Which opioids in case of mast cell activation disorders?

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Clinical Implications box

Patients suffering from 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 hyper-reactive, or both, in one or multiple tissues. Classification of mast cell disorders is divided in 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 suffering from mast cell activation can experience symptoms associated with sudden and massive mast cell-mediators release: e.g. urticaria, pruritus, angioedema, anaphylaxis, 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 cells activation differs depending of the opioid type, and 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, remifentanil, did not induce histamine release from any type of mast cell (3,4). Consequently, these latter are preferred to treat patients with mast cell disorders requiring opioids (2).

Tramadol is an opioid receptor agonist and also inhibits monoamines reuptake. Only one study have 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 dogs (7) and is well tolerated in human in case of severe morphine-induced itch (8). Consequently, tramadol and hydromorphone could be proposed to patients suffering 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 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 cases safety reports (ICSRs) included in the preferred term “urticaria”, according to the Medical Dictionary for Regulatory Activities classification, until the 5th April 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 others 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 cut-off for signal detection was defined as a lower boundary of the ROR 95% CI greater or equal to 1, and number of reports greater or equal to 3 (9).

A total of 476 442 ICSRs of urticaria were reported in the WHO pharmacovigilance database, on the 5th April 2018. Table 1 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 while 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 a 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 (ADR) are under-reported, especially non-serious ADR 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 WHO pharmacovigilance database for appropriate adjustment on potential confounders.

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 suffering from 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 1. Disproportionality analysis of urticaria reports associated with opioids

Opioids	**Cases of "urticaria"**	**Non-cases**	**ROR [95%CI]**
Hydromorphone	166	13493	0.42 [0.36-0.49]
Tramadol	1663	89988	0.63 [0.60-0.66]
Fentanyl	816	114094	0.24 [0.23-0.26]
Morphine	1736	55712	1.06 [1.01-1.11]
Codeine	491	11563	1.44 [1.32-1.58]
Meperidine	1701	23673	2.45 [2.33-2.57]