

Anaphylactoid Reactions to Narcotic Analgesics

***Malcolm M. Fisher,¹ David G. Harle,²
and Brian A. Baldo^{*,2}***

*¹Intensive Therapy Unit, Royal North Shore Hospital of Sydney,
St. Leonards NSW 2065 and Department of Anaesthesia,
University of Sydney; and ²Kolling Institute of Medical Research,
Royal North Shore Hospital and Department of Medicine,
University of Sydney, Sydney, Australia*

NARCOTIC ANALGESICS AND HISTAMINE RELEASE

The narcotic analgesics are among the most commonly prescribed drugs in hospitals and are administered to 30–41% of patients (1). Although these drugs produce potent and serious side effects, anaphylactoid reactions to the drugs have rarely been described (2), and compared to neuromuscular blocking drugs, induction agents, and colloids, their “antigenic” safety is impressive.

Many of the narcotics are potent histamine releasers, and to this effect has been attributed many of the anaphylactoid responses that have been documented (3–5). The direct pharmacological release of mediators, such as histamine, by opioid narcotics is likely to occur more frequently than true type I immediate hypersensitivity reactions to the drugs. It has been shown that morphine-induced plasma histamine release produces cardiovascular abnormalities that can be blocked by H₁ and H₂ antihistamines in combination (6). Morphine releases histamine from rat peritoneal mast cells (7) and human skin mast cells (8,9), but not basophils (7) or pulmonary mast

*Author to whom all correspondence and reprint requests should be addressed.

cells (C. Hirshman, personal communication). Morphine and meperidine (pethidine) appear to be the most potent releasers of histamine with naloxone, alfentanil, and nalbuphine the least potent. In a study by Levy and colleagues (8), 16 volunteers were tested intradermally with a number of narcotics at a concentration of 5×10^{-4} M. The results revealed that morphine, meperidine, fentanyl, and sufentanil produced both wheal and flare responses, although no response was observed with naloxone, alfentanil, and nalbuphine. Butorphanol produced a significant wheal but no flare, whereas naloxone attenuated cutaneous wheal and flare responses to fentanyl but only the flare response to morphine.

Although under some circumstances cutaneous phenomena are associated with elevated plasma histamine levels (10), the cutaneous allergoid phenomena associated with parenteral morphine and butorphanol are not associated with increased plasma histamine levels, suggesting that considerable cutaneous release occurs before plasma levels rise (11). Although controlled studies have shown cardiovascular abnormalities resulting from the direct histamine-releasing effects of morphine (3,6), morphine may produce hypotension by other mechanisms (12,13) and the correlation between plasma histamine levels and hypotension is poor (13).

Flacke and colleagues (3) studied histamine release resulting from four narcotics during surgery, and found meperidine caused greater release than morphine and little release occurred with fentanyl or sufentanil. The results of the study could have been influenced by one patient who may have had an anaphylactic reaction to meperidine.

In another study, it was shown that massive doses of fentanyl produced fewer cardiovascular effects than doses of morphine used routinely in cardiac anesthesia (14). Since fentanyl is between 80–200× as potent an analgesic as morphine, the authors conclude that fentanyl administration may be a more direct way of avoiding histamine-induced effects on the peripheral circulation.

Since Herxheimer (15) first suggested that morphine was contraindicated in asthma because of its histamine-releasing effects, this belief appears to have become enshrined in folklore, and has been reiterated as recently as 1989 (16). There is no evidence to

support this belief. Indeed, the converse, that direct histamine release does not produce bronchospasm, is the view best supported by the evidence. Although patients who spontaneously develop asthma have elevated venous plasma histamine levels (17), no direct histamine-release study has produced bronchospasm. Indeed, a cogent argument can be made that, if significant bronchospasm occurs in an "anaphylactoid reaction," it is likely that the reaction is immune-mediated (18). One can further argue that the direct histamine-releasing effects of drugs given in normal dosage do not cause severe clinical anaphylaxis in normal patients.

NARCOTIC ANALGESICS AND IMMUNE FUNCTION

It is well known that heroin addicts are more susceptible to infectious disease, and studies in animals show suppressed immune function, probably related to activation of the hypothalamo/pituitary/adrenal axis (19).

ANAPHYLAXIS TO NARCOTIC ANALGESICS

Such reactions are extremely rare. The comprehensive review of Boileau and colleagues (20) listed reactions to dextromoramide (2), pentazocine (1), phenoperidine (1), morphine (2), meperidine (1), and fentanyl (3). Other cases have been described for meperidine (21,22), codeine phosphate (23), papaveretum (24), and fentanyl (25-27).

In the report of Bennett et al. (25), an anaphylactic reaction to fentanyl was confirmed by a positive intradermal test 1 mo after the reaction, suggesting the likelihood of specific IgE antibodies to fentanyl on the subject's skin mast cells. Another report of possible fentanyl anaphylaxis occurred in a subject who received fentanyl and alloferin intraoperatively and had positive intradermal tests to both drugs (26). The report of Zucker-Pinchoff and Ramanathan (27) concerned a reaction to epidurally administered fentanyl. Intradermal testing with the drugs suggested an anaphylactic reaction, and previous exposure to the drug supported the diagnosis.



Fig 1. Histogram showing uptakes of ^{125}I -anti-human IgE, and reflecting uptakes of human IgE antibodies, by morphine, codeine, and control solid phases used with cord, "normal," and "allergic" sera and serum from a subject who experienced a life-threatening anaphylactic reaction following administration of papaveretum. Ten normal sera from nonallergic, healthy adults were used. The ten "allergic" sera used were from adult subjects allergic to house dust mites and/or grass pollens, but not opioid alkaloids. Open bars represent reactions with cord serum; hatched bars, reactions with "normal" sera; black bars, reactions with "allergic" sera; and dotted bars, reactions with serum from the subject who reacted to papaveretum.

DETECTION OF IgE ANTIBODIES REACTIVE WITH MORPHINE AND CODEINE BY RADIOIMMUNOASSAYS

Radioimmunoassays for the detection of serum IgE antibodies reactive with morphine and codeine have been recently reported (24). Results obtained with serum from a subject who experienced a life-threatening anaphylactic reaction to papaveretum, and was shown by intradermal skin testing to be allergic to papaveretum and morphine, are summarized in Fig. 1. With both morphine- and codeine-Sepharose, strongly positive uptakes were obtained with serum from the subject. In contrast, the results with control solid phases and serum controls proved to be negative.

Prior to these studies, Levy and Rockoff (22) had detected IgE antibodies to meperidine in a patient who reacted to the drug, but no details of methods or controls were given. It is likely that, as with

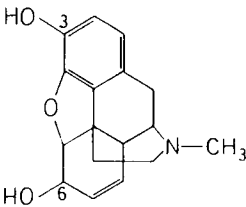
Structure	Allergenic determinant identified
	N-methyl, Cyclohexenyl ring with hydroxyl at C-6

Fig. 2. IgE-binding determinant identified on the morphine molecule. The allergenically dominant feature of the determinant is the methyl substituent attached to the *N*.

the neuromuscular blocking drugs (NMBDs) as the technology to detect drug-specific IgE to narcotics develops, a greater number of severe “anaphylactoid” reactions will be found to be IgE-mediated.

Identification of Morphine Allergenic Determinant

Hapten-inhibition studies were performed to verify the specificity of binding of the detected IgE antibodies and identify the morphine allergenic determinant (24). Using morphine and a number of structural analogs, as well as meperidine, methadone, and fentanyl, it was concluded that the structural features of the IgE binding determinant on morphine comprised the cyclohexenyl ring with a hydroxyl group at C-6 and, most importantly, a methyl substituent attached to the *N* atom (Fig. 2). Meperidine and methadone were found to crossreact weakly with the subject's IgE antibodies.

Cross-Sensitivity Among Narcotics

Too few patients have been studied to determine accurately the likelihood of clinical cross-sensitivity among narcotics. Cutaneous testing in the case described by Zucker-Pinchoff and Ramanathan

(27) suggested possible crossreactivity among fentanyl, alfentanil, sufentanil, and meperidine. Interestingly, morphine did not produce any allergic response 3 h and 24 h after the initial reaction to fentanyl, and it was concluded that morphine did not seem to crossreact with fentanyl and its derivatives.

In the report of an anaphylactic reaction to papaveretum described by Harle et al. (24), cutaneous testing and hapten inhibition of IgE antibody binding suggested clear crossreactivity between morphine and codeine, some crossreactivity with nalorphine, methadone, and meperidine (which was administered uneventfully), and no crossreactivity with fentanyl.

Specificity of IgE Antibodies that React with Morphine

In 1983, Baldo and Fisher (28) showed that morphine HCl interacted strongly with IgE antibodies in the sera of subjects allergic to NMBDs. On a molar basis, the alkaloid was frequently almost as potent an inhibitor of the binding of IgE to the NMBD solid phase as the NMBD implicated in the subject's anaphylactic reaction. The basis of the crossreactivity between morphine and the NMBDs was shown to be the presence of quaternary or tertiary ammonium groups in the compounds, and this structural similarity is readily apparent if one examines molecular models of morphine and *d*-tubocurarine (29). Later studies confirmed these findings and demonstrated that employment of a morphine solid phase provided a valuable supplementary test when screening for IgE antibodies that react with substituted ammonium groups (29).

Even though the IgE antibodies in the sera of NMBD-allergic subjects frequently interact with morphine, these subjects are invariably able to tolerate morphine and show no allergic manifestations. This is believed to be because the NMBDs contain at least two substituted ammonium groups, which permits the crosslinking of adjacent IgE molecules on a mast cell necessary for allergic mediator release, whereas morphine contains only one such group. In the one morphine-allergic subject we have closely studied so far, the morphine-reactive serum IgE antibodies were found to be complementary to the *N*-methyl group and the cyclohexenyl ring with a hydroxyl at C-6, that is, structures encompassing, but also additional to, the substituted ammonium group (24). Unlike

the NMBDs, then, morphine appears to have only a single allergenic determinant group of this type on the molecule, suggesting that allergic reactivity to the compounds is mediated via protein or membrane binding of the drug (30,31). It remains possible that more than one identical, or similar allergenic determinant(s) on morphine, distinct from the determinant already identified, and capable of crosslinking IgE-antibodies, may be found. It should be emphasized, however, that apart from penicillins and some alkylating agents, evidence for conjugation of drugs to carriers is almost always lacking (32). Leaving aside this question, another question with both fundamental and applied implications remains, namely, would a NMBD, such as succinylcholine, *d*-tubocurarine, or alcuronium, provoke an allergic reaction in a subject with type I IgE-mediated hypersensitivity to morphine or codeine? Although the similarity of the NMBD and morphine antigenic sites can be clearly demonstrated by immunological inhibition studies, most if not all patients allergic to NMBDs receive narcotics uneventfully. In the subject we investigated (24), skin tests to *d*-tubocurarine and pancuronium were negative, and pancuronium was given uneventfully 6 wk after the anaphylactic reaction. Given the apparently rare occurrence of immediate hypersensitivity reactions to morphine, the question of possible clinical cross-sensitivity between this narcotic and NMBDs will probably be difficult to answer unequivocally for some time to come. Table 1 presents a summary of findings when sera from the two groups were compared in direct binding and inhibition studies. Examination of more sera from morphine-allergic subjects would reveal the number and nature of allergenic determinants on the morphine molecule. Clearly, if some of these determinants do not encompass the tertiary ammonium group, crossreactions with NMBDs would not be expected.

DIAGNOSIS

Intradermal testing has been used for the diagnosis of anaphylactic reactions to narcotic analgesics (22,24–27,33). Because of the potent cutaneous histamine-releasing effects of meperidine and morphine, dilutions of 1:100,000 are needed for intradermal testing. Where possible, tests for drug-reactive IgE antibodies should

Table 1
Summary of Typical Results of Direct Binding and Inhibition
Studies on Drug-Reactive IgE Antibodies in Sera from Subjects
Allergic to Morphine or Neuromuscular Blocking Drugs

Serum from morphine- reactive subject	Serum from neuromuscular blocking drug ¹ -reactive subject
Direct Binding	
Reaction of IgE antibodies with drug solid supports	
Morphine > choline > <i>d</i> -tubocurarine > alcuronium	Choline > morphine > <i>d</i> -tubocurarine > alcuronium
Inhibitions	
Morphine-Sepharose: ² Morphine, codeine >> <i>d</i> -tubocurarine > > alcuronium, succinylcholine, choline, atracurium, metocurine	Morphine-Sepharose: Morphine >> <i>d</i> -tubocurarine >> alcuronium, succinylcholine
	Choline-Sepharose: Succinylcholine ≥ morphine ≥ <i>d</i> -tubocurarine ≥ alcuronium

¹For example, succinylcholine.

²Order of inhibitory potency.

also be used to confirm the case history and skin test results. As experience is gained with specific IgE tests for drugs, and particularly when assays are developed for a broader spectrum of narcotic drugs, these assays may become the diagnostic method of choice, since cutaneous testing with potent histamine releasers can be difficult to interpret.

CONCLUSION

Although reports in the literature of severe anaphylactic reactions to narcotics are rare, they occur, and it may be that such reactions are true IgE-mediated reactions, rather than direct histamine release as has been previously believed. Cross-sensitivity

between individual opioid derivative members of the fentanyl group of drugs appears likely.

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