

Metaxalone (Skelaxin) and Serotonin Toxicity (Serotonin Syndrome): Warning of Potential for Fatalities if Combined with Serotonin Re-uptake Inhibitors

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Abstract

Evidence has emerged that **Metaxalone (Skelaxin)** is a weak monoamine oxidase inhibitor (MAOI) which when used in large doses may be sufficiently potent to induce **serotonin toxicity (ST)** (aka Serotonin Syndrome), but only if and when it is combined with a serotonin reuptake inhibitor (SRI). Metaxalone was introduced just over 50 years ago and is used widely for the treatment of musculoskeletal pain.

It was approved in the days when less extensive pharmacological data concerning drugs existed. Now, theoretical computational (*in silico*) techniques allow a degree of useful prediction of the likely receptor and enzyme targets of drugs (this has shown metaxalone to be a weak MAOI). This, combined with the fact that it is an ‘oxazolidinone’, structurally and pharmacologically related to antibiotics like linezolid, which definitely do exhibit both MAOI potency, and also the clinical effect of inducing ST, suggests the wisdom of vigilance concerning the probability of ST with metaxalone also.

As of Dec 2015 several case reports have described what is probably severe ST in patients who have received metaxalone in combination with an SRI. The fact that such reports have only recently emerged may, at least partly, reflect the increasing knowledge and understanding of ST. The importance of such understanding has been highlighted recently by various incorrect and misleading warnings emanating from several drug regulatory agencies (WHO, FDA etc.) concerning ST. These misleading warnings include triptans and antiemetic drugs like ondansetron. The explication of why it is logical to dismiss ondansetron (and triptans) as a suspects, but conclude that Metaxalone is ‘guilty’, contains valuable lessons in understanding pharmacology, toxicology and serotonin toxicity (1-3). The same applies to methylthionium (methylene blue). These lessons have, evidently, not yet gained general recognition despite all the computers in use, nor have the appropriate interaction warnings been successfully incorporated into clinical management protocols.

Keywords: Metaxalone, oxazolidinone antibiotics, linezolid, MAOIs, methylthionium (methylene blue), moclobemide, SSRIs, SRIs, SNRIs, cyclobenzaprine, drug interactions, Serotonin Toxicity, Serotonin Syndrome, severe, fatal, warning.

Background

Perhaps we should not be too surprised that an understanding of **serotonin toxicity (ST)** mechanisms is continuing to provide useful elucidation of the probable mode of action of various drugs (2). The utility of such an understanding has been clearly illustrated by the story of methylene blue, dealt with extensively both on my website and in my peer reviewed publications (3). More recently its utility has been exemplified in the rebuttal of the warnings issued about triptans and ST (3-5) and about ondansetron and ST (6).

The above review (3) explained how an understanding of the potencies and mechanisms of ST, and their important interactions, leads to precise and reliable predictions. Almost the only possible explanation of severe ST involving usual therapeutic doses of drugs is the classic and potentially fatal interaction of an MAOI with an SRI.

This chain of events was started in Nov 2014 when Dr Pete Bentham alerted me to recent case reports suggesting severe ST involving metaxalone (7, 8). After some investigation I posted a warning:

<http://www.psychotropical.com/metaxalone-skelaxin-and-st>

The fact that metaxalone has been used for such a long time (more than 50 yrs) with no apparent reports of ST would at first seem to make ST unlikely: after all one might suppose it surely would have occurred and been reported somewhere? Maybe it has been and no-one has yet unearthed the reports? (which seems to be the case, see below) I have attempted to ascertain this, with limited success, it is not as easy as one might think. Such considerations notwithstanding, all this suggest that it is a weak MAOI, probably reversible, like moclobemide. Therefore, it is only when it is ingested in large doses and in combination with a serotonin reuptake inhibitor (SRI) that ST is exhibited.

That is precisely the same picture that we do indeed see with the reversible MAO-A selective drug moclobemide (9, 10). Some people tried using combinations of moclobemide and SSRIs, but it proved to be a rather delicate and brave balancing act which could (and did) easily go seriously amiss (11, 12): there were deaths, some published, some only reported to me privately. Most people stopped doing it fairly quickly. I summed it up with this comment: ‘The above data indicate clearly that such combinations represent a predictably risky strategy. Moclobemide, if combined with any drug exhibiting significant SRI potency, produces a risk of severe ST and also the possibility of fatalities even with ‘therapeutic’ doses.’ (12).

I recap on this story because there are close parallels and lessons between moclobemide, linezolid and metaxalone whereby small increases in dosage (or increases in blood levels due to pharmaco-kinetic interactions) may rapidly lead to catastrophic and fatal toxicity.

The current evidence about metaxalone provides a warning signal that is sufficiently strong that it mandates further investigation. One arm of this investigation should be the effort to ascertain whether other cases of toxicity with this drug involve typical ST manifestations and whether these have only occurred in the presence of (S)SRIs (which is what I would confidently predict). So far that would appear to be the case. It would be surprising if there were not a few cases of severe or fatal ST from metaxalone overdoses in subjects on SRIs out there somewhere.

Update: Case Reports

These initial cases (7, 8) were brought to my attention by Dr Pete Bentham. My research since then has revealed further previously reported, by unrecognised, cases where metaxalone appears to be implicated in ST (13, 14). There is a further report this year, 2015, of 2 cases of probable ST involving ODs of metaxalone and therapeutic doses of an SRI (15), exactly as I predicted in my original warning a year ago.

<http://www.psychotropic.com/metaxalone-skelaxin-and-st>

There are also one or two post-mortem toxicology reports of suicides or deaths that that involve metaxalone & SRIs. In these cases there is usually no information indicating symptoms before death, so establishing that such cases represent ST is impossible. Nevertheless these do constitute another suspicious signal (16-18).

The Huska and Martini cases (13, 15) fall into that minuscule group of case reports about ST in the last decade which are actually useful. They both contain elements which immediately make one think it is likely to be severe ST involving an MAOI and an SRI. The patients presented acutely complaining of feverishness and shaking, temperatures rose rapidly, and they exhibited severe tremulousness, shivering, hyperreflexia and muscle rigidity.

This is very much the classic picture of ST with dramatic and rapid onset dominated by neuro-muscular symptoms and resolving rapidly following cessation of medication (and the use of cyproheptadine). It is instructive to compare these cases with the cyclobenzaprine cases (see below) and the poor cases put forward by the FDA and used to justify the idea of ST with ondansetron: those cases, quite apart from not meeting formal diagnostic criteria, just do not look like ST.

The other metaxalone cases described are all 'probable' or 'definite' ST and involved an SRI, except for one of the cases reported by Bosak. The investigation of this case involved steps to ascertain what drugs had been taken as part of the overdose, but as is so often the case, sources of information were limited and of uncertain reliability. Although drug

screening showed no other known SRI drugs it remains entirely possible the patient had ingested an SRI prior to the overdose.

These cases provide a very strong indication that metaxalone is MAOI. The detailed reasoning that justifies this statement is contained in the other extensive information about ST, both in my peer-reviewed papers, and on this website. In short, it is the same as the picture we see with moclobemide. Overdoses of moclobemide alone do not cause serotonergic symptoms or ST, but when it is mixed with even small doses of SRIs serious cases of ST are frequent, and fatal cases are well-documented. Thus, we would expect no signs of ST with metaxalone by itself, but we would expect it if large doses of metaxalone are combined with therapeutic doses of an SRI.

That is precisely what the above cases illustrate.

New Data on Metaxalone

Another avenue of investigation is to establish more precisely the likelihood of it being a significant MAO inhibitor. This can be done with computer modelling techniques, and there is good reason for pursuing this because many similar compounds have been studied in the search for antibiotics (19) and one of them, that has now been on the market for some time, linezolid, definitely has significant MAOI activity at high, but sometimes clinically achieved, blood levels and has caused definite ST (20). The other main possibility is to actually assay its MAO activity *in vitro* using similar techniques to those we (Ramsay et al.) used for MB (21). Its ability to modify the tyramine pressor response would also give additional information as would testing in a rat model of ST e.g. see (22). However, that is all time and money. It would be worth doing if there is someone out there with the time and money.

Colleagues that I contacted (in 2014) about this responded promptly and calculations using theoretical modelling on computers (*in silico* modelling) indicated that the drug is indeed a weak monoamine oxidase inhibitor. We have Prof Yelecki in Turkey to thank for this (see acknowledgements below). Prof Yelecki's computed value is 4.3 μmol for the inhibition of MAO-A and 3.5 μmol for MAO-B: this puts it in the same ballpark as moclobemide and linezolid. Other variables such as metabolism and the degree of brain penetrance mean that prediction of the potency in the human brain is not presently possible with any accuracy. Nevertheless, there is a strong indication that this drug has clinically relevant MAOI activity in high doses.

It is precisely because accurate estimation of the potency of drug effects at the relevant receptors in the human brain is so difficult to ascertain that the occurrence or absence of ST with drug combinations is a useful tool for revealing whether the concentrations are actually reaching

clinically relevant levels and altering central serotonin neurotransmission.

More and higher quality data from toxicology databases of overdoses in humans would therefore be of great value, because it would establish the frequency and severity of ST with different doses and combinations of drugs. Unfortunately, despite recommendations made nearly 20 years ago (23), such data is not routinely collected.

A Note About Cyclobenzaprine

It is also worth noting in passing that one of the other drugs used in the same context as metaxalone is cyclobenzaprine. This drug has also been implicated in possible cases of ST, although there do not appear to be any clear cases of severe toxicity like the ones above with metaxalone (24-26). Previous discussion on this question prompted a similar chain of events to be set in motion as is related above. *In silico* modelling by Tudor Oprea's group has suggested that cyclobenzaprine is a weak SRI, comparable to amitriptyline (27, 28).

I will discuss these useful and interesting results about cyclobenzaprine in a separate commentary when I have time. In this immediate context the current data on cyclobenzaprine serves to illustrate this interesting and important point about the drug interactions that precipitate ST. If cyclobenzaprine is a significant SRI in humans then we would expect it to cause serotonergic symptoms, or even ST, when it is taken in overdose (which, like amitriptyline, it does **not** seem to do), but we would not expect it to cause major ST when combined with other (S)SRIs. This is because both drugs are working by the same mechanism of action and our current understanding indicates clearly that this does not lead to any greater elevation of serotonin than would be expected by simply increasing the dose of one or other of the SRI drugs. However, if cyclobenzaprine were to be mixed with an MAOI then the story would be dramatically different and severe life-threatening ST would be likely. Because MAOIs are not used very frequently the result is that cases of ST emerging with cyclobenzaprine would be expected to be rather less common than cases with metaxalone (other things being equal). This is because a lot of people in the general community are taking (S)SRI drugs (like 5-10%) so you do not have to have a very big series of metaxalone overdoses before it becomes inevitable that a proportion of them will have ingested both drugs.

Conclusion

The subtle twist appears to be that metaxalone is just sufficiently weak as an MAOI that in general circumstances it does not cause problems when combined with SRIs. Perhaps it is only in patients who ingest large, supra-therapeutic doses, or develop particularly high blood levels, that

have a risk of ST with SRIs. And thus metaxalone has managed to stay under the radar for half a century. In some ways it most closely resembles linezolid which definitely increases serotonin-mediated side effects, but rarely provokes severe toxicity (20, 29-31).

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