

Methylene Blue and Serotonin Toxicity

Abstract

This is the story of how an understanding of the spectrum concept of serotonin toxicity led to the hypothesis, then the experimental validation, of the potent MAOI-A potency of methylene blue. This is important because it is used for various purposes, including as a dye during surgical procedures. It does cause fatal interactions in people who have been taking SRI drugs prior to surgery — this information is not yet contained in any guidelines concerning drugs and anaesthesia. The story further highlights the apparent inability of drug regulatory agencies such as the FDA, EMA, and MHRA to understand toxicity related drug interactions — they have issued a number of unhelpful and incorrect statements about this problem which have mislead doctors.

Introduction

My collaborators and I showed that **Methylene Blue MB** (aka Methylthioninium chloride) is an potent monoamine oxidase inhibitor (MAOI) *in vitro* [i.e. in test tube experiments] and that in humans it causes potentially fatal serotonin toxicity (serotonin syndrome) when combined with serotonin reuptake inhibitors [1, 2].

There have been many deaths in humans due to serotonin toxicity precipitated by this interaction

As I write this updated version [amended June 2012] of the story about MB the reverberations of the American FDA warning are beginning to echo around the Internet spreading significant misinformation. It is enough to say that the FDA warning is unlikely to result in much useful increase in anyone's knowledge or understanding, because it contains significant mistakes and lists many drugs which are not involved in serotonin toxicity as being a danger. This is counter-productive.

I have not posted anything on MB since 2009 is because I have been concentrating on getting scientific papers published in the peer-reviewed literature to make the scientific community more aware of this problem. I have now published various contributions to the medical literature about this which I list here for completeness, and the historical record.

Publications concerning MB, up to June 2012: [1-14].

Summary: Essential basic knowledge

Methylene blue is a **potent** monoamine oxidase inhibitor (**MAOI**) that interacts with serotonin reuptake inhibitors — both selective and non-selective, SRI/SSRI — to induce **severe potentially fatal serotonin toxicity ST (serotonin syndrome)**: a severe reaction is **likely with therapeutic doses** of such MAOI/SRI combinations and can often be fatal.

I have published a review of human cases of ST with MB and SRIs which establishes that **this toxic reaction is ST** [1] beyond reasonable doubt, even though the regulatory agencies [in UK, USA and Europe] have not got up to speed with this yet [this remains the case in 2022]. The theoretical underpinning of the pharmacology of the interaction is both established and understood and there is no room for doubt or equivocation. The MHRA and the FDA warnings have been/are poor and unhelpful, they have been amended once and may have

been amended again by the time you read this [15, 16]), yet they still have not got it right.

The MHRA and the FDA warnings are still deficient and erroneous

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-serious-cns-reactions-possible-when-methylene-blue-given-patients>

Key symptoms and the effect of anaesthesia

Progressively: Tremor, then hyperreflexia (especially lower limbs), clonus (inducible, spontaneous, ocular), rigidity, hyperthermia. Autonomic overactivity (diaphoresis, BP, mydriasis, gut) and mental state change (excitement, confusion in late stage).

But: anaesthesia changes the emerging signs and symptoms because anaesthesia itself treats ST. It lowers brain temperature and disguises and or suppresses symptoms like tremor & hyperreflexia. Thus, post anaesthesia ST may present after 30-60 minutes as agitation/confusion and the hyperreflexia etc. may be muted and only noted on careful examination. As the cooling effect of anaesthesia wears off hyperthermia can increase rapidly (over a few hours) leading to death [12, 17].

History

My web site introduces me as: ‘... an internationally acknowledged authority on **serotonin toxicity (ST)**, sometimes called **serotonin syndrome (SS)**, and an expert on other sorts of drug interactions, side effects and adverse effects’. Hence my interest in, and recognition of, this problem of serotonin toxicity with Methylthioninium chloride (methylene blue).

Since my initial ‘alert’ [18] and web site posting in 2006 about serotonin toxicity from combinations of MB + **(selective) serotonin reuptake inhibitor interactions ((S)SRIs)**, further serious cases, and several fatalities from probable or definite ST have been reported or recognised. It is usual in such circumstances for reported cases to be only a proportion of actual cases, and the questions to my website and cases reported to me also indicate that. There are two retrospective case series of relevance, Kartha [19] & Sweet [20].

There are now more than a dozen case reports. Indeed, there are unlikely to be many further case reports that are sufficiently interesting to be worthy of publication, as many journal editors have already concluded. Reports that have been submitted, which do not add anything to the existing literature, are likely to be rejected on the basis that they are of insufficient novelty value or interest. That lengthy explanation of the status is appropriate because it represents a straw poll of opinion among the experts in the field. In other words what they are saying is it is fully documented, and more case reports will not add anything of value.

The UK MHRA data also contains several cases, including one typical case of ST that was fatal. However, most of the MHRA data is of little value for assessing ST, particularly because there is no definite information about previous and current drug treatment: it merely confirms that most cases of CNS toxicity look like ST even from the minimal information available.

That in vitro study I initiated, courtesy of Rona Ramsay in St Andrews, yielded data unequivocally demonstrating that Methylene Blue is a potent inhibitor of monoamine oxidase A (MAO-A) in vitro [2] with a K_i of 27 nM — that is potent. This clarifies why it precipitates serious and potentially fatal serotonin toxicity if

combined with (S)SRIs [3, 21], as moclobemide and the old monoamine oxidase inhibitors (MAOIs) do.

SSRIs include 'Prozac' like drugs (SSRIs) and other drugs that act as SNRIs, and the tricyclic antidepressant (TCA) clomipramine, the opioids tramadol and meperidine (aka pethidine), and venlafaxine, duloxetine, chlorpheniramine etc.; see [18] Table 2, or my web site, for an authoritative list.

Many published lists contain multiple errors and misinformation (that includes the MHRA & FDA material which contain elementary errors

Mixtures of MAOIs (in this instance Methylthioninium [aka methylene blue]) combined with SRIs (of any sort, specific or non-specific) are the **only** cause of serious (i.e., potentially fatal) serotonin toxicity. Such mixtures produce an elevated risk of toxicity and should be studiously avoided.

This new finding of potent MAO-A inhibition by MB is important because it is used intra-venously in surgery for thyroid operations at doses of 2-10 mg/kg, for methaemoglobinuria (1-2 mg/kg) and for resistant hypotension in septic shock and anaphylaxis [22-24]; cardiac surgery [25-28]; ifosfamide encephalopathy [29]; priapism [30]; also trials in dementia ([31], abstract only) and manic-depressive illness have been completed (Alda, M, Dalhousie Nova Scotia, [32]) and malaria (see <http://clinicaltrials.gov>) and chromo-endoscopy [33].

And then there is the odd, and mostly forgotten story of its use in amniocentesis [34-36] where it caused fetal abnormalities like ileal atresia, and possible deaths: the deaths seem to have been skated over. Even more alarmingly the same mistakes appear to be being repeated with toluidine blue (Tolonium Chloride) [37] and Azure B [38]. It is also used for various other staining biopsy purposes by various routes and doses, e.g., it is injected into inter-vertebral discs, up fallopian tubes, into ileostomies etc.

New Human Data, May 2009 and Onward

The dangerous irony is that, although thought of as merely a dye by non-pharmacologically orientated surgeons, it is a potent drug. As of May 2009, there are good new studies of its human pharmacokinetics, reviewed by Stanford and Gillman [9]. The Ramsay and Gillman paper on *in vitro* activity [2] established that MB is a potent inhibitor of MAO-A with a K_i of 27 nM and that it binds in the active site of MAO-A. The most recent human data established MB plasma concentrations after an IV dose of 0.75 mg kg⁻¹ (usual therapeutic doses are 1-7 mg kg⁻¹) as being a peak of 500-600 ng ml⁻¹ in plasma [33, 39, 40]. The mean $T_{1/2}$ was 13.6±3.7 h. The peak value of 500 ng ml⁻¹ represents a concentration of 1.6 µM in plasma, indicating that the concentration inside cells is likely to reach a level that inhibits MAO-A, even at the low dose of 0.75 mg kg⁻¹. At higher concentrations MB also inhibits Nitric Oxide synthase (NOS): the formation of L-citrulline by NOS is completely inhibited by 30 µM MB [41, 42], and it inhibits soluble guanylate cyclase (cGC) [43, 44]. I have a case reported to me via the website of definite ST with only 1 mg kg⁻¹, which fits the above estimate. That has now been published [8].

Various evidence suggests MB helps memory and neuronal degeneration [45-49]. It may also have (like some other MAOIs, see Youdim) acetylcholinesterase antagonist activity [50]. Wischik also proposes MB dissolves Tau polymers isolated from Alzheimer disease brains, and prevents Tau aggregation in cell models in the high nM concentration range (150 - 580 nM) and also reverses Tau pathology in the brain [31, 51]. MAO-A inhibition probably occurs at a lower concentration than Tau inhibition. In view of previous evidence about MAOIs and Parkinson disease and dementia [52, 53] it will be interesting to learn to what extent this is related to its MAOI activity.

The older studies of its pharmacokinetics [54, 55] are probably outdated (see above) but suggested: an estimated terminal half-life of 5.25 h (recent estimates

14 hrs); the area under the concentration-time curve was, oral dose, 9 nmol/min/ml vs. IV 137 nmol/min/ml. i.v. IV probably results in much higher concentrations in brain. See also [56, 57]. The LD50 in sheep is ~40mg kg⁻¹. However, there is some doubt about the accuracy of some of these older estimations.

For some clinical situations it may be relevant to note that MB appears to prevent the febrile response: Riedel has demonstrated MB completely blocked the febrile response to lipopolysaccharide (LPS) [58].

I said before 'My guess is that at > 0.5 - 1 mg per kg intra-venously it will be active as an MAOI.' And it seems that was a good guess. When injected into tissues the systemic availability may be less, and the dose probably lower, thus, these situations are less likely to give rise to ST interactions. Please contact me if you have any views or experience on this and I will update this doc as needed. Try to remember to fill out adverse drug reaction reports for the authorities in your country, it is clear this is often forgotten about.

Summary of The Current Evidence

- We have irrefutable evidence that mixing MAOIs and SRIs, in therapeutic doses, gives an elevated risk of severe ST, and definitely does precipitate fatalities.
- We have strong evidence that Methylthioninium chloride (methylene blue) is a potent (at nanomolar concentrations) MAO-A inhibitor *in vitro*, and strong evidence it is active *in vivo*.
- We know that many of the cases in question have exhibited symptoms typical of ST (and ST is not easily confused with other conditions), and of a severity only seen with mixtures of MAOI + SSRI (*ipso facto*, this is convincing evidence that MB is an MAOI in humans, not only in test tubes).
- We know paralysis and anaesthesia are good effective treatment for ST, and therefore modify the symptoms (particularly hyperthermia), we would expect these post-operative cases to be atypical.
- We know that in Sweet's & Kartha's series of 325 patients only those on SSRIs pre-operatively got symptoms, and not a single patient of the 280 who were not on SRIs got symptoms.

This constitutes strong presumptive evidence that serotonin toxicity is the most likely explanation and constitutes a strong cause-effect link to explain the observations. I cannot see, nor have I seen proposed, any remotely plausible alternative explanation.

If MB [aka Methylthioninium] is judged to be indicated cessation of SRIs must be accorded a high priority indeed (with due consideration of elimination half-life), prior to treatment/procedure/surgery. Other types of drugs with serotonin-mediated actions (the word "serotonergic" is mis-used) are not implicated in significant toxicity e.g. tryptans, mirtazapine, bupropion,, tricyclic antidepressants (except clomipramine) etc. See [18].

How the Story Started

In 2005 David Bogod, the editor of the journal Anaesthesia, invited me to write an editorial concerning case reports and serotonin toxicity [3]. Anaesthesia had already published an interesting case report by Martindale et al of 'Neurological sequelae following methylene blue injection for parathyroidectomy', although that report had not then been recognised as a possible example of ST [59]. One of my routine Google searches for SS/ST in early 2006 led me to an unpublished report on the internet by Rosenbaum [60], who, most astutely in my opinion, suggested the symptoms and signs observed in that patient might be serotonin toxicity (ST), resulting from an interaction between methylene blue and a

serotonin reuptake inhibitor (SSRI). Rosenbaum noted the similarities to the Martindale report. I immediately corresponded with Rosenbaum, to encourage him to publish his case in a peer reviewed Journal (he never got round to it), and to let him know that in my opinion he was correct, and furthermore that this strongly suggested (because of the severity of symptoms) that methylene blue must be a monoamine-oxidase inhibitor. I searched for information concerning methylene blue and MAOI activity, with some success, and submitted a comment to Bogod (Anaesthesia) concerning this [3], particularly because the case illustrated the problems and potential of case reports, the subject of my previous Anaesthesia editorial. As they were preparing to go to press with my letter the editor contacted me to say they had received another report that he thought I might wish to comment on. Indeed, it seemed likely that this was indeed another case of ST [61]. All subsequently discovered/recognised published reports, as of May 2012, are tabulated below.

The key issue to grasp (see figure below, ST triangle) is that severe degrees of ST, involving *therapeutic* doses of (S)SRIs, only occur following combination with MAOIs [3], but not with other drugs (with other mechanisms of action (cf. the misinformation in the MHRA warning)). These few cases therefore indicated (one could *almost* say proved) that methylene blue must possess significant potency as an MAOI. See diagrams and figures below that illustrate the details of symptoms, interactions, and severity.

A search of the existing standard texts (Goodman and Gilman, Rang and Dale, British National Formulary, Martindale etc) revealed no information or suggestion that Methylene Blue is an MAOI: however other older, and some recent literature did support a degree of MAO inhibition [62-64], but one of uncertain potency and relevance in relation to humans. I therefore sought the assistance of Rona Ramsay at St Andrews, an expert in the field of assessing MAOI potency, who took on the task of assaying MAO inhibition by methylene blue. The rest, as they say, is history.

SRIs have been in use for more than three decades. Clomipramine has been in use since 1966- France, 1968- UK, before fluoxetine, 1986-USA, 1988- UK. MB has been used for parathyroid surgery since ~ 1971. It would be astonishing if substantial numbers of patients taking them had not been operated on with procedures that utilize the infusion of methylene blue. Since (we now know) that it is a potent MAOI one would expect a large number of reports of toxicity; there are few. This is similar to the situation that pertained for decades with pethidine and imipramine [65, 66]. In my opinion the most parsimonious explanation is that ST had occurred but had not been recognised, or the relevance of the reactions seen had not been appreciated: cf. pethidine, imipramine, linezolid [67]. The fact that most of the cases now uncovered have been reported as 'encephalopathy' re-enforces my point. This is congruous with the documented history of failure to recognise serotonin toxicity when it occurred frequently between 1955 and 1982 without recognition [68], usually caused by MAOIs + imipramine or clomipramine or pethidine.

It would be interesting to know if, in retrospect, experienced practitioners recognise that they have indeed seen ST symptoms (particularly clonus, hyperreflexia, pyrexia and agitation/confusion) in such cases (see Kartha [19] below). Patients are usually slightly hypothermic post-operatively. A recent study of 1300 patients found a mean aural temperature of 35.8°C [69]. Anaesthetics greatly reduce both brain metabolism and temperature, inducing brain and body hypothermia [70-74]. After a single pentobarbital dose of 50 mg/kg, i.p. brain temperature dropped 4.0-4.5 °C [75]. Post-operative cases of ST are most unlikely to be hyperthermic by the usual criteria. Other signs may be muted also. Careful and repeated examination for clonus (especially ocular), hyperreflexia and tremor (masked by post-op shivering) are recommended.

Errors in Official Warnings: MHRA, FDA, EMA

The MHRA in the UK issued an incomplete and misleading warning [15] in Jan 2008, but have discounted the Ramsay paper, a copy of which they were provided with prior to its publication in May 2007. They have also failed to reference my 2006 paper, or use the term serotonin syndrome or serotonin toxicity [21]. Both their warning and their response to my written communication to them, and to this web post, have been factually inaccurate and muddled. They have indicated they do not wish any further communications or information, and have declined to explain why they have deliberately chosen not to inform doctors of the potential for fatality from ST. Their further update of April 2009 does little to improve things [16], it again fails to mention MAOI inhibition by MB, and fails to mention the fatality in their own case data. One must wonder what on earth is going on in their heads; if anyone can throw any light on that, do let me know. They need to get their act together and get up to speed on this issue. NB I have also written to the FDA who did not even deign to reply: talk about hubris.

The FDA and EMA (European Medicines Agency) and MHRA materials for doctors (product information etc.) do not explain the entirely predictable incidence of ST nor mention MB is a potent MAOI. Doctors need to know this to understand what is going on and to treat patients correctly.

Failure to state MB is an MAOI and failure to warn by providing explicit information about potentially fatal ST is inexplicable, and, with our current knowledge, inexcusable.

Health Canada Get it Right

Health Canada have issued [Feb 2011] this succinct and correct information:

“Serotonin toxicity/serotonin syndrome has been reported when methylene blue was administered intravenously in patients also receiving other drugs with serotonin reuptake inhibition properties. Several of these cases required admission to intensive care unit.” [76].

So, you see, it is possible. That is about all a well-informed doctor needs to know in an emergency.

Currently Known Cases: Methylene Blue and ST

[I have not bothered to add the further cases as of this updating in 2021]

Currently known cases relevant to methylene blue and serotonin toxicity are: [12, 17, 19, 59-61, 77-86], this includes the old new case I have uncovered [77] about which Clare Stanford and I have published a ‘correction’ (see below) that also reviews MB pharmacology. Note: Patel [87] has been included in the paper by Ng [83], the case does not meet any criteria to justify even a suggestion of ST, and no SSRI had been taken pre-op, thus this case is irrelevant in this context. Ng says, of Patel, ‘Only one of the seven case reports did not meet the diagnostic criteria, as a serotonergic agent had not been administered’, his meaning is unclear. His report is of six cases, most of which had been previously postulated to be ST and had already been commented on. His table assigning diagnosis contains multiple errors.

Table: Cases of ST with MB (up to June 2012): Certainty of Diagnosis and Severity

Case reference (chronological order)	Certainty of diagnosis of ST	Severity of clinical state	Comments
1) Stanford [77]	Definite	Severe	MB used, but not mentioned in original report
2) Martindale [59]	Definite	Severe	'Rotational nystagmus', represents ocular clonus
3) Bach [79]	Probable	Moderate	'A suggestion of clonus, forced dorsiflexion of feet' *
4) Majithia [80]	Probable/definite	Severe	'Nystagmus', was very probably ocular clonus *
5) Mathew [61]	Definite	Severe	MH queried, tremor, agitation, temperature 40°C
6) Rosenbaum [60]	Definite	Severe	The first recognised case. 'Agitated, tachycardic and diaphoretic ... lower extremity rigidity'. T38.3°C
7) Khan [81]	Probable/definite	Severe	'Confused, agitated, jerky movement of all four limbs' *
8) Mihai [82]	Possible	N/A	'Agitated and restless ... unable to speak no response to verbal command ... no limb weakness, ... no focal neurological signs'
9) Ng [83]	Probable/definite	Severe	'Agitated, disoriented, moving all limbs purposelessly ... increased tone in all limbs' and 'rapid, fluid eye movements' represents probable ocular clonus *
10) Shanmugam [84]	Definite	Severe	'confused and agitated ... temperature 40°C, myoclonic jerks, fine tremors, dilated pupils, shivering, hyperactive reflexes, hypertonicity'
11) Khavandi [85]	Probable/definite	Moderate	'agitated and restless', 'myoclonic movements of the lower limbs, brisk reflexes', T 37.5° C)
12) Schweibert [8]	Definite	Severe	'Confusion, agitation, aphasia, ocular clonus, mydriasis, hyperreflexia and arterial hypertension'. Dose 1 mg kg⁻¹
13) Rowley [86]	Definite	Severe	'38.1°C (rectal), end-gaze nystagmus, hypertonia, diaphoresis, agitated, Duloxetine.
14) Heritier Barras [17]	Definite	Severe	Severe hyperthermia 42.3°C, rigidity, shivering, inducible clonus, hyperreflexia, diaphoresis.
15) Top [12]	Definite	Fatal	Severe hyperthermia 43.1°C, ocular clonus, hyperreflexia, diaphoresis. Venlafaxine 150 mg daily, MB 9 mg/kg

Other cases have crossed my desk in various confidential contexts, none of them contradict anything stated herein. Sadly, the WHO database is usually only accessible on payment of a fee (that I, personally, cannot afford), but they have told me they have 102 reports of toxicity. Anders Viklund is kindly trying to get more information for me, I will give more details if and when those are available. I am trying to help producers to update their product information texts (the Australians have already initiated that, to their credit). I am not aware of the

WHO acting on this yet, it would be worth their serious consideration because in many areas of the world MB is apparently being issued to doctors without proper warnings. If you are aware of any cases that might be relevant please let me know via email

Case Series: Kartha and Sweet

It is noteworthy that two case series exist, in Nov 2006 Kartha [19] and in March 2007 Sweet [20]. It might be useful to re-examine such series [I have approached these authors but they are not willing/able to provide any further information, perhaps there are medico-legal concerns].

Kartha reported 12 cases of 'toxic metabolic encephalopathy' (which, in my opinion, are likely to represent serotonin toxicity) from a retrospective analysis of 193 patients operated on for parathyroidectomy using methylene blue: one patient died (possibly of serotonin toxicity). All 12 with 'toxic metabolic encephalopathy' were on SSRIs pre-operatively: i.e. of the total of 28 patients who were on SSRIs (in the series of 193) 12/28 had 'toxic metabolic encephalopathy'. It is almost certain that had these patients been fully assessed for the symptoms of serotonin toxicity the % exhibiting significant serotonin toxicity symptoms would have been in excess of 50%. This paper was published after my August 2006 review, I was unable to take its valuable data into account (I 'found' it 6/2008).

Sweet & Standiford report on a series of 132 cases, 17 had SSRIs pre-op. None of those who had no prior use of SSRIs got symptoms, 5/17 (30%) who did take SSRIs pre-op did get symptoms. They considered the possible explanation of serotonin toxicity but did not favour it because of the symptom profile. In my opinion the main reason for the different and varying symptom profile is treatment: i.e. these subjects were coming out of anaesthesia which is an effective treatment for serotonin toxicity. The rate at which various drugs are cleared, especially relaxants, probably plays a key role in suppressing hyperreflexia etc. Also, as Rosenbaum points out (personal communication) symptoms that obscure ST, such as shivering, are common on emergence from anaesthesia. I would observe also that it is certain that a proportion of the patients on SSRIs were either on sub-therapeutic doses of SSRI or were non-compliant; the real denominator in the fractions needs to be adjusted lower, in my opinion by at least 30%, i.e. ~12/20 not 12/28). The nominator is also certain to be too low (missed cases), the % experiencing a reaction is probably between 50 & 75%.

Both these series (totalling 325 patients) concur in the finding *only* those patients on SSRIs experienced symptoms. The odds are thousands to one that it is the pharmacological property of serotonin reuptake inhibition that is the key to this adverse interaction. There is no other known property these drugs possess in common that could explain things. Both these series also support my supposition that these cases had previously been going unrecognised/unreported. From my detailed knowledge of the history of serotonin toxicity that is exactly what I would predict. To restate it simply: Doctors do not see what they are not looking for. This is an important point to appreciate because it seems that a major stumbling block for many people who do not have a good understanding of serotonin toxicity (and the spectrum concept) is the comparative rarity of (reported) cases relative to the presumed large number of cases where Methylthionium chloride (methylene blue) and SSRIs must have been used together.

Other Data: Mostly Poor Case Reports

Ng [83] summarised some cases in 2008 and added, *post hoc*, his opinion that they may represent serotonin toxicity. He has insufficiently recognised the previous work [6], and the implications of the fact methylene blue is an MAOI on the risk of toxicity. Hence his contribution is incomplete, misleading and incorrect in

some details. He has not acknowledged prior references which stated clearly that serotonergic mechanisms, specifically serotonin toxicity, had been concluded to be the explanation by other authors right from the start. In his introduction he states: ‘to consider this diagnosis [serotonin syndrome] in previous, *unexplained* reports of adverse reactions amongst patients undergoing parathyroidectomy using methylene blue.’ Thus, his introduction is disingenuous because the cases were not ‘unexplained’ at all; his contribution is not original or useful, indeed it probably meets the definition of plagiarism.

It is impossible, in this context, to avoid repeating my comment about poor case reports which is elaborated in detail in my editorial ‘Extracting value from case reports: lessons from Serotonin toxicity (serotonin syndrome)’[18]. Poorly informed comment based on faulty case reports bedevils the whole issue and causes much confusion. ‘Plus ça change, plus c’est la même chose’, as Alphonse said [88].

Several other commentators had previously speculated about serotonergic mechanisms, even if they did not make the connections and appreciate the implication that Methylthioninium chloride (methylene blue) must be an MAOI. Since we have touched on the area of precedence, acknowledging prior contributions, plagiarism and learning from history, it is most appropriate to give due credit to Clare Stanford [77] (the 1st author is her sister), they came tantalisingly close to getting it right: A decade later I can now, with Clare’s help, complete the circle! (see [9]).

The Stanford Report: History and Education

When I checked the fine details of the various accumulated references (to update my web posting- viz this doc, in June 2008) my attention was drawn to the correspondence relating to Bach [79] from Siebert [89], Howard [90] and Palmer [78] that highlighted the apparent anomaly of the earliest potentially related report from (Clare & sister) Stanford in 1999 [77], which, although similar, did not report the use of Methylthioninium chloride (methylene blue).

That Stanford report is important, interesting and educative and I abridge the abstract below:

‘... postoperative delirium ... during recovery from anaesthesia. Features **agitation**, confusion, **uncontrolled limb movements**, **abnormal ocular function** (KG-probably horizontal ocular oscillations- not nystagmus), hypertension, **pyrexia**, **brisk reflexes**, **ankle clonus** and raised creatine kinase. ... had been taking paroxetine. ... had many features in common with problems associated with, the serotonin syndrome and the malignant neuroleptic syndrome. We offer several alternative explanations for this event, all of which rest on disruption of serotonergic and/or dopaminergic transmission.’

NB The bolded features are typical/pathognomonic of serotonin toxicity. This degree of severity could only result from MAOI + SSRI: ergo, the patient must have received an MAOI, somehow. (see diagram/figure).

The report does not mention Methylthioninium chloride (methylene blue) but does say the operation was a parathyroidectomy. That is why other commentators (Bach [79], Siebert [89], Howard [90] and Palmer [78]) ‘wrote it off’ as different. I hope readers will by this stage be sufficiently informed about serotonin toxicity to guess the remainder of the story. Yes, I emailed Clare Stanford to ask her to provide more information and check for omissions in her report: Yes, Methylthioninium chloride (methylene blue) was used. Therefore, hers was the 1st report involving Methylthioninium chloride (methylene blue) where the possibility of ST was suggested, even if she did not realize it for ten years.

This illustrates the predictive power of the spectrum concept of serotonin toxicity, as detailed in my reviews [1, 18]. To fully and properly understand the

situation a brief review of serotonin toxicity is required. Look at the diagrams/figures in the other sections which will help). Don't worry if it takes a minute or two to twig: there have been several peer reviewers of a couple of my published papers who have clearly not understood the intricacies of the spectrum concept of serotonin toxicity, despite being reviewers for eminent journals, and have made silly comments.

Conclusions

- 1) Mixing methylene blue with SRIs frequently and predictably causes severe serotonin toxicity: cease SRIs, with appropriate washout periods, beforehand. This applies to intra-venous use at doses of approximately 0.5 – 1 mg per kg or greater, the risk with smaller doses via other routes is still uncertain, but oral doses of 200-400 mg produce blood levels that would be predicted to be sufficient to cause an interaction.
- 2) Make sure you know the following drugs which are significant serotonin reuptake inhibitors from (7), table 2. Paroxetine, sertraline, fluoxetine, fluvoxamine, (es)citalopram. (des)Venlafaxine, milnacipran, duloxetine, sibutramine, Clomipramine, imipramine. Tramadol, meperidine (pethidine), dextromethorphan, dextropropoxyphene pentazocine, Chlorpheniramine, brompheniramine, (fentanyl is most unlikely to be significantly serotonergic in usual doses).
- 3) Remember patients may forget to mention drugs recently ceased. Because fluoxetine has an elimination half-life of up to 7+ days it may be present in significant amounts more than one month after cessation.
- 4) Be aware of the signs and symptoms of serotonin toxicity, especially hyperreflexia, clonus, and how to treat it and be aware that post-anaesthetic cases are expected to present with modified signs and symptoms.
- 5) The 'corrected' % of patients experiencing a reaction post operatively (see above) may be as high as 50% - 75%.
- 6) The question of interactions between opioid analgesics (pethidine, tramadol, fentanyl etc) and MAOIs is dealt with in detail in another of my reviews [91].
- 7) The UK MHRA & FDA & EMA warnings are only partially correct, unhelpful, and in need of significant revision. They do not explain the entirely predictable incidence of ST nor mention MB is a potent MAOI. Doctors need to know this in order to treat patients correctly.
- 8) Other agencies (including professional associations and colleges) might consider issuing information and guidance (some have done already [5, 92], well done).
- 9) Some suppliers of Methylthionium chloride (methylene blue) have already modified their PIs to state MB is a potent MAOI and may precipitate lethal ST with SRI. Those that have not may be held to have failed to give due warning of material risks.

References

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