

Which opioids in case of mast cell activation disorders?



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Clinical Implications

- Patients with mast cell activation symptoms with opioids should avoid codeine and morphine, because of histamine release. Our data suggest that tramadol and hydromorphone are valuable alternatives in this case.

TO THE EDITOR:

Mast cell disorders are characterized by an excessive mast cell accumulation, or hyperreactive, or both, in one or multiple tissues. Mast cell disorders are classified into primary (including mastocytosis), secondary (including physical urticarias), and idiopathic mast cell disorders (including idiopathic anaphylaxis).¹ Mast cell activation releases vasoactive mediators such as histamine and tryptase. Therefore, patients with mast cell activation can experience symptoms associated with sudden and massive mast cell mediator release, for example, urticaria, pruritus, angioedema, anaphylaxis, and abdominal pain. The release of mast cell mediators may be precipitated by a variety of stimuli, including drugs, such as nonsteroidal anti-inflammatory drugs, iodinated contrast agents, antibiotics, and opioids.

Mast cell activation differs depending on the opioid type, and the comparison of the systemic release of histamine has been investigated.² Morphine, codeine, and meperidine provoke histamine release in a concentration-dependent manner.^{3,4} Fentanyl and its derivatives, alfentanil and remifentanil, did not induce histamine release from any type of mast cell.^{3,4} Consequently, these are preferred to treat patients with mast cell disorders requiring opioids.²

Tramadol is an opioid receptor agonist and also inhibits monoamine reuptake. Only one study has explored its ability to induce histamine release but was not conclusive.⁵ Nevertheless, this drug is supposed not to release histamine.⁶ Hydromorphone is a pure opioid agonist. This drug induced minimal histamine release in dogs⁷ and is well tolerated in human in case of severe morphine-induced itch.⁸ Consequently, tramadol and hydromorphone could be proposed to patients with mast cell disorders. However, robust data are still lacking to confirm this hypothesis.

To further address this issue, we performed a disproportionality analysis using data from the World Health Organization (WHO) pharmacovigilance database Vigibase by a case-noncase study. Given the tight link between histamine and urticaria, we used this adverse reaction as a proxy of the opioid ability to induce histamine release. We therefore extracted all individual case safety reports (ICSRs) included in the preferred

term “urticaria,” according to the Medical Dictionary for Regulatory Activities classification, until April 5, 2018. We calculated the reporting odds ratio (ROR) of urticaria associated with tramadol, hydromorphone, fentanyl, morphine, codeine, and meperidine. ROR was calculated using the following formula: $ROR = (a/c)/(b/d)$ with (a) the number of urticaria reports with the opioid drug, (b) the number of reports other than urticaria with the opioid drug, (c) the number of urticaria reports with all other drugs in Vigibase, and (d) the number of all other reports with all other drugs in Vigibase excluding urticaria. According to the European Medicines Agency, the cutoff for signal detection was defined as a lower boundary of the ROR 95% CI greater than or equal to 1, and number of reports greater than or equal to 3.⁹

A total of 476,442 ICSRs of urticaria were reported in the WHO pharmacovigilance database, on April 5, 2018. Table I displays the results of the disproportionality analysis of urticarial case reports associated with opioids. We found that morphine, codeine, and meperidine were associated with an increased reporting of urticaria, whereas tramadol, hydromorphone, and fentanyl were not. Meperidine showed the higher disproportionality signal among opioid drugs.

These results were consistent with previous literature: urticaria was significantly less reported with fentanyl than with other opioids such as morphine and meperidine. Moreover, according to this disproportionality analysis, tramadol and hydromorphone were not associated with increased reports of urticaria.

Histamine-releasing properties could be partially explained by chemical structures: morphine and meperidine have a phenylpropylamine structure, and fentanyl has an anilidopropylamine structure.⁶ Yet tramadol is chemically close to methadone, a phenylpropylamine derivative, and hydromorphone is a semisynthetic derivative of morphine.

This disproportionality analysis displays several limitations. Adverse drug reactions (ADRs) are underreported, especially nonserious ADRs including urticaria. Opioids are drugs used for several decades, so we do not suspect a temporal bias. Another issue is the lack of information in the WHO pharmacovigilance database for appropriate adjustment on potential confounders.

The occurrence of urticaria is the consequence of mast cell activation and release of mediators. Herein, we demonstrated the absence of pharmacovigilance signal concerning urticaria with fentanyl, tramadol, and hydromorphone. These drugs could induce less symptoms of mast cell activation and could be interesting alternatives for patients with mast cell disorders and requiring analgesics. These results are not definitive recommendations and need to be confirmed by further prospective controlled studies.

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TABLE I. Disproportionality analysis of urticaria reports associated with opioids

Opioids	Cases of "urticaria"	Noncases	ROR [95%CI]
Hydromorphone	166	13,493	0.42 [0.36-0.49]
Tramadol	1663	89,988	0.63 [0.60-0.66]
Fentanyl	816	114,094	0.24 [0.23-0.26]
Morphine	1736	55,712	1.06 [1.01-1.11]
Codeine	491	11,563	1.44 [1.32-1.58]
Meperidine	1701	23,673	2.45 [2.33-2.57]

ROR, Reporting odds ratio.

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REFERENCES

1. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med* 2015;373:163-72.
2. Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA. Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxycodone. *Anesthesiology* 1985;62:124-9.
3. Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by mu-opioid receptors: an *in vivo* microdialysis study in human skin. *Anesth Analg* 2004;98:364-70.
4. Stellato C, Cirillo R, de Paulis A, Casolaro V, Patella V, Mastronardi P, et al. Human basophil/mast cell releasability. IX. Heterogeneity of the effects of opioids on mediator release. *Anesthesiology* 1992;77:932-40.
5. Barth H, Giertz H, Schmal A, Lorenz W. Anaphylactoid reactions and histamine release do not occur after application of the opioid tramadol. *Agents Actions* 1987;20:310-3.
6. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012;40:216-35.
7. Guedes AGP, Papich MG, Rude EP, Rider MA. Comparison of plasma histamine levels after intravenous administration of hydromorphone and morphine in dogs. *J Vet Pharmacol Ther* 2007;30:516-22.
8. Katcher J, Walsh D. Opioid-induced itching: morphine sulfate and hydromorphone hydrochloride. *J Pain Symptom Manage* 1999;17:70-2.
9. European Medicines Agency; EudraVigilance Expert Working Group. Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System (EMA/106464/2006 rev.1). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.pdf. Accessed April 27, 2017.