Anesthesiology
55:292–296, 1981

The Use of H_1 and H_2 Histamine Antagonists with Morphine Anesthesia: A Double-blind Study

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High doses of morphine can produce significant cardiovascular effects generally attributed to histamine release. The authors examined the possibility that H_1 and H_2 histamine antagonists might prove beneficial in preventing these responses. In a randomized double-blind study, four groups of 10 patients each received 1 mg/kg morphine and either a placebo, diphenhydramine (H_1), cimetidine (H_2), or both of the histamine antagonists. The morphine-placebo group demonstrated a marked elevation in plasma histamine levels (880 ± 163 to 7437 ± 2684 pg/ml), a decrease in systemic vascular resistance (SVR) (15.5 to 9.0 l torr/(l·min^{-1}) and diastolic BP (71 ± 3 to 45 ± 4 torr) and an increase in cardiac index (CI) (2.4 ± 0.2 to 3.0 ± 0.2 l·min^{-1}·m^{-2}). The administration of either cimetidine or diphenhydramine with morphine provided minimal protection. Those patients who received morphine and both antagonists demonstrated significant attenuation of these responses (CI 2.5 ± 0.2 to 2.5 ± 0.1 l·min^{-1}·m^{-2}; SVR 17.4 to 14.6 torr/(l·min^{-1}) although plasma histamine levels showed a comparable increase (1059 ± 222 to 7653 ± 4242 pg/ml). These data demonstrate directly that many of the hemodynamic effects of morphine can be attributed to histamine release. They further demonstrate that significant hemodynamic protection can be obtained by the use of histamine antagonists and the combination of H_1 and H_2 antagonists is superior to either given alone. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: morphine. Histamine: cimetidine; diphenhydramine; release.)

MORPHINE is widely used as the principal anesthetic agent in patients undergoing cardiac surgery primarily because of its lack of cardiac depression.[1,2] The usefulness of this agent is sometimes compromised by the occurrence of significant hemodynamic alterations, particularly hypotension, most commonly attributed to histamine release.[3–5] This assumption has generally been based upon indirect evidence (*i.e.*, the presence of flushing and urticaria), because of the lack of a sensitive and accurate assay for plasma histamine levels.

The recent development of such an assay[6,7] coupled with the development of H_1 and H_2 histamine receptor antagonists prompted a reexamination of the role of histamine in morphine anesthesia. This study was undertaken to determine: 1) the quantitative effect of intravenous morphine on plasma histamine levels; 2) the relationship of plasma histamine to hemodynamic variables; and 3) the ability of prior administration of H_1 and H_2 histamine blockers to attenuate these hemodynamic responses.

Methods

Forty patients scheduled for elective coronary artery bypass graft surgery were selected for study. Mean age was 56 ± 8 years, all patients were without signs or symptoms of congestive heart failure and had ejection fractions of at least 0.50 at the time of cardiac catheterization. All patients had been receiving propranolol for at least six weeks, with the last dose approximately 12 h prior to anesthesia. Informed consent was obtained in all cases and the protocol was approved by the Human Studies Committee of the hospital.

All patients were monitored continuously via an oscilloscope and a direct writing recorder with the standard limb lead II and lead V_5 of the electrocardiogram. Radial, pulmonary artery, and central venous catheters were placed under local anesthesia. A face mask was applied for delivery of oxygen and control measurements and blood samples for histamine and arterial blood gases were obtained.

Each patient received either 4 mg/kg cimetidine, 1 mg/kg diphenhydramine, a combination of the two, or an equivalent volume of placebo. Following this pretreatment they received 1 mg/kg morphine. There were four groups of 10 patients each: Group 1—placebo plus morphine; Group 2—cimetidine plus morphine; Group 3—diphenhydramine plus morphine; and Group 4—cimetidine plus diphenhydramine plus morphine. The order of patient allocation to these groups was randomized and double blind. The active and placebo medications, prepared by Smith, Kline and French Laboratories were identical

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Received from the Departments of Anaesthesia and Surgery, Harvard Medical School and the Anesthesia and Surgical Services, Massachusetts General Hospital, Boston, Massachusetts 02114. Accepted for publication February 28, 1981. Supported in part by a grant from Smith, Kline and French Laboratories. Presented in part at the annual meeting of the American Society of Anesthesiologists, St. Louis, October 1980.

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TABLE 1. Group 1: Morphine Only*

Period	$\overline{BP}$ (torr)	Diastolic BP (torr)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	HR (beats/min)	SVR ($torr/l \cdot min^{-1}$)	Venous Histamine (pg/ml)
I Control	88 ± 4	71 ± 3	2.4 ± 0.2	57 ± 2	15.5 ± 1	880 ± 163
II Placebo	85 ± 3	67 ± 2	2.6 ± 0.1	57 ± 2	14.8 ± 1	657 ± 98
III One-third in	79 ± 5	61 ± 4†	2.8 ± 0.1†	58 ± 2	12.2 ± 1‡	2467 ± 1208†
IV 2 min after	61 ± 4‡	45 ± 4‡	3.0 ± 0.2†	59 ± 3	9.0 ± 1‡	7437 ± 2684‡
V 5 min after	73 ± 8	59 ± 7‡	2.9 ± 03	64 ± 4	11.5 ± 1‡	4980 ± 1681‡
VI 10 min after	74 ± 5	57 ± 5‡	2.7 ± 0.2	59 ± 4	12.7 ± 1†	3037 ± 1090‡

* Values are means ± SE.
† $P < 0.05$ compared to control.
‡ $P < 0.01$ compared to control.

in appearance and volume, numbered and otherwise unlabeled.

Following control measurements, the numbered medication was administered. Measurements were repeated at 15 min and the inspired oxygen content was reduced to 50 per cent by the addition of nitrous oxide. Morphine was then administered IV at the rate of 5–10 mg/min, iv metocurine was added slowly for a total dose of 0.3 mg/kg to allow for controlled respiration to maintain Pa_{CO_2} within normal limits.

Five sets of measurements and samples were obtained: after the test drug, after one-third the total dose of morphine and metocurine (0.1 mg/kg), and at 2, 5, and 10 min after administration of the total dose of both drugs. At the time of the two-min measurement, the anesthesiologist in charge of the patient had the option of instituting therapy for hypotension, if present, in the form of a phenylephrine infusion. This decision was based upon clinical judgement.

During each period, measurements were made of heart rate, mean ($\overline{BP}$) and diastolic blood pressure, mean pulmonary artery ($\overline{PA}$) and pulmonary capillary wedge ($\overline{PCW}$) pressure, central venous pressure (CVP) and cardiac output (in duplicate) by thermal dilution technique (CO). Systemic vascular resistance (SVR) was calculated as the ratio of $\overline{BP}$ and CO from these measurements. Samples for arterial blood gases and for arterial and mixed venous plasma histamine levels were also obtained. The histamine assay was by a single isotope radioenzymatic method with a sensitivity of 100 pg/ml.[7] All samples were analyzed in duplicate and intra- and interassay variations were less than 10 percent.

Intragroup data were analyzed for significance using a correlated *t* test. Intergroup data were subjected to an analysis of variance.

Results

Arterial blood gases reflected the change in inspired oxygen content but were otherwise unremarkable throughout the period of the study in all four groups. The changes in $\overline{PA}$ and $\overline{PCW}$ did not achieve statistical significance nor did the variations in PVR. There was no significant difference between arterial and mixed venous histamine levels and venous levels only are reported in the tables.

GROUP 1—PLACEBO AND MORPHINE (TABLE 1)

There was a 10-fold peak increase in plasma histamine levels within 2 min of the morphine administration at which time the decreases in $\overline{BP}$, diastolic BP, and SVR were most pronounced. The increase in cardiac index (CI) was also greatest at this point. There was a gradual return toward control values but it should be noted that eight of the 10 patients required the administration of phenylephrine. SVR decreased as plasma histamine increased as did the diastolic $\overline{BP}$ (fig. 1).

GROUP 2—CIMETIDINE AND MORPHINE (TABLE 2)

This group followed a pattern similar to Group 1. The cimetidine alone produced no significant changes. The peak changes in SVR and plasma histamine again occurred within 2 min of morphine administration. This decrease in SVR was significant compared to control but less than in Group 1 (6.5 *vs.* 4.4 $torr/(l \cdot min^{-1})$, $P < 0.01$). Six patients in this group received phenylephrine after the 2-min measurements.

GROUP 3—DIPHENHYDRAMINE AND MORPHINE (TABLE 3)

The administration of diphenhydramine alone produced a significant increase in heart rate. As in the previous groups, the peak morphine effect was seen within 2 min with significant decreases in diastolic BP and SVR but less than seen with morphine alone [13 *vs.* 26 torr, $P < 0.01$ and 5.5 *vs.* 6.5 $torr/(l \cdot min^{-1})$, NS, respectively]. Five patients in this group received phenylephrine after the 2-min measurements.

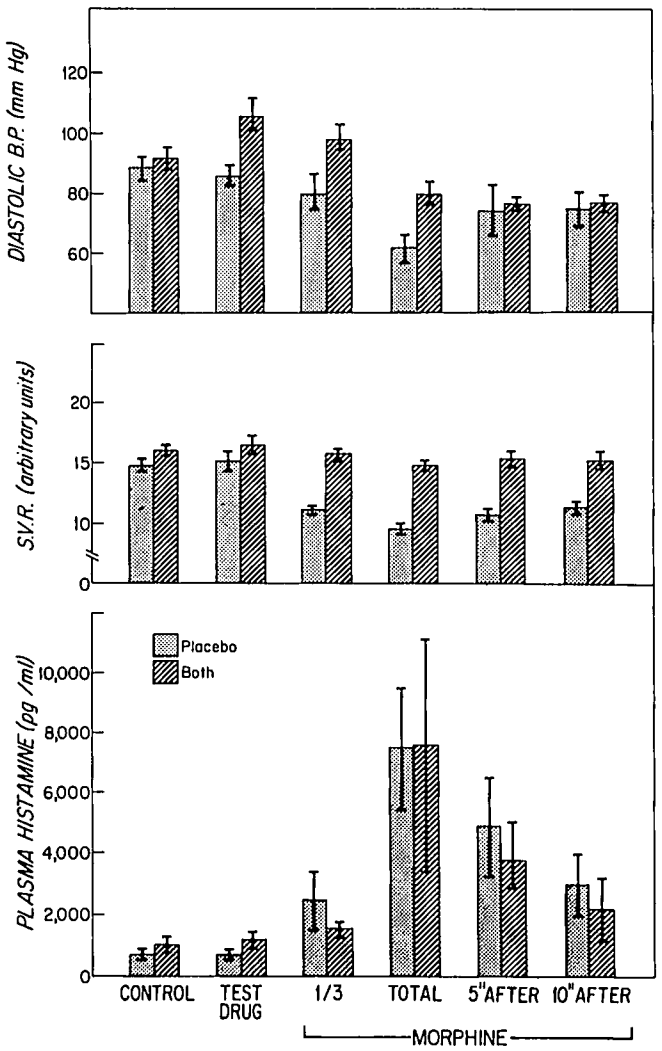

FIG. 1. This depicts the relationship between plasma histamine levels, SVR and diastolic BP for Groups 1 and 4. Note that the diastolic BP and SVR appear to be inversely related to the plasma histamine levels in the placebo group (Group 1). This relationship is distorted in Group 4 (see text).

GROUP 4—CIMETIDINE, DIPHENHYDRAMINE, AND MORPHINE (TABLE 4)

Following administration of both histamine antagonists there was a significant increase in heart rate, diastolic BP and $\overline{BP}$. Within 2 min of morphine administration, peak histamine levels were obtained. Despite a seven-fold increase in plasma histamine there was no significant change in CI or diastolic BP. No patient in this group required phenylephrine.

When this group is compared with Group 1, the decrease in SVR is significantly less (2.8 *vs.* 6.5 torr/($l \cdot min^{-1}$), $P < 0.05$) as is the decrease in diastolic BP (7 *vs.* 26 torr, $P < 0.01$) and the change (or lack of it) in CI (2.4 ± 0.2 to 3.0 ± 0.2 *vs.* 2.5 ± 0.2 to 2.5 ± 0.1 $l \cdot min^{-1} \cdot m^{-2}$, $P < 0.05$) although comparable increases in plasma histamine occurred. Stated another way, the relationship between venous histamine levels and changes in SVR and diastolic BP is distorted in the presence of H_1 and H_2 antagonists (Fig. 1).

Discussion

The predominant effect of endogenous histamine release in humans is a generalized dilatation of terminal arterioles which may lead to a profound decrease in systemic blood pressure.[8] Morphine has long been recognized to cause a histamine release, the effect being to some extent dependent upon the rate of administration.[1,2,5] The rate of administration utilized in this study (5–10 mg/min) was one that is used clinically and was sufficient to cause this release. These data quantitate the increase in plasma histamine levels following the administration of 1 mg/kg morphine. This increase was accompanied by an increase in CI and a decrease in SVR and diastolic BP. Thus, it is reasonable to assume that histamine release will account for much of the cardiovascular effects of morphine. The significance of these data is that the actual measurements of histamine were obtained and that they indeed correlate with the hemodynamic changes.

It is unlikely that metocurine or nitrous oxide played a significant role in histamine release. In a previous study utilizing the same techniques but without the morphine, no significant changes in plasma histamine levels were noted.[9] This is compatible with the majority of published evidence which would suggest that in humans, at these doses, metocurine has little histamine effect[10,11] or significant ganglionic blocking activity.[12,13] It is possible to postulate that metocurine somehow acts synergistically with morphine in producing histamine release under these conditions. Such a possibility is unlikely and unnecessary to explain the histamine response noted here, since morphine has been reported to produce similar hemodynamic responses in the absence of metocurine.[2]

The hemodynamic changes can also reasonably be attributed to the histamine increases rather than the effect of either nitrous oxide or metocurine. The major effects of nitrous oxide, if they occur, would be to decrease CI and increase PVR,[2] but such changes are unlikely in patients with normal ventricular function such as these.[14] The administration of metocurine at this dose level should not have significant cardiovascular effects. It is apparent from table 1 that in period III when only 0.1 mg/kg metocurine had been administered there was already a significant increase in CI and decrease in SVR paralleling the increased histamine levels recorded.

TABLE 2. Group 2: Morphine–Cimetidine*

Period	$\overline{BP}$ (torr)	Diastolic BP (torr)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	HR (beats/min)	SVR ($torr/l \cdot min^{-1}$)	Venous Histamine (pg/ml)
I Control	81 ± 3	63 ± 3	2.7 ± 0.3	60 ± 3	18.4 ± 3	1020 ± 136
II Cimetidine	81 ± 3	62 ± 2	2.7 ± 0.2	60 ± 3	17.1 ± 3	1248 ± 249
III One-third in	83 ± 4	64 ± 4	3.0 ± 0.3	62 ± 3	15.9 ± 2	2064 ± 713
IV 2 min after	64 ± 4‡	47 ± 3‡	2.5 ± 0.2	55 ± 4	14.0 ± 2‡	4300 ± 1355†
V 5 min after	62 ± 3‡	47 ± 3‡	2.4 ± 0.2	56 ± 3	14.4 ± 2†	1117 ± 168
VI 10 min after	69 ± 3	51 ± 3†	2.2 ± 0.2†	53 ± 3	18.7 ± 3	1453 ± 297

* Values are means ± SE.
† $P < 0.05$ compared to control.
‡ $P < 0.01$ compared to control.

The decision to administer phenylephrine at the 2-min postmorphine period, based upon clinical judgement, shows a remarkable correlation with the effectiveness of the histamine antagonists. Eighty per cent of the placebo patients received phenylephrine, 60 per cent of the cimetidine patients and 50 per cent of the diphenhydramine patients but none of the Group 4 patients. Because of the administration of phenylephrine at the time of the peak hypotensive effect, little can be said about subsequent hemodynamic changes. For this reason we have emphasized the measurements obtained at 2 min postmorphine.

It is interesting to note that in Group 1 patients there was not a significant increase in heart rate with the histamine release. Histamine is postulated to have both inotropic and chronotropic effects on the heart,[15–17] and one would anticipate that the levels produced were sufficient for a rate effect. Recent evidence also indicates that during anaphylaxis in humans, histamine release produces a sympathoadrenal discharge.[18] The same study shows that tachycardia, if it occurs, is related more to plasma norepinephrine concentrations than histamine. It is possible that there was sufficient residual beta blockade in our patients to prevent a rate response. Alternatively, the chronotropic effect of histamine may have been blocked by our patient's intrinsic heart disease or by a centrally mediated bradycardia induced by the high dose of morphine.

Previous experimental work demonstrated that the use of H_1 blockers alone provided only partial hemodynamic protection[19,20] and that H_2 blockers were necessary as well.[20,21] The development of a clinically useful H_2 blocker, cimetidine, provided the necessary

TABLE 3. Group 3: Morphine–Diphenhydramine*

Period	$\overline{BP}$ (torr)	Diastolic BP (torr)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	HR (beats/min)	SVR ($torr/l \cdot min^{-1}$)	Venous Histamine (pg/ml)
I Control	88 ± 6	70 ± 4	2.5 ± 0.1	52 ± 1	17.8 ± 2	664 ± 57
II Diphenhydramine	100 ± 6	78 ± 5	2.8 ± 0.2	62 ± 2†	18.2 ± 2	901 ± 200
III One-third in	96 ± 4	77 ± 4	2.9 ± 0.2†	63 ± 2†	17.0 ± 2	2186 ± 1135
IV 2 min after	71 ± 4‡	57 ± 4‡	2.7 ± 0.1†	61 ± 3†	12.3 ± 1†	4498 ± 2566†
V 5 min after	74 ± 5†	58 ± 4‡	2.6 ± 0.1	55 ± 1	14.0 ± 1†	1672 ± 623
VI 10 min after	79 ± 6	63 ± 5	2.5 ± 0.1	54 ± 1	15.9 ± 2	1174 ± 373

* Values are means ± SE.
† $P < 0.05$ compared to control.
‡ $P < 0.01$ compared to control.

TABLE 4. Group 4: Morphine–Cimetidine–Diphenhydramine*

Period	$\overline{BP}$ (torr)	Diastolic BP (torr)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	HR (beats/min)	SVR ($torr/l \cdot min^{-1}$)	Venous Histamine (pg/ml)
I Control	91 ± 4	68 ± 3	2.5 ± 0.2	56 ± 5	17.4 ± 1	1059 ± 222
II Cimetidine Diphenhydramine	105 ± 5†	78 ± 5†	2.8 ± 0.2	72 ± 5‡	18.4 ± 1	1269 ± 206
III One-third in	97 ± 4	75 ± 4	2.7 ± 0.1	67 ± 5	16.8 ± 1	1525 ± 247
IV 2 min after	79 ± 4‡	61 ± 3	2.5 ± 0.1	57 ± 4	14.6 ± 1†	7653 ± 4242‡
V 5 min after	75 ± 2‡	61 ± 3	2.3 ± 0.1	56 ± 3	15.6 ± 1	3835 ± 1776†
VI 10 min after	76 ± 2‡	60 ± 3	2.1 ± 0.1	53 ± 3	15.5 ± 2	2240 ± 1267

* Values are means ± SE.
† $P < 0.05$ compared to control.
‡ $P < 0.01$ compared to control.

tool for patient studies.[21,22] In our studies, the decrease in SVR was smallest in the group which received both cimetidine and diphenhydramine. The fact that protection was less when either antagonist was administered alone confirms that both H_1 and H_2 receptors are involved in the response in humans.

It is apparent from these data, that cimetidine alone has few, if any, cardiovascular effects while diphenhydramine alone can produce significant changes in heart rate and blood pressure.

The protection achieved in this study was not complete. Since the action of the histamine blockers is competitive at the receptor site, this would suggest that either larger doses of H_1 and H_2 histamine antagonists might provide more complete protection or that other mechanisms are involved as well.

These data support the conclusion that the administration of morphine in humans stimulates significant histamine release which correlates with the major hemodynamic response, *i.e.*, a decrease in BP and SVR and an increase in CI. Prior administration of H_1 and H_2 histamine antagonists provides greater protection from these responses than either drug given alone.

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