

MAOIs and opioid analgesics

Abstract

The serotonin reuptake inhibitor potency of most of the commonly used opioid analgesics is now known from quality *in vitro* data: that means we can predict confidently which are potentially able to cause serotonin toxicity when mixed with MAOIs. This data substantiates my previous interpretation concerning which of these drugs can cause ST. The most important predictions, made from the spectrum concept of serotonin toxicity, concerned the widely used drug fentanyl, and its congeners. Fentanyl is now established to have no significant serotonin reuptake inhibitor potency and it can be concluded that it poses no risk of serotonin toxicity when mixed with MAO inhibitors (or any other ‘serotonergic’ drugs).

Introduction

The first thing to state and be clear about is this: the interaction that is possible and occurs occasionally between MAOIs and larger doses of opioid analgesics, is serotonin toxicity (ST). It occurs because some opioid analgesics are weak serotonin reuptake inhibitors (SRIs). Other non-opioid analgesics (NSAIDs, paracetamol etc.) are safe because they are bereft of SRI activity and therefore cannot cause ST.

It is as simple as that, although you could be forgiven for not understanding that, because most of the literature, **including relevant product information**, is confused on this issue.

See also MAOIs and anaesthesia; <https://psychotropical.com/maois-and-anaesthesia/>

First, perfectly safe: codeine, oxycodone, hydrocodeine, dihydrocodeine, morphine, hydromorphone, oxymorphone, heroin, buprenorphine, fentanyl (and congeners).

Second, a bit risky (but unlikely to cause serious problems in usual therapeutic dose when given only once or twice): Pethidine (meperidine), methadone, dextropropoxyphene, pentazocine, dextromethorphan, tramadol, and tapentadol.

Although the product information produced by the FDA in conjunction with drug companies is generally of high quality [1] the issue of ST drug interactions is a striking and consequential exception, for reasons that are opaque to me.

Those reading this, who have not previously read the [introduction to ST](#), should do so before continuing with this, unless they are already knowledgeable about ST.

Concern over which opioid analgesics are safe in combination with MAOIs has persisted for 50 years, is common, and causes a lot of worry, expense, confusion, disagreements between healthcare providers, and disruption in routine clinical care. It is an archetypal example of the trouble and expense caused by unnecessary, overcautious, and mis-informed warnings given by (non-clinical) ‘experts’ who do not have to take responsibility for the chaos and expense they cause — with the best of intentions I am sure; but as the proverb goes

The road to hell is paved with good intentions*

Meaning number one seems to be most commonly understood as 'correct' but is a concrete interpretation which I suspect is consequent upon a 'religious' mindset. Atheists may be more likely to adopt the second meaning which implicitly recognises that having good intentions can lead to evil actions (like the Spanish inquisition or burning Witches). Contemporary examples, like Catholics and paedophilia, may upset those of delicate sensibilities — the ready-retreat to claiming offence from something is an epidemic, especially when it is something people are unwilling or unable to face-up to.

Opioids and SRI potency

My 1998 review paper 'Serotonin syndrome: history and risk' [2] analysed reported cases of ST in the world literature up till then, some of which involved opioids: various of my other papers (e.g., my main review of such data in the British J. Anaesthesia [3]) contains data relevant to this question.

Pethidine caused a few deaths in the 1960s before the risk was appreciated: note that this drug interaction was not recognised as ST until described as such in my review. The risk of serious ST with one intra-muscular injection of 50-75mg of Pethidine is probably low, say 1 in 10 or less [4], but this risk escalates with increasing and successive doses, especially because Pethidine has a long half-life. In practice most patients on MAOIs who get given an average size dose of Pethidine will probably not develop serious symptoms; however, there is a small chance that one dose would produce a reaction sufficiently severe to be fatal, if unrecognised and not dealt with appropriately.

The current situation: data from Rickli (2018)

The confusion is compounded by the poor quality of medical publications on this subject. These are not refereed to a standard that maintains the integrity of the scientific literature. The recent paper by Rickli et al. [5] is another example of this; although their data on the SRI potency of a number of these opioids at the human cloned serotonin transporter (hSERT) is a useful addition to the previously sparse data available, **their analysis of ST cases is highly misleading and erroneous.**

Their results (expressed as IC₅₀s) were in K_i nM: Dextromethorphan 68, Methadone 230, Pethidine 1600, Tramadol 3300 Tapentadol 3300 (fentanyl > 10,000).

Replication of these results in other laboratories is required
before we can have confidence in them

Codd's [6] values were: (K_i in nM) methadone (14), dextromethorphan (23), levomethorphan (36), levorphanol (86), dextrorphan (400), tramadol (528), propoxyphene (30,000).

Rickli's attempt to correlate the SRI potency of opioids with their propensity to precipitate ST is of no use whatsoever. This is because the cases they include are clearly not reliably ascertained as ST — it is indeed worse than that, it is misleading and mis-directs people. They mistakenly suggest there are 45 reported cases of ST involving fentanyl in the peer-reviewed literature [7-18] — that view should not be relied on and is incorrect. They also looked at the cases reported in the WHO database (reliability of these is even worse than case reports, if that is possible). No matter what caveats and limitations they (correctly) expressed in

* Interpretations of this saying: 1) There is no value in simply planning to do good if you do not truly do it; or 2) People who believe their intentions are good often end up doing bad things (the law of unintended consequences), as exemplified by Catholics who 'lie for God' and cover-up paedophilia.

their discussion, readers are going to see their figure 1, seemingly illustrating that nearly 400 cases of ST have been reported with fentanyl. The quality of that data is such that it cannot be regarded as being accurate or reliable. Indeed, it cannot reasonably be described as 'scientific data' without putting an unconscionable strain on the semantic integrity of the English language.

Not a single one of those case reports is a definite case of ST where fentanyl is likely to have been the causative agent

'Data' like that simply make a nonsense of the scientific literature and anyone who trades in that currency needs to think more critically about their scientific thinking and methods.

See also my separate commentary on ST and MB:

<https://psychotropic.com/methylene-blue-serotonin-toxicity-syndrome/>

That elaborates on something I have published previously [19] about the lack of ST exhibited in the two large surgical case-series of patients exposed to SSRIs and methylene blue [20, 21]. Those reports constitute an inadvertent but useful 'experiment' of the putative SRI potency of fentanyl which was used regularly in these cases. If fentanyl was an SRI (sufficiently potent to cause serious ST if mixed with MAOIs, viz. MB) then cases would have been evident in this series: however, no case exhibited toxicity who had not been taking SRIs pre-operatively, i.e. of the 280 cases (325 - 45) who had MB, but no SRI pre-operatively, none showed toxicity, whereas 38% of those who took SRIs did have toxicity. Thus, it can be reliably inferred that fentanyl is not a significant SRI in usual circumstances.

This data [5, 22] substantiates previous conclusions.

Just as ST can be caused by mixing MAOIs with antidepressants which have SRI activity, the same is true for analgesics.

Fortunately, as with the TCAs (most of which do not have sufficient SRI potency), most analgesics are sufficiently weak in respect of SRI potency that this property is of no clinical relevance, even after over-doses.

The situation, as far as clinical practice is concerned, is clear.

First, it can be re-stated confidently that: codeine, oxycodone, hydrocodone, dihydrocodeine, morphine, hydromorphone, oxymorphone, buprenorphine, fentanyl (and congeners), are perfectly safe.

The following analgesics have occasionally caused ST reactions (including some deaths): pethidine (meperidine), dextropropoxyphene, pentazocine, dextromethorphan, tramadol; we can probably add tapentadol [23-26] and methadone, because although there are, to my knowledge, no definite clinical cases, their SRI potencies do suggest they may be in the 'at-risk' bracket, but only if combined with MAOIs.

They cannot cause serious ST when combined with other SRIs.

The Walczyk paper [25] about tapentadol (by pharmacists) purports to describe a case of ST with tapentadol and duloxetine — this case is clearly utterly unconvincing as ST (as opined by Prof Isbister himself, a toxicologist, with Prof Whyte, in the Hunter toxicity Service [24]): however, its SRI potency might possibly be sufficient for it to cause ST in combination with MAOI, but not by itself, nor with another SRI, nor even in overdose.

Note: if you search the literature, you will see that some years ago both Professor Isbister and I published a number of rebuttals of these kinds of poor case reports in journals. Our publications did no good, nobody reads them, cites them, or takes any notice of them and the publication of poor and valueless case reports continues in an unabated stream. It illustrates how the scientific literature has become an impediment to knowledge as much as a facilitator of it.

Summary

When patients are taking MAOIs, some opioid analgesics are sufficiently potent as serotonin reuptake inhibitors to precipitate serotonin toxicity. In usual doses, used once or twice post-operatively, they are unlikely to cause severe serotonin toxicity. Repeated, and larger, doses carry a significantly higher risk and fatalities have occurred.

References

1. McMahon, D. and S.H. Preskorn, *The package insert: who writes it and why, what are its implications, and how well does medical school explain it?* Psychiatr Pract, 2014. **20**(4): p. 284–90.
2. Gillman, P.K., *Serotonin Syndrome: History and Risk*. Fundamental and Clinical Pharmacology, 1998. **12**(5): p. 482–491.
3. Gillman, P.K., *Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity*. British Journal of Anaesthesia, 2005. **95**(4): p. 434–441.
4. Evans-Prosser, A., *The use of pethidine and morphine in the presence of monoamine oxidase inhibitors*. British Journal of Anaesthetics, 1968. **40**: p. 279.
5. Rickli, A., *Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome*. Brit J Pharmac, 2018.
6. Codd, E.E., et al., *Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception*. Journal of Pharmacology and Experimental Therapeutics, 1995. **274**(3): p. 1263–70.
7. Reich, M. and D. Lefebvre-Kuntz, *[Serotonergic antidepressants and opiate analgesics: a sometimes-painful association. A case report]*. Encephale, 2010. **36 Suppl 2**: p. D119–23.
8. Rastogi, R., R.A. Swarm, and T.A. Patel, *Case scenario: opioid association with serotonin syndrome: implications to the practitioners*. Anesthesiology, 2011. **115**(6): p. 1291–8.
9. Gollapudy, S., V. Kumar, and M.S. Dhamee, *A case of serotonin syndrome precipitated by fentanyl and ondansetron in a patient receiving paroxetine, duloxetine, and bupropion*. J Clin Anesth, 2012. **24**(3): p. 251–2.
10. Mugele, J., K.A. Nanagas, and L.M. Tormoehlen, *Serotonin Syndrome Associated With MDPV Use: A Case Report*. Ann Emerg Med, 2012.
11. Larson, K.J., et al., *Myoclonus in patient on fluoxetine after receiving fentanyl and low-dose methylene blue during sentinel lymph node biopsy*. J Clin Anesth, 2014.
12. Samartzis, L., et al., *Linezolid is associated with serotonin syndrome in a patient receiving amitriptyline, and fentanyl: a case report and review of the literature*. Case Rep Psychiatry, 2013. **2013**: p. 617251.
13. Gaffney, R.R. and I.R. Schreiber, *Serotonin Syndrome in a Patient on Trazodone and Duloxetine Who Received Fentanyl following a Percutaneous Liver Biopsy*. Case Rep Gastroenterol, 2015. **9**(2): p. 132–6.
14. Hillman, A.D., et al., *Serotonin syndrome caused by fentanyl and methadone in a burn injury*. Pharmacotherapy, 2015. **35**(1): p. 112–7.
15. Koury, K.M., B. Tsui, and P. Gulur, *Incidence of serotonin syndrome in patients treated with fentanyl on serotonergic agents*. Pain Physician, 2015. **18**(1): p. E27–30.

16. Robles, L.A., *Serotonin Syndrome Induced by Fentanyl in a Child: Case Report*. Clin Neuropharmacol, 2015. **38**(5): p. 206–8.
17. Shah, N.D. and A.B. Jain, *Serotonin syndrome presenting as pulmonary edema*. Indian J Pharmacol, 2016. **48**(1): p. 93–5.
18. Franco, D.M., et al., *Case report of a fatal intoxication by Nucynta*. Am J Forensic Med Pathol, 2014. **35**(4): p. 234–6.
19. Gillman, P.K., *Fentanyl and serotonin toxicity*. British Journal of Anaesthesia, 2009: p. <http://bjaoxfordjournals.org/cgi/eletters/95/4/434#4135>.
20. Kartha, S.S., et al., *Toxic metabolic encephalopathy after parathyroidectomy with methylene blue localization*. Otolaryngology – Head and Neck Surgery, 2006. **135**(5): p. 765–8.
21. Sweet, G. and S.B. Standiford, *Methylene-blue-associated encephalopathy*. Journal of the American College of Surgeons, 2007. **204**(3): p. 454–8.
22. Barann, M., et al., *Effects of opioids on human serotonin transporters*. Naunyn Schmiedeberg Arch Pharmacol, 2015. **388**(1): p. 43–9.
23. Raffa, R.B., et al., *Mechanistic and functional differentiation of tapentadol and tramadol*. Expert Opin Pharmacother, 2012. **13**(10): p. 1437–49.
24. Russo, M., D. Santarelli, and G. Isbister, *Comment on "Probable Tapentadol-Associated Serotonin Syndrome After Overdose"*. Hospital pharmacy, 2017. **52**(4): p. 248–248.
25. Walczyk, H., et al., *Probable tapentadol-associated serotonin syndrome after overdose*. Hospital pharmacy, 2016. **51**(4): p. 320–327.
26. Mullins, M.E. and W.H. Dribben, *Comment on Tapentadol and Serotonin Syndrome*. Hospital pharmacy, 2017. **52**(4): p. 246–247.