

Pharmacologically Induced Histamine Release: Sorting Out Hypersensitivity Reactions to Opioids

by Fanny Li, Pharm.D.

Self-reports of opioid “allergy” are common in clinical practice, with patients often referring to symptoms more suggestive of an extension of the pharmacologic action of the drug rather than a “true” immune-mediated reaction. Even though opioids are capable of inducing Type I hypersensitivity reactions with repeat exposures, true anaphylactic reactions with an immunologic basis are rare.¹⁻⁴ Rather, many reported reactions occur on first-exposure and/or lack demonstrated immunologic mechanisms. Such non-allergic hypersensitivity reactions can manifest as pruritus, flushing, hives, and/or hypotension, and thereby present a clinical dilemma for the prescriber attempting to balance the risk of potentially serious consequences of allergic reactions against the therapeutic goal of optimal pain management.^{5,6} This article will review the pathophysiology of the different types of opioid allergic reactions to aid in distinguishing between true drug allergy—which may lead to anaphylaxis and cardiovascular collapse on re-challenge—and non-allergic histamine release. In addition, this article will discuss immune-mediated cross-sensitivity reactions between opioids. Applying this information to the treatment of patients will help prescribers avoid some adverse consequences of the administration of opioids and assist them in choosing rational alternatives for patients with documented intolerance.

Almost all opioid analgesics cause direct histamine release as one of their pharmacologic actions.^{3,7,8} Without immunologic involvement, these reactions are termed “pharmacologically induced histamine release” or simply “non-allergic” reactions.⁵ The release of histamine into the extracellular space may result in dilation of venules, an increase in vascular permeability, contraction of smooth muscles, and stimulation of mucous gland secretion.⁸ Unlike Type I hypersensitivity reactions which are IgE-mediated and cause the release of multiple inflammatory mediators, non-IgE mediated reactions are thought to only involve histamine release from mast cells without the simultaneous generation of either prostaglandins or leukotrienes.^{7,9} This pure histamine release appears to be due to an idiosyncratic susceptibility of some mast cells and, as demonstrated by the inability of naloxone to decrease the histamine release caused by morphine, is thought to be independent of opiate receptors.^{7,10-13}

Mast cell heterogeneity may explain why pharmacologically induced histamine release reactions are not associated with the systemic reactions and anaphylactic symptoms of true opioid allergies.^{14,15} For example, after *in vitro* opioid exposure, cutaneous mast cells exhibited histamine release while those obtained from the lungs, adenoids, tonsils, colon, and heart did not.^{14,15} As additional data suggest, direct histamine release may loosely correlate with the opioid chemical source, and be dependent on the concentration of the opioid to which the mast cells are exposed.^{12,13,16} With the exception of meperidine, the “naturally” occurring compounds (e.g., morphine

(Continued on page 14)

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Sorting Out Hypersensitivity Reactions to Opioids (continued)

Morphine, codeine, and meperidine tend to cause more histamine release than other opioids. Moreover, the effect appears to be concentration-dependent and unrelated to analgesic potency.

and codeine) appear to be more potent in their ability to cause histamine release than the “synthetic” and “semi-synthetic” compounds (see Table I).^{12,13,16-19} Fentanyl, on the other hand, has been demonstrated *in vitro* and *in vivo* to produce little change in histamine release from baseline.^{13,19,20} Interestingly, one study that combined intradermal testing with biopsy from the skin-test site demonstrated that fentanyl is capable of producing cutaneous wheal and flare reactions in the absence of mast cell degranulation.¹² The clinical implications of this finding for fentanyl are unknown.

In summary, morphine, codeine, and meperidine tend to cause more histamine release than other opioids. Moreover, the effect appears to be concentration-dependent

Table I: Classification of Chemical Source and Experimental Histamine Release Characteristics of Various Opioids^{7,24}

Opioid	Classification of Chemical Source	Relative Histamine Release
Buprenorphine	Semi-synthetic	No data
Codeine	Natural	High
Fentanyl	Synthetic	Low
Hydrocodone	Semi-synthetic	No data
Hydromorphone	Semi-synthetic	Low
Levorphanol*	Semi-synthetic	Low
Meperidine	Synthetic	High
Methadone	Synthetic	Low
Morphine	Natural	High
Nalbuphine	Semi-synthetic	No data
Oxycodone	Semi-synthetic	Low
Oxymorphone*	Semi-synthetic	Low
Propoxyphene*	Synthetic	No data

*Non-formulary at UWMC

Patients with documented or suspected IgE-mediated allergic reactions or prior anaphylaxis to an opioid should not be re-challenged with the offending agent without first consulting an allergist.

Currently, too few cases of true IgE-mediated opioid allergic reactions have been reported to accurately predict the likelihood of cross-allergenicity between opioids.

and unrelated to analgesic potency. For patients presenting with symptoms suggestive of non-allergic histamine release, countering the acute reaction with antihistamines and changing to an opioid less likely to cause histamine release is recommended (see Table I). Philbin, et al., recommends that the elevated histamine levels and histamine-related cardiovascular abnormalities from morphine may best be blocked by use of a combination of type 1 and type 2 histamine receptor antagonists (such as diphenhydramine 25-50mg IV or PO with ranitidine 50mg IV or 150mg PO) prior to opioid administration.¹⁷ For parenterally administered opioids, slowing the rate of infusion may also be helpful in reducing histamine release.^{20,21} The use of mast cell stabilizers, such as oral cromolyn, have not been studied in this context.

Unlike non-allergic histamine release, Type I hypersensitivity reactions are IgE-mediated, generalized reactions involving multiple organ systems, and are potentially life-threatening. Typical features include hives, bronchospasm or respiratory distress, laryngeal edema, hypotension, and even acute vascular collapse.^{6,22} Taking into consideration the extent of systemic involvement, and whether symptoms are the result of first or repeated opioid exposure, one may distinguish between immune- and non-immune-mediated reactions. Patients with documented or suspected IgE-mediated allergic reactions or prior anaphylaxis to an opioid should not be re-challenged with the offending agent without first consulting an allergist.

Currently, too few cases of true IgE-mediated opioid allergic reactions have been reported to accurately predict the likelihood of cross-allergenicity between opioids.³ Since immune-mediated reactions depend on the affinity of the allergic determinant, or binding site, of the opioid molecule for the IgE antibody (see Figure 1), the relative degree of binding to IgE has been used to assess the likelihood of cross-sensitivity between opioids in

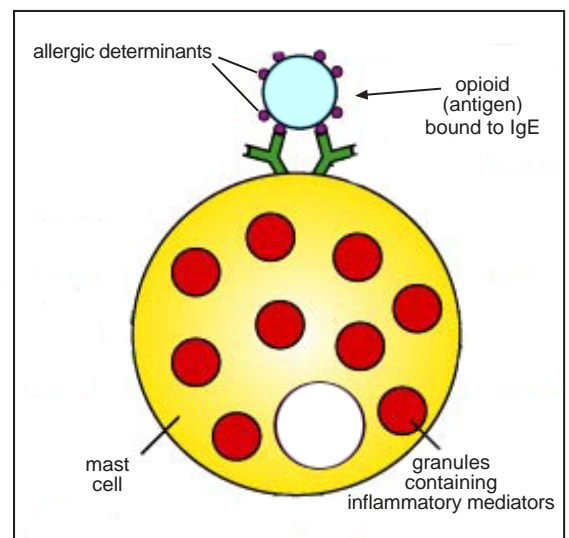


Figure 1. Release of the inflammatory mediators of allergic reactions is dependent on the affinity of the antigen for IgE.

(Continued on page 15)

While immune cross-sensitivity among opioids is not well-defined, categorization of opioids by chemical class and allergic determinant is useful to guide prescribers in cautiously choosing between alternatives in patients who have a history of Type I hypersensitivity.

experimental models. In one model, assays using isolated morphine-specific IgE antibodies showed equal binding affinity for codeine, half the affinity for meperidine and methadone, and less for fentanyl.² Largely based on this work, the likelihood of cross-sensitivity is thought to be highest among opioids who are members of the same chemical class. The three main opioid chemical classes and their members are shown in Figure 2. Among the members of the phenanthrene class, the methyl substituent attached to the nitrogen atom and the hydroxyl group attached at position 6 of the cyclohexene ring (see morphine example shown in sidebar below) have been proposed as specific IgE allergic determinants.^{2,23} As shown in Figure 2, grouping opioids by structural class and allergic determinant can serve to guide the selection of an alternative when true hypersensitivity is encountered clinically. However, caution with this approach is warranted because the administration of any opioid to a patient with a true hypersensitivity may pose some risk.

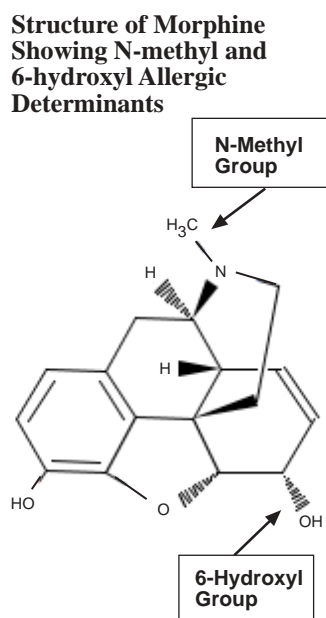
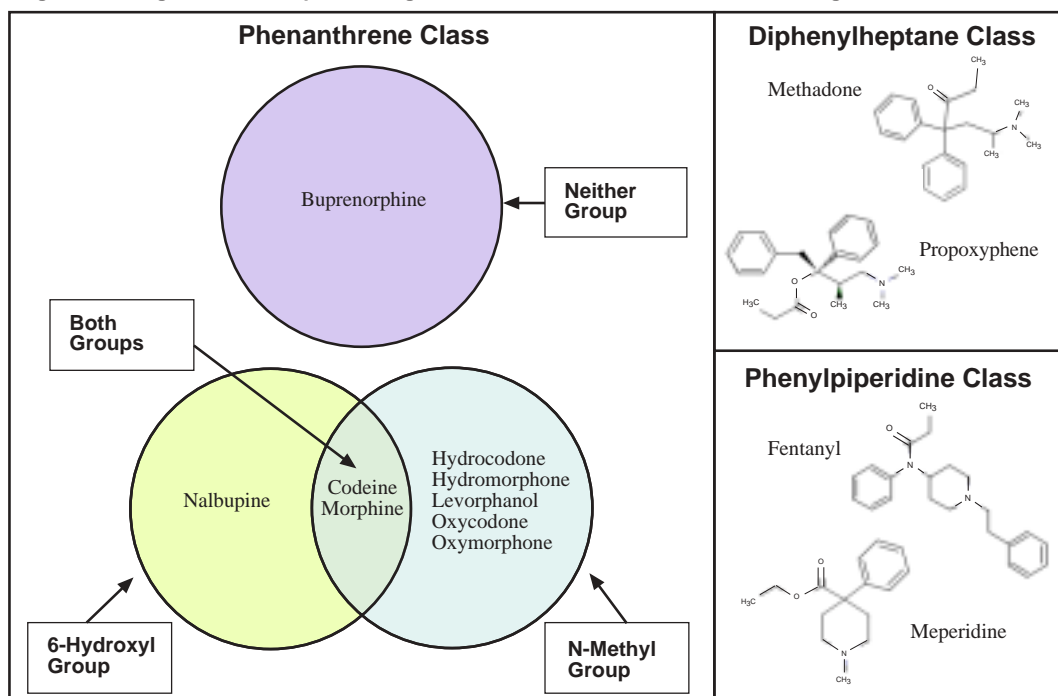


Figure 2. Categorization of Opioid Analgesics Based on Structural Class and Allergic Determinants 2,23,24



In conclusion, opioid reactions from immune- and non-immune-mediated histamine release may be difficult to distinguish. Obtaining a detailed patient history is the first step in assessing whether a self-reported “allergy” is immune or non-immune in nature. An elevated histamine level in association with a high IgE level detected by radioallergosorbent test (RAST) is the most reliable indicator of true allergy;⁴ however, radioallergosorbent tests have not been validated for routine clinical use. Life-threatening anaphylactic reactions to opioid analgesics are rare, and while immune cross-sensitivity among opioids is not well-defined, categorization of opioids by chemical class and allergic determinant is useful to guide prescribers in cautiously choosing between alternatives in patients who have a history of Type I hypersensitivity. Likewise, if the presentation is consistent with the more common isolated histamine release, the cautious use of histamine blockers in conjunction with opioids less likely to cause histamine release is recommended. For both types of patients, the use of non-opioid alternatives such as acetaminophen, aspirin, or NSAIDs should also be considered.

References available upon request.

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Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s) [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Pregabalin (Lyrica)	Capsule: 50, 75, 100, 150, 200, 225, 300mg	Anticonvulsant	Adjunct for therapy of partial-onset seizures	No more than 75mg BID, or 50mg TID
Added to formulary restricted to use by HMC Epilepsy Clinic physicians.				

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

Reminder: IV-to-Oral Conversion for Hospitalized Patients Receiving Target Medications

Automatic therapeutic interchange is approved for all UW Medicine inpatients receiving a target IV medication when the following criteria are met:

1. Functioning gastrointestinal tract

- Tolerating at least 1000mL/day of oral fluids or 40mL/h of enteral nutrition; Tolerating other oral medications.
- Able to swallow or has a functioning NG/feeding tube in place. (Only those medications available in liquid formulations or which can be crushed/suspended in liquid will be given via feeding tubes.)

2. Clinically stable

- For antimicrobial therapy the patient must be afebrile (temperature less than 38°C) for at least 24 hours, and if leukocytosis was initially present the WBC must be decreasing.
- For digoxin, the patient must be hemodynamically stable.

Exclusion criteria:

- Patients with an unreliable absorption of oral/enteral medications (i.e., patients with severe diarrhea, short bowel syndrome, active inflammatory bowel disease, grade 3 or 4 mucositis, active gastrointestinal bleeding, or emesis).
- Patients on vasopressors (>2 mcg/kg/minute of dopamine).
- Patients receiving fluoroquinolone therapy that are also receiving oral divalent cation therapy and/or enteral feedings.

Target Medications = Ciprofloxacin, Digoxin, Fluconazole, Lansoprazole, Levofloxacin, Linezolid, Metronidazole, Moxifloxacin, Pantoprazole, Ranitidine, and Rifampin.

Vol. 35, No. 4

Pharmacologically Induced Histamine Release: Sorting Out Hypersensitivity Reactions to Opioids, 13-15

Reminder: IV-to-Oral Conversion for Target Medications, 16
March P&T Committee Actions, 16



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