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Anaphylaxis following Administration of Papaveretum. Case Report: Implication of IgE Antibodies that React with Morphine and Codeine, and Identification of an Allergenic Determinant

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IgE antibodies that reacted with morphine and codeine were detected in the serum of a subject who experienced a life-threatening anaphylactic reaction following the administration of Omnopon-Scopolamine® (papaveretum-hyoscine). Hapten inhibition studies with morphine and a number of structurally-related analogues revealed that morphine and codeine were the most potent inhibitors of IgE binding to a morphine-solid phase. Nalorphine, meperidine, and methadone were also good inhibitors of IgE binding, but naltrexone, buprenorphine, and fentanyl proved to be poor inhibitors. From a detailed examination of structure-activity relationships, the authors conclude that the important structural features of the morphine allergenic (that is, IgE binding) determinant comprises the cyclohexenyl ring with a hydroxyl group at C-6 and, most important of all, a methyl substituent attached to the N atom. The authors' findings suggest that morphine analogues administered to such a patient may provoke clinical anaphylaxis. Hyoscine reacted weakly with IgE antibodies in the subject's serum, but this was thought to be due to weak cross-reaction between this compound and morphine. (Key words: Allergy, drug: anaphylaxis. Analgesics, opioid: morphine, codeine.)

SEVERE ANAPHYLACTOID reactions to drugs used in anesthesia are an increasing problem in many countries. With neuromuscular relaxants in particular, many reactions are attributed to the well-documented direct histamine-releasing effects of the drugs. In addition, however, neuromuscular relaxant-specific IgE antibodies have been recently detected in the sera of the majority of patients who, even in the absence of previous exposure,[1–6] experience life-threatening anaphylactoid reactions. It has been argued that it is unlikely that the direct histamine-releasing effects of drugs can produce life-threatening reactions in healthy patients.¶**

Opioids such as morphine and meperidine are potent histamine-releasing drugs[7] and anaphylactoid reactions to these drugs although extremely rare, have been attributed to this effect.[7–9] IgE antibodies specific to meperidine have been detected.[10]

Papaveretum is a mixture of opioids containing 47.5–52.5% morphine, 2.5–5.0% codeine, 16.0–22.0% narcotine, and 2.5–7.0% papaverine.[11] In this report the authors describe a life-threatening anaphylactoid reaction to papaveretum when the drug was used as a preanesthetic medication and the subsequent detection of morphine- and codeine-reactive IgE antibodies. Using the methodology the authors have developed for the study of neuromuscular relaxants, the authors have also identified the drug allergenic determinant structures that interact with the IgE antibody combining sites on morphine and investigated the degree of cross-reactivity with other opioids.

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Materials and Methods

A 50-yr-old woman presented for repair of an incisional hernia. She gave no history of allergy or atopy, but brought two units of autologous blood with her to the hospital because she had "gone into shock" on two previous occasions while undergoing anesthesia for cesarian section. The records of these episodes 20 and 17 yr previously were not available, although three subsequent anesthetics had been uneventful. In two of these for which records were available, she received meperidine as the

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¶ Fisher MM, Baldo BA: Anaphylactoid reactions during anaesthesia. Clinics in Anaesthesiology 2:677–692, 1984.

** Fisher M McD. Direct histamine release in anaesthesia and surgery: Unanswered questions. Discussion about a protocol of a controlled clinical trial: Induction of anaesthesia and perioperative risk. Theoretical Surgery 3:145–147, 1988.

sole opioid. The subject weighed 74 kg and was given Omnopon-Scopolamine® (papaveretum-hyoscine) im as preanesthetic medication and calcium heparin 5000 units subcutaneously for prophylaxis against venous thrombosis. Within 5 min of the injection, she developed profuse sweating, nausea, chest pain, palpitations, hypotension, and transient loss of consciousness. Her pulse was not palpable and she was given 500 ml of Haemaccel®, a synthetic colloid, and transferred to Prince of Wales Hospital, Sydney, by paramedics who administered a further 500 ml of Haemaccel. On admission, her blood pressure was 85/60 and she was given 500 ml of 5% Stable Plasma Protein Solution (SPPS) which increased her blood pressure to 110/80. She was given naloxone 0.8 mg iv on admission with little effect. Over the next 3 h, however, her blood pressure decreased to 85/50 and appeared to respond to 50 mg of hydrocortisone iv. The subject was discharged the following day. Six weeks later after intradermal testing she was anesthetised uneventfully with thiopental, fentanyl, and pancuronium following preanesthetic medication with meperidine, atropine, and calcium heparin. Postoperative analgesia was provided with meperidine. Blood was obtained from the patient 6 weeks after the time of intradermal testing and the serum stored at −20° C.

Over the past 14 yr we have developed and evaluated a system of investigating anaphylactoid reactions to anesthetic drugs using conventional investigations. This system involves the use of diagnostic skin testing performed 4–6 weeks after a reaction, using dilutions of drugs that have been shown not to produce wheal and flare reactions in nonreacting patients. For determining the nature of the antibody involved, we use a radioimmunoassay (RIA) in which the drug is coupled to an insoluble carrier and IgE antibodies that bind to the drug and can be detected by incubation with specific ^{125}I-antihuman-IgE to determine semiquantitatively the antibody levels. The allergenic determinant(s) on the drug, and drugs with likely cross-reactivity can then be determined by performing inhibition experiments where the serum is preincubated with structurally related compounds that can be shown to inhibit the binding of the IgE antibodies in the patient's sera to the drug solid phase. With this patient, the investigation was performed in the following manner. Intradermal testing was carried out 6 weeks after the reaction using 0.01-ml injection of drugs into the forearm of the patient in accordance with the current published protocol.[12] Control patients were not used and d-tubocurarine 1 mg/ml and saline were used as positive and negative controls, respectively.

Coupling of drugs to carriers for RIA testing was performed in the following manner. The optimum *p*H, temperature and time of incubation for the coupling of morphine and codeine to activated Sepharose were determined. Coupling conditions for optimal complexes occurred when morphine hydrochloride and codeine phosphate (15 mg in 3 ml of water) were separately covalently coupled to 400 mg of Epoxy-activated Sepharose 6B (Pharmacia Australia Pty. Ltd., N.S.W.) by adjusting the *p*H to 12.0 with 2.5 M NaOH and gently shaking at 30° C for 20 h. The gels were washed with water, 0.1 M borate buffer *p*H 8.0, 0.1 M acetate buffer *p*H 4.0, and water. Excess reactive sites were blocked by incubating the gels with 1 M ethanolamine (*p*H 9) for 4 h. Finally the gels were washed as above and resuspended in water (8 ml). Ethanolamine-Sepharose complex was prepared by using 150 mg of ethanolamine and 250 mg of activated Sepharose.

With the preparation of hyoscine-Sepharose complex, Epoxy-activated Sepharose 6-B (150 mg) was added to aliquots of hyoscine hydrobromide (20 mg) in water (3 ml) and the *p*Hs were adjusted to 11.2, 11.6, 12.0, and 12.4, respectively. The gels were then treated as above.

Radioimmunoassay tests for IgE-specific antibodies against morphine, codeine and hyoscine were performed according to the following protocol. Serum (50 μl) was added to 4 mg of the solid-phase complex (morphine-, codeine-, hyoscine-, or ethanolamine-Sepharose, or Sepharose alone) and left at room temperature for 3 h. Tubes were then washed and centrifuged three times with phosphate-buffered saline *p*H 7.4 (PBS) containing Tween 20 (0.1%) before adding 20000–30000 cpm per tube of ^{125}I-antihuman IgE (Pharmacia Australia Pty. Ltd., N.S.W.). After standing overnight, tubes were washed three times and counted in a Packard Auto-Gamma Spectrometer. The presence of reactive IgE antibodies in a serum was determined by the percent radioactive uptake of ^{125}I-antihuman IgE, *i.e.*, the percent of counts added.

Inhibition assays to verify the specificity of binding of the detected IgE antibodies and identify the drug allergenic determinant were performed by using the following method. Patient serum (50 μl) diluted 1:4 (saline), was incubated for 1 h with 50 μl of a solution of the inhibitor being tested before addition of the morphine-Sepharose drug solid phase support (4 mg in 80 μl). After 3 h, tubes were washed and centrifuged three times with PBS-Tween before the addition of ^{125}I-antihuman IgE (20000–30000 cpm/tube). After overnight incubation at room temperature, tubes were washed three times and counted.

Control sera used in the RIA consisted of pooled cord serum that does not contain IgE, serum from ten adults allergic to house dust mite and/or grass pollen on whom the clinical diagnosis had been confirmed by radioactive uptakes of 10–45% with RAST testing to the appropriate allergen discs, and sera from nonallergic healthy adult hospital staff members.

The drugs and other compounds used in the RAST studies were ethanolamine, Tween 20, nalorphine hydro-

bromide, naltrexone hydrochloride, naloxone hydrochloride, and hyoscine hydrobromide (Sigma Chemical Co., St. Louis, Mo); methadone hydrochloride (Wellcome Australia Ltd., N.S.W.); fentanyl citrate (Janssen Pharmaceutica Pty., Ltd., N.S.W.); codeine phosphate (Drug Houses of Australia Pty., Ltd., N.S.W.); buprenorphine hydrochloride (Reckitt and Coleman Pharmaceuticals, N.S.W.); heparin calcium (Calciparine), papaverine hydrochloride, heparin sodium and atropine sulphate (David Bull Laboratories Pty., Ltd., Dee Why, Australia); hyoscine butylbromide (Boehringer Ingelheim Pty., Ltd., N.S.W.); thiopental sodium (Abbott Laboratories, N.S.W.); pancuronium bromide (Organon, Oss.); morphine hydrochloride and meperidine hydrochloride were donated by Roche Products Pty., Ltd., Dee Why, Australia.

Results

Skin Tests

Results of intradermal testing are summarized in table 1. Separate intradermal administration of the drugs produced clear, positive reactions to papaveretum and morphine at 1:100,000 dilution. A flare but no wheal response was observed with the positive control drug d-tubocurarine. In contrast, all the other drugs tested, and saline, produced negative results.

Detection of Morphine- and Codeine-Reactive IgE Antibodies

Table 2 summarizes results obtained from direct binding RIA studies in which morphine- and codeine-Sepharose were incubated with control sera or serum from the patient. With morphine-Sepharose, the patient's serum gave an uptake of ^{125}I-antihuman IgE of 30.1%. An uptake of 14.1% was obtained with the same serum using codeine-Sepharose. By contrast, control solid supports of ethanolamine-Sepharose and Sepharose alone gave uptakes of only 0.6%. A cord serum and sera from ten normal subjects and ten adult subjects allergic to allergens other than drugs all gave uptakes of 0.6% or less with the morphine- and codeine-Sepharose solid phases and the control supports.

Table 1. Skin Test Response of Subject to Intradermal Injections* of Morphine and Some Other Drugs

Drug	Concentration	Dilution	Wheal (cm)	Flare (cm)
Saline	0.9%	—†	—	—
d-Tubocurarine	1 mg/ml	—	—	2.5
Papaveretum	20 mg/ml	1:100,000	0.7‡	2.5 × 3§
Morphine	10 mg/ml	1:100,000	1	2.5 × 3
Fentanyl	50 μg/ml	1:100	—	—
Meperidine	50 mg/ml	1:10,000	—	—
Atropine	600 μg/ml	1:1,000	—	—
Hyoscine	400 μg/ml	1:1,000	—	—
Calcium heparin	5000 U/ml	1:1,000	—	—
Sodium heparin	1000 U/ml	1:1,000	—	—
Thiopental	25 mg/ml	1:100	—	—
Pancuronium	2 mg/ml	1:100	—	—

* Solution of drug in 0.01 ml.
† No wheal or flare reaction observed.
‡ One diameter.
§ Two diameters measured at right angles.

Table 2. IgE Antibodies to Morphine and Codeine in Serum from a Patient who Experienced an Anaphylactic Reaction following Administration of the Drug

Sera	Radioactive uptake (%) of ^{125}I-antihuman IgE with Sepharose linked to:			
	Morphine	Codeine	Ethanolamine	Sepharose alone
Control subjects				
Cord	0.4	0.4	0.5	0.4
Normal*	0.5 ± 0.1†	0.5 ± 0.1	0.6 ± 0.2	0.5 ± 0.2
Allergic‡	0.6 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Patient	30.1	14.1	0.6	0.6

* Ten adult subjects (nine females/one male).
† Mean ± SD.
‡ Ten adult subjects allergic to house dust mites and/or pollens but not opioid alkaloids.

Tests for Hyoscine-Reactive IgE Antibodies

The highest uptake of ^{125}I-antihuman IgE with the subject's serum relative to the uptakes obtained with a cord and a normal serum occurred when hyoscine had been coupled to activated Sepharose at *p*H 11.6. The serum gave an uptake of 2.4% compared to uptakes of 0.8% and 0.9% with the cord and normal sera, respectively.

Specificity of the Morphine-Reactive IgE Antibodies

In order to determine the specificity of the IgE antibodies in the serum of the patient, inhibition studies were performed with morphine, codeine, and a number of structurally-related analogues using morphine-Sepharose. Inhibitory responses obtained when the compounds were used with the patient's serum are shown in figure 1 and the percent inhibitions of IgE binding to morphine-Sepharose using 200 nmol of each compound are shown in figure 2. Morphine and codeine proved clearly to be the most potent inhibitors of IgE-binding and closely paralleled each other over the concentration range 16–1600 nmol with 200 nmol producing 72% inhibition with both drugs. The next best inhibitor, nalorphine, was markedly weaker, producing 46% inhibition with 200 nmol of com-

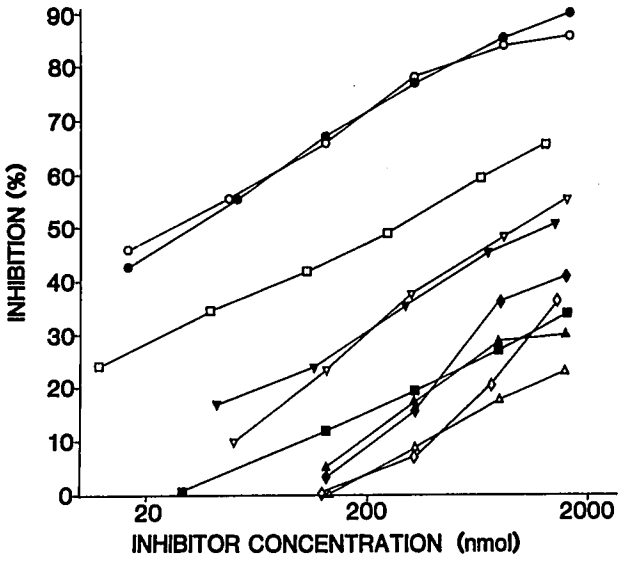
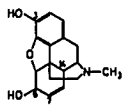
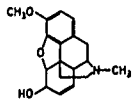
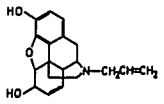
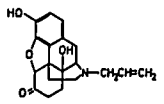
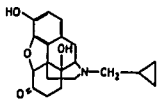
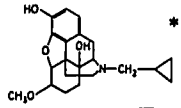
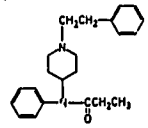
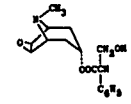
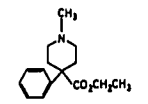
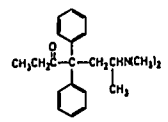


FIG. 1. Inhibition by morphine and a number of structurally related analogues, of IgE binding in the patient's serum to morphine-Sepharose complex. The serum was used at a dilution of 1:4. Key to symbols: (○) morphine; (●) codeine; (□) nalorphine; (■) naloxone; (△) naltrexone; (▲) buprenorphine; (▽) meperidine; (▼) methadone; (◇) fentanyl; (◆) hyoscine.

pound. Meperidine and methadone proved to be very similar in inhibitory potency with both drugs producing 31% inhibition with 200 nmol of compound. Naloxone and buprenorphine were only weakly active with 200 nmol of drug showing 15% and 11% inhibition, respectively, while fentanyl and naltrexone were essentially inactive at this inhibitory concentration. In the range 600–1600 nmol, however, the four poorest inhibitors, naloxone, buprenorphine, fentanyl, and naltrexone, showed significant inhibition (23–36%). Although hyoscine produced only 9% inhibition at 200 nmol, 40% inhibition was achieved with 1600 nmol of the drug. Papaverine did not inhibit IgE binding over the concentration range 160–1600 nmol.

Discussion

The relevance of studies such as these to anesthesiologists is related to subsequent drug exposure. Fisher,[13] showed that several life-threatening reactions to drugs used in anesthesia were related to a failure to communicate, failure to investigate, and failure to appreciate the possibility of cross-sensitivity. When a reaction is due to the direct histamine-releasing effects of a drug, which is often assumed, a subsequent reaction could be prevented by use of antihistamines or a slower rate of infusion. The expression "anaphylactoid" may mean that no evidence of an immunological basis to the reaction exists or that such a basis has not been detected. In many cases in the literature, the reaction is classified as anaphylactoid be-

Compound	Structure	Inhibition (%) of IgE antibody binding to morphine-Sepharose with 200 nmol of compound
Morphine		72
Codeine		72
Nalorphine		46
Naloxone		15
Naltrexone		3
Buprenorphine		11
Fentanyl		3
Hyoscine		9
Meperidine		31
Methadone		31

*Buprenorphine contains an endoetheno bridge between C_6 and C_{14} and a 1-hydroxy-1, 2, 2 -trimethylpropyl substitution on C_7.

FIG. 2. Inhibition of morphine-IgE antibody interaction by morphine and some structural analogues.

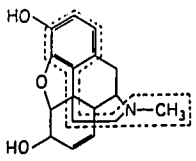
cause an immunologic basis has not been sought or has not been sought appropriately. As technology is developed to detect drug-specific antibodies, it appears that a considerable number of responses previously thought to be nonimmunological that occur in relation to anesthesia have an immunological basis.

In previous studies with sera from patients who experienced life-threatening anaphylactic reactions during anesthesia, we developed RIAs for the detection of drug-reactive IgE antibodies to neuromuscular blocking drugs[1–6] and the induction agent thiopental.[14,15] Drug-reactive IgE antibodies to the antibacterial agents trimethoprim[16,17] and sulfamethoxazole,[18] as well as to the antibiotics penicillins and cephalosporins (unpublished), have also been detected. Based on the successful methodology used in the development of RIAs for these drugs, we attempted to develop a drug-specific immunoassay as a diagnostic test for immediate-type hypersensitivity to morphine and to examine the molecular basis of IgE-binding by the drug.

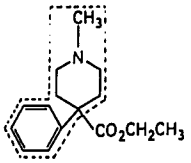
The patient proved to be skin-test positive to morphine, papaveretum, and the histamine-releasing agent d-tubocurarine, but negative to all the other drugs tested (table 1) suggesting that the life-threatening anaphylactic-like reaction experienced by the subject was probably produced by morphine. The response to the control drug of d-tubocurarine was less than is normally seen, suggesting that the patient's cutaneous response to the histamine-releasing drugs was diminished. This response does not, however, compromise the relevance of the positive tests that are due to a different mechanism. Histamine-releasing drugs used as controls in skin testing are primarily used to suggest that negative responses to other drugs may be false-negatives if histamine releasing capability is impaired. Further evidence to support the conclusion that the subject reacted clinically to morphine was obtained from direct binding immunoassay studies (table 2) that revealed the patient's serum had significant levels of morphine- and codeine-reactive IgE antibodies. In the preparation of the morphine- and codeine-solid phase supports, the mode of coupling of the drugs to the bisoxirane-activated carrier was probably through the nucleophilic hydroxyl groups attached at position 6 of the morphine and codeine nuclei. The direct binding and inhibition studies confirmed that both drugs had bound to the activated support.

Using the RIA for hyoscine, binding of IgE antibodies in the patient's serum to the drug-solid phase was weakly positive. This finding is consistent with the skin test results where hyoscine did not produce a positive response in the subject. It seems likely therefore that morphine and/or related alkaloids present in papaveretum provoked the life-threatening anaphylactic reaction in the patient. The results obtained with inhibition experiments using the patient's serum and morphine-Sepharose support this conclusion.

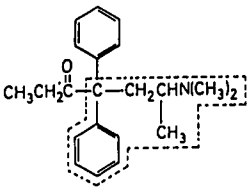
In analysing the hapten inhibition results, a similar structural determinant was recognized in each of the cross-reacting compounds. The two best inhibitors, morphine and codeine, were practically identical in inhibitory potency. These two drugs vary only in the composition of the group attached at position 3 where morphine has a hydroxyl and codeine a methoxy group. This suggests that the complementary IgE antibodies in the patient's serum do not recognize this region of the morphine molecule. With nalorphine, which differs from morphine only by the substitution of a propylene group for the methyl group on the ring N atom, a significant decrease in inhibitory potency was observed. This suggests that the composition of the group attached to the N atom is important for IgE antibody recognition. Naloxone, which varies from nalorphine in having a keto group at C-6, a single bond instead of a double bond between C-7 and C-8, and a hydroxyl group on C-14, was markedly weaker than morphine as an inhibitor. This leads to the conclusion that the cyclohexenyl ring is important for IgE binding since the differences between nalorphine and naloxone are confined to this region of the molecule. Naloxone, although weakly active, was a better inhibitor than naltrexone, which differs from the former compound only in having a cyclopropylmethyl instead of an allyl substituent attached to the N. This further suggests that the substituent attached to the N atom is a critical feature of the allergenic determinant. The inhibition exhibited by both meperidine and methadone are surprising at first sight, but on close examination of the structures, it can be seen that both compounds contain structural features that are similar to those found in morphine. In particular, all three compounds share a sequence of an aromatic ring separated from the N atom by three C atoms with a methyl group attached to the N atom (figs. 2 and 3). Thus, four of the five best inhibitors morphine, codeine, meperidine, and methadone, producing inhibitory values at 200 nmoles of 72%, 72%, 31%, and 31%, respectively) have methyl groups attached to the N atom while nalorphine contains a methylene (CH_2) group. With fentanyl, (3% inhibition at 200 nmol, but 20–36% inhibition in the range 700–1600 nmoles) a sequence of atoms including an additional N atom shows some similarity to morphine (figs. 2 and 3). Taking all of the inhibition results into account, we conclude that the important structural features of the morphine allergenic (that is, IgE-binding) determinant comprise the cyclohexenyl ring with a hydroxyl group at C-6 and, most important of all, a methyl substituent attached to the N atom. The weak inhibitory activity demonstrated by hyoscine is probably a reflection of the ring N-methyl group on the molecule since a methyl substituent attached to a ring N appears to be a critical,



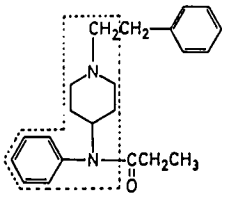
Morphine



Meperidine



Methadone



Fentanyl

FIG. 3. Structure of morphine and structures of some of the compounds that cross-reacted (weakly in the case of fentanyl) with the morphine-reactive antibodies detected in the patient's serum. The similar structural sequences in the different compounds thought to be involved in IgE-binding are outlined by dashed lines. Other compounds that showed significant cross-reactivity are not shown since the putative determinant in the morphine structure is either common (codeine), similar (nalorphine, where the N-methyl of morphine is replaced by an N-propylene group) or similar but with some more pronounced differences (naloxone, naltrexone, and buprenorphine).

but not the only, feature of the IgE-binding determinant of morphine.

As more sera from subjects allergic to morphine are examined for IgE antibodies that react with the drug, it will be interesting to see what structural variations, if any, occur to the morphine determinant identified here.

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