context, their patient was hyperthermic. These two states are aetiologically and clinically distinct.

The uncorrected misspelling of cyproheptadine as ‘ciproheptadin’ surely tells us more about the inexperience of the referees.

Their conclusion section opens with the ungrammatical and oxymoronic sentence, ‘Though widely known, published and reviewed, methylene blue interactions with SSRI/SnRI and serotonin toxicity is still a relatively unknown entity.’ Widely known, but unknown. The authors are confused. When they refer to serotonin toxicity as an ‘unknown entity’ they are not telling us what is known about the subject, they are telling us what they themselves do not know about the subject, but that is hardly worthy of publication. And they do not know about it because they do not know how to do a proper literature search, nor how to select and evaluate what they find. If editors and referees are going to let this kind of amateur effort into print the literature is doomed to become a mass of ill-informed unhelpful verbiage. I would argue it has got to that point already, at least in serotonin toxicity, which is my area of expertise.

‘Based on our literature search, the majority of cases are self-limiting ...’; yes, death is self-limiting. This statement is dangerously poorly informed and utterly unhelpful. It depends a bit on the dose! ‘sola dosis facit venenum’ (the dose makes the poison’), as the old, and true, pharmacological adage goes.

In brief, the authors’ conclusions are confused and clearly do not evince an understanding of the problem. There is no question that there is an absolute contraindication to giving even small doses of methylene blue to patients who are already taking drugs with significant therapeutic activity as serotonin reuptake inhibitors (9-11). Failure to recognize, emphasize and abide by this prohibition will lead to fatalities, as it already has done (11), and as it nearly did do in this case.

The key issue, and one which these authors do not appear to address in any substantive way, is how on earth was it possible for a known fatal interaction not to be flagged by the systems and safeguards that should have been in operation in their hospital? Even if the surgeon thought MB was just a pretty-coloured blue liquid? how did the pharmacist who, presumably, supplied it, not flag the interaction.

Writing as someone who provides medico-legal opinions in such situations, this hospital, and the pharmacists and doctors concerned, may benefit from the knowledge that I would advise my consulting legal firm for the plaintiff that they were prosecuting a non-defensible case. A case such as this could easily lead to major permanent disabilities or death and the financial liability would potentially be in the millions for the relevant defendants. Any hospital that does not have well-established systems for preventing such incidents is exposing themselves to serious liability.

References

1. Naik, A and Rincon-Aznar, C, Delayed Recovery from General Anaesthesia: A Post-operative Diagnostic Dilemma and Implications of ICU Management of Serotonin Toxicity. Case report. *The Journal of Critical Care Medicine*, **2015**. 1(4): p. 174–178.
2. Gillman, PK, CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity. *J Psychopharmacol (Oxf)*, **2011**. 25(3): p. 429–3.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20142303
3. Sampson, M, McGowan, J, Cogo, E, Grimshaw, J, et al., An evidence-based practice guideline for the peer review of electronic search strategies. *J. Clin. Epidemiol.*, **2009**. 62(9): p. 944–52.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19230612
4. Helmer, D, Savoie, I, Green, C, and Kazanjian, A, Evidence-based practice: extending the search to find material for the systematic review. *Bull. Med. Libr. Assoc.*, **2001**. 89(4): p. 346–52.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11837256
5. Lasserre, K, Expert searching in health librarianship: a literature review to identify international issues and Australian concerns. *Health Info Libr J*, **2012**. 29(1): p. 3–15.
<http://www.ncbi.nlm.nih.gov/pubmed/22335285>
6. Gillman, PK, Extracting value from case reports: lessons from serotonin toxicity. *Anaesthesia*, **2006**. 61: p. 419–422.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16674612
7. Gillman, PK, Mechanisms, management and measurement in atropine induced hyperthermia. *Anaesth Intensive Care*, **2009**. 37(2): p. 322–323.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19400503
8. Gillman, PK, Neuroleptic malignant syndrome, poor science and inaccurate measurements. *J Psychopharmacol (Oxf)*, **2010**: p. 20 May 2010, 10.1177/0269881110367461.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20488833

9. Adler, AR, Charnin, JA, and Quraishi, SA, Serotonin Syndrome: The Potential for a Severe Reaction Between Common Perioperative Medications and Selective Serotonin Reuptake Inhibitors. A&A Case Reports, **2015**. 5(9): p. 156-159.

10. Larson, KJ, Wittwer, ED, Nicholson, WT, Weingarten, TN, et al., Myoclonus in patient on fluoxetine after receiving fentanyl and low-dose methylene blue during sentinel lymph node biopsy. J. Clin. Anesth., **2014**.

<http://www.ncbi.nlm.nih.gov/pubmed/25499271>

11. Top, WM, Gillman, PK, de Langen, CJ, and Kooy, A, Fatal methylene blue associated serotonin toxicity. Neth. J. Med., **2014**. 72(3): p. 179-81.

<http://www.ncbi.nlm.nih.gov/pubmed/24846936>