

Drug safety interaction warning. Methylthioninium chloride (Methylene Blue) is a potent MAOI and causes potentially fatal serotonin toxicity (serotonin syndrome) when combined with serotonin reuptake inhibitors. Updated December 2008

Introduction

My web site introduces me as: '... an internationally acknowledged authority on **serotonin toxicity (ST)**, sometimes called **serotonin syndrome (SS)**, and also 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). My publication credentials can be accessed readily, e.g. via the National Library of Medicine <http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&term=Gillman%20PK>

Since my initial 'alert' (1) and web site posting in 2006 about serotonin toxicity from combinations of Methylthioninium (Methylene Blue) + (**selective serotonin reuptake inhibitor interactions ((S)SRIs)**), further serious cases, and two fatalities (from probable or definite ST) have been reported/recognised. There are two retrospective case series of relevance, Kartha (2) & Sweet (3), and, as of Dec 2008, 12 case reports (1 as yet unpublished) (4-13). I am also aware of several other cases through my website. The MHRA data also contains several cases, including one typical case of ST that was fatal. In my 2006 paper (1) I stated 'Further corroboration and quantification of Methylene Blue's potency [as an MAOI] is in progress to establish the degree of effect in the doses used in surgery.' (Hereafter I shall use the term **serotonin toxicity (ST)**).

That in vitro study that I initiated, courtesy of Rona Ramsay in St Andrews, has yielded data unequivocally demonstrating that Methylene Blue is a potent inhibitor of **monoamine oxidase A (MAO-A) *in vitro*** (14). This clarifies why it precipitates serious and potentially fatal serotonin toxicity if combined with (S)SRIs (1, 15), just as moclobemide and the old **monoamine oxidase inhibitors (MAOIs)** do. SSRIs include all 'Prozac' like drugs (SSRIs) as well as other drugs that act as SRIs like the **tricyclic antidepressant (TCA)** clomipramine, tramadol, meperidine (aka pethidine), sibutramine, venlafaxine, duloxetine, chlorpheniramine etc. See (16) Table 2, or my web site, for an authoritative list. NB many published lists contain multiple errors and mis-information (that includes the official MHRA warning).

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

This new finding of potent MAO inhibition by Methylthioninium is important because it is used intra-venously in surgery for thyroid operations at doses of 2-10 mg/kg, for methaemoglobinuria and for resistant hypotension in septic shock and anaphylaxis (17-19); cardiac surgery (20-23); ifosfamide encephalopathy (24); priapism (25); also trials in dementia ((26), abstract only) and manic-depressive illness have just been completed (Alda, M, Dalhousie NS, as yet unpublished). And then there is the odd, and seemingly mostly forgotten story of its use in amniocentesis (27-29) where it caused fetal ileal atresia, and possible deaths: the deaths seem to have been skated over. Even more alarmingly the mistakes appear to be being repeated with toluidine blue (Tolonium Chloride) (30). 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.

The sad irony is that although thought of as a dye, especially by non-pharmacologically orientated surgeons, it is a very potent drug. Current research indicates it has nano-molar potency for MAO-A (14) and low micromolar for NO synthase, but even at 1 mM concentration it is a poor inhibitor of soluble guanylyl cyclase (31).

My guess is that at > 0.5 - 1 mg per kg **intra-venously** it will be active as an MAOI. When injected into tissues the systemic availability will be less, and the dose probably lower, so these situations are unlikely to give rise to ST interactions. Please contact me if you have any views or experience on this so I can update this doc as needed. Try to remember to fill out adverse drug reaction reports for your country's authorities, it is clear this is often forgotten about, especially when people are struggling to get stuff published.

I sum up my view of the evidence thus:

- We have irrefutable evidence that mixing MAOIs and SRIs, in therapeutic doses, gives a high risk of severe ST, and definitely precipitates fatalities.
- We have very strong evidence that Methylthioninium chloride (methylene blue) is a very potent (at nanomolar concentrations) MAO-A inhibitor in vitro, and also strong evidence it is active *in vivo*.
- We know that many of the cases in question have exhibited symptoms either pathognomonic or typical of ST, and of a severity only seen with mixtures of MAOI + SSRI (ipso facto, this is very strong evidence that MB is an MAOI).
- We know paralysis and anaesthesia are good effective treatment for ST, and therefore modify the symptoms (particularly hyperthermia), so 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 who was not on SRIs got symptoms (the same applies to all known case reports also).

This constitutes very strong presumptive evidence that serotonin toxicity is the most likely explanation, and also constitutes a very strong cause-effect link to explain all the observations.

If Methylthionium is judged to be indicated SRIs must be ceased, prior to treatment/procedure/surgery. Other types of serotonergic drugs are not implicated in significant toxicity e.g. tryptans, mirtazapine, bupropion, lithium, tricyclic antidepressants etc. See (16).

The story

In 2005 David Bogod, the editor of the journal *Anaesthesia*, invited me to write an editorial concerning case reports and serotonin toxicity (15). *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 (5). One of my routine google searches for SS/ST in early 2006 led me to an unpublished report on the internet (still available as of Dec 2008) by Rosenbaum (9), 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: medical.mhaus.org [see link](#) accessed Dec 2008

I immediately corresponded with Rosenbaum, in order to encourage him to publish his case in a peer reviewed Journal (he never got round to it, but it is still up on the web site), 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 concerning this (1), 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 very likely that this was indeed another case of ST (8). All subsequently discovered/recognised reports, as of Sept 2008, are listed below.

The key issue to grasp (see ST triangle below) is that severe degrees of ST, involving *therapeutic* doses of (S)SRIs, only occur following combination with MAOIs (16), but not with other serotonergic drugs (with other mechanisms of action (cf. 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 for 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 (32-34), but one of uncertain potency and relevance in relation to humans. I therefore sought the assistance of Rona

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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.

SRIIs have been in use for more than three decades. Clomipramine has been in use since 1966- France, 1968- UK, well 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 (35, 36). In my opinion the most parsimonious explanation is that ST has occurred but has not been recognised, or the relevance of the reactions seen has not been appreciated: cf. pethidine, imipramine, linezolid (37). The fact that most of the cases now uncovered have been reported as 'encephalopathy' reinforces my point. This is congruous with the well documented history of failure to recognise serotonin toxicity when it occurred frequently between 1955 and 1982 without recognition (38), 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 (2) below). Patients are usually slightly hypothermic post-operatively. A recent study of 1300 patients found a mean aural temperature of 35.8°C (39). Anaesthetics greatly reduce both brain metabolism and temperature, inducing brain and body hypothermia (40-44). After a single pentobarbital dose of 50 mg/kg, i.p. brain temperature dropped 4.0-4.5 °C (45). So post-operative cases of ST are most unlikely to be hyperthermic by the usual criteria. Other signs may well be muted also. Careful and repeated examination for clonus (especially ocular), hyperreflexia and tremor (masked by post-op shivering) are recommended.

The MHRA warning

The MHRA in the UK issued an incomplete and misleading warning (46) 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 (1). 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. See below for a full analysis of that.

Currently known cases: methylene blue and possible or probable ST

Currently known cases relevant to methylene blue and serotonin toxicity are: (2, 4-13, 47), this includes the old new case I have uncovered (4) about which Clare Stanford and I have just submitted a 'correction' (see below). Note: Patel (48) has been included in the paper by Ng (12), the case does not meet *any* criteria to justify a even a suggestion of ST, and no SSRI had been taken pre-op, so this case is irrelevant in this context. Ng says, of Patel, 'Only one of the seven case reports

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did not meet the diagnostic criteria, as a serotonergic agent had not been administered', his meaning is unclear. His report is really 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, because it does not correctly interpret the Hunter Serotonin Toxicity Criteria.

Table: Cases of ST with MB (up to Dec 2008): certainty of diagnosis and severity

Case reference (chronological order)	Certainty of diagnosis of ST	Severity of clinical state	Comments
1) Stanford (4)	Definite	Severe	MB used, but not mentioned in original report
2) Martindale (5)	Definite	Severe	'Rotational nystagmus', represents ocular clonus
3) Bach (6)	Probable	Moderate	'A suggestion of clonus, forced dorsiflexion of feet' *
4) Majithia (7)	Probable/definite	Severe	'Nystagmus', was very probably ocular clonus *
5) Mathew (8)	Definite	Severe	MH queried, tremor, agitation, temperature 40°C
6) Rosenbaum (9)	Definite	Severe	The first recognised case. 'Agitated, tachycardic and diaphoretic ... lower extremity rigidity'. T38.3°C
7) Khan (10)	Probable/definite	Severe	'Confused, agitated, jerky movement of all four limbs' *
8) Mihai (11)	Possible	N/A	'Agitated and restless ... unable to speak no response to verbal command ... no limb weakness, ... no focal neurological signs'
9) Ng (12)	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 (13)	Definite	Severe	'confused and agitated ... temperature 40°C, myoclonic jerks, fine tremors, dilated pupils, shivering, hyperactive reflexes, hypertonicity'
11) Khavandi (49)	Probable/definite	Moderate	'agitated and restless', 'myoclonic movements of the lower limbs, brisk reflexes', T 37.5° C)

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).

If you are aware of any cases that might be relevant please let me know via email or 'contact me' at www.psychotropic.com.

It is especially noteworthy that two case series exist, in Nov 2006 Kartha (2) and in March 2007 Sweet (3). Other recent case series exist, e.g. Han's series of 473 patients (21) that make no mention of 'encephalopathy' or ST. It might be useful to re-examine such series [I have approached these authors several times but they have not offered any further information].

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 all 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 just after my August 2006 review so 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 very 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; so 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), so the real % 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 therefore about a million to one

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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 almost all 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 Methylthioninium chloride (methylene blue) and SSRIs must have been used together.

Ng (12) has summarised some more of the cases and added, *post hoc*, his opinion that they may represent serotonin toxicity. He has insufficiently recognised the previous work (50), and the implications of the fact methylene blue is an MAOI on the risk of toxicity. Hence his contribution is misleading and incorrect in some details. He has not acknowledged the references and extensive assistance I gave him, which stated clearly that serotonergic mechanisms, specifically serotonin toxicity, had previously 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.' They were not 'unexplained' at all; his contribution is not original. The paper is best ignored.

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)'(15). 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 (51).

Several other commentators had previously speculated about serotonergic mechanisms, even if they did not quite make all 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 (4)(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!

When I checked the fine details of all 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 (6) from Siebert (52), Howard (53) and Palmer (47) that highlighted the apparent anomaly of the earliest potentially related report from (Clare & sister) Stanford in 1999 (4), which, although very similar, did not report the use of Methylthioninium chloride (methylene blue).

That Stanford report is so important, interesting and educative that 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 (6), Siebert (52), Howard (53) and Palmer (47)) 'wrote it off' as different. I hope readers will by this stage be sufficiently well informed about serotonin toxicity to guess the remainder of the story. Yes, I emailed Clare to ask her to provide more information and check for omissions in her report: Yes, Methylthioninium chloride (methylene blue) was used. So 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.

All this illustrates the predictive power of the spectrum concept of serotonin toxicity, as detailed in my most recent review (54). To fully and properly understand the situation a brief review of serotonin toxicity is required.

Serotonin toxicity, Serotonin syndrome: summary

This section is inserted for those who want a quick update / summary: it may be skipped by those already familiar with the topic—but the new diagram may help. See below.

Serotonin toxicity (ST) is an iatrogenic drug-induced toxidrome displaying the characteristics of a synaptic serotonin concentration-related phenomenon. The term ST is preferable because serotonin syndrome (SS) insinuates an idiosyncratic reaction like malignant hyperthermia (MH) or neuroleptic malignant syndrome (NMS). ST is important because potentially fatal combinations of therapeutic drugs are sometimes inadvertently administered. Also, many texts contain incomplete and erroneous information concerning which drugs are capable of precipitating ST, and its mechanism, symptoms and treatment. Such texts include the British National Formulary, Australian Medicines Handbook, and even 'Goodman and Gilman' and Rang & Dale, and now the MHRA.

The generally poor understanding of serotonin toxicity has been highlighted, more recently, by the availability of several drugs, not used as antidepressants, that possess the property of monoamine oxidase inhibition. It was the accidental discovery of the mood elevating properties of iproniazid, in the trials for

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tuberculosis around 1955, that led to the discovery of the monoamine oxidase inhibiting properties of those drugs, and to the development of the original MAOI antidepressants. The first patient to die as a result of serotonin toxicity was a doctor, in the original trials of iproniazid, who was given pethidine (55) i.e. a combination of MAOI + SRI. So it's a long story, a saga even!

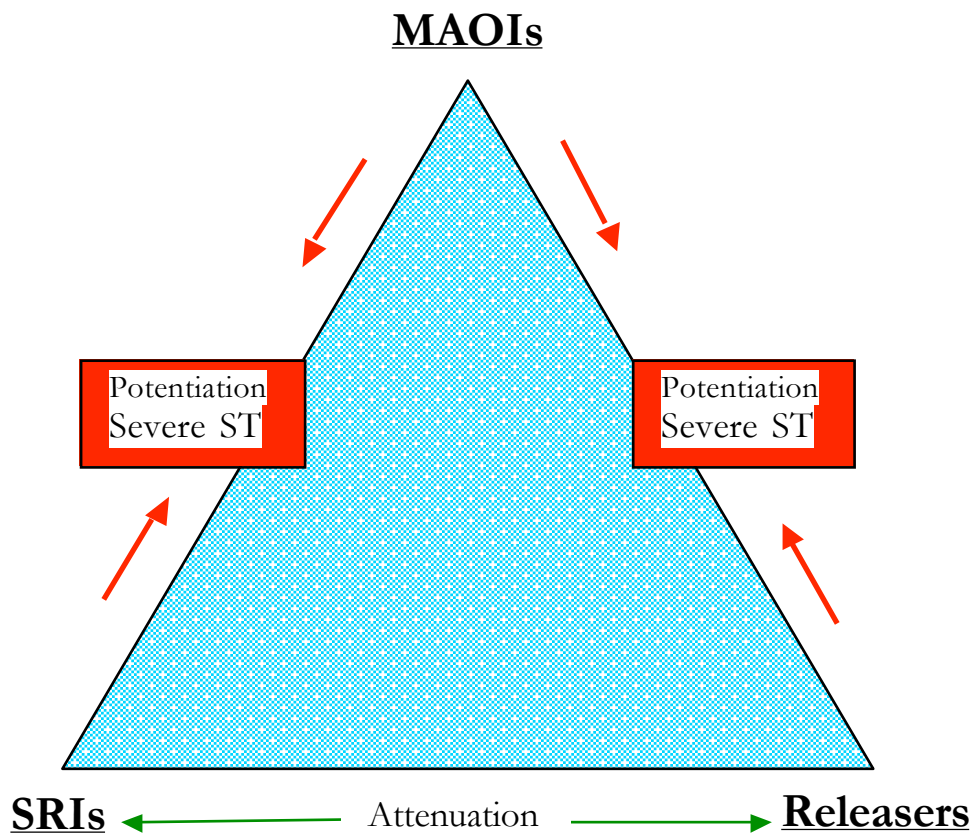
In 50 years the wheel has now gone full circle, in that the latest new drug causing this problem is again an anti-microbial, linezolid, that also has significant activity as an MAOI. Thus history repeats itself, and we demonstrate how slowly and painfully we learn from history, and how quickly we forget its lessons (56). Students of the history of medicine may, by this time, be exhibiting wry smiles as they recollect the original work, going back to the nineteenth century, following the discovery of inorganic dyes from petroleum, and how Paul Ehrlich studied their antimicrobial properties. These eventually resulted in the discovery of the tricyclic psychotropics, including antihistamines, and the tricyclic antidepressants, and the Neuroleptics (all based on the Methylene Blue nucleus).

The evidence relating to serotonin toxicity from Professor Whyte's research group (HATS) series of 2,222 serotonergic overdoses has been published in a seminal series of papers (57-64). Other recommended papers concerning serotonin toxicity are: (37, 38, 65-76).

STT

Figure: The serotonin toxicity triangle

The ultimate guide to understanding serotonin toxicity (serotonergic drug interactions): the only three classes of drugs involved in serious ST are: MAOIs, serotonin reuptake inhibitors, and releasers, like MDMA (ecstasy).



The clinical features of serotonin toxicity

The typical clinical features of ST in humans, are (i) neuromuscular hyperactivity: tremor, clonus, myoclonus and hyperreflexia, and, in the advanced stage, pyramidal rigidity; (ii) autonomic hyperactivity: diaphoresis, fever, tachycardia, tachypnoea and mydriasis; and (iii) altered mental status: agitation, excitement, with confusion in the advanced stage only. Descriptions of the clinical presentation may be found elsewhere (57, 69). Whyte concludes ... 'only clonus (inducible, spontaneous or ocular), agitation, diaphoresis, tremor and hyperreflexia were needed for accurate prediction of ST as diagnosed by a clinical toxicologist.' If, *in the presence of a potent serotonergic agent*, the single sign of spontaneous clonus is present, then ST may be reliably diagnosed.

The spectrum concept explains ST as a progression of serotonergic effects mediated by the degree of elevation of intra-synaptic serotonin. These range from serotonin-related side effects (at therapeutic doses) through to toxicity, and culminate in death with MAOI / SRI combinations. The three important mechanisms are serotonin reuptake inhibition (SRI), MAO inhibition and pre-synaptic release. The only *therapeutic* drugs implicated in *severe* reactions are: overdose of MAOIs-alone, combinations of MAOIs with either SRIs, or the only clinically available serotonin releaser, amphetamine (methylphenidate is not a risk (16, 77)).

The data suggests that about 50 per cent of patients who have ingested the weak 'RIMA' moclobemide, in combination with SRIs, will exhibit at least moderately severe ST (cf. Kartha). SSRIs alone do not result in severe ST or pyrexia in excess of 38.5c (65) which indicates they have a ceiling effect.

Understanding ST as a form of poisoning reveals the importance of knowing the degree to which different drugs are capable of elevating brain serotonin, indeed the relative frequency and severity of ST with different drugs (and combinations) is useful in refining hypotheses about the potency and actions of those drugs (16).

Death can result from a single dose of an SRI when errors are made in a patient already on an MAOI, as two recent deaths illustrate. The Otte case (imipramine 225 mg), in a European teaching hospital (78), and also Cassens (79). Neither were treated with 5-HT_{2A} antagonists. It is entirely predictable the same thing will happen when linezolid or Methylene Blue achieve substantial MAO inhibition, which they do, in a dose dependent manner.

Since paralysis and anaesthesia constitute effective treatment of severe serotonin toxicity exhibiting hyperpyrexia, the clinical picture on emergence from anaesthesia will be modified. Further reviews like Kartha's, of series of patients, may help clarify the way in which the symptoms differ (from the usual presentation in the absence of anaesthesia). Post-operatively, previously suppressed serotonin toxicity will 'emerge' as the effects of anaesthesia wear off.

The good news is Methylthioninium chloride (methylene blue) itself is safe, but because it is an MAOI the potential interaction with SRIs must be avoided, and other possible pharmacodynamic interactions considered.

Conclusions

- 1) Mixing methylene blue with SRIs causes serotonin toxicity: cease SRIs, with appropriate washout periods, beforehand. This definitely 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 probably negligible.
- 2) Make sure you know the following drugs which are significant serotonin reuptake inhibitors from (7), table 2. Paroxetine, sertraline, fluoxetine, fluvoxamine, (es)citalopram. Venlafaxine, milnacipran, duloxetine, sibutramine, Clomipramine, imipramine. Tramadol, meperidine (pethidine), dextromethorphan, dextropropoxyphene pentazocine (fentanyl is unlikely to be significantly serotonergic in usual doses), Chlorpheniramine, brompheniramine.
- 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 another of my reviews (37).
- 7) The UK MHRA warning is unhelpful and is in need of revision.
- 8) Other agencies (including professional associations and colleges) might consider issuing information and guidance (some have done already (80), well done).
- 9) Some suppliers of Methylthioninium chloride (methylene blue) have already modified their PIs.

The MHRA warning

The MHRA in UK issued a warning (46) in Jan 2008, but appear to have discounted the Ramsay paper, a copy of which they were provided with prior to its publication in May 2007, and have failed to reference or mention my 2006 paper (1). The MHRA warning is unclear and does not explain the implicated drugs, the mechanism or the risks. Indeed it fails to mention ST or the fact that Methylthioninium chloride (methylene blue) is an MAOI at all. It is difficult to see how withholding this crucial information from doctors can serve any good purpose: indeed it can be considered negligent because it also has implications for the safe administration of other drugs, quite apart from the interaction with SRIs.

The MHRA data also has several extra unpublished cases: one deserves particular mention, because even the vestigial details provided allow **a confident diagnosis of ST**. The case involved clomipramine as the pre-operative SRI, and the symptoms reported were: 'Hypertonia, Clonus, Serotonin syndrome, Convulsion, Coma, Cerebral disorder, Multi-organ failure', culminating in death. However, there is no mention of **typical and fatal ST** in the MHRA warning. A

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review of their stance would be well advised, or they will appear lamentably distant from a diligently researched and well informed position.

The MHRA warning contains significant errors, omissions and mis-information (e.g. it incorrectly refers to mirtazapine and bupropion as 'serotonergic' drugs). These errors detract from its usefulness and introduce an element of confusion that is likely to lead clinicians to make misconceived and faulty decisions that will have negative consequences (e.g. it suggests avoiding Methylthioninium with drugs that have 'serotonergic' activity, whereas it is only SRIs that pose a danger). The MHRA warning does **not** contain the key word serotonin syndrome (or serotonin toxicity).

I sent them [the original V. of] this document and received the response below (abridged), which confirms their mis-understandings, mis-information and confusion. I suggest clinicians remind themselves of the limitations imposed on the MHRA and its 'committees' and how this influences the content and wording of the statements they issue:

"The Agency works in the context of a product's licensed indications. In the UK, methylthioninium is licensed for managing methaemoglobinaemia only; other uses fall outside the licence ('marketing authorisation'). However, it is recognised that occasionally medicines need to be used in an 'off-label' way, but this increases the clinician's professional responsibility. Any communication from the Agency needs to be carefully worded so as not to endorse 'off-label' use."

and

"Your (sic) say that the Agency seemed unaware of the paper you co-authored with Dr Ramsay and her colleague¹. In fact we had been in touch with Dr Ramsay ..."

I stated initially (trying to be polite and tactful) '... appear to have been unaware of the Ramsay paper or my input', but had in fact already changed that to 'but appear to have discounted the Ramsay paper, a copy of which they were provided with prior to its publication in May 2007, and have failed to reference or mention my 2006 paper'; because, of course, I knew full well they had a copy. Thus, discounting it without even referencing it, could be considered an error of judgement.

Your article says that Drug Safety Update 'incorrectly refers to mirtazapine and bupropion as serotonergic drugs' ... Mirtazapine is also associated with serotonin syndrome, even when used alone (81, 82) Clinicians consider it to possess significant serotonergic activity (we realise that you don't accept this!).

Yes indeed the Drug Safety Update 'incorrectly refers to mirtazapine and bupropion as serotonergic drugs'. The case reports given above as references to justify that constitute very poor evidence indeed: especially because those same case reports were robustly rebutted by two prominent ST commentators (83, 84), as well as being discussed in a dedicated review elsewhere in the context of extensive contrary evidence (54). It is poor academic scholarship to quote references without including information or comment on published comments and rebuttals. It is also careless and lazy since a single mouse click is all that is required to obtain that information: viz.

<http://www.ncbi.nlm.nih.gov/pubmed/12671522?dopt=Citation>

The animal evidence for significant serotonergic effects of mirtazapine has also
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been discredited in a lengthy and detailed paper by Millan (85).

The phrase 'we realise that you don't accept this!' is a puerile attempt at patronization which merely serves to demonstrate the MHRA's collective confusion between what constitutes evidence and fact, and what constitutes interpretation and opinion. There is **no** good evidence that mirtazapine does have substantive clinically relevant serotonergic effects, and, contrary-wise, there is good positive evidence that it lacks significant serotonergic effects: hence informed opinion must be that it very probably has no significant serotonergic effects in humans, or rats. It is not appropriate for science to 'accept' propositions for which there is no good replicated evidence; so no, I do not accept it. And the same applies to bupropion: there is not a skerrick of evidence it precipitates ST and it has no serotonergic effects; Stahl recently described it as being 'devoid of clinically significant serotonergic effects' (86, 87).

"Crucially, if inhibition of monoamine oxidase were a significant pharmacological action of methylthioninium, then one would expect the usual interactions with tyramine in foods and with drugs."

This comment indicates a lack of understanding of the clinical situation: No-one is feeding them cheese whilst they are undergoing parathyroidectomy. These patients are 'nil by mouth'. And then 'usual interactions ... with drugs', that means, primarily, ST (SS) caused by SSRIs, which is exactly what this whole business is about.

"In contrast, Sweet and Standiford specifically say that none of their 5 reports was consistent with the serotonin syndrome and Kartha and colleagues characterise their 7 (sic) cases simply as 'transient toxic metabolic encephalopathy'."

Yes, most people who do not know much about ST (especially, with due respect, surgeons) do say such things, that is why the 50 year history of ST is littered with unrecognised reports. Recognising ST is not something that falls within the area of expertise of your average surgeon, so it is not scientific, or realistic, to put much weight on their opinion about this. Kartha's series was, of course, 12 cases, not 7, I quote 'The 193 patients in the study were divided into two groups. Group A (n = 12) contained patients who experienced postoperative neurological sequelae.'

"They [MHRA] also considered experimental evidence for other mechanisms of toxicity such as increased serotonin synthesis caused by methylthioninium-induced reduction in nitric oxide production (32).

Wegener's paper (32) does not consider the possibility that methylthioninium is an MAOI, but the observation, that it raises serotonin levels, strongly supports that it is an MAO-A inhibitor, and the observations are most parsimoniously explained by that. Also, 'other mechanisms of toxicity such as increased serotonin synthesis' would mean it was ST anyway, so the logic has broken down here.

"Another suggestion is that methylthioninium causes confusion, hyperthermia, and sympathetic overactivity through an antimuscarinic effect (8)."

Having discounted moderately strong evidence from (inter alia) Kartha's large case series this advances an unfounded speculation proffered in a case report (8) referencing Pfaffendorf's work (88). Pfaffendorf's reference does not support an antimuscarinic effect, nor have the cases reported demonstrated features of the

antimuscarinic toxidrome, nor is there even a putative mechanism to explain why SSRIs alone should precipitate this.

The final MHRA letter 'self-justification' paragraph reads

"Since none of the putative mechanisms seemed compelling, the short article in *Drug Safety Update* did not tackle this aspect, nor did it include *serotonin syndrome* as a key term. In any case, the article focussed (sic) on what clinicians should do rather than on pharmacology."

I see, so 'what clinicians should do' does not depend on pharmacology? A novel approach indeed.

I suggest clinicians remind themselves of the limitations of 'committees' and take all sources of evidence into consideration in deciding how best to serve their patients.

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