

Opiate-sensitivity: clinical characteristics and the role of skin prick testing

S. M. S. NASSER and P. W. EWAN

Department of Medicine, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, UK

Summary

Background The value of skin prick testing in opiate-sensitive individuals is uncertain as opiates cause non-specific weals by direct degranulation of mast cells.

Objective To define whether skin prick test (SPT) responses to opiates in opiate-sensitive individuals are different to those seen in the normal population and to describe the clinical characteristics of this group of subjects.

Methods The SPT responses of eight opiate-sensitive subjects to morphine 10 mg/mL, pethidine (meperidine) 50 mg/mL and papaveretum 15.4 mg/mL at four different concentrations (undiluted, 1/10, 1/50 and 1/100) were compared with the responses of 100 (32 atopic) non-opiate-sensitive control subjects. Four of the opiate-sensitive subjects had a clinical history of asthma, rhinitis or urticaria on occupational exposure to morphine. One subject developed urticaria with codeine, one developed urticaria and asthma with morphine and diamorphine and two subjects reacted to intravenous papaveretum with anaphylaxis or urticaria. Five out of the eight cases had opiate sensitivity confirmed by single-blind placebo-controlled oral challenge.

Results Skin prick tests to all three opiates were not significantly different when the eight opiate-sensitive subjects were compared with either the entire normal control group or the subgroup of 47 definite opiate-tolerant controls that had previously received opiates for clinical indications. Furthermore, there were no significant differences in size of opiate SPT responses between atopic and non-atopic control subjects. In the control subjects, there was a positive correlation in SPT weal size between the three opiates.

Conclusion Skin prick testing is not useful in the diagnosis of opiate sensitivity and placebo-controlled challenge should be considered.

Keywords: anaphylaxis, asthma, opiate, morphine, pethidine, papaveretum, rhinitis, skin prick test, urticaria

Clinical and Experimental Allergy, Vol. 31, pp. 1014–1020. Submitted 26 April 2000; revised 24 August 2000; accepted 18 November 2000.

Introduction

There are insufficient data on the use of skin prick testing in the diagnosis of opiate sensitivity. Opiates such as morphine, codeine and synthetic opioids such as pethidine can cause direct mast cell degranulation without the presence of specific IgE antibodies [1]. This effect is only partially antagonized by naloxone, implying

a mechanism that is not dependent on opiate receptors [1,2]. A further issue is mast cell heterogeneity with differential responses to the direct degranulating effect of diverse opiates. For example, human skin mast cells degranulate *in vitro* in the presence of morphine [3] but human lung, intestinal or heart mast cells do not release histamine with a similar stimulus [4]. This suggests that systemic reactions to opiates/opioids can theoretically occur either by an IgE-mediated allergic mechanism or by massive mediator release from skin mast cells, or alternatively by a change in mast cell phenotype to allow

Correspondence: P. W. Ewan, Department of Allergy and Clinical Immunology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. E-mail: pamela.ewan@addenbrookes.nhs.uk

Table 1 Individual weal diameters to each opiate concentration for the eight opiate-sensitive subjects

Case number	Weal size diameter (mm)							
	1	2	3	4	5	6	7	8
<i>Morphine</i>								
10 mg/mL	3	4	5	4	5	2	4	4
1 mg/mL	3	3	0	3	0	0	3	2
0.2 mg/mL	2	2	0	2	0	0	3	2
0.1 mg/mL	0	0	0	0	0	0	2	2
<i>Papaveretum</i>								
7.7 mg/mL	3	5	0	4	3	5	3	5
0.77 mg/mL	0	3	0	0	0	2	0	2
0.15 mg/mL	0	0	0	0	0	1	0	0
0.077 mg/mL	0	0	0	0	0	0	0	0
<i>Pethidine</i>								
50 mg/mL	4	0	2	5	3	4	4	2
5 mg/mL	2	0	2	0	0	2	0	1
1 mg/mL	0	0	2	0	0	0	0	0
0.5 mg/mL	0	0	0	0	0	0	0	0
-ve control	0	0	0	0	0	0	0	0
Histamine	4	5	5	5	5	4	7	6

pharmacological degranulation in mast cells outside the skin.

IgE antibodies to morphine and codeine have been detected in the serum of a subject who experienced a life-threatening anaphylactic reaction following the administration of a papaveretum-hyoscine combination [5]. Intradermal tests to papaveretum (a mixture of 47.5–52.5% morphine, 2.5–5% codeine, 16–22% narcotine and 2.5–7% papaverine) and morphine demonstrated positive weal and flare responses. However, in that study control subjects were not tested for their intradermal response and skin prick test (SPT) results were not reported, leaving the issue of skin prick testing in opiate sensitivity unresolved.

Codeine has been used as a positive control in skin prick testing for many years, although histamine is now more commonly used. Skin prick tests in normal individuals with codeine demonstrated a positive reaction in 39 of 56 subjects [6]. The sensitivity of urticaria-prone skin to codeine has been calculated as 100 times greater than for normal skin [7] but this is more likely to be a reflection of greater mast cell density in the skin of patients with chronic idiopathic urticaria [8] than due to an IgE-mediated mechanism. Positive weal and flare responses have also been documented to morphine, codeine, meperidine and to endogenous opiates on intradermal testing [9]. Skin biopsies taken from normal subjects after intradermal morphine injection have demonstrated mast cell

degranulation when examined by electron microscopy, providing convincing evidence for a direct effect of morphine on the skin mast cell population [10].

In our clinic we have had a number of cases of opiate sensitivity and because of the direct mast cell degranulating action of opiates, we sought to question the validity of skin prick testing as a means of discriminating between opiate-sensitive and opiate-insensitive subjects. We have carried out SPT to some of the most commonly used opiates/opioids in clinical practice (morphine, papaveretum and the synthetic opioid pethidine) on eight subjects who presented with clinical sensitivity to an opiate. Their responses have been compared with 100 control subjects without a history of opiate sensitivity. The relevance of skin prick testing to opiates in clinical practice is discussed.

Methods

Control subjects

Eighty-two healthy control subjects (29 male) of mean age 39.6 (range 21–80) years working at the authors' hospital were skin prick tested to morphine, papaveretum and pethidine. Twenty-nine subjects had a history of atopic disease (asthma, childhood eczema or seasonal allergic rhinitis) and 29 subjects had received at least one of the opiates for clinical indications previously (24 pethidine, five morphine and three papaveretum). In addition, 18 patients (six male) of mean age 61.4 (range 24–84) years, admitted for orthopaedic operations and who were to subsequently receive either morphine or pethidine in the postoperative period, were skin prick tested preoperatively. Three of these patients had a history of atopic disease and none experienced adverse reactions to opiates when given as analgesia postoperatively. There were no adverse reactions during skin prick testing.

Skin prick tests

In each subject SPTs were performed over the flexor aspect of the right arm. Each of the 100 subjects was skin prick tested to stock concentrations of morphine 10 mg/mL, pethidine 50 mg/mL and papaveretum 15.4 mg/mL and at dilutions (in physiological saline) of 1/10, 1/50 and 1/100. Any patient who demonstrated a positive reaction at 1/100 dilution was further tested to that opiate at a dilution of 1/1000. A fresh lancet was used for each opiate and skin prick testing was started at the most dilute concentration, wiping the lancet between pricks. A negative control solution of physiological saline and positive control of histamine (10 mg/mL) were included with each test. An adequate positive control weal diameter was taken to be at least 4 mm greater than negative control to exclude the

possibility of antihistamine ingestion. The negative control weal diameter was subtracted from each opiate/opioid skin prick weal.

Case 1. Occupational morphine-induced asthma This was a 28-year-old woman who worked as a formulation scientist involved in morphine manufacture. She had a history of intermittent cough since the age of 19 years which had not been diagnosed as asthma and for which she was not taking treatment. Her cough had become worse within a few months of joining the company 5 years ago. Her work involved intermittent periods of morphine exposure and when working with morphine she had paroxysms of coughing and her peak flow decreased from a baseline of 500 L/min to 390 L/min. After a period of morphine exposure it usually took 2 weeks before her peak flows returned to baseline. In hospital, she underwent a single blind placebo-controlled morphine inhalation challenge. She received incremental exposure to morphine by pouring morphine powder from one container into another and doubling the number of 'pours' and hence the time of exposure at 15 minute intervals. Lactose powder was used as control and the challenges were carried out on separate days more than 2 weeks apart. On the morphine challenge day she developed rhinitis with sneezing and rhinorrhoea, conjunctivitis and a decrease in peak flow from 500 to 430 L/min (14% decrease) at 3 min of morphine exposure. Placebo challenge was negative. She underwent oral morphine sulphate challenge with 1 mg, 5 mg and 7 mg at 60-min intervals. This led to pruritus and erythema of her neck followed by erythema and urticaria of her arm.

Case 2. Papaveretum-induced anaphylaxis This 45-year-old woman suffered severe bronchospasm, hypotension with an unrecordable blood pressure and asystole immediately after receiving intravenous 7.7 mg Omnopon (papaveretum) 90 min into a hysterectomy. Premedication was with temazepam and salbutamol and anaesthesia had been induced uneventfully with thiopentone, fentanyl and vecuronium, followed by enflurane and halothane. She was resuscitated with 2 mg adrenaline, DC cardioversion, intravenous fluids and methylprednisolone. Postoperatively she had lip and periorbital angioedema. She was given eight doses of pethidine for postoperative pain without reaction. She had received six previous general anaesthetics, which included fentanyl, without problems. SPTs with fentanyl and vecuronium were negative and there was no history of latex allergy.

Case 3. Occupational morphine-induced urticaria This 29-year-old man had worked as a granulation technician in the manufacture of morphine and dihydrocodeine for 8 years. His job entailed mixing raw material to produce

granules. Skin exposure to morphine powder produced an urticarial rash which usually occurred on his wrists and neck. Dihydrocodeine exposure at work produced no symptoms and he was able to tolerate oral dihydrocodeine. Single-blind placebo-controlled morphine inhalation challenge was performed as in case 1 and this led to nasal congestion which resolved by 4 h. There was no decrease in FEV₁ or symptoms of asthma and there was no reaction to placebo (powdered lactose). Oral morphine challenge with 5 mg followed by 10 mg at 60-min intervals produced a generalized pruritus and three areas of giant urticaria on the face and trunk. An additional skin prick to codeine test was included in this case and was positive at the stock concentration of 60 mg/mL but negative at a dilution of 1/10.

Case 4. Occupational morphine-induced asthma and rhinitis This 28-year-old man had worked as a technician in the manufacture of morphine for 5 years. He had no history of asthma but after working for 18 months he developed rhinitis and severe attacks of asthma on exposure to morphine at work. His symptoms resolved when he stopped manufacturing morphine but would return on even brief accidental morphine exposure with rhinitis and severe wheezing. Single-blind placebo-controlled morphine inhalation challenge was performed as in case 1 and he developed severe rhinitis and wheeze with an 18% decrease in peak flow rate. There was no reaction to placebo. Oral morphine challenge with 5 mg and 10 mg at 60-min intervals led to generalized erythema, nasal congestion and late wheezing at 6 h with a decrease in peak flow rate of 10%. This was repeated 4 weeks later with similar results.

Case 5. Occupational morphine-induced asthma and rhinitis This 33-year-old man had suffered with asthma and allergic rhinitis as a child. He was not taking any regular treatment when he started working as a technician involved in the manufacture of morphine 6 years ago. Soon after joining the company he noticed a return of his asthma symptoms and required regular inhaled corticosteroids, which resulted in an improvement in symptoms. Four years later he developed morphine-induced nasal obstruction, rhinorrhoea, an itchy palate and wheeze on minimal exposure to morphine. Brief skin contact with morphine powder produced an erythematous, scaly rash. When he stopped working with morphine a few months later he noticed an immediate improvement in both his rhinitis and asthma and he was able to halve his inhaled corticosteroid dose. Single-blind placebo-controlled morphine inhalation challenge was performed as in case 1 and this led to immediate symptoms of nasal obstruction, rhinorrhoea and wheezing at 2 h with an 8% reduction in both FEV₁ and

PEFR. There was no reaction to placebo challenge. Oral morphine challenge with 5 mg, 10 mg and 20 mg at 60-min intervals produced a late-phase asthmatic reaction at 15 h with severe wheezing and dyspnoea which persisted for several days.

Case 6. Codeine and pethidine sensitivity This 42-year-old woman had a 10-year history of severe facial angioedema following ingestion of codeine, aspirin and all non-steroidal anti-inflammatory drugs (NSAIDs). There was no history of laryngeal oedema, asthma or rhinitis with any drug. She had no history of atopic disease and skin tests to *Dermataphagoides pteronyssinus*, cat and grass pollen were negative. She underwent incremental oral codeine challenge with 7.5 mg, 15 mg, 30 mg and 60 mg at hourly intervals and 45 min after the 60 mg dose developed intense erythema and urticaria over the face, scalp, neck and upper chest. There was no dyspnoea or hypotension although she felt faint and she required treatment with IV hydrocortisone 200 mg and chlorpheniramine 10 mg. Several weeks later she underwent an oral challenge to pethidine with incremental doses of 12.5 mg, 25 mg and 50 mg at hourly intervals. At 1 hour after the 50 mg dose she developed generalized pruritus, facial erythema and angioedema and felt faint and unwell. There was a small decrease in blood pressure from a baseline of 122/76 to 95/59. She required treatment with IV hydrocortisone 200 mg, chlorpheniramine 10 mg and 500 mL N/saline with overnight observation.

Case 7. Morphine and diamorphine sensitivity This 34-year-old man was diagnosed with cystic fibrosis at age 14. For 4 years he had had recurrent episodes of abdominal pain from a variety of diagnoses including pancreatitis, appendicitis and several episodes where the cause was not identified. He had a history of at least 20 hospital admissions with abdominal pain requiring opiate analgesia. During his most recent admission he received 20 mg oral morphine sulphate and 30 min later developed a generalized urticarial rash with wheeze and dizziness. Later on the same day he was given diamorphine intravenously and within a few minutes developed similar symptoms. He recovered with treatment by 1 hour. There was no history of opiate sensitivity from previous admissions and he had received both opiates on several occasions in the past without reaction. Further episodes of pain were treated with the opioid tramadol without incident. He had no history of atopy or other drug reactions. Challenge with either morphine or diamorphine was not felt necessary on either clinical or safety grounds. In order to further define his opiate sensitivity and to allow a wider range of future treatment options he underwent incremental pethidine challenge with an oral dose of 25 mg followed by 50 mg

at 90-min intervals. He tolerated both doses without reaction.

Case 8. Morphine sensitivity This 42-year-old female doctor had a 3-year history of pressure and heat-induced urticaria. She was atopic with grass pollen-induced hay fever but no history of asthma. Eleven years earlier she had been given papaveretum as a single agent, intravenously, following a Caesarian section and immediately developed generalized urticaria. More than 20 years ago she had taken a kaolin and morphine mixture for diarrhoea and developed angioedema of the face. She has avoided codeine and pethidine ever since.

Data analysis

Spearman's rank correlation coefficient was used to detect an association between the sizes of the SPT weals after the undiluted stock concentration of each opiate. The Mann–Whitney *U*-test for unpaired non-parametric variables was used to compare the size of the weal diameter after undiluted opiate between the eight opiate-sensitive subjects and the 47 control subjects who were known to be opiate-tolerant. The Mann–Whitney *U*-test was also used to compare weal size diameters between the atopic and non-atopic control populations for each undiluted opiate SPT.

Results

Subjects

A total of one hundred control subjects underwent skin prick testing and there were no adverse reactions. There were no adverse reactions to skin testing in the eight opiate-sensitive subjects.

Skin prick tests

Individual SPT results for the eight opiate-sensitive subjects are shown in Table 1. A comparison of the SPT results of the 100 normal controls with the eight opiate-sensitive subjects at individual concentrations of morphine and pethidine are shown in Figs 1 and 2, respectively. The eight opiate-sensitive subjects demonstrated similar SPT results to the 100 control subjects for each of the three opiates tested. The SPT weal diameters to undiluted opiate in the opiate-sensitive subjects were similar to the weal diameters obtained in the 47 known opiate-tolerant control subjects for morphine ($P > 0.1$), papaveretum ($P > 0.1$) and pethidine ($P > 0.1$). None of the eight opiate-sensitive subjects had a SPT weal size of more than 3 mm greater than negative control for any of the diluted opiate concentrations. Amongst the control subjects, only 8/100

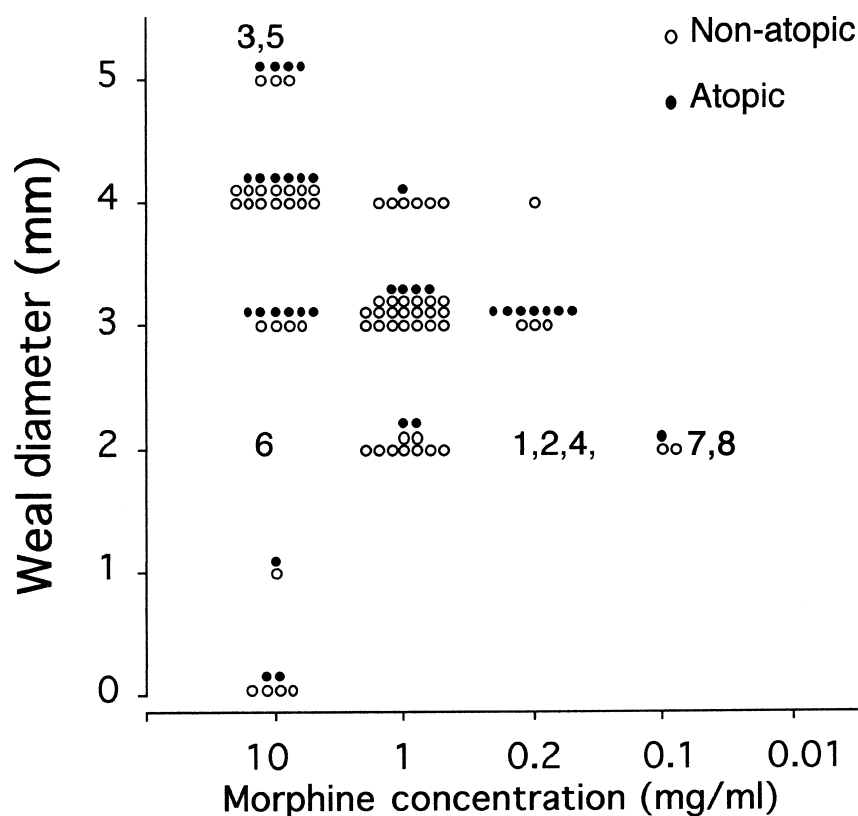


Fig. 1. Skin prick test weal size diameter resulting from the lowest morphine concentration (stock: 10 mg/mL) that gave a weal size diameter of at least 2 mm greater than negative control. Each subject has one plot. ○ = non-atopic; ● = atopic.

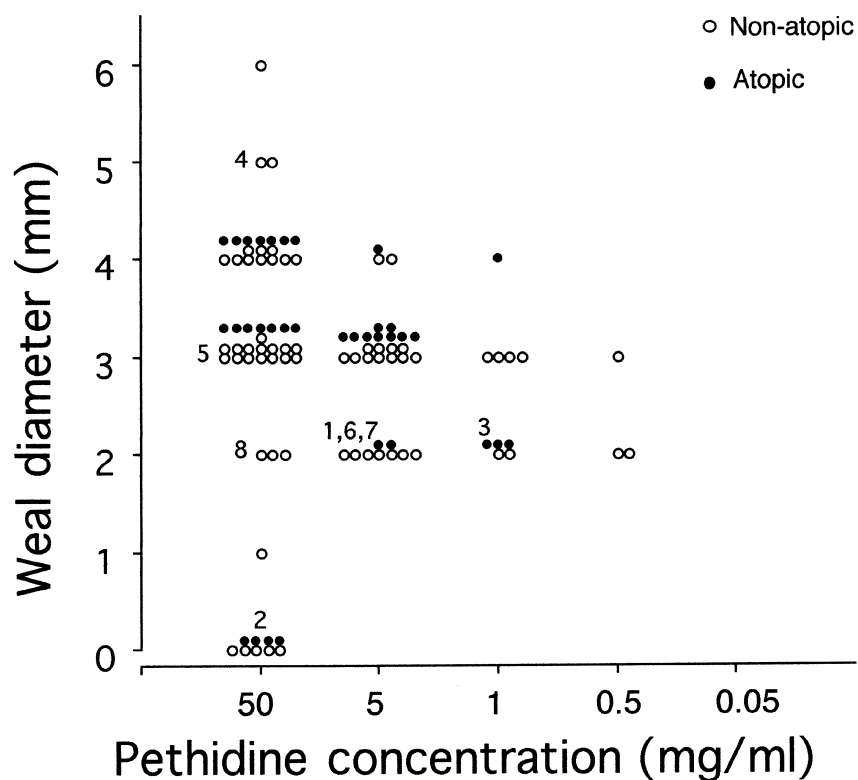


Fig. 2. Skin prick test weal size diameter resulting from the lowest pethidine concentration (stock: 50 mg/mL) that gave a weal size diameter of at least 2 mm greater than negative control. Each subject has one plot, the control subjects ($n = 100$) are denoted by circles and the eight opiate-sensitive subjects by numerals. ○ = non-atopic; ● = atopic.

for morphine and papaveretum and 4/100 for pethidine, had a SPT weal size that was 4 mm or greater than negative control for any opiate concentration except for the undiluted stock concentrations.

The 32 clinically atopic control subjects demonstrated similar opiate SPT weal responses to the 68 non-atopic subjects. There were no statistically significant differences between the atopic and non-atopic groups for size of SPT weal after morphine, papaveretum or pethidine. There was a significant correlation in weal size after the undiluted stock concentrations when a comparison was made between morphine and papaveretum ($r = 0.443$; $P < 0.001$), morphine and pethidine ($r = 0.48$; $P < 0.001$) and between papaveretum and pethidine ($r = 0.332$; $P < 0.01$).

Discussion

Our results clearly demonstrate that in all eight cases of opiate-sensitivity, skin prick testing was not of diagnostic value. The SPT weal diameters in our eight opiate-sensitive subjects were similar to the 100 control subjects and did not significantly differ from 47 known opiate-tolerant control subjects. In addition, by defining the normal SPT responses to morphine, papaveretum and pethidine, future cases of clinical opiate sensitivity can be compared in order to establish whether known cases of IgE-mediated opiate sensitivity have larger SPT responses.

Opiate sensitivity is relatively uncommon and we have therefore examined 82 subjects who had either no previous exposure to opiates or had not reacted adversely to them. In order to strengthen the control population we examined a further 18 subjects who subsequently received opiates for postoperative analgesia and did not have an adverse reaction. Skin prick test results in these 18 subjects were not significantly different to the 82 control subjects in the first group. The diagnosis of opiate sensitivity was confirmed in five of our eight cases by either inhaled or oral morphine or codeine challenge. Each of these was performed in a single-blind placebo-controlled manner. We did not perform challenge testing in case 2 because of the severity of her reaction and because of the clear temporal relationship between administration of intravenous papaveretum and the anaphylactoid reaction. In addition, she had negative SPTs to fentanyl and vecuronium and there was no clinical evidence of latex sensitivity, ruling out sensitivity to the other agents to which she was exposed. Case seven had two reproducible intolerant reactions to morphine and diamorphine in hospital and because of the severity and clear-cut nature of the reactions a challenge was not considered justified. Similarly, case 8 had one immediate reaction to intravenous papaveretum supported by an earlier intolerant reaction to oral morphine and therefore clinical opiate challenge was considered unjustified.

We chose to skin prick test using morphine and papaveretum because these were the drugs to which our eight opiate-sensitive subjects had reacted. Papaveretum is a mixture of opiates and contains codeine. Pethidine was added because it is a synthetic opioid and *in vitro* studies have shown it to have less direct mast cell degranulating activity than the naturally occurring opiates [1]. Furthermore, subject 2 was able to tolerate pethidine after she had reacted to papaveretum and if the SPTs had been useful for diagnosis they would have allowed us to identify whether our opiate-sensitive subjects could tolerate a synthetic opioid. The concentrations of opiate/opioid chosen were the commercially available 'stock' concentrations contained in an ampoule with the amounts per millilitre approximating to a single dose. It was considered more relevant to test at concentrations employed in clinical practice rather than to use equimolar concentrations of the opiates/opioid. Furthermore, our decision to include a 1/50th concentration was vindicated as the majority of both controls and opiate-intolerant individuals had negative responses at 1/100th dilution for all three opiates.

Four out of eight cases had occupational symptoms on exposure to powdered morphine. We therefore challenged these subjects by creating an atmosphere of morphine powder of increasing concentration. We did not consider it ethical to perform similar challenges in normal controls because of the risk of sensitization. However, five other opiate workers without a strong clinical suspicion of opiate-sensitivity were also challenged with negative results (data not shown). Placebo challenges carried out in a similar manner with powdered lactose were negative in each case.

It is noteworthy that there was a significant correlation in weal diameter between the three opiates, suggesting a similar mode of action for mast cell degranulation and therefore making it unlikely that specific IgE was involved. Subjects 7 and 8 developed weal and flare responses to 1/100 dilution of morphine but had negative responses at 1/1000 dilution, raising the possibility that they may have IgE-mediated responses detected by skin prick testing. There were only three control subjects with an equivalent response and two of these were known to tolerate opiates. If we are to assume that their reaction was IgE-mediated then it is surprising that their SPTs to higher concentrations of morphine did not give larger weals to those observed. Furthermore, the size of the weals observed at 1/100 dilution was not sufficiently distinguishable from the control population to advocate skin-prick testing as an appropriate investigation in opiate-sensitive subjects.

A number of studies have examined the *in vitro* effect of naturally occurring, synthetic and endogenous opiates on mast cell and basophil degranulation. In a study using isolated rat mast cells [1], morphine, codeine and pethidine induced histamine release in a similar concentration range.

The opiate receptor antagonist naloxone only partially inhibited morphine- and codeine-induced histamine release. By contrast, pethidine induced a slow histamine release which was less affected by naloxone. The authors therefore concluded that there is a similar mechanism for histamine release induced by morphine and codeine, whereas the synthetic opioid pethidine has a different mode of action.

The total incidence of opiate sensitivity is unknown, and the differential incidence of anaphylactoid and anaphylactic reactions to opiates is also not known. Only one possible case of an IgE-mediated reaction to papaveretum [5] and three other possible cases of sensitivity to pethidine, morphine and fentanyl [11,12] have been described in the literature. We did not develop a serum IgE assay for opiates nor is there one available commercially and we have therefore not reported serum IgE levels to the three opiates. Consequently, we cannot be sure whether our eight opiate-sensitive subjects experienced IgE or non-IgE mediated reactions. Our eight cases experienced opiate-induced symptoms of rapid onset, comprising asthma, rhinitis, urticaria and anaphylaxis, which are considered to be caused by an IgE-mediated process. It is therefore probable that at least some of our eight subjects experienced IgE-mediated reactions and that opiate-mediated IgE cross-linking on the surface of skin mast cells led to little additional mast cell mediator release compared with the direct degranulating effect of these compounds.

Alternatively, all eight opiate-sensitive subjects may have had non-IgE mediated reactions because their SPT results equated with our control population and because all the opiate-induced weals peaked within 5 min, suggesting that direct mast cell degranulation was responsible for local release of histamine. Furthermore, there was no significant difference in weal diameter on skin prick testing for the three opiates between the atopic and non-atopic members of the control population.

We conclude that skin prick testing is not helpful in the diagnosis of opiate-sensitivity and that direct placebo-controlled challenge is necessary to make the diagnosis.

References

- 1 Grosman N. Histamine release from isolated rat mast cells: effect of morphine and related drugs and their interaction with compound 48/80. *Agents Actions* 1981; 11:196–203.
- 2 Shanahan F, Lee TD, Bienenstock J, Befus AD. The influence of endorphins on peritoneal and mucosal mast cell secretion. *J Allergy Clin Immunol* 1984; 74:499–504.
- 3 Lawrence ID, Warner JA, Cohan VL et al. Purification and characterization of human skin mast cells. Evidence for human mast cell heterogeneity. *J Immunol* 1987; 139:3062–9.
- 4 Tharp MD, Kagey Sobotka A, Fox CC, Marone G, Lichtenstein LM, Sullivan TJ. Functional heterogeneity of human mast cells from different anatomic sites: *in vitro* responses to morphine sulfate. *J Allergy Clin Immunol* 1987; 79:646–53.
- 5 Harle DG, Baldo BA, Coroneos NJ, Fisher MM. Anaphylaxis following administration of papaveretum. Case report: Implication of IgE antibodies that react with morphine and codeine, and identification of an allergenic determinant. *Anesthesiology* 1989; 71:489–94.
- 6 Lin RY, Erlich ER, Don PC. Skin prick test responses to codeine, histamine, and ragweed utilizing the Multitest device. *Ann Allergy* 1990; 65:222–6.
- 7 Cohen RW, Rosentreich DL. Discrimination between urticaria-prone and other allergic patients by intradermal skin testing with codeine. *J Allergy Clin Immunol* 1986; 77:802–7.
- 8 Natbony SF, Phillips ME, Elias JM, Godfrey HP, Kaplan AP. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983; 71:177–83.
- 9 Casale TB, Bowman S, Kaliner M. Induction of human cutaneous mast cell degranulation by opiates and endogenous opioid peptides: evidence for opiate and nonopiate receptor participation. *J Allergy Clin Immunol* 1984; 73:775–81.
- 10 Levy JH, Adelson D, Walker B. Wheal and flare responses to muscle relaxants in humans. *Agents Actions* 1991; 34:302–8.
- 11 Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Reanim* 1993; 12:97–104.
- 12 Baldo BA, Fisher MM. Diagnosis of IgE-dependent anaphylaxis to neuromuscular blocking drugs, thiopentone and opioids. *Ann Fr Anesth Reanim* 1993; 12:173–81.