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FDA Warning About Methylene Blue & Serotonin Toxicity [issued 7/26/2011 & modified]

Keywords

MAOI, methylene blue, serotonin syndrome toxicity, drug safety, drug interaction, SSRIs, fatal, FDA, EMA, MHRA, inaccuracy, plagiarism

Summary

The various recent warnings from the FDA [latest seems to be 20/10/11] about serotonin toxicity involving methylene blue are still incomplete, misleading to clinicians and contain errors. Other agencies [EMA, MHRA] have issued similarly poor information, but **Health Canada have got it succinctly correct**. The FDA info is also a blatant example of plagiarism, a fraudulent practice recently decried in a Lancet editorial (1). Worldwide the product information (packet inserts) for doctors about MB are currently still poor and many fail to warn that **MB is an MAOI which interacts with SRIs** to cause a significant chance of **serious or fatal serotonin syndrome toxicity**.

Introduction

A brief introduction to the background of this serious adverse drug interaction is necessary. I am Doctor P K Gillman and I am an internationally recognised authority on the complex subject of serotonin toxicity. I have specifically reviewed the potentially fatal occurrence of serotonin toxicity with methylene blue [aka methylthioninium] when it is given with SRIs, first in 2006 and more recently in 2010.

I posted a well-referenced warning about this in 2006 (updated 2009) **five years before the FDA**. This update supersedes my initial post, but

has the same title (/methblue_toxicity_v2.doc) in order to preserve pre-existing links.

http://www.psychotropical.com/docs/methblue_toxicity_v2.doc

Note: there is further information about ST MB etc. on my new web site

<http://psychotropical.info/index.php?page=methylene-blue>

As I was preparing to update the information on my website to reflect my most recent papers (2-5), and other data, further warnings, commented on below, were put out by the FDA which are still unsatisfactory.

The Canadians got it right: short, sweet and accurate; key symptoms correct, precipitating drugs correct. Why can't the FDA manage that even when they are spoon-fed a good template? See Health Canada:

http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2011/methylene_blue-bleu_nth-aah-eng.php

This post highlights the errors and misleading info in the FDA warning. I offered to help them improve the info, but they declined to even reply to emails.

There is much other relevant information elsewhere on my site and in my published papers: read on.

FDA Safety Announcements/Communications

The first has now been followed up by two more (6)

<http://www.fda.gov/Drugs/DrugSafety/ucm263190.htm#sa>

<http://www.fda.gov/Drugs/DrugSafety/ucm276119.htm>

On the face of it one might applaud this FDA 'Safety Announcement' about the risk of serotonin toxicity with methylene blue. But also, note that the UK MHRA issued a similar warning [also somewhat misleading] in both 2008 & 2009 (7, 8). And the Canadians also in Feb 2011.

However, further consideration of the FDA warning leads to a different perspective. But, be warned, good scholarship it is not.

Considering the power, stature and resources of the FDA these warnings represents an egregious example of poor scholarship and tardiness. But, the latest is a useful improvement.

First, the title "...serotonergic psychiatric medications", think about it. It is imprecise, unscientific and wrong. The term "serotonergic" has no defined or agreed meaning, some such drugs are not "psychiatric" at all, and the term "psychiatric medications" is bad use of language (solecism).

Then, look at the three references that they give, which are the same even in this latest version (9-11). The most recent is four years old—2007. If that is what they are basing this advice then on why did it take

them five years to reach their conclusion and issue this ‘updated’ advice? However, if they are basing it on something else, where are the citations? My review, published [online] more than a year ago [Feb 2010] (3), provides many more cases and references and restates my detailed hypothesis and explanation of the mechanism.

I remain almost speechless. It beggars belief to suppose the FDA are so incompetent that they are unaware of all this more recent, and more edifying, research. So what is going on?

Plagiarism and hubris would explain it, challenged competence may be the icing on their cake.

Americans are recognized, on the other side of the pond, as being visually impaired when it comes to noticing and quoting non-American literature: it is a sort of scientific hegemony. It is dishonest, it is plagiarism. It does them no credit.

Misinformation and Errors

This FDA document contains misinformation and errors. The most important of these are:

- Failure to explain that MB is a potent MAOI [now corrected, but without attribution]
- Failure to explain that MAOIs (like MB) predictably interact with SRIs and precipitate potentially fatal ST [now partially corrected, without attribution]
- The use of an imprecise and outdated description of ST
- The listing of drugs as implicated which do not precipitate ST (because they have no serotonergic action)
- Failure to mention how anaesthesia may modify presentation

The consequence of this is that it will presumably lead to the FDA promulgating changes in product information sheets [better late than never, but they could have used the time to get it correct!] which are neither based on sound science, nor substantive evidence. That is a major negative outcome.

See below for further details.

Plagiarism and Attribution

Now we come to the matter of attribution in relation to the contents of this warning. A cornerstone of good science is building your case on the foundations of previous evidence. An ethical principle of science is giving credit to that previous work, by appropriately citing the original papers. Not to do this is grossly improper academic conduct and is plagiarism (1). Plagiarism means putting forward other people’s work and ideas without giving them any credit [and thereby implicitly assigning

credit to yourself]. It is intellectual theft. It is cheating, lying, dishonesty (the dictionary definition is ‘stealing somebody’s work or idea’). Otherwise know as copying the example of Presidents.

This FDA document exemplifies two instances of obvious plagiarism. Firstly, not attributing the original idea describing how methylene blue interacts with SRIs thereby producing a clinical picture that is highly likely to be serotonin toxicity (12). Secondly, they have now stated that MB is a monoamine oxidase inhibitor. This can only be based on our work, which was the first clear and unequivocal demonstration that it is a potent reversible and selective inhibitor of monoamine oxidase-A (13). Failure to cite these two pieces of important evidence, which are central to their discussion, is plagiarism.

The FDA warning states that MB “Is a potent, reversible monoamine oxidase inhibitor (MAOI).” [almost accurate, it is actually a highly potent & *selective* MAO-A inhibitor]. They have lifted this from ‘our’ paper (13) but they have not acknowledged it by citing the reference. Neither have they referred to my review and analysis of all the case reports (3), most of which they seem to have missed, nor other papers on pharmacology, ST etc.

Product Information Sheets

I do not wish to nitpick about the various other mistakes in this document, but nevertheless, it is important to note some of them, because the FDA are responsible for getting manufacturers to change their product information sheets. If this is the standard of their analysis on the subject, these information sheets are going to be filled with incorrect and misleading information for which there is no scientific basis. That is obviously undesirable.

Incidentally, one or two manufacturers have already altered their product information on my direct advice, a commendable example of common sense and expediency.

Because it seemed obvious that the authorities in the English-speaking world were being rather slow on the uptake concerning this I simply contacted some manufacturers with the evidence and suggested that they alter their product information sheets.

Incorrect Information

The FDA information on the diagnosis of serotonin toxicity is second rate (see (14, 15), and their list of drugs that might induce it was, and continues to be, an exhibition of pharmacological ignorance (e.g. see (3, 16, 17). For example, they list all tricyclics (that is 6 mistakes straight off), mirtazapine, nefazodone, trazodone, maprotiline and bupropion (total= 11 mistakes), all of which are devoid the significant serotonergic activity and cannot cause serotonin toxicity. That is a pretty impressive list of mistakes, and the references given below fully justify calling these

mistakes. There is no room for equivocation, they have got it badly wrong. Since these are commonly used drugs one imagines this may create unnecessary chaos in surgical departments who imagine they now have to cease these drugs or risk being sued, because the FDA have said so.

For the average medical practitioner the situation can be summed up very concisely (see Health Canada). It is only drugs that have significant potency as serotonin reuptake inhibitors that are a significant risk. Other types of serotonergic drugs (a poorly defined and unsatisfactory term) do not appear to be capable of elevating serotonin to a problematic extent (if combined with MAOIs). The only possible exception I would make is Lithium.

The FDA have failed to quote many important recent references. It is also noticeable that the document is entirely Amero-centric, as unfortunately is so much of the American literature. That is especially inappropriate since almost all the original research about ST is 'non-American'. I am sure my UK associates will not regard that as a revelatory statement. But the general audience need to be aware that Americans are a bit up themselves citation-wise.

Bad science results in bad policy.

Put simply, if I had been asked to referee this as a journal publication it would have taken me only a few minutes to decide to advise the editor against publication. Bad title, bad references, 95% chance it is a bad paper.

Devoting time and energy to any further criticism of this FDA document is a bit pointless. It would be better to read my recent review paper (3).

Google and Wikipedia: Better Info Than FDA

One last observation. Both Google and Wikipedia have arguably been providing, for nearly five years, better info than the FDA.

Perhaps one or two folk at the FDA could profitably adopt the habit of logging on to [this website](#) every morning when they arrive at work.

Have a thinking day at the FDA.

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