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Jerry Kalangara, Sudheer Potru & Merin Kuruvilla

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REVIEW



Clinical Manifestations and Diagnostic Evaluation of Opioid Allergy Labels – A Review

Jerry Kalangara, Sudheer Potru and Merin Kuruvilla 

ABSTRACT

While opioids represent one of the most common medication allergy labels, these labels are often unsubstantiated in clinical practice. The removal of erroneous opioid allergy labels has a unique importance in the population with acute or chronic pain. The current approach to patients with pseudo-allergy to opioids is switching to an alternative opioid with less histamine release. Thus, allergy labels to relatively lower potency opioids such as codeine may be feasibly result in the prescription of stronger medications like fentanyl that would otherwise not be indicated.

This narrative review provides an overview of the epidemiology and clinical manifestations of opioid allergy labels commonly encountered by pain management practitioners along with recommendations for evaluation and management.

A literature search of PubMed was performed using the comprehensive MeSH term, “Opioid Allergy”.

In recent years, it has become apparent that a substantial proportion of patients labeled as opioid allergic are found to be tolerant of these agents. Opioid skin testing and IgE assays are of limited application. DPT is the yet underutilized gold standard for diagnosis. There is also an increasing call for studies evaluating basophil activation testing in opiate allergy.

Opioid allergy labels require a closer look especially in view of the current opioid epidemic. The low likelihood of true reactivity, combined with the conceivable clinical relevance of an opioid allergy label, calls for further characterization of this label in populations with acute or chronic pain diagnoses. Future directions should include larger prospective studies with systematic evaluation and classification of opioid allergy labels to determine future viability of opioid use.

Abbreviations: EHR: electronic health record; NMBA: neuromuscular blocking agent; IgE: immunoglobulin E; MC: mast cell; GPCR: G-protein coupled receptor; MRGPRX2: mas-related G-protein receptor; QAI: quaternary ammonium ions; SCAR: severe cutaneous adverse reaction; AGEF: acute generalized exanthematous pustulosis; SDRIFE: symmetrical drug-related intertriginous and flexural exanthema; BAT: basophil activation testing; DPT: drug provocation testing

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Epidemiology

Opioids represent one of the most common medication allergy labels documented in the electronic health record (EHR), accounting for 48% of allergy alerts in one series (1). They are also frequently implicated in anaphylaxis (9.8 per 10,000) based upon EHR documentation (2). Despite this high prevalence, true immunological hypersensitivity among these patients is exceedingly rare. The vast majority of opioid allergies are non-immunologic, or “anaphylactoid”. Further, opioid allergy labels are often

unsubstantiated in clinical practice. Opioids have among the highest rates of uneventful EHR allergy alert overrides, attributed to non-allergic gastrointestinal symptoms or other adverse effects triggering these labels (3). This may also be due to the fact that most of the prior literature describing immediate drug hypersensitivity to opioids has relied on clinical history alone without further workup (4). Cases of true opioid allergy confirmed by drug provocation testing are largely limited to case reports (5, 6). In one

Jerry Kalangara, MD, and Sudheer Potru, MD, are with the Division of Pain Medicine, Emory University School of Medicine, Atlanta, Georgia, USA. Merin Kuruvilla, MD, are with the Division of Pulmonary, Allergy and Critical Care, Emory University School of Medicine, Atlanta, Georgia, USA.

CONTACT Merin Elizabeth Kuruvilla, MD  merin.ek1@gmail.com 1365 Clifton Rd NE, Bldg A, 3rd Flr, Atlanta, GA 30322, USA.

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Table 1. Classification of medication classes within the opioid family.

Structural class	Agent	Source	Effect at opioid receptor
Diphenylheptanes Phenanthrenes	Methadone	Synthetic	Full opioid agonist
	Buprenorphine	Semi-synthetic	Partial mu agonist
	Butorphanol	Synthetic	Mixed agonist-antagonist
	Codeine	Opium alkaloid (natural)	None (converted to morphine)
	Heroin	Semi-synthetic	Full agonist
	Hydrocodone	Semi-synthetic	Full agonist
	Hydromorphone	Semi-synthetic	Full agonist
	Levorphanol	Synthetic	Mixed agonist-antagonist
	Methylnaltrexone	Synthetic	Mu-receptor antagonist
	Morphine	Opium alkaloid (natural)	Full agonist
	Nalbuphine	Synthetic	Mixed agonist-antagonist
	Naltrexone	Synthetic	Antagonist
	Oxycodone	Semi-synthetic	Full agonist
	Oxymorphone	Semi-synthetic	Full agonist
	Papaverine	Opium alkaloid (natural)	Full agonist
	Thebaine	Opium alkaloid (natural)	Full agonist
Phenylpiperidines	Alfentanil	Synthetic	Full agonist
	Carfentanil	Synthetic	Full agonist
	Fentanyl	Synthetic	Full agonist
	Meperidine	Synthetic	Full agonist
	Remifentanil	Synthetic	Full agonist
	Sufentanil	Synthetic	Full agonist
	Tramadol	Synthetic	Weak/selective mu agonist

recent cohort of 98 subjects with diagnoses of opioid allergy, this label was borne out in only 15% of patients by drug provocation testing (7).

Thus, there is a significant dearth of literature pertaining to hypersensitivity reactions provoked by opioids, specifically with respect to symptoms, cross-reactivity patterns, and diagnostic techniques. Moreover, there is no literature to date describing the prevalence of opioid allergy in a chronic pain population. Most cases of opioid hypersensitivity to date have originated from the perioperative setting where opioids have been implicated in ~2% of allergic reactions (8). Even this is likely to be an overestimate due to the absence of validated tests. Erroneous opioid allergy labels might not only overlook alternative culprits such as neuromuscular blocking agent (NMBA) allergy but also result in needless avoidance measures. These ramifications would potentially be extensive in a chronic pain population, amidst a national opioid epidemic, as will be discussed later. This review provides an overview of the manifestations of opioid allergy and strategies for appropriate diagnosis and management of these labels.

Pathogenesis

Nomenclature—Immunologic Versus Non-Immunologic Anaphylaxis

True type I immediate drug hypersensitivity or immunologic anaphylaxis implies the presence of

drug specific IgE acting through its high affinity receptor (FcεRI) on mast cells (MCs) and basophils, driving mediator release including histamine, tryptase, platelet activating factor, and cysteinyl leukotrienes. However, an increasing proportion of drug allergy is being attributed to non-immunologic anaphylaxis, which is characterized by immediate reactions that are not IgE-triggered but occur with direct MC activation and mediator release. In contrast to type I anaphylaxis which requires prior exposure for IgE development, non-immunologic anaphylaxis is often elicited by the first dose of the culprit drug. Historically, these non-immunologic reactions have been termed “pseudoallergic” or “anaphylactoid,” but are now deemed as anaphylactic since independent of the underlying mechanism, both kinds of reactions may be clinically indistinguishable.

Mechanisms of Opioid-Induced Immunologic Anaphylaxis

Most drug molecules are too small to be immunogenic on their own and act as haptens or prohaptens in order to elicit IgE-mediated immunity (9). The specific mechanisms through which opioids generate specific IgE are largely unknown. Further, there is only a single case report that identifies the allergenic epitope that

binds to specific IgE antibody for morphine and codeine (10).

Mechanisms of Opioid Induced Non-Immunologic Anaphylaxis

There are two main mechanistic pathways proposed to mediate direct MC degranulation: activation through stimulation of opioid receptors and direct G-protein coupled receptor (GPCR) activation. It is currently unknown whether one is preferentially activated over the other or whether the two pathways overlap. A classification of medication classes within the opioid family has been outlined in Table 1 for reference.

Opioid Receptor Stimulation

Human cutaneous MCs express mRNA for mu (μ) and delta (δ) opioid receptors, but not for kappa (κ) opioid receptors (11). The stimulation of these receptors by opioids triggers intracellular signaling pathways associated with G-protein, mitogen-activated protein kinase, and phospholipase C activation (11), which ultimately lead to mediator release. Codeine, but not its synthetic analog meperidine, has been shown to preferentially activate the μ -receptor on human cutaneous MCs causing mediator production (11). This might explain the especial predilection of lower potency opioids, such as codeine and morphine, to induce MC degranulation in a concentration-dependent manner compared to other opioids. Even endogenous opioid peptides including dynorphin, enkephalin, and β -endorphin, are capable of activating human cutaneous MCs (12). A central μ -receptor-mediated mechanism is also supported by descriptions of clinical response of pruritus to μ -receptor antagonists (13, 14).

On the other hand, higher-potency compounds like fentanyl and its derivatives does not induce histamine release from MCs and are consequently preferred to treat patients with opioid allergy labels. Similarly, methadone, tramadol and hydromorphone do not appear to trigger histamine release. These disparities in histamine-releasing properties could potentially be explained by their chemical structures: morphine and meperidine have a phenylpropylamine structure, while fentanyl has an anilidopropylamine structure.

However, further data is necessary to confirm this hypothesis.

MRGPRX2 Receptor Stimulation

Opioid induced MC degranulation is only partially inhibited by naloxone *in vivo*, implying an additional opioid receptor independent mechanistic component for non-immunologic anaphylaxis (15). Recently, McNeil et al. demonstrated that MC driven immediate drug hypersensitivity can be mediated by the engagement of the MC receptor Mas-related G-protein receptor (MRGPRX2) (16). While clinically indistinguishable from classic IgE/Fc ϵ RI-dependent MC degranulation, drug occupancy of the MRGPRX2 receptor is a novel non-immune mechanism of MC driven immediate hypersensitivity. Several opioid compounds including codeine, morphine, and their major metabolites were recently observed to bind this same GPCR (17). Computer-based modeling studies have been used to predict specific binding sites (Glu164 and Asp184) for positively charged opioids on these receptors (18). These have been validated by subsequent mutagenic studies in which mutant receptors lacking these negative charges lose reactivity for opioids.

The Pholcodine Hypothesis

Pholcodine is a morphine analog marketed as an antitussive that has been linked with a unique propensity to induce neuromuscular blocking agent (NMBA) anaphylaxis (19). This opioid appears to have an especially high primary IgE sensitizing potential to its major allergenic epitope—quaternary ammonium ions (QAI), which it shares with NMBAs. Presensitization with IgE antibodies to these QAI epitopes through pholcodine ingestion leads to recognition of cross-reacting QAIs in NMBAs resulting in perioperative anaphylaxis.

The mechanism behind this selective IgE sensitization to pholcodine, that differs structurally from morphine and codeine only by a single morpholinyl-ethyl-3 group at position 3, remains unknown. However, this hypothesis has proven valid in explaining differences in the frequency of NMBA anaphylaxis in Norway and Sweden for the same time period (20). 11% of atopic

individuals and 6% of blood donors in Norway were IgE sensitized to pholcodine in the early 2000s, and this was associated with a 200 to 300 times increased risk of NMBA anaphylaxis. Per Norwegian estimates, this translated into an increased risk for the general population from 1/5200 to 1/20. This is in stark contrast to Sweden, a country unexposed to pholcodine at the time, where IgE sensitization as well as NMBA anaphylaxis was very rarely diagnosed. Furthermore, following the withdrawal of pholcodine from the Norwegian market in 2007, there was a significant decrease in both the prevalence of IgE sensitization as well as reported cases of NMBA anaphylaxis (19).

Clinical Features

Non-Immunologic Anaphylaxis/ Anaphylactoid Reactions

Several opioids are potent histamine releasers and most opioid reactions are pseudoallergic in nature. In contrast to IgE-mediated drug allergy, pseudoallergy does not require prior exposure to the culprit agent, can be dose dependent, and is characterized by flushing, itching and hives. The most frequent symptom is pruritus that occurs to some degree almost universally with codeine and morphine. These reactions are rarely severe, and but seldom progress to bronchospasm or hypotension. This is because MCs in different anatomical sites appear to be functionally different in terms of response to opioid medications. Several studies have reproduced isolated cutaneous MC degranulation following a morphine challenge, but absence of effect on human cardiac, gastrointestinal, or pulmonary MCs (21, 22). This explains the prominence of cutaneous MC-mediated pruritus and hives rather than systemic reactions resembling anaphylaxis.

Anaphylactoid reactions also appear to be quicker in onset but short-lived clinically in comparison with IgE-FcεRI dependent reactions that are often prolonged in their course. This observation correlates with *in vivo* studies that demonstrate a more rapid and transient response to MRGPRX2-mediated degranulation, as opposed

to a more protracted and intense reaction after FcεRI stimulation (23).

Immunological (IgE-FcεRI) Anaphylaxis

Despite the frequent use of opioids, true IgE-mediated hypersensitivity is exceedingly infrequently and rarely bolstered by formal causality assessment. In one report, a diagnosis of meperidine-induced anaphylaxis was supported by positive selective prick testing to meperidine as compared with negative results in ten control subjects (24). Similar findings were reproduced in a case of perioperative anaphylaxis to fentanyl (25). Other reports are usually hampered by the unknown specificity of *in vitro* testing, and omission of skin testing in appropriate control subjects. As previously mentioned, the allergenic epitope in morphine and codeine that binds to its specific IgE was characterized in a mere single case report (10).

Other Cutaneous Manifestations

While scant, delayed hypersensitivity reactions mediated by T cells may occur with opioid use. There have been several reports of contact dermatitis to morphine and heroin in an occupational setting among nurses, physicians, and pharmaceutical workers with associated positive patch test reactions (26–28). This has also been observed with transdermal buprenorphine (29). Severe cutaneous adverse reactions (SCARs) have been but seldom reported. Isolated cases of acute generalized exanthematous pustulosis (AGEP) are described in the literature (30). Other manifestations have included fixed drug eruption secondary to dextromethorphan (31), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) from codeine confirmed by drug challenge (32). There is also a single account of codeine induced drug induced hypersensitivity syndrome (33).

Cross-Reactivity Patterns

The accurate prediction of clinical cross-reactivity among opioids is precluded by the limited number of patients studied. As a rule, natural and

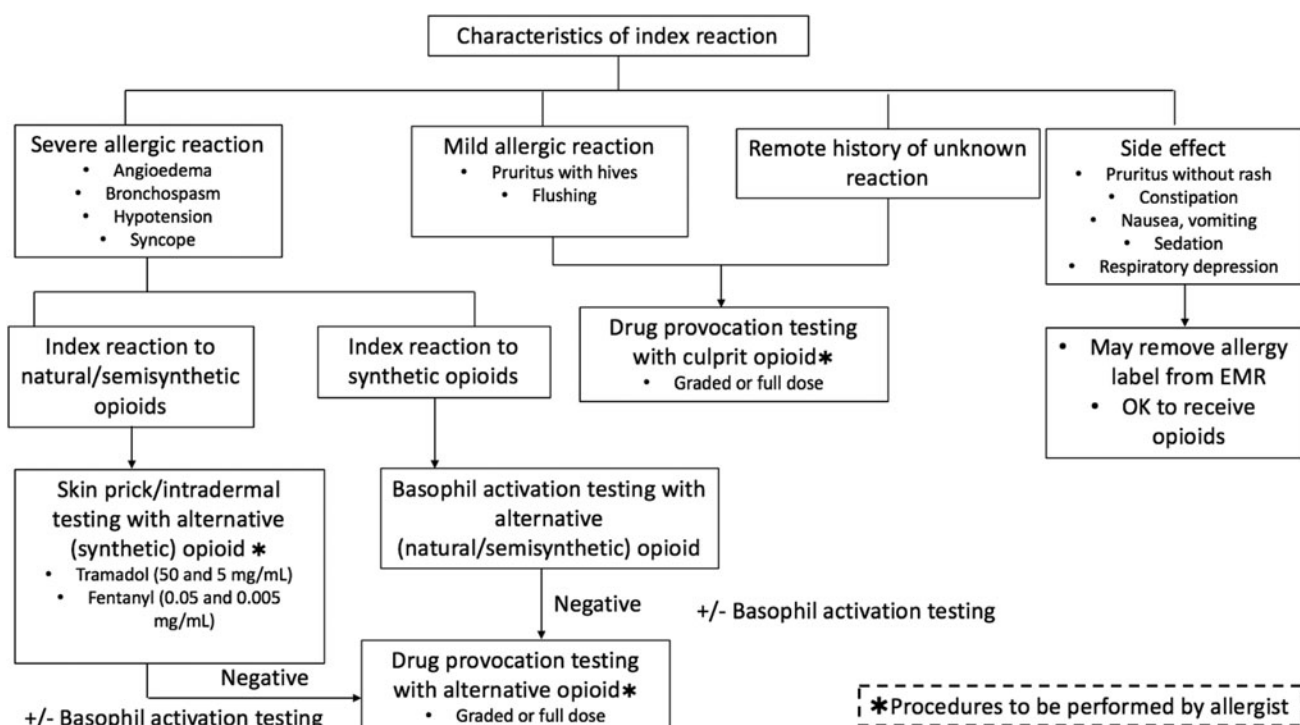


Figure 1. Algorithm to diagnostic approach of opioid allergy labels for the pain practitioner.

semisynthetic opioids are structurally very similar and should not be used in the setting of a true allergy to any of these derivatives. For instance, codeine should be avoided in those with a morphine allergy since it is metabolized to morphine. Further, hapten-inhibition studies with phenanthrenes such as morphine have demonstrated clear cross-reactivity with other phenanthrenes (codeine), and also to a partial extent with phenylheptanes (methadone) and phenylpiperidines (meperidine), but none with fentanyl (10).

Similarly, cross-sensitivity has been suggested among fentanyl, alfentanil, sufentanil, and meperidine (34). These synthetic agents have been used however in those intolerant to natural/semisynthetic agents without incident. In the recent cohort reported by Li et al. (7), subjects with documented allergy to natural opioids (morphine and codeine) tolerated synthetic opioids (such as fentanyl) uneventfully, suggesting an absence of cross-reactivity between these two groups.

Opioid Allergy and the Opioid Epidemic

The management of chronic pain is challenging, and thus many physicians still routinely prescribe

opioids for treatment of chronic pain (35). Opioid medication prescribing in the United States has decreased substantially since 2012, but the number of days' supply in each prescription has increased annually since 2006. Opioids remain among the most prescribed medications in the United States, with one (hydrocodone/acetaminophen) in the top ten, three within the top sixty, and five within the top 200 (36).

The annual number of overdose fatalities secondary to opioids has quadrupled in the past two decades, in parallel with the numbers of prescriptions for opioid analgesics. Anaphylactic reactions have been postulated to be responsible for a proportion of heroin overdose deaths (37, 38). Postmortem blood tryptase levels were significantly elevated in a third of 22 heroin users with sudden injection-related deaths (38). Similarly, elevated serum tryptase concentrations along with increased eosinophil cationic protein (ECP) were measured in another postmortem blood sample study of 48 heroin-related deaths (37). In conjunction with the observation that several of these deaths could not be accounted for by blood morphine levels alone, the authors speculated that elevated tryptase might reflect a causal association. However, a statistically significant

increase in tryptase levels was noted after intravenous heroin injection in another report that did not result in clinical adverse reactions (39). While this finding calls into question the relevance of elevated postmortem tryptase in heroine fatalities, it should still be borne in mind that alternative systemic reactions beyond overdose related respiratory depression may contribute to the mechanism of death in heroin related fatalities.

Diagnostic Methods

The evaluation of opioid allergy begins with reviewing the clinical history and symptoms of the index reaction, which guides subsequent diagnostic workup. The key to diagnosis lies in distinguishing reactivity from direct histamine release versus true IgE-mediated MC activation, as well as elucidating the clinical relevance of positive specific IgE results. Both of these goals are fraught with complications as detailed below. An algorithm delineating a suggested approach to suspected opioid allergy is outlined in Figure 1.

Skin Testing

The routine skin testing of all patients with a past reaction to opioids is not indicated since IgE-mediated anaphylaxis is rare. There would be a potential role for opioid skin testing in the setting of a severe multi-systemic anaphylactic reaction, however, this is associated with the inherent problem of histamine release and false positive reactions. In fact, codeine, by inducing skin wheal reactivity, has long been used as a positive control for allergy skin prick testing.

Skin tests may be applied in the setting of reactions to fentanyl and tramadol, that produce minimal to no histamine release from cutaneous MCs (21, 40). A positive intradermal test to fentanyl citrate 0.5 ng/ml was observed in one patient with perioperative anaphylaxis, and supported by negative skin tests in 30 control subjects at a higher concentration (25). However, another case report of a pediatric patient with perioperative anaphylaxis attributed to fentanyl developed recurrent reaction during a subsequent procedure without fentanyl (41). As a rule,

opioids should also be tested in normal control subjects to rule out symptoms caused by histamine release and irritant effects. In addition, higher dilutions of tested opioids have been applied to circumvent histamine release with mixed results. Some have stated that morphine can actually be used for skin testing at low molar concentrations, however, prick tests in different concentrations were not significantly different among opiate sensitive subjects and opiate tolerant controls in another study (42).

In Vitro Testing for Opioid Specific IgE

The use of *in vitro* assays is complicated by the unavailability of validated opioid specific IgE testing. There has only been limited investigation into identifying the allergenic structure of opioids (10) and thus there exist only a handful of studies applying IgE immunoassays to opioid medications exist. Rare cross-reacting IgE antibodies that recognize methadone, fentanyl, morphine and meperidine were identified in the same report (10). Armentia et al. suggested that the commercially available IgE assay to *Papaver somniferum* seed (poppy seed), particularly the oil body fraction, is useful in detection of opioid allergy (43). This was based on findings in a cohort of 203 subjects with perioperative anaphylaxis and positive opioid challenges, in which opium seed IgE testing had 64.2% sensitivity and 98.4% specificity for opioid sensitization (43).

Conversely, Van Gasse et al. concluded in a recent study of 22 patients that IgE assays to poppy seed and morphine are not useful to diagnose opioid allergy based on discrepancy between testing and challenge outcomes (44). The authors attributed this to a high false positive rate, secondary to prevalence of specific IgE antibodies to these compounds in approximately 10% to 15% of the general population. Further, as stated previously, a positive specific IgE to morphine may just represent a marker for sensitization to substituted ammonium determinants which are present not only in opioids but also NMBAs and several other drugs. This is supported by the retrospective review of anesthetic records in patients with perioperative anaphylaxis—those with positive morphine IgE had subsequent uneventful

administration of fentanyl and other synthetic opioids (45). Therefore, the pertinence of positive opioid specific IgEs if performed should be verified by graded drug challenges.

Basophil Activation Testing (BAT)

Basophil activation testing (BAT) is a flow cytometry assay that is being increasingly applied to diagnose immediate drug allergy. Basophils express high levels of the IgE receptor FcεRI and upregulate surface activation markers CD63 and CD203c after stimulation with culprit drug (45). However, they barely express MRGPRX2 on their surface and are thus unresponsive to opioids. This is reinforced by basophil studies that did not demonstrate any histamine release following stimulation with opioid drugs, suggesting that MCs were the primary source (40). Presently, BAT is the only *in vitro* method to potentially discriminate between IgE versus non-IgE mediated reactions, due to functional differences between basophils and cutaneous MCs. Moreover, in patients allergic to pholcodine, BAT appears to be selectively positive to this agent only and not to codeine and morphine despite structural similarity (46). Thus, BAT may constitute an asset to explore the presence of an MRGPRX2-triggered endotype, especially in the setting of positive skin tests and negative BAT (45).

Mast Cell Mediators

Measurement of MC mediator release can be useful for diagnosis of an acute reaction, the most widely used of which is total serum tryptase. MC tryptase is liberated early in the course of an allergic reaction, often showing serum levels >11.5 ng/ml. However, it is time sensitive, peaking within 1-2 hours and normalizes after 5-6 hours of symptom onset (47).

Histamine is the first released MC mediator; while serum elevation is consistent with anaphylaxis it has an extremely short half-life of 20 minutes. Thus, plasma histamine measurement is of limited utility in the clinical setting. On the other hand, histamine metabolites—*N*-methylhistamine or *N*-methylimidazoleacetic acid—may be

measured in urine and can be detected for 24 hours following the acute event (47).

Drug Provocation Testing (DPT)

Drug provocation testing (DPT), or drug challenge, is considered the “gold standard” in the diagnosis of several forms of drug allergy (48). It consists of the supervised and controlled administration of a culprit drug to exclude hypersensitivity, thus avoiding erroneous allergy labels and overdiagnosis of drug allergy. DPTs have been shown to be safe after risk stratification and using individualized protocols, when performed by experienced allergists. They may be performed as full dose or graded challenges, the latter starting with 1/100 to 1/10 of the final dose at 30- to 60-minute intervals.

Given the conspicuous over-labeling of opioid allergy and absence of reliable skin or *in vitro* tests, most patients would require DPT to confirm or rule out diagnosis. This again does not separate pharmacologic effect from true immunologic allergy. The importance of performing DPTs in workup of opioid allergy was recently highlighted in a retrospective cohort of 98 patients, involving DPTs to various opioid agents gathered over an 8-year period (7). Only 15% of this cohort were confirmed to be truly allergic. In a multivariate analysis of the index reaction symptoms and drug hypersensitivity, a history of hypotension and angioedema were significantly associated with positive challenge outcomes. This suggests that a history of these symptoms may be predictive of genuine reactions. Overall, there is thus a high risk of overestimating opioid allergy prevalence in the absence of DPTs. Similar findings were noted in a smaller study of 8 opioid allergic patients (42). There was no correlation between skin test results at various dilutions and oral challenge outcomes, emphasizing the redundancy of skin testing in most situations.

Management

The acute management of allergic reactions to opioids consists of standard anaphylaxis therapies (antihistamines, steroids, epinephrine). Naloxone has been used successfully in the acute reversal of

opioid-induced pseudoallergic reactions that fail to respond to standard of care (10).

The prevention of recurrent pseudoallergic reactions from opioids has centered upon three principles: [1] the substitution of opioids with non-opioid medications, [2] identification of an alternative opioid that is tolerated, and [3] pre-emptive administration of H1/H2 antihistamines.

Prophylaxis with antihistamines is an effective tool to improve opioid tolerability in those with cutaneous reactions. While the principles delineated above suffice for most opioid allergic patients, there is an extremely small fraction that fails to respond to these measures. There is limited evidence that this refractory population may tolerate continuous opioid infusions with gradual dose escalations (49). This has been attributed to the dose dependence of opioid induced histamine release, and lower peak serum concentrations with continuous infusions as opposed to boluses.

Reports of desensitization for opioid hypersensitivity are anecdotal and limited to case reports (50, 51). This may be due to the fact that non-IgE mediated reactions are not amenable to desensitization. In fact, there is recent evidence that MRGPRX2, in contrast to other GPCRs, is resistant to desensitization. Conversely, the prolonged stimulation of this reception actually leads to the induction of a Ca^{2+} response and enhanced degranulation (15).

Conclusions

In recent years, it has become apparent that a substantial proportion of patients labeled as opioid allergic are found to be tolerant of these agents. Opioid skin testing and IgE assays are of limited application. DPT is the yet underutilized gold standard for diagnosis, but this entails physician supervision in a controlled environment.

The removal of erroneous opioid allergy labels has a unique importance in the population with acute or chronic pain. The current approach to patients with pseudo-allergy to opioids is switching to an alternative agent with less histamine release. Thus, allergy labels to relatively lower potency opioids such as codeine may be feasibly result in the prescription of more potent medications like fentanyl that would otherwise not be

indicated. The low likelihood of true reactivity, combined with the conceivable clinical relevance of an opioid allergy label, calls for further characterization of this label in populations with acute or chronic pain diagnoses.

Future directions should include larger prospective studies with systematic evaluation and classification of opioid allergy labels to determine future viability of opioid use. Also, it is yet unknown whether pharmacogenomics (such as CYP2D6 polymorphism in codeine metabolism) plays a role in predilection to allergy. There is also an increasing call for studies evaluating BAT in opiate allergy (52). Opioid allergy is thus far a largely overlooked area in drug allergy research, and requires a closer look especially in view of the current opioid epidemic.

Disclosure statement

The author reports no conflict of interest. The author alone is responsible for the content and writing of the article.

ORCID

Merin Kuruvilla  <http://orcid.org/0000-0002-2668-4418>

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