Original Article

Opioid Hypersensitivity: Predictors of Allergy and Role of Drug Provocation Testing

Philip H. Li, MBBS, MRes (Med), MRCP[a,b], Kok Loong Ue, MBChB, MRCP[a], Annette Wagner, MD[c], Ryszard Rutkowski, MD, PhD[d], and Krzysztof Rutkowski, MD, MRCP[a] *London and Cambridge, United Kingdom; Pokfulam, Hong Kong; and Bialystok, Poland*

What is already known about this topic? IgE-mediated opioid hypersensitivity is rare; many reactions are due to direct mast cell degranulation. Opioid skin testing and sIgE are of limited use. Drug provocation testing (DPT) is an underutilized "gold standard" for diagnosis.

What does this article add to our knowledge? Opioid allergy is overdiagnosed. DPT confirms allergy only in a small minority. Angioedema or hypotension as an index reaction increases the likelihood of true opioid allergy. Most codeine/morphine allergic patients tolerate fentanyl, a synthetic opioid.

How does this study impact current management guidelines? Opioid DPT help avoid incorrect diagnosis/over-diagnosis. Angioedema or hypotension as an index reaction might predict the likelihood of true allergy. DPT are safe when performed by experienced clinicians after risk stratification and using individualized protocols.

BACKGROUND: True IgE-mediated hypersensitivity to opioids is rare and many reactions are due to direct mast cell degranulation. Opioid drug provocation testing (DPT) is the gold standard for diagnosis but is underutilized.
OBJECTIVE: The objective of this study was to evaluate the clinical characteristics and predictors of opioid hypersensitivity, as well as outcomes of opioid DPT.
METHODS: Patients referred for opioid DPT over the past 9 years were studied. Patient characteristics, indications for opioid use, symptoms of index reaction, and outcomes of DPT were analyzed. Association analysis was performed to study variables associated with a diagnosis of opioid hypersensitivity.
RESULTS: Of the total of 98 patients referred with suspected opioid hypersensitivity, 15 (15%) were diagnosed with opioid allergy. Angioedema (odds ratio [OR]: 5.66; 95% confidence interval [CI]: 1.49-21.47; $P = .011$) and hypotension (OR: 5.00; 95% CI: 1.15-21.70; $P = .032$) were significantly more frequent in opioid allergic patients than those with a negative DPT. Patients who received opioids during anesthesia were significantly more likely to be opioid allergic (OR: 6.74; 95% CI: 2.05-22.13; $P = .001$). In contrast, a negative association was identified with patients who received opioids for analgesia (OR: 0.27; 95% CI: 0.08-0.86; $P = .008$).
CONCLUSIONS: Only 15% of our cohort were diagnosed with opioid allergy, emphasizing the importance of DPT in preventing erroneous overdiagnosis. Patients with a history of angioedema or hypotension as their index reaction were significantly more likely to be opioid allergic. DPT are safe when performed by experienced clinicians after risk stratification and using individualized protocols. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Allergy; Hypersensitivity; Opioid; Predictors; Provocation; Skin testing*

The term "opioids" refers to all natural, semisynthetic, and synthetic morphine-like drugs. Naturally occurring alkaloids or opiates, such as morphine and codeine, are found in the resin of the opium poppy (*Papaver somniferum*). Semisynthetic opioids, such as oxycodone and pholcodine, are derived from chemical modifications of natural opiates. Fully synthetic opioids, such as fentanyl and pethidine, are artificially synthesized from chemicals that are not derived from natural opiates.[1] Opioids are the most potent and commonly prescribed analgesics. The consumption of opioids has more than tripled over the past 20 years, and the demand for morphine-based opiates rose to 416 tons in morphine equivalent in 2014.[1] Despite this, true IgE-mediated immediate hypersensitivity reactions are rare. Some studies implicate opioids in around 2% of cases of perioperative

[a]Department of Allergy, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[b]Division of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Pokfulam, Hong Kong
[c]Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
[d]Department of Respiratory Diagnostics, Medical University of Bialystok, Bialystok, Poland
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Corresponding author: Krzysztof Rutkowski, MD, MRCP, Department of Allergy, Great Maze Pond, 2nd Floor, Bermondsey Wing, London SE1 9RT, United Kingdom. E-mail: chris.rutkowski@gstt.nhs.uk.
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Abbreviations used
DPT- Drug provocation testing
sIgE- Specific IgE
SPT- Skin prick testing
ST- Skin test

anaphylaxis, but this is likely to be an overestimate due to the lack of validated testing methods.[2,3] Most reactions to opioids are non-IgE-mediated due to direct mast cell degranulation and histamine release at clinically used doses.[4,5] Worryingly many patients are mislabeled with opioid allergy even in the absence of diagnostic evidence or relevant allergy testing. This can not only lead to unnecessary drug avoidance, but other culprits of drug hypersensitivity reactions can be missed. The use of skin tests (ST) in diagnosis is questionable, and because of the histamine releasing properties of most opioids, ST results are not significantly different between opioid allergic patients and tolerant controls.[6] Some opioids, for example, fentanyl and tramadol, do not provoke direct mast cell degranulation.[5,7-9] Similarly, the value of specific IgE (sIgE) testing has been questioned mainly because positive results to morphine and pholcodine have been found in 5% of blood donors and 10% of patients with other allergies but no history of opioid allergy.[10,11] Both skin prick testing (SPT) and sIgE may provide additional information provided their inadequacies are taken into consideration and never interpreted in isolation. Additional steps such as higher dilutions of tested opioids for SPT and appropriate inhibition studies for sIgE may also be considered. In most cases, the diagnosis of a true immediate hypersensitivity ultimately depends on drug provocation testing (DPT) with the index opioid.[4,12] However, it is often difficult to differentiate pharmacological from allergic symptoms. There is little published data available to a practicing allergists/immunologists faced with such diagnostic dilemma. Although not indicated in every case, DPT with opioids appear underutilized because of the lack of validated protocols, limited clinic capacity, and sometimes physicians' inexperience and apprehension.

In our practice, patients suspected to be allergic to opioids are referred for DPT only after careful risk stratification. It relies on a clinical and drug history review, assessment of serial serum tryptase levels, exclusion of other possible agents, and appropriate allergy testing. In this pragmatic retrospective study, we evaluated the clinical characteristics and predictors of opioid allergy as well as outcomes of patients referred for opioid DPT.

METHODS

We reviewed all available records of patients referred for opioid DPT at Guy's and St Thomas' NHS Foundation Trust (London, UK) and Cambridge University Hospitals NHS Foundation Trust (Cambridge, UK) between 2008 and 2016. This included patients who underwent DPT and those who, in view of their undisputed history, were diagnosed clinically without the need for DPT. Data extracted included gender and age, suspected index opioid (ie, the opioid implicated in the allergic reaction), indication for its use and symptoms of index reaction, other concomitantly administered agents, history of spontaneous urticaria, opioid ST and sIgE results, baseline serum tryptase levels, symptoms, and outcomes of DPT. ST were performed only in patients with suspected fentanyl and tramadol allergy (opioids devoid of direct histamine releasing properties). Tramadol hydrochloride 50 and 5 mg/mL (Meda Pharmaceuticals, Bishop's Stortford, UK) and fentanyl citrate 0.05 and 0.005 mg/mL (Janssen Cilag Ltd, Bucks, UK) were used for skin prick and intradermal testing, respectively. Measurements of pholcodine and morphine sIgE were performed using ImmunoCAP (Thermo Fisher Scientific, Göteborg, Sweden). Tested opioids included codeine, fentanyl, meptazinol, morphine, oxycodone, pethidine, tramadol, and papaveretum (a mixture of morphine, codeine, and papaverine). Patients were grouped depending on the clinical setting where opioids had been used: during anesthesia or for analgesia, antitussive, or "other" action in an outpatient or inpatient setting. Symptoms of index reactions were categorized based on the definition criteria for anaphylaxis into skin (urticaria, pruritus, flushing, rash), angioedema, respiratory (dyspnoea, wheeze/bronchospasm, stridor, hypoxemia), gastrointestinal (nausea, vomiting, abdominal pain), hypotension, and "others"/unclassified.[13,14] DPT protocols were tailored to individual patients. All patients underwent DPT with the same opioid implicated in the index reaction. Index drugs were administered in a graded fashion at 30- to 60-minute intervals, for example, oral morphine sulfate (Oramorph, 10 mg/5 mL; Boehringer Ingelheim Ltd, Bracknell, UK): 5, 10, and 20 mg; codeine phosphate (25 mg/5 mL; Thornton & Ross Ltd, Linthwaite,

TABLE I. Patient characteristics, indications for opioid use, symptoms of index reaction, and outcomes of provocation testing

	Total (n = 98)	Allergic (n = 15)	Nonallergic (n = 83)
Demographics			
Age (median, range)	43 (12-76)	44 (12-66)	43 (13-76)
Male	26 (27%)	2 (13%)	24 (29%)
History of spontaneous urticaria	12 (12%)	1 (7%)	11 (13%)
Concomitant and suspected agents	46 (47%)	10 (67%)	36 (43%)
Clinical setting of opioid use			
For analgesia	59 (60%)	5 (33%)	54 (65%)
During anesthesia	29 (30%)	10 (67%)	19 (23%)
As antitussive	4 (4%)	0	4 (5%)
Other indications for referral*	5 (5%)	0	5 (6%)
Index reactions			
Skin (urticaria, pruritus, flushing, rash)	56 (57%)	8 (53%)	48 (58%)
Angioedema	37 (38%)	10 (67%)	27 (33%)
Respiratory (dyspnoea, wheeze, stridor, hypoxemia)	20 (20%)	7 (47%)	13 (16%)
Gastrointestinal (nausea, vomiting, abdominal pain)	12 (12%)	2 (13%)	10 (12%)
Hypotension	16 (16%)	6 (40%)	10 (12%)
Other*	9 (9%)	0	9 (11%)
Opioids			
Codeine	34 (35%)	5 (33%)	29 (35%)
Fentanyl	3 (3%)	1	2 (2%)
Meptazinol	1	0	1
Morphine	55 (56%)	8 (53%)	47 (57%)
Oxycodone	1	1	0
Papaveretum	1	0	1
Pethidine	1	0	1
Tramadol	2 (2%)	0	2 (2%)

*See the text for description.