Histamine Release during Morphine and Fentanyl Anesthesia

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High doses of morphine produce peripheral vasodilation and frequently significant hypotension. These effects are thought to be due, in part, to the release of histamine. One putative advantage of high-dose fentanyl anesthesia is its relatively small effect on peripheral vascular resistance. In a randomized study, the authors examined the possibility that the hemodynamic differences between morphine and fentanyl might be attributable to histamine release. Fifteen patients were studied prior to coronary artery bypass surgery. Subjects received an infusion of morphine (1 mg·kg⁻¹, iv at 100 µg·kg⁻¹· min⁻¹ [n = 8]) or fentanyl (50 µg·kg⁻¹ at 5 µg·kg⁻¹·min⁻¹ [n = 7]). Patients in the morphine group had an average 750 per cent peak increase in plasma histamine accompanied by a significant decrease in mean arterial pressure (−27 mmHg) and systemic vascular resistance (−520 dyne·s·cm⁻⁵). The greatest decrease in systemic vascular resistance occurred in those patients with the highest levels of plasma histamine (r = −0.81). Patients in the fentanyl group had no change in plasma histamine and no decrease in arterial pressure or systemic vascular resistance. Cardiac output and heart rate were comparable between the two groups. Differences in the release of histamine account for most, if not all, of the different effects of morphine and fentanyl on the peripheral vasculature. (Key words: Anesthesia: cardiovascular. Anesthetics, intravenous: morphine; fentanyl. Blood pressure: drug effects; vascular resistance. Histamine.)

HIGH DOSES of morphine and fentanyl are routinely used for intravenous anesthesia in patients with minimal circulatory reserve. It is well documented that clinically useful doses of these drugs produce little in the way of myocardial depression.[1,2] In volunteers and cardiac surgical patients, morphine usually produces a transient or sustained decrease in systemic vascular resistance.[1,3–5] In contrast, when Stanley introduced the use of fentanyl–oxygen anesthesia, he noted that even 50 µg·kg⁻¹ of fentanyl produced little change in peripheral vascular tone.[2]

Morphine is known to release histamine in humans, although until recently the evidence for this was indirect, i.e., flushing and urticaria.[6] In a recent study from our laboratory, Philbin et al.[7] have shown that morphine does indeed produce large increases in plasma histamine and that histamine antagonists block the accompanying va-

sodilation. To our knowledge, fentanyl has not been described as producing clinically observable signs of histamine release.

The development of a sensitive radioenzymatic assay for histamine[8] and its recent improvement[9] now make it possible to measure the small changes in plasma histamine that are produced by alkaloids of the sort used in anesthesia. The present study was designed to compare the histamine released by high doses of morphine and fentanyl in cardiac surgical patients. At the same time, we have correlated plasma histamine with changes in several hemodynamic variables.

Methods

Fifteen patients scheduled for elective coronary artery bypass surgery were studied according to an institutionally approved protocol after giving informed consent. None had signs or symptoms of congestive heart failure, and all had ejection fractions of at least 0.50 at the time of cardiac catheterization. All patients had been receiving propranolol for at least 6 weeks, with the last dose given approximately 12 h prior to anesthesia. Premedication was mg·kg⁻¹ intramuscular morphine 0.1 mg·kg⁻¹ and scopolamine 0.4 mg.

Patients were randomly allocated to a morphine or fentanyl treatment group. After placement of radial and pulmonary artery catheters while patients were under local anesthesia, control hemodynamic values were recorded. We measured radial artery pressure (BP), pulmonary artery pressure (PA), central venous pressure (CVP), and cardiac output (CO) by thermodilution. Systemic vascular resistance (SVR) was calculated as $\frac{BP - CVP}{CO} \times 80$. Radial arterial and mixed venous (pulmonary arterial) blood samples (5 ml) were collected for determination of plasma histamine.

Oxygen was administered by mask, and the narcotic infusion was begun via an IMED® volumetric pump. Morphine (1 mg·kg⁻¹, total dose) was administered at a rate of 100 µg·kg⁻¹·min⁻¹. Fentanyl (50 µg·kg⁻¹, total dose) was given at a rate of 5 µg·kg⁻¹·min⁻¹. The total dose of morphine and the rate of administration were those routinely used for cardiac surgical procedures at this institution. The fentanyl dose and infusion rate approximated those described by Stanley.[2]

Metocurine 0.3 mg·kg⁻¹ was administered concomitantly over a 5-min period. Respiration was assisted, then
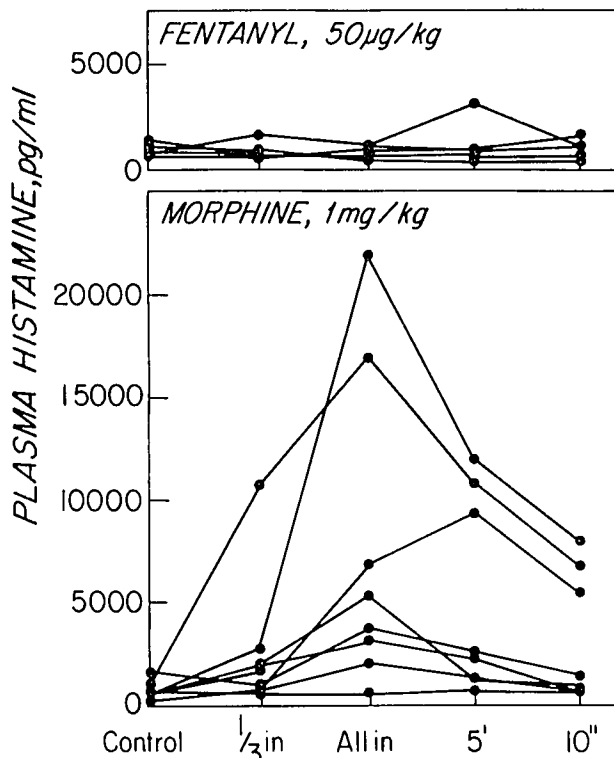
FIG. 1. Individual data for plasma histamine from arterial samples taken at the times indicated. Differences in peak response were highly significant ($P < 0.005$).

controlled, and normocarbia was confirmed by periodic monitoring of arterial blood gases. Hemodynamic measurements and blood samples were taken at five points in all: control; after administration of one third of the total dose of narcotic; and at 0, 5, and 10 min following the drug infusion. The patients were not intubated or surgically stimulated during the period of measurement and sample collection. We did not adopt strict criteria for the use of pressors, but phenylephrine was administered when deemed appropriate by the attending anesthesiologist.

Blood samples were collected in heparinized glass tubes and placed immediately on ice. All assays were done in blind fashion. The histamine assay used was a modification of the single isotope radioenzymatic assay of Beaven which has been previously described.[9] This assay is linear over the clinically useful range and has a sensitivity sufficient to detect levels less than 100 pg· ml^{-1}. Significant differences in plasma histamine levels and in hemodynamic variables were determined by correlated t tests. Change in systemic vascular resistance was compared with plasma histamine by simple correlation. A logarithmic transformation was used since the histamine response is not normally distributed.

Results

In agreement with our previous study of morphine-induced histamine release,[7] there were no significant differences between arterial and mixed venous plasma histamine levels; only arterial levels are reported here. There were no significant differences in baseline plasma histamine between the morphine and fentanyl groups, and these values were all within the normal range for our laboratory. The administration of fentanyl caused virtually no change in plasma histamine at any point measured (fig. 1). The morphine group had an average 750 per cent peak increase in plasma histamine, but, as in the case of our previous studies,[7,9] there was a wide range of response. This varied from no detectable increase in plasma histamine to a peak histamine level of 20 ng·ml^{-1}. The latter approaches the level previously reported in anaphylactic reactions.[10] Plasma histamine after 0.33 mg·kg^{-1} of morphine was not a good predictor of the response to the total dose.

In the morphine group, the peak elevation in plasma histamine corresponded very well with the maximal decrease in systemic vascular resistance (-520 ± 80 dyne· s·cm^{-5}) and in mean blood pressure (-27 ± 4 mmHg) from control values (fig. 2). In contrast, the fentanyl group had no change in plasma histamine, no drop in systemic vascular resistance, and no fall in mean blood pressure. Figure 3 shows that the change in systemic vascular resistance following the administration of morphine was inversely correlated with plasma histamine ($r = -0.81$). This indicates that those patients with the largest increases in histamine had the greatest hemodynamic responses.

Hemodynamic data collected at 5 and 10 min following drug administration must be interpreted cautiously since seven of eight morphine patients received phenylephrine. None of the patients receiving fentanyl required pressor support.

Cardiac output rose slightly in patients given morphine ($P < 0.05$) and did not change significantly in those given fentanyl. Heart rate did not change significantly in either group, perhaps because of residual beta blockade.

Discussion

The classic work of Schmidt and Livingston demonstrated tachyphylaxis to the hypotensive effect of morphine in dogs.[11] Since that study, it has generally been assumed that histamine was somehow involved in the systemic response to morphine, although direct proof was lacking. The circumstantial evidence, however, was strong: intradermal injection of morphine produced a "triple response" (redness, flare, and wheal). Intrave-

nous injection of morphine or histamine produced hypotension, flushing, itching and urticaria.

Feldberg and Paton utilized a perfused cat gastrocnemius preparation and a relatively non-specific bioassay to demonstrate histamine release by three opiate alkaloids.[12] Schachter found that meperidine induced a dose-related release of histamine from cat skin.[13] Johnson and Moran showed that morphine released histamine from rat peritoneal mast cells without disrupting the cells themselves,[14] although high concentrations of morphine were required.

Unfortunately, most *in vivo* studies of drug-induced histamine release have been restricted to the massive effects of insect venoms and the phenylethylamine polymer 48/80.[6] Low molecular weight basic amines, such as morphine and other anesthetic drugs, release amounts of histamine that are well below the sensitivity of unmodified biological and fluorometric assays unless relatively large blood samples are taken and elaborate steps
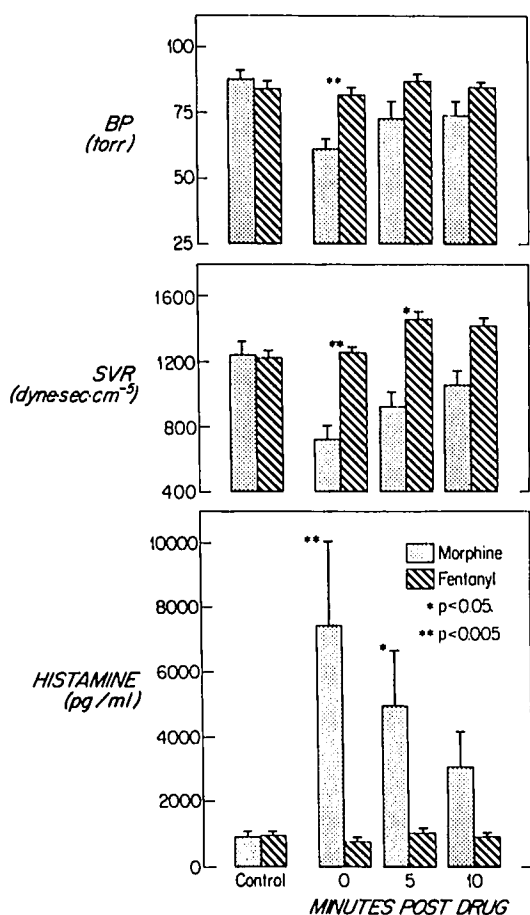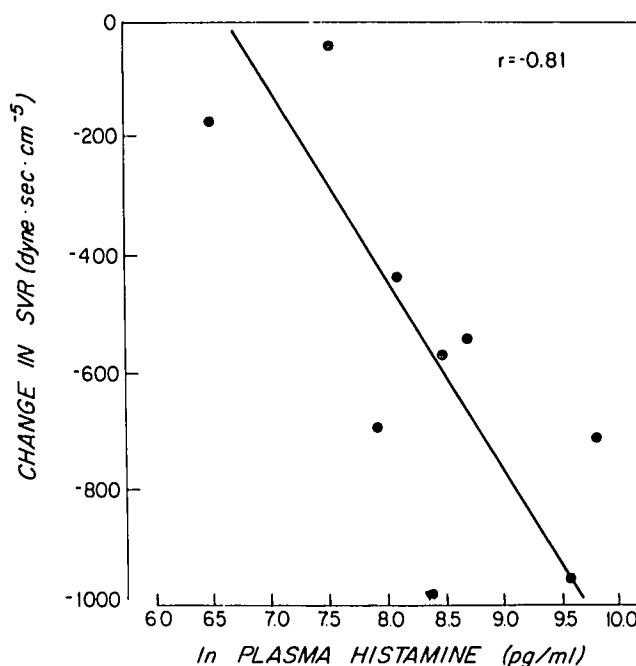
FIG. 3. Correlation of plasma histamine (logarithmic transformation, see text) with peak change in systemic vascular resistance for patients given morphine. Data for fentanyl are not included since neither variable changed significantly in this group.

are introduced to concentrate and separate histamine from interfering substances. Lorenz and co-workers used such a technique to measure histamine released by plasma expanders and induction agents.[15] The enzymatic isotopic assay used in this study has a sensitivity of 100 $pg \cdot ml^{-1}$ and requires as little as 50 μl plasma. Thus, it has been possible to make direct, repeated measurements of the changes in plasma histamine produced by clinically useful drugs. In a previous study we used this technique to show that d-tubocurare produces a dose-related increase in plasma histamine that correlates very well with the degree of observed hypotension.[9] Philbin *et al.*[7] have recently confirmed the early *in vitro* morphine studies by demonstrating that 1 $mg \cdot kg^{-1}$ morphine can release significant amounts of histamine. In that study, hypotension and decreased systemic vascular resistance also correlated well with elevations in plasma histamine, and most of these hemodynamic effects were blocked by pretreatment with diphenhydramine and cimetidine. This would suggest that histamine release plays an important role in determining vasomotor tone following the administration of morphine.

Opiates may produce hypotension in other ways, however. In 1972, Lowenstein *et al.*[16] studied the vascular effects of morphine on the isolated, separately perfused canine gracilis muscle. They showed that there were two mechanisms responsible for the loss in peripheral vas-

FIG. 2. Data for plasma histamine (from fig. 1), mean arterial pressure and systemic vascular resistance at the times indicated (mean ± SEM). Asterisks indicate significant differences ($*P < 0.05$; $**P < 0.005$).

cular resistance: first, there was a local direct vasodilator effect and second, a centrally mediated loss of vasomotor tone. The second effect requires intact innervation and is potentiated when baseline sympathetic tone is high. We had no *a priori* reason to believe that fentanyl or any other opioid should behave differently from morphine in this regard.

The results in the present study confirm prior observations that even massive doses of fentanyl produce fewer cardiovascular effects than doses of morphine routinely used in cardiac anesthesia. Furthermore, it seems clear that in this patient population, almost all of the hemodynamic difference can be accounted for by differences in the release of histamine. Baseline systemic vascular resistance and mean arterial pressure were virtually identical in the two groups. As expected, patients given morphine became hypotensive; plasma histamine rose by 750 per cent, systemic vascular resistance dropped by 42 per cent, and the two variables were well correlated. In the fentanyl group, mean arterial pressure did not change, and there was no significant change in either plasma histamine or systemic vascular resistance.

Other factors potentially influencing the hemodynamic responses (*e.g.*, nitrous oxide, metocurine) were constant between the two groups. Hypotension secondary to narcotic-induced bradycardia might not have been demonstrable in the face of residual beta blockade, but this too should have been consistent for both groups.

The opiate doses selected have clinical relevance, although they are not equianalgesic. Fentanyl is variably considered to be 80 to 200 times as potent an analgesic as morphine (probably closer to 200 if one is considering peak effect). Assuming a comparable potency ratio still holds in this high dose range, one would expect roughly five times more opiate effect (*e.g.*, analgesia) after 50 μg·kg^{-1} of fentanyl than after 1 mg·kg^{-1} of morphine. There is, of course, no reason to assume that histamine release is at all related to interaction at opiate receptors. The amount of histamine released probably relates primarily to the concentration of drug achieved at mast cell membranes. It is therefore reasonable to assume that histamine release will be least with extremely potent drugs such as fentanyl since clinically useful effects occur at extremely low concentrations.

The rapid intravenous administration of morphine exposes tissues to transient, high concentrations of the drug. The hemodynamic effects may be minimized by slowing the rate of infusion (thereby decreasing histamine release), or pretreating with histamine antagonists (blocking the histamine effect at end organs). On the basis of this study, the use of fentanyl would seem to be a more direct way to avoid histamine-induced effects on the peripheral circulation.

References

1. Wong KC, Martin WE, Hornbein TF: The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. ANESTHESIOLOGY 38:542–548, 1973
2. Stanley TH, Webster LR: Anesthetic requirements and cardiovascular effects of fentanyl oxygen and fentanyl diazepam oxygen anesthesia in man. Anesth Analg (Cleve) 57:411–416, 1978
3. Canahan TJ, Ominsky AJ, Wellman H, et al: A prospective random comparison of halothane and morphine for open-heart anesthesia: One year's experience. ANESTHESIOLOGY 38:528–535, 1973
4. Lowenstein E, Hallowell P, Levine FH, et al: Cardiovascular response to large doses of intravenous morphine. N Engl J Med 281:1389–1393, 1969
5. Samuel IO, Unni VKN, Dundee JW: Peripheral vascular effects of morphine in patients without preexisting cardiac disease. Br J Anaesth 49:935–939, 1977
6. Rothschild AM: Histamine release by basic compounds, Handbook of Experimental Pharmacology, XVIII/Part I. Edited by Silva M. Berlin, Springer-Verlag, 1966, pp 386–430
7. Philbin DM, Moss J, Akins CW, et al: The use of H_1 and H_2 histamine antagonists with morphine anesthesia: A double blind study. ANESTHESIOLOGY 55:292–296, 1981
8. Beaven MA, Jacobsen S, Horakova Z: Modification of the enzymatic isotopic assay of histamine and its application to measurements of histamine in tissues, serum, and urine. Clin Chim Acta 37:91–103, 1972
9. Moss J, Rosow CE, Savarese JJ, et al: Role of histamine in the hypotensive action of d-tubocurarine in man. ANESTHESIOLOGY 55:19–25, 1981
10. Moss J, Fahmy NR, Sunder N, et al: Hormonal and hemodynamic profile of an anaphylactic reaction in man. Circulation 63:210–213, 1981
11. Schmidt, CF, Livingston AE: The action of morphine on the mammalian circulation. J Pharmacol Exp Ther 47:411–441, 1933
12. Feldberg W, Paton WDM: Release of histamine from skin and muscle in the cat by opium alkaloids and other histamine liberators. J Physiol (Lond) 114:490–509, 1951
13. Schachter M: The release of histamine by pethidine, atropine, quinine and other drugs. Br J Pharmacol 7:646–654, 1952
14. Johnson AR, Moran NC: Inhibition of the release of histamine from rat mast cells: The effect of cold and adrenergic drugs on release of histamine by 48/80 and antigen. J Pharmacol Exp Ther 175:632–640, 1970
15. Lorenz W, Doenicke A: Histamine release in clinical conditions. Mt Sinai J Med (NY) 45:357–386, 1978
16. Lowenstein E, Whiting RB, Bittar DA, et al: Local and neurally mediated effects of morphine on skeletal muscle vascular resistance. J Pharmacol Exp Ther 180:359–367, 1972