Spectrum concept of serotonin toxicity

by Dr Ken Gillman | Last updated Oct 21, 2021 | Published on Nov 13, 2014 | Serotonin Toxicity, Anti-Depressants

Introduction: The dose effect relationship

In my opinion it is crucial to understand and remember, when considering the risks of drugs that affect serotonin, that **serotonin toxicity (ST)** behaves as would be expected of a synaptic serotonin concentration-related phenomenon. If you do not have a clear understanding of the synergistic effects that drugs, working by a different mechanisms, are capable of producing, then it is not possible to understand serotonin-mediated interactions or ST. A reasonable knowledge of basic pharmacology and neuronal mechanisms is required to understand why and how different kinds of drugs may interact.

ST is a synaptic serotonin concentration-related phenomenon

ST is an iatrogenic toxidrome — because it is a form of poisoning toxidrome is the correct terminology and should be used in preference to the word syndrome. The concept of a toxidrome (from toxic + syndrome) is more appropriate and accurate [1]: it insinuates a characteristic clinical picture typical of the toxicity of a particular class of drugs with specific major actions (e.g. serotonin-mediated, anti-muscarinic, etc.).

Changes characteristic of increased serotonin in the central nervous system typically result from the specific or selective serotonin reuptake inhibitors (SSRIs). These changes are more pronounced following supra-therapeutic doses and overdoses, and they merge in a continuum with toxic effects [2-4].

I have long advocated the 'spectrum concept' of ST which emphasises the role that progressively increasing serotonin levels play in mediating the clinical picture as side effects merge into toxicity.

The spectrum concept provides both a framework for understanding the subject, and the disparate literature, and makes testable predictions about the frequency and severity of toxicity. The proven illustration of this was my prediction of the MAOI effect of **Methylene Blue (MB)** [5, 6], a drug that had been in use for 50 years! We showed it to be a nanomolar potent inhibitor of MAO-A [7].

Reports of interactions between drugs that produce supposed ST cannot be understood or evaluated without understanding the clear-cut evidence for the spectrum effect, which is based on animal experiments, general pharmacological knowledge, and other basic scientific medical knowledge. Incidentally, that is a good part of the underlying science which makes it possible to reject with confidence some of the sillier papers that have been offered, like the one from Professor Taylor at the Maudsley [8] which I have criticised elsewhere

The animal and human evidence for the dose effect relationship is detailed below, especially in relation to the seminal and unique HATS toxicology data from Professor Ian Whyte's group in Newcastle, Australia.

The dose-effect relationship is the term used to describe the effects of progressive elevation of serotonin, either by raising the dose of one drug, or combining it with another serotonergic drug, which can produce considerably greater elevations of serotonin.

Thus, the most frequent (and perhaps the only) combination of therapeutic drugs likely to elevate serotonin to that toxic degree is the combination of monoamine

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oxidase inhibitors (MAOIs) with serotonin reuptake inhibitors (SRIs). Serotonin releasers, like MDMA, can cause fatalities if mixed with MAOIs.

The degree of risk of ST provides insights about the nature and extent of a drug's serotonin-mediated effects. For example, it clearly shows that mirtazapine, which has no serotonin-mediated toxicity, has no significant serotonin-mediated effects, and is not in fact a dual action drug [9-12].

There has been debate about which receptors mediate which components of the physiological syndrome (various twitches and movements, see Jacobs [1]. Isbister's review of the animal research has clarified the picture [2] and agrees with my preliminary analysis in the 1998 review [3]: there is little doubt about how to reduce pathological consequences of hyperpyrexia and deaths related to large elevations of serotonin (>50 times basal levels): and that is by blocking 5-HT2A receptors, not 5-HT1A or DA receptors. However, it may be noted that most clinical toxicologists take the view that when people are suffering from poisoning related to drugs, the less extra drugs you give them the better. They therefore generally advise not to use specific antidotes. The favoured approach, in addition to supportive care and active cooling, is sedation with benzodiazepines.

Gillman and Whyte have developed the spectrum concept of serotonin toxicity, which predicts and explains the severity of toxicity in relation to the combinations of drugs ingested. The spectrum concept is central to developing an overall understanding of this complex field.

It is possible to make deductions concerning the potency of serotonergic actions of drugs thought, or claimed, to have such properties, from a consideration of the data herein (see below). It is clear that amitriptyline does not produce serotonin toxicity in over-dose, or with monoamine oxidase inhibitors, nor have clinical obsessive-compulsive disorder efficacy. It is therefore reasonable to suppose its serotonin reuptake inhibitor potency is not clinically relevant [9, 13].

Hopefully the demonstrated value of systematically collected toxicity data (as exemplified by the HATS data from Professor Ian Whyte), as highlighted in this document, will (eventually) persuade others to make the efforts needed to follow Ian Whyte down this path as suggested in my 1998 review conclusion:

> It is proposed that more systematic national collection of toxicity data is essential in order to quantify the relative risk of serotonin syndrome with various combinations of serotonergic drugs

Potentially Fatal Combinations

General physicians may note that for therapeutic drugs the only cases that have been life-threatening or fatal, as a result of ST, have resulted from combinations of a **monoamine oxidase inhibitor (MAOI)** and a **serotonin reuptake inhibitor (SRI)** but not from other combinations of drugs with serotonin-mediated effects (e.g. not from monoamine oxidase inhibitors combined with lithium or L-tryptophan or nefazodone or mirtazapine, nor from SSRIs with anything other than MAOIs).

Examples of specific drug combinations that may produce severe toxicity, and may require life-saving treatment are:

- An irreversible MAOI (in normal dose) plus any serotonin reuptake inhibitor (in normal dose), such as:
- Tranylcypromine (or phenelzine) + clomipramine or venlafaxine or any SSRI
- Tranylcypromine (or phenelzine) + tramadol or pethidine
- Any Reversible Inhibitor of Monoamine oxidase-A (RIMA) like moclobemide (in high doses of 600 – 1200 mg or more), Mehylene blue or (rarely) high doses of linezolid [14] plus any serotonin reuptake inhibitor (in normal dose). For example,

moclobemide (or linezolid) + clomipramine or venlafaxine or any SSRI or SRI analgesic like tramadol.

F/Note: the mixture of MDMA, ecstasy (3,4-methylenedioxymethamphetamine) with moclobemide (but not SSRIs) is likely to precipitate potentially fatal ST.

In the above instances this demonstrated human toxicity is consonant with the findings showing greater elevations of serotonin in animal experiments.

Animal evidence

There is a clear dose effect relationship in animal work. Evidence supporting the dose effect relationship accumulated, most notably in a series of papers by Marley and Wozniak (1983-85) [4-9] and has been clearly confirmed more recently by Nisijima's group [10-12]. All this work shows proportionally greater increases in both 5-HT levels and fatalities resulting from more potent combinations as above.

Nisijima's group has done the most recent work. In their 2003 paper using clorgyline (2mg/kg) + 5-Hydroxytrypophan (100mg/kg) this produced an elevation of brain 5-HT of 1200 fold and all rats died within 90 min of drug administration. This contrasts with their 2004 paper in which they reduced the dose to clorgyline 1.2mg/kg + 5-Hydroxytrypophan 80mg/kg. In this 2nd experiment no rats died before sacrifice at 360 mins post drug administration. Furthermore the degree of elevation of 5-HT was less; 40 fold versus 1200 fold. This demonstrates an unequivocal dose effect relationship.

In Marley's experiments greater elevations of brain 5-HT, and higher death rates, occurred with inhibition of MAO-A and MAO-B together than with individually. Also in Nisijima's work changes in dopamine were smaller, and with glutamate much smaller, and may be secondary, or even an epiphenomon.

[4-20]. I have reviewed Marley's work in more detail [3]. This extensive body of research indicates that whatever drug combinations are used to raise serotonin levels there is a dose-effect relationship. This dose effect relationship is mediated through the final common pathway of elevated brain serotonin levels and the degree of elevation has an increasingly great effect on body temperature and mortality.

Human evidence

In humans the evidence clearly and unequivocally indicates that the severity of serotonin-mediated side effects, moving along the spectrum towards ST, is dose related and occurs frequently with larger doses of SSRIs and more frequently in overdoses* (see [1]. Data substantiating this interpretation comes from the HATS database, which has the considerable virtue of being a large series of consecutive poisonings from a toxicology unit with a defined catchment area. These have been documented and reported by Professor Ian Whyte and his team who have published a series of seminal papers in this field and are expert at assessing toxicity in general, and ST in particular.

*SRIs in overdose cannot cause life-threatening toxicity via ST

History

The history of the spectrum concept may be traced to Hilton, Lane, and Gillman who all mentioned or discussed it briefly in 1997. It was formally defined and elaborated, with a discussion of the animal evidence, by Gillman in 1998. Radomski and Dursun proposed a subdivision into three groups (on the basis of severity):

"(1) Mild state of serotonin-related symptoms; (2) serotonin syndrome (full-blown form); (3) toxic states".

This is in agreement with the spectrum concept, although not formulated in those specific terms.

Whyte et al have published the elements that constitute the picture, originally, in various forms from the HATS data [15-27].

L-tryptophan

Studies using L-tryptophan, going back to the 1950s, demonstrated unequivocal evidence of a dose-effect relationship, with the appearance of hyper-reflexia and mild coldness, but not hyper-pyrexia, when large doses of 4-5 g were combined with MAOI. Oates seminal paper [28] demonstrated a dose effect relationship; and was also the first to propose the presently accepted mechanism for ST.

Although L-tryptophan is little used my most practitioners now it is instructive to note old observations about it. These may be an example of how understanding ST may provide an insight into the mechanism, and extent to which drugs raise serotonin. By itself L-tryptophan appears to do little for depression or brain 5-HT level — it probably increases 5-HT about as little as mirtazapine — viz. approx. 50-150% over 'baseline', noting that baseline is a rather poorly defined concept and not a fixed entity. It can help sleep noticeably. When combined with MAOIs it provides modestly improved antidepressant efficacy and, in animal models, greater increases in brain 5-HT than MAOIs alone.

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