



Methylene Blue: Understanding Drug Interactions



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Perhaps the most prominent concern patients and prescribers have regarding methylene blue is the risk of serotonin syndrome. This can result from the interaction of methylene blue with other drugs that affect serotonin and monoamine oxidase inhibitors (MAOIs). MAOIs are deaminators of neurotransmitters, resulting in deactivation of, and affecting the number of, neurotransmitters in the synaptic cleft, thereby regulating neurotransmitter levels and brain mood function.

Methylene Blue and Serotonin Syndrome

There are two subtypes of MAOIs: MAO-A and MAO-B. MAO-A affects the deamination of serotonin, norepinephrine, epinephrine, and melatonin, whereas MAO-B breaks down phenethylamine and benzylamine. Dopamine, tyramine, and tryptamine are metabolized by both MAO-A and MAO-B. Methylene blue in particular only affects MAO-A.

Because of this effect on MAO-A, the use of intravenous methylene blue has been associated with the development of serotonin syndrome¹⁻⁸. Because of the severity of the interaction, in published drug databases (i.e UpToDate LexiDrug, Clinical Pharmacology, etc.), the interaction is listed as a “Avoid Combination (X)” and/or “Level 1 (Contraindicated).”

For this reason, many patients and practitioners avoid the use of methylene blue⁹⁻²⁶. However, much of the data supporting the contraindication and interaction is based on the use of intravenous methylene blue, or extrapolation of similar drugs that work on MAOIs. That said, these are not actual accounts of methylene related drug interaction.

Oral vs Intravenous

Indeed, after several searches in scientific literature, only a single case report was found describing a possible link between oral methylene blue and serotonin syndrome²⁷. This discrepancy is expected, and reported events could be because the pharmacokinetics of intravenous methylene blue are different than that of oral methylene blue. Obviously, intravenous administration results in quicker and higher peak levels compared to oral delivery²⁸. These higher peaks also correlate with the concept that the methylene blue interaction with other medications is dose related, $>5\text{mg/kg}$ ²⁹.

In summary, nearly the entirety of the information on methylene blue causing serotonin syndrome is either theoretically based on pharmacodynamics or is pharmacokinetically based on the use of parenteral methylene blue used in a hospital setting. The corresponding fast infusion and high peak levels more likely approach the 5mg/kg suggested threshold for serotonin syndrome to occur.

Clinical Research on Methylene Blue

Renewed clinical interest in the use of oral methylene blue only truly reignited after the publication of the Zheng article in BMC Microbiology back in 2020, for use in treating Bartonella³⁰. Since then, thousands of patients across the United States have received oral methylene blue for numerous indications. However, to date, there has been no formal collection of data to correlate the use of compounded oral methylene blue with adverse reactions or serotonin syndrome.

Therefore, because of this void in data and information, recommendations regarding the use of methylene blue concomitantly with medications and supplements that affect serotonin or MAOI should be done conservatively and on an individualized basis. Practitioners should keep in mind patients' weight, age, and dosing of the methylene blue and the other medications or supplements the patient may be using.

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References

1. Ng BK, Cameron AJ, Liang R, Rahman H. Serotonin syndrome following methylene blue infusion during parathyroidectomy: a case report and literature review. *Can J Anaesth*. 2008;55(1):36-41. [PubMed 18166746]
2. Shanmugam G, Kent B, Alsaidwadi T, Baskett R. Serotonin syndrome following cardiac surgery. *Interac Cardiovasc Thorac Surg*. 2008;7(4):656-657. [PubMed 18334520]
3. Schwiebert C, Irving C, Gillman PK. Small doses of methylene blue, previously considered safe, can precipitate serotonin toxicity. *Anaesthesia*. 2009;64(8):924. [PubMed 19604213]
4. Stanford BJ, Stanford SC. Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paroxetine? *J Psychopharmacol*. 1999;13(3):313-317. [PubMed 10512094]
5. Nicolaou G, Lee D. Methylene blue-induced serotonin syndrome presenting with ocular clonus and failure of emergence from general anesthesia. *Can J Anaesth*. 2016;63(7):896-897. [PubMed 26943644]
6. Pollack G, Pollack A, Delfiner J, Fernandez J. Parathyroid surgery and methylene blue: a review with guidelines for safe intraoperative use. *Laryngoscope*. 2009;119(10):1941-1946. [PubMed 19598213]

7. Hencken L, To L, Ly N, Morgan JA. Serotonin syndrome following methylene blue administration for vasoplegic syndrome. *J Card Surg.* 2016;31(4):208-210. [PubMed 26934199]
8. Sweet G, Standiford SB. Methylene-blue-associated encephalopathy. *J Am Coll Surg.* 2007;204(3):454-458. [PubMed 17324781]
9. Lloyd JT and Walker DR, "Death After Combined Dexamphetamine and Phenelzine," *Br Med J*, 1965, 2:168. [PubMed 14304064]
10. Nymark M and Nielsen IM, "Reactions Due to the Combination of MAOIs With Thymoleptics, Pethidine, or Methylamphetamine," *Lancet*, 1963, ii:524. [PubMed 14065430]
11. Krisko I, Lewis E and Johnson JR, "Severe Hyperpyrexia Due to Tranylcypromine-Amphetamine Toxicity," *Ann Intern Med*, 1969, 70:559. [PubMed 5775035]
12. Pettinger WA and Oates JA, "Supersensitivity to Tyramine During Monoamine Oxidase Inhibition in Man. Mechanism at the Level of the Adrenergic Neurone," *Clin Pharmacol Ther*, 1968, 9:341. [PubMed 5649986]
13. Pettinger WA, Soyangco F, and Oates JA, "Inhibition of Monoamine Oxidase in Man by Furazolidone," *Clin Pharmacol Ther*, 1968, 9:442. [PubMed 5655478]
14. Stern IJ, Hollifield RD, Wild S, et al, "The Anti-Monoamine Oxidase Effects of Furazolidone," *J Pharmacol Exp Ther*, 1967, 156:492-9. [PubMed 6028876]
15. Suphanklang J, Santimaleeworagun W, Supasynhd O. Combination of Escitalopram and Rasagiline Induced Serotonin Syndrome: A Case Report and Review Literature. *J Med Assoc Thai.* 2015;98(12):1254-1257. [PubMed 27004312]
16. Zoloft (sertraline) [prescribing information]. New York, NY: Pfizer Inc; December 2017.
17. Viibryd (vilazodone) [prescribing information]. Irvine, CA: Allergan USA Inc; January 2017.
18. Lexapro (escitalopram) [prescribing information]. Madison, NJ: Allergan USA Inc; January 2019.
19. Trintellix (vortioxetine) [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; July 2019.
20. Paxil (paroxetine) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; January 2017.
21. Fluvoxamine [prescribing information]. Baudette, MN: ANI Pharmaceuticals, Inc.; January 2017.
22. Prozac (fluoxetine) [prescribing information]. Indianapolis, IN: Lilly USA, LLC; January 2017.
23. Celexa (citalopram) [prescribing information]. Madison, NJ: Allergan USA, Inc.; December 2018.
24. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352(11):1112-1120. [PubMed 15784664]
25. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM.* 2003;96(9):635-642. [PubMed 12925718]
26. Sternbach H. The serotonin syndrome. *Am J Psychiatry.* 1991;148(6):705-713. [PubMed 2035713]
27. Zuschlag ZD, Warren MW, K Schultz S. Serotonin toxicity and urinary analgesics: a case report and systematic literature review of methylene blue-induced serotonin syndrome. *Psychosomatics.* 2018;59(6):539-546. [PubMed 30104021]
28. Peter C, Hongwan D, Kupfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharm* 2000;56:247-250.
29. Ginimuge PR, Jyothi SD. Methylene blue: revisited. *J Anaesthesiol Clin Pharmacol.* 2010 Oct-Dec;26(4):517-520.
30. Zheng X, Ma X, Li T, et al. Effect of different drugs and drug combinations on killing stationary phase and biofilms recovered cells of *Bartonella henselae* in vitro. *BMC Microbiology* 2020;20(87):1-9

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