

CASE REPORTS

Pharmacological stimuli in asthma/urticaria

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ABSTRACT

Background: The use of opioids as analgesics is becoming increasingly widespread, which may have repercussions in patients with urticaria or asthma, as these agents frequently cause adverse reactions.

Material and methods: We present three patients who developed allergic reactions after receiving codeine: two patients who developed acute urticaria, and a third asthmatic patient receiving specific immunotherapy who developed bronchospasm. Skin prick-testing (SPT) and intradermal reaction (IDR) tests with various opioids were performed, followed by controlled oral challenge. Prick tests and IDR were also carried out in 20 controls.

Results: Similar SPT and IDR results were recorded in the three patients and in the controls. In the case of controlled oral challenge with codeine, patient 1 suffered bronchospasm, while patient 2 developed generalized urticaria. The test was not performed in the third patient. All of the patients tolerated tramadol 50 mg without problems. We advised the use of tramadol as analgesic and fentanyl or remifentanyl as anesthetics.

Discussion: In these types of manifestation, the pharmacological properties of the opioids used are highly important, particularly as regards their histamine-releasing potential. Codeine, morphine and pethidine present the greatest histamine-releasing

capacity, while tramadol, fentanyl and remifentanyl do not release histamine and their use is thus recommended in pulmonary disease requiring opioid administration.

Cutaneous symptoms are more frequently caused by opioids than by respiratory symptoms, since these drugs act on the M_{TC} mast cell population, which is more prevalent in the skin than in the lungs. Some of this action is inhibited by naloxone.

Conclusions: In most patients, these reactions are not IgE-mediated. Consequently, SPT and IDR are of little diagnostic value, and controlled oral challenging with the suspect drug or with one of the non-histamine releasing agents should be used. The patch test is useful in occupational contact dermatitis.

Key words: Opioids. Codeine. Asthma. Urticaria.

INTRODUCTION

An increasing number of drugs help to improve the life of patients, particularly in relation to the management of pain. The most widely used agents are anti-inflammatory drugs that are already known to us and which may affect pathologies commonly seen in our practice, such as asthma and urticaria, in some patients.

The use of opioids is not unusual in analgesic treatment, and as we will see, these substances can also cause problems in such pathologies. The opioids are divided into several groups¹:

– Morphine group: *morphine, oxycodone, hydrocodone, heroine, noscapine, dextrometorphan, oxymorphone, levorphanol, tramadol, buprenorphine, codeine* (*Naloxone* and *Naltrexone* as antagonists).

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- Piperidine: *meperidine, loperamide, diphenoxylate, fentanyl, sufentanil, alfentanil, remifentanyl*.
- Methadone group: *methadone, levomethadyl, dextropropoxyphene*.

These agents can produce frequent adverse reactions, such as¹: nausea, vomiting, sedation, respiratory depression, muscle rigidity, bradycardia or itching.

MATERIAL AND METHODS

We present three patients with clinical manifestations after codeine ingestion.

Case 1

A 27-year-old asthmatic woman sensitized to *D. pteronyssinus* and *D. farinae*, and in her fourth year of immunotherapy, appeared asymptomatic except for some respiratory infections. She suffered three episodes of dyspnea and wheezing related to the ingestion of paracetamol and codeine. She had tolerated paracetamol alone but had not taken codeine later. Skin prick-testing and IDR were performed with opioids. Controlled oral challenges with codeine and tramadol were carried out.

Case 2

A 32-year-old woman presented with rhinoconjunctivitis, sensitized to grass, *Cupressus arizonica* and animal dander. Previously she had neither cutaneous symptoms nor asthma.

She consulted 30 minutes after taking acetylsalicylic acid (ASA) and codeine for a respiratory infection, with a clinical picture of generalized acute urticaria that disappeared within a few hours with

Controlled oral challenge with tramadol was well tolerated (table III).

To summarize, the patient developed bronchospasm in response to codeine, and was able to tolerate tramadol (fig. 1).

Patient 2

He skin prick-test and IDR results are the same that patient 1 (table I).

Controlled oral challenge showed complete tolerance of ASA, reaching the therapeutic dose. Controlled oral challenging with codeine 30 mg was carried out. The patient tolerated 1/8 of the dose without problems, though 40 minutes after ingesting 1/4 of the dose she developed itching and hives on the back. We therefore administered ebastine 20 mg. Fifty-five minutes later she presented generalized urticaria; dexchlorpheniramine and methylprednisolone were thus administered, after which the clinical picture resolved within 55 minutes.

Tryptase levels were determined, obtaining the following results:

- Generalized urticaria: 15 µg/l
- Two hours later: 9 µg/l
- Baseline: 7 µg/l

Controlled oral challenge with tramadol 50 mg was carried out, without adverse effects.

Patient 3

The results obtained are similar of the other patients (table I). Controlled oral challenge with tramadol was carried out without incidents.

Controls

The following results were obtained:

Table I

Skin prick-test and intradermal reaction in the three patients

	PRICK				IDR				
	1/1	1/10	1/10 ²	1/10 ³	1/10 ²	1/10 ³	1/10 ⁴	1/10 ⁵	1/10 ⁶
Codeine		+	+	–					
Morphine		–	–	–	+	+	+	+	–
Tramadol	–				+				
Petidine	–				+				
Fentanyl	–				–				

Table II
Spirometric control of the challenge test with codeine (30 mg) in patient 1

Codeine 30 mg	PEF	CVF	FEV1	MMEF 75/25
Basal	7.14 (106 %)	3.67 (94 %)	3.17 (99 %)	86 (109.6 %)
1/4 Dose	6.48 (96 %)	3.38 (87 %)	2.94 (92 %)	86 (109.6 %)
1/2 Dose	6.50 (96 %)	3.13 (80 %)	2.78 (87 %)	89 (112 %)
After 15'	5.14 (76 %)	2.72 (70 %)	2.43 (76 %)	89 (112 %)
Terbutaline	7.44 (110 %)	3.50 (90 %)	3.14 (98 %)	89 (112 %)

Table III
Spirometric control of the challenge test with tramadol (50 mg) in patient 1

Tramadol	PEF	CVF	VEMS	MMEF 75/25
Basal	7.06 (105 %)	3.64 (94 %)	3.12 (98 %)	85.1 (107 %)
1/2 DOSE	6.74 (114 %)	3.88 (99 %)	3.28 (103 %)	86 (109.6 %)
1/1 DOSE	7.80 (116 %)	3.84 (98 %)	3.28 (102 %)	85.1 (107 %)

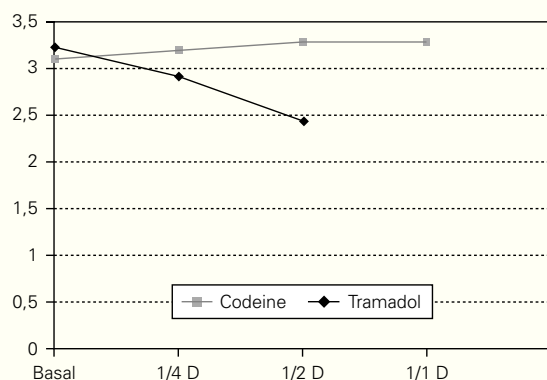


Figure 1.—Difference between challenge test to codeine and tramadol.

Without contact:

- Codeine: 8 Prick-test+
- Morphine: 7 Prick-test+. All IDR positive up to 1/10⁵; 9 positive up to 10⁶
- Tramadol: 2 Prick-test+. IDR 9+
- Pethidine: 1 Prick-test+. IDR 10+
- Fentanyl: 1 Prick-test+ IDR 0+

With contact:

- Codeine: 9 Prick-test+
- Morphine: 9 Prick-test+. IDR 9+ up to 1/10⁶, 1 up to 1/10⁵

- Tramadol: 0 Prick-test+. IDR 10+
- Pethidine: 2 Prick-test+. IDR 8+
- Fentanyl: 1 prick-test+. IDR 8+

All patients were advised to use tramadol as analgesic and fentanyl and remifentanyl as anesthetics.

DISCUSSION

The singularities of opioids deserve a brief review of their pharmacokinetic characteristics¹.

Codeine

This drug is a pure opioid agonist. It is used in application to moderate pain, cough and constipation. In some cases in Europe it is ineffective due to the high prevalence of fast extensive debrisoquine metabolizers.

Codeine can produce adverse effects requiring a differential diagnosis: cutaneous symptoms (itching, urticaria, rash, angioedema, erythema multiforme, erythema nodosum, occupational eczema). Respiratory: bronchospasm. Others: hypotension (when administered i.v.), pseudo-scarlatiniform fever.

The mechanisms of action underlying these clinical conditions may be: *a)* Hypersensitivity: one case has been described of IgE mediated response to morphine with cross-reactivity to codeine²; *b)* Histamine release: highly potent; *c)* Ganglionic vasomotor depression and block: causes important hypotension.

To summarize, we have seen that the prick-test and IDR are of scant utility³; indeed, such testing is used as positive control in France, in the same way in which histamine is used in Spain. Therefore, in those cases where the clinical history is insufficient, only controlled oral challenging can yield a diagnosis. In occupational contact eczema among workers who manipulate codeine, it is recommended to perform patch-tests with codeine phosphate a concentration of 0.1 %⁴.

Morphine

This drug is a powerful analgesic, with high histamine-releasing potential that occasionally causes respiratory depression. Skin prick-testing and IDR are likewise of little help in this case, and the diagnosis must be based on the clinical findings or controlled oral challenge. Another case of IgE response to morphine has been reported in Spain, in addition to the case commented above with cross-reactivity to codeine.

There have also been reports of occupational cases with clinical conditions in which the symptoms are cutaneous or respiratory.

Tramadol

This drug is not a pure agonist, and its mechanism of action is partially mediated by its metabolite (o-demethyltramadol), which is a pure μ -agonist and possesses another still unknown mechanism. It acts upon the central nervous system binding to α_2 -adrenergic receptors, and also exerts some serotonergic action. This is why the drug is contraindicated in patients receiving treatment with monoamine oxidase (MAO) inhibitors and in epilepsy.

Tramadol produces very little respiratory depression, and even in intubated patients with mechanical ventilation it neither reduces pO_2 nor increases pCO_2 . It is the opioid recommended for asthma by the *British Journal of Anaesthesia*⁵. In addition, tramadol is not a histamine-releasing drug.

It seems to be a good alternative for these patients, though only controlled oral challenge is able to confirm this.

Fentanyl and remifentanyl

These substances are μ -agonists used as anesthetics and also to some extent as analgesics, because of their rapid metabolism. They are not histamine-releasing drugs, and constitute the anesthetics recommended for patients with pulmonary pathology⁵.

In these cases fentanyl and remifentanyl seem to be acceptable options in patients of this kind⁵.

Pethidine-meperidine

This is the most powerful opioid formulation, as well as the one of the most intense histamine-releasing agents. A case of IgE-mediated pethidine hypersensitivity has been reported⁶.

General Comments

In the study of opioids, adverse reactions, skin prick-testing and IDR are of scant value and can thus be omitted. The only way to diagnose these patients

is by means of controlled oral challenge, and in highly suspicious cases we may search for specific IgE targeted to the opioid in question. Patch-testing is very useful in occupational contact eczema⁴.

Many substances induce histamine release, including opioids. In these clinical situations PGD_2 and LTC_4 can be determined – the corresponding values being 10-fold lower than in IgE-mediated reactions.

There are two types of mast cells: M_{TC} (mostly in skin) and M_T in the lungs⁷. Opioids exert comparatively greater action upon M_{TC} , which is why skin symptoms are the most common expression in these patients⁷. Naloxone partially inhibits this action⁷.

CONCLUSIONS

We have presented three patients with clinical pictures of asthma and urticaria following codeine ingestion, attributable to the histamine-releasing action of the drug. All of them tolerated tramadol without problems.

The most common of these adverse effects are not IgE-mediated. Resorting to opioids that do not mediate histamine release, such as tramadol, fentanyl and remifentanyl, can solve the problem.

Skin prick-testing and IDR to opioids are of scant diagnostic utility, and the gold standard in these patients is controlled oral challenge.

Patch-tests in occupational contact eczema are usually used in workers suffering problems when manipulating morphine and codeine⁴.

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