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Assessment of Opioid Cross-reactivity and Provider Perceptions in Hospitalized Patients With Reported Opioid Allergies

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Abstract

Background: The incidence of opioid allergy cross-reactivity in hospitalized patients with historical opioid allergies remains unknown. **Objectives:** The purpose of this study was to characterize the incidence of newly suspected IgE-mediated reactions (IMRs) based on clinical criteria among patients with a chart-documented opioid allergy and to assess clinician perceptions of opioid allergies. **Methods:** This retrospective cohort study was conducted in hospitalized adults with a historically documented opioid allergy who received a subsequent opioid. The primary outcome was the incidence of allergic cross-reactivity between clinical and chemical opioid classes in patients with historical IMRs (H-IMRs) identified by clinical criteria, ICD-9 diagnosis codes, or allergic reaction treatment. Secondary outcomes included the incidence of opioid intolerances incorrectly documented as allergies and a survey to clinicians to assess the impact of opiate warnings on prescribing practices. **Results:** A total of 499 patients with historical opioid allergies were included. H-IMR to an opioid of any class was not significantly associated with IMR cross-reactivity to the same or any other class, with cross-reactivity rates ranging from 0% to 6.7%. Of the historical chart-documented allergies, 249 reactions (50%) were determined to be intolerances. A total of 461 (92.5%) patients successfully tolerated readministration of opioids despite a chart-documented allergy, and 8 (1.6%) patients developed possible IMR (7 pruritus, 1 possible anaphylaxis). Survey results (n = 54) indicated that opiate allergy warnings were neutral or unlikely to change opiate prescribing. **Conclusions:** The risk of IMRs caused by opioids is low in patients with H-IMRs to opioids. Opioid allergy documentations may propagate alert fatigue and unwarranted prescribing changes.

Keywords

analgesics, opioid, narcotics, opiate alkaloids, hypersensitivity, anaphylaxis, drug hypersensitivity/prevention and control

Introduction

Opioid analgesics are consistently among the most widely used drugs in the hospital and outpatient settings.[1] These medications are generally well tolerated, and there is presumably a very low incidence of true anaphylactic responses to opioids.[2,3] An accepted theory is that because of the endogenous production of opioid-like substances, true IgE-mediated allergies to opioids do not exist.[1] However, many opioids possess the ability to cause mast cell degranulation and subsequent histamine release independent of IgE antibodies, which can lead to reactions mimicking an IgE-mediated reaction (IMR).[2] Opioids are often classified by their molecular structure; opioids within the same class possess similar characteristics in regard to histamine-releasing properties, adverse effect profiles, and potential for IgE-binding inhibition.[2,4,5] Direct opioid-receptor mediated vasodilation can cause flushing that mimics the allergic response.[2] Symptoms of both of these pseudo-allergic responses may be difficult to distinguish from that of true IMRs.[1] Diagnosis of such a reaction poses a challenge in clinical practice. Opioid skin testing has produced inconsistent results in patients with previous IgE reactions to opioids[2,6-8] and is largely affected by the limited availability of drug-specific IgE assays. As a result, the diagnosis of hypersensitivity reactions often remains by clinical manifestation. Regardless of the allergic response pathway to an opioid, opioid reactions may be classified as a clinically meaningful allergic response (requiring additional diagnostic tests or interventions surrounding the

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reaction) or an intolerance related to the pharmacology and adverse effect profile of the drug. Decades often occur between an inciting reaction and a patient's recall of an event. As such, patients may not remember reaction details or may misinterpret common adverse effects as allergies.[6,7,9] These factors can lead to inaccurate chart documentation of adverse effects as allergies. Electronic alerts triggered by misclassified opioid allergies may be unnecessarily contributing to clinician alert fatigue and may result in suboptimal pain management, compromised patient safety, and lower quality of overall patient care.[10,11] In a review of pediatric allergies, only 14% of documented reactions were considered true drug allergies, which led to removal of 93% of incorrectly reported allergies from patient charts, of which 50% were opioid agents.[11]

Allergic cross-sensitivity between opioid classes may theoretically occur based on molecular structure. However, cross-sensitivity between opioid classes has not been well defined. Further information on the true incidence of IgE-mediated opioid reactions and allergic cross-sensitivity may improve prescribing practices and reduce the burden of unnecessary prescribing alerts because up to half of allergy warnings pertain to narcotic agents, including opioids.[10]

The purpose of this study was to determine the incidence and severity of true IMRs based on clinical description, symptomatic presentation, and temporal association among patients with a chart-documented opioid allergy who were rechallenged with opioid therapy for the management of pain.

Methods

Study Design

This study was a single-center retrospective cohort study approved by the Colorado Institutional Review Board. Included patients were 18 to 89 years old admitted to our institution between January 1, 2013, to December 31, 2017, who self-reported or had a chart documented history of an opioid allergy on admission and subsequently received an opioid medication during their stay. Exclusion criteria were pregnancy; prisoners; cognitively challenged patients; patients receiving concomitant nonopioid medications for which they had a documented allergy; patients admitted for the primary diagnosis of anaphylaxis, angioedema, or any other allergic condition; or prior study enrollment.

Primary Outcome

The primary outcome of the study was to determine the incidence of allergic cross-reactivity between the 3 different clinical classes of opioid medications. In addition, the incidence of allergic cross-reactivity between opioid chemical classes was also evaluated. Patients were first grouped by these clinical classes of opioids on the basis of their allergy history (Table 1). Historically documented opioid allergy was then classified as a possible historical IgE-mediated reaction (H-IMR) or an intolerance reaction based on temporal association and symptomatic presentation. IMRs were classified by the presence of any of the following criteria immediately after opioid administration: the appearance of rash, urticaria, pruritus or throat swelling; or the requirement of treatment with epinephrine, diphenhydramine, or steroids; or a new ICD-9 code for anaphylaxis. Reactions that did not include at least 1 of these characteristics were classified as opioid intolerances. Additionally, chart-documented opioid reactions that had no clinical information regarding the nature of the allergic reaction or intolerance (unknown reaction) were considered intolerances. Commonly reported symptoms of opioid intolerances included headache, gastrointestinal upset, anxiety, sedation, and hallucination. These H-IMRs were then isolated and compared with the incidence of newly suspected IMRs on opioid rechallenge on subsequent admission. Those who developed an IMR on administration of an opioid from a different class than the opioid of their H-IMR were considered to be cross-reactive. If a patient reacted to multiple classes of opioids within a temporal period of opioid receipt, each opioid class was considered a unique instance in order to determine cross-reactivity rates. These rates were compared with the rate of an IMR after readministration of an opioid within the same class for which the patient reported a historical allergy.

Secondary Outcomes

Secondary outcomes included determining the incidence of opioid intolerance reactions being incorrectly documented as opioid allergies and determining the impact that documented opioid allergies have on opioid prescribing practices.

Patient charts were reviewed to determine the nature of their chart-documented allergy. IMRs and intolerance reactions were determined according to the methods described above. Reactions that listed no details or symptoms were classified as "unable to determine." IMR rates on opioid rechallenge between patients with H-IMR, historical intolerance, and an unknown reaction were compared.

Health care professionals practicing at our institution voluntarily completed a survey regarding opioid allergies and prescribing practices. Survey participants included doctors, pharmacists, physician assistants, nurse practitioners, and nurses from a variety of different inpatient settings, trainee levels, and years of experience. Surveys were managed using the Qualtrics© survey software package. Participants were grouped into cohorts based on clinician-reported witness or nonwitness of an anaphylactic

Table 1. Opioid Medication Classes (Chemical and Clinical).

Clinical Classification					
Origin		Natural	Semisynthetic	Synthetic	
Agent		• Codeine • Morphine	• Hydrocodone • Hydromorphone • Oxycodone • Oxymorphone	• Buprenorphine • Fentanyl • Meperidine • Methadone • Tapentadol • Tramadol	
Chemical Classification[a]					
Structure	Phenanthrenes	Benzomorphans	Phenylpiperdines	Diphenylheptanes	Phenylpropylamines
Agent	• Buprenorphine • Codeine • Morphine • Hydrocodone • Hydromorphone • Oxycodone • Oxymorphone	• Diphenoxylate • Loperamide • Pentazocine	• Fentanyl • Meperidine	• Methadone • Propoxyphene	• Tapentadol • Tramadol

[a]Representative agents for each chemical structure based on non-zero use in this study.

reaction associated with opioid administration. They were then questioned with regard to the effect of documented opioid allergies on their prescribing and administration practices. Questions consisted of various patient scenarios, including documented IMRs versus documented intolerance reactions and how such allergies affect their decision to prescribe/administer opioid medications from the same or different opioid classes.

Statistics

All statistical analyses were conducted using the JMP SAS© software. For the primary outcome, a Fisher exact test was utilized to compare the proportion of novel IMR development from use of an opioid within the same class as the documented H-IMR compared with use of an opioid from a different class than that described.

For the secondary outcomes, a Fisher exact test was also utilized to compare the proportion of new IMRs in patients with H-IMR compared with patients with a history of intolerance or an unknown reaction. For survey data, results were collected in the form of a 5-point Likert scale to measure clinician opinions regarding the likelihood of prescribing opioids in select clinical scenarios (1 = *extremely likely*, 2 = *moderately likely*, 3 = *neither likely nor unlikely*, 4 = *moderately unlikely*, and 5 = *extremely unlikely*). Analysis of survey results was performed using the Wilcoxon rank-sum test. Across all testing, a 2-sided P value of <0.05 was considered statistically significant.

Results

Patient Demographics

A total of 9973 patients met inclusion criteria. Of these, 499 patients were randomly selected to be included in the study using a random number generator as a sampling of convenience (http://www.randomnumbergenerator.com). Key demographics included a mean age of 59.5 years, mean length of hospital stay of 5.25 days, mean number of concurrent allergies of 2.3, and a sex distribution that was 27% male and 73% female (Table 2). All demographics were found to be nonsignificantly different between patients with H-IMR, historical intolerance, and an undetermined reaction, except for small differences in age. Older patients were significantly more likely to have a documented intolerance reaction. A proportion of patients had multiple chart-documented allergies that spanned across multiple opioid classes (27% of patients with H-IMR had allergies to multiple opioid classes).

Primary Outcome

Allergic cross-reactivity rates are reported in Table 3. Because there were patients with historical allergies to multiple opioid classes, each allergy instance and rechallenge was considered unique and separated for the purpose of data analysis. In addition, 2 patients developed a novel IMR that was temporally associated with rechallenge of agents from multiple opioid classes. These were considered unique instances for data analysis regarding cross-reactivity. None

Table 2. Baseline Patient Demographics.

Baseline Characteristics					
Characteristic	All Patients (n = 499)	H-IMR (n = 212)	Historical Intolerance (n = 249)	Undetermined Reaction (n = 38)	*P* Value[a]
Mean age in years (SD)	59.5 (15.75)	56.4 (16)	62 (15.3)	60 (13.5)	0.01
Sex	• Male: 27% • Female: 73%	• Male: 22.6% • Female: 77.4%	• Male:29.3% • Female:70.7%	• Male: 34.2% • Female: 65.7%	>0.05
Mean length of hospital stay in days (SD)	5.25 (5.3)	4.8 (5.12)	5.5 (5.4)	5.5 (5.4)	0.4
Mean number of concurrent allergies (SD)	2.3 (2.8)	2.6 (2.8)	1.97 (2.6)	2.5 (3.6)	0.06
Historical Allergy Documentation[b]					
Natural chart allergy (%)	351 (70.3%)	154 (72.6%)	172 (69.1%)	25 (65.8%)	0.57
Semisynthetic chart allergy (%)	152 (30.5%)	63 (30.0%)	82 (32.9%)	7 (18.4%)	0.16
Synthetic chart allergy (%)	112 (22.4%)	60 (28.3%)	41 (16.5%)	11 (28.9%)	0.005

Abbreviations: H-IMR, historical IgE-mediated reaction.
[a]*P* values reflect differences between patients based on classification of historical allergy as either H-IMR, historical intolerance, or undetermined reaction.
[b]Percentages are determined by proportion of each allergy classification (H-IMR, historical intolerance, or undetermined) that was observed for each opioid class with reported allergy. Some patients reported allergies to opioids from multiple classes, which accounts for the percentage totals above 100% in each column.

of the opioid classes was found to have statistically significant differences in the development of IMR following administration of an opioid from a different class than the originating opioid class that induced a historical IgE reaction. Rates of IMR on opioid rechallenge were low among patients with H-IMR to natural and semisynthetic agents. No patient with H-IMR to a synthetic agent experienced IMR on opioid rechallenge from an agent in any opioid class.

In addition, we classified opiates based on 5 chemical classifications (phenanthrenes, phenylpiperidines, phenylpropylamines, diphenylheptanes, and benzomorphans; Table 1). Largely, phenanthrenes accounted for the highest number of H-IMRs (n = 190), with both phenanthrenes and phenylpiperidines accounting for the most administered opiate classes, respectively (Supplemental Table 1). Rates of IMR in patients with H-IMR to the phenanthrene opiate class who subsequently received a phenanthrene compared with those who received a phenylpiperidine were 3.03% versus 3.19%, respectively ($P > 0.99$; Supplemental Table 1). No IMRs occurred in patients with an H-IMR to any of the other 5 classes on rechallenge. We did not identify any patient with an allergy to a benzomorphan documented in our cohort.

Secondary Outcomes

Incidence of True IgE-Mediated Allergic Reactions. The prevalence of IMRs and intolerance reactions were determined using retrospective chart review. Of all patients evaluated, only 212 (42%) of the documented opioid allergies were determined to be potentially IgE-mediated allergic responses. A total of 249 (50%) were determined to be intolerance reactions to opioid adverse effects, and 38 (8%) were unable to be determined because of incomplete chart documentation. In patients with an H-IMR, 6 (2.8%) patients subsequently developed a newly suspected IMR on rechallenge (Table 4). In patients with a history of intolerance, 2 (0.8%) patients subsequently developed a newly suspected IMR on rechallenge. No patient with an unknown or unrecalled opioid allergy history reacted with an IMR on readministration of an opioid.

In our cohort, 98% of patients with documented opioid allergies did not experience an IMR on opioid rechallenge (Table 4). Of the 8 patients who did experience an IMR after opioid readministration, 7 experienced pruritis as their only or their primary symptom, with 2 having additional symptoms of urticaria (1 patient) and throat swelling (1 patient). Of these 8 patients, 5 received an antihistamine, and 2 received no medications to treat the IMR. One patient received an antihistamine and was already receiving an epinephrine infusion for a cardiothoracic procedure. The patient was continued on the opioid therapy after cessation of the vasopressor. Of note, 2 of these patients received multiple opioids at the time of their IMR. The 1 remaining patient had a self-reported anaphylactic reaction. The treatment for this reaction was a 1-time dose of an antihistamine. No clinician made any notation of any symptoms suggestive of anaphylaxis and the patient still received 3 subsequent doses of the offending opioid agent after the alleged anaphylaxis (Naranjo Score: 1, Possible).

Post Hoc Analysis on the Incidence of True IgE-Mediated Allergic Reactions. Because we observed such low rates of IMR among our studied population, a second cohort was designated with a more targeted definition to isolate

Table 3. Opioid Cross-reactivity Rates Among Patients With H-IMRs.

	Total Administrations	No IMR	IMR	Rate (%)	*P* Value[a]
Patients with H-IMR to natural opioid (n = 154)					
Natural readministration	16	15	1	6.7	N/A
Semisynthetic administration	129	125	4	3.2	0.45
Synthetic administration	85	83	2	2.4	0.41
Administration of any opioid of another class	138	134	4	2.9	0.43
Patients with H-IMR to semisynthetic opioid (n = 63)					
Natural administration	14	14	0	0	0.57
Semisynthetic readministration	47	43	4	6.9	N/A
Synthetic administration	41	38	3	7.9	>0.99
Administration of any opioid of another class	50	47	3	6.4	0.71
Patients with H-IMR to synthetic opioid (n = 60)					
Natural administration	11	11	0	0	>0.99
Semisynthetic administration	52	52	0	0	>0.99
Synthetic readministration	25	25	0	0	N/A
Administration of any opioid of another class	63	63	0	0	>0.99

Abbreviations: H-IMR, historical IgE-mediated reaction; IMR, novel IgE-mediated reaction on rechallenge; N/A, not applicable because it is the reference proportion.
[a]*P* values compare the incidence of newly suspected IMR to the same class of the documented opioid allergy with the incidence of newly suspected IMR to a different opioid class. Some patients concomitantly received opioids from 2 or more classes prior to reaction, in which each medication was considered an individual incidence.

Table 4. Reaction Rates on Opioid Readministration as Classified by Chart Allergy History.

		Reaction Development		
		No Reaction (n = 462)	Suspected IMR (n = 8)	Intolerance (n = 29)
Allergy history	Any historically reported opioid IgE allergy (n = 212)	189 (89.2%)	6 (2.8%)	17 (8%)
	Any historically reported opioid intolerance (n = 249)	235 (94.4%)	2 (0.8%)	12 (4.8%)
	Unclassified historical opioid reaction (n = 38)	38 (100%)	0	0

Abbreviation: IMR, IgE-mediated reaction.

additional IMRs to validate the screening abilities of our initial search criteria for IMRs and to explore a population with a higher proportion of allergic reactions based on allergic history and medications administered during their hospitalization. Another 290 unique patients were reviewed following the same inclusion criteria as described above, with the addition of requiring diphenhydramine and either epinephrine or steroids administered during their stay. This targeted cohort revealed that based on allergy history, receipt of an opiate, and a suspected treatment of an allergic response, that 77/290 (26.5%) patients experienced an IMR on opioid rechallenge. Of these reactions, pruritus was the only or the primary symptom reported in the majority of IMR cases. There was 1 additional case of anaphylaxis. The patient's clinician noted that the patient experienced respiratory difficulty and wheezing following opioid administration. These symptoms were resolved following administration of antihistamine, steroid, and intramuscular epinephrine. Since this reaction occurred, the patient has received the same opioid on 3 separate occasions with no allergic response, and the reaction has been removed from the patient's chart allergy (Naranjo Score: 4, Possible). Combining the reactions from both our main cohort and this higher risk post hoc cohort, the absolute rate of observed possible anaphylaxis was 2/789 patients (0.25%).

Impact of Documented Opioid Allergy on Opioid Prescribing. A total of 54 clinicians comprising nurses (20%), pharmacists (63%), doctors (10%), and nurse practitioners or physician assistants (7%) completed the study survey (Supplemental Table 2). The mean practice experience was 8.6 years, and the majority of clinicians who participated in the study currently practice in the critical care (53%) or internal medicine (31%) settings. Across 465 years of practice experience, 10 (18.5%) clinicians reported witness of opioid-associated

anaphylaxis during their career, whereas 44 (81.5%) clinicians had not witnessed opioid-associated anaphylaxis in their career. Survey results revealed that there were no significant differences in the perceptions regarding opioid prescribing and warnings between clinicians who had witnessed opioid anaphylaxis during their career and those who had not. There were no significant differences between clinicians who had or had not witnessed opioid-associated anaphylaxis and whether chart warnings of opioid allergies affected their opioid prescribing practices (median Likert score of 3; interquartile range [IQR] = 2-4). Chart warnings regarding opioid intolerances on subsequent opioid prescribing were scored with median likelihoods of 3.5 (IQR = 2.75-4.25) and 4 (IQR = 3-4) in the opioid anaphylaxis witness and nonwitness groups, respectively. The perceived likelihood of cross-reactivity between opioid classes was scored with medians of 3.5 (IQR = 2.75-5) and 4 (3-4) in the opioid anaphylaxis witness and nonwitness groups, respectively (Supplemental Table 2).

In the hypothetical scenarios created for survey respondents, prescribing response varied according to nature and severity of opioid allergy as compared with intolerance (Supplemental Table 3). Less than 15% of clinicians were willing to prescribe, administer, or verify the same opioid if the chart warning was a result of an unknown reaction. Similarly, less than 10% of clinicians were willing to prescribe, administer, or verify the same opioid if the chart warning exhibited a mild IMR (rash and itching). Less than 2% of clinicians were willing to prescribe, administer, or verify the same opioid if the patient had a chart history of a severe IMR (anaphylactoid symptoms).

Discussion

This was the first study to systematically characterize opioid cross-reactivity rates comprehensively in a clinical setting. Results of this study indicate that the rates of symptoms reflective of IgE-mediated allergies to commonly administered opioids are low. Prior allergic history to an opioid did increase the likelihood of reaction on readministration of an opioid of a different class. The observed opioid cross-reactivity rates in this study were similar to those between penicillin and other β-lactam antibiotics (cephalosporins, carbapenems).[12] In addition, this study revealed that 50% of documented opioid allergies were unlikely to be true IgE-mediated allergies and were more feasibly attributable to patient intolerance of opioid adverse effects. Finally, charted allergies to opioids were unlikely to affect prescribing among clinicians, even if they had witnessed anaphylaxis to an opioid agent during their practice.

Previous research has determined that as few as 15% of patients presenting with suspected IgE-mediated hypersensitivity to opioids based on clinical presentation produced a positive drug reaction for a provocation test.[13] These results imply that the IMRs we isolated may conservatively overestimate true rates of allergic reactions. Because pruritus was the most common symptom isolated in this study, it is feasible that many of these reactions were not IgE mediated in nature and that the low rates of reactivity are a conservative overestimate of true opioid allergy rates in this cohort. In an analysis of drug allergy alert overrides, one study revealed that 88.7% of drug allergy alerts for opioid analgesics are overridden.[10] They reported an overall trend of drug allergy alerts increasing at an alarming rate,[10] which highlights the critical importance of pruning alerts to avoid distracting clinicians from potentially dangerous reactions. With the robust increase in opioid prescribing observed in the United States over the past 2 decades, this class of drugs represents an opportune target for reduction of unnecessary alert generation resulting from allergic cross-reactivity alone. Findings from this study indicate the need for further evaluation of the utility of electronic alerts when prescribing opioids to patients with documented opioid allergies. This may provide an opportunity to reduce the burden of clinician alert fatigue and improve the quality of patient care delivered.

Limitations

The low rates of reactions in this study may not be truly representative of the true prevalence of IgE allergies to opioids or the incidence of cross-reactivity across clinical classes of opioids. The scarcity of reaction rates in this study limits our confidence in stating differences in cross-reactivity among different classes. We attempted to overcome this limitation with analysis of our follow-up cohort of patients with higher likelihood for allergic reactions, but still found low rates of IMR following opioid rechallenge. In addition, rates of cross-reactivity observed in this study may be a conservative overestimation of true rates of cross-reactivity because of classifying patients who reacted to multiple simultaneous opioid agents as unique instances. The incomplete documentation of reactions in many of the patients' charts may affect the validity of our retrospective IMR characterization. Because this was a single-center study, our results may have reduced generalizability. Furthermore, the lack of availability of a test for confirmed classification of type I hypersensitivity makes it difficult to differentiate between true IgE allergy and opioid-induced pruritus, which comprised the majority of allergic manifestations observed in this study. Despite thorough research and chart review, our determination of IMRs based on temporal association of opioid administration and symptomatic presentation inevitably leaves room for error in allergy classification.

Conclusions and Relevance

The results of this retrospective study indicate that the rates of IgE reactions in patients with a history of a chart-documented opioid allergy remain low and that chemical or clinical opioid class was not sigificantly associated with risk of recurrent allergic reactions. This was the first study to comprehensively assess potential cross-reactivity rates across clinical and chemical opioid classes. There was no association with prior allergy to a clinical class of an opioid and cross-reactivity with any other opioid class. Because of the retrospective nature of this study, careful interpretation of true allergy rates is warranted. However, application of these data may aid clinics in the future management of patients with chart-documented opioid allergies.

Authors' Note

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Declaration of Conflicting Interests

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Supplemental Material

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