Histamine Release by Narcotics and Muscle Relaxants in Humans

Jonathan Moss, M.D., Ph.D.,* and Carl E. Rosow, M.D., Ph.D.†

It has been postulated for a long time that commonly used narcotics and neuromuscular blocking agents can cause hemodynamically significant histamine release in humans. This proposition is based primarily on the demonstration of histamine release in isolated tissues in experimental animals and the clinical observation that intravenous drug administration can mimic exogenous histamine infusion. While these experiments are suggestive, the high dose of drugs required to effect histamine release in many in vitro studies and the species-specific characteristics of histamine release render extrapolation difficult. The lack of specific H1 and H2 antagonists has made much of the clinical data difficult to interpret. Improvements in assay methods only recently permitted the systematic measurement of drug-induced histamine release.

The purposes of this article are to review the literature, which demonstrates that commonly used narcotics and neuromuscular blocking agents can cause dose-related increases in plasma histamine in humans; to demonstrate further that these increases in plasma histamine are temporally and quantitatively related to observed cardiovascular changes; and to review clinical strategies that attenuate the cardiovascular changes in humans. These strategies include altered rate of administration and the use of H1 and H2 receptor antagonists. Drug design also will be considered, because structural changes can increase potency and specificity, while reducing nonspecific effects like histamine release.

Preclinical Experiences

Uvnas and Thon have described a relatively simple in vitro model for histamine release using mast cells harvested from rat peritoneal fluid. This method has been utilized extensively and has become a standard screening test for histamine release by drugs. Morphine and d-tubocurarine, among other drugs, cause a dose-related release of histamine from rat mast cells without disrupting the cells themselves (Fig. 1). A possible defect of this method is that relatively high concentrations of the releasing drugs are required to effect release. In clinical practice, such levels rarely are achieved. Thus, the rat mast cell preparation is a qualitative rather than a quantitative screen.

Other investigators have performed elegant studies using perfused skin and muscle preparations in an attempt to demonstrate that histamine is released when narcotics and muscle relaxants are administered in perfusate. Feldberg and Paton used a perfused cat gastrocnemius preparation and a guinea pig ileum bioassay for histamine in order to compare the effects of three naturally occurring opiate alkaloids. Schachter found that meperidine induced a dose-related release of histamine from cat skin. Related opiate alkaloids that appear to release histamine are nalorphine, papaverine, thebaine, and sinomenine. None of the latter drugs have been tested at more than one dose level.

More recently, in vivo experiments have been carried out to study blood and plasma histamine after the administration of anesthetic agents to animals. While it has been possible to demonstrate the massive release of histamine by agents such as insect venom or the

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Histamine release

**Fig. 1.** Release of histamine from rat mast cells. The ordinates are the release of histamine as a percentage, corrected for spontaneous release, from *in vitro* preparations of rat peritoneal and pleural mast cells. The abscissae are the molar concentrations of the drugs. The points are the mean of 5–10 experimental values; the bars indicate SEM. (Data are reproduced by permission of the authors and the *Journal of Pharmacology and Experimental Therapeutics.* Ellis HV, Johnson AR, Moran NC: Selective release of histamine from rat mast cells by several drugs. J Pharm Exp Ther 175:627–631, 1970.)

yethylamine polymer 48/80, other agents, such as morphine alkaloids or *d*-tubocurarine, which are relatively weak releasers, could not be studied. The lack of a sensitive, reliable method to assay plasma histamine has hampered these investigations.

Measurement of histamine, in whole blood is less desirable than direct plasma measurement, because histamine from basophils and platelets is included in the determination. Nevertheless, several studies in animals have suggested doses of curare, which cause paralysis and also cause an increase in total blood histamine with concomitant hemodynamic changes.42–44,75 Zeppa et al. demonstrated that blood histamine increased fivefold in dogs given meperidine (5 mg/kg IV).74 Shurig et al. measured plasma histamine and hemodynamic changes in dogs given either butorphanol (0.75 mg/kg) or morphine (3 mg/kg) and found that histamine release and hemodynamic changes occurred after morphine administration but not after the administration of butorphanol.62

Savarese et al. attempted to quantify histamine release indirectly by measuring the “autonomic margin of safety” for a number of neuromuscular blocking agents.59 The doses that produced twitch depression in cats were compared with those that elicited vagal and ganglionic blockade. The delayed depressor response in arterial pressure was used as an all-or-none indicator of histamine release. No measurements of plasma histamine were made, but the cardiovascular data were utilized to construct quantal dose–response curves for presumed histamine release in these animals. Potency to effect the delayed depressor response in cats appeared to correlate with the ability to produce flushing and hypotension in surgical patients. A possible defect of this method is that the anesthetized cat may fail to detect compounds that marginally release histamine in humans. Recent experience with the investigational neuromuscular blocking compound BW444 documents the relative insensitivity associated with the cat model.2 Thus, while it may be possible to rule out those drugs that are potent histamine releasers in humans, it may be difficult to extrapolate in marginal cases.21,46

In addition to the *in vitro* studies and animal experiments, there are numerous clinical case reports and clinical studies that demonstrate that the administration of narcotics and neuromuscular blocking agents in usual doses can cause tachycardia, hypotension, and peripheral vasodilatation—signs that may be mimicked by the infusion of histamine.24,25,31,32 Interpretation of individual case reports often is rendered difficult because of the concomitant use of multiple agents and the difficulty in distinguishing between direct and immunologically mediated histamine release. There are now relatively simple tests that permit “*a posteriori*” demonstration of immunologically mediated drug reactions in most cases.17,25 In this review, we shall concentrate on the anaphylactoid or nonimmunologically mediated histamine release by narcotics and muscle relaxants.

Few clinical studies have been performed that have systematically examined plasma histamine following the administration of anesthetic agents. Usual histamine levels in human plasma are 1 ng/ml.4–7,20,24,33–38 This level
is well below the sensitivity of unmodified biologic and fluorometric assays, unless elaborate steps are introduced to concentrate and separate histamine from interfering substances. The development of the enzymatic isotopic assay for histamine and its recent improvement make it possible to detect histamine in blood, plasma, and other body fluids, with a sensitivity of 0.1 ng/ml. Lorenz has used a sophisticated fluorometric assay to measure histamine release by succinylcholine, alocin, and pancuronium, but only one dose level of each drug was tested. These studies by Lorenz et al. have demonstrated elevations in plasma histamine following the administration of barbiturates and propanidid. The extent to which increased levels of plasma histamine actually contributed to the hemodynamic responses they observed is unclear.

Clinical Studies

Few clinical studies have been performed that have examined plasma histamine systematically after the administration of anesthetic agents. To demonstrate histamine release by neuromuscular blocking agents and narcotics, we have measured plasma histamine following administration of several drugs with different structures, duration of action, and metabolism.

We have utilized a radioenzymatic assay to measure plasma histamine following the administration of multiple relaxants with different structures, durations of action, and metabolic pathways. In a recent study, we administered d-tubocurarine to a series of 21 patients undergoing elective orthopedic procedures. Each patient received fentanyl (3 μg/kg) followed 2 min later by thiopental (6 mg/kg). These patients then were ventilated with O₂/N₂O. Four minutes after the administration of thiopental, d-tubocurarine (0.25–0.75 mg/kg) was given intravenously as a rapid bolus. Plasma histamine was measured before and at 2 and 5 min after the administration of neuromuscular blocking agent. The short plasma half-life for histamine, probably under 2 min, makes it likely that any histamine released by the barbiturate would not have been observed. Blood pressure and heart rate were measured at each event.

Following the administration of d-tubocurarine, significant changes in heart rate, blood pressure, and plasma histamine were observed. Hemodynamic changes and changes in plasma histamine followed a similar time course. Figure 2 demonstrates the individual data points for venous plasma histamine achieved before the administration of d-tubocurarine (event 3) compared with 2 and 5 min after the administration of various doses of the drug. While higher doses of d-tubocurarine cause increases in the mean level of plasma histamine 2 min after administration, it is clear that there is significant variability in the peak plasma histamine after a given dose. It also appears, however, that there is a
quantal dose–response relationship, i.e., that as the dose of d-tubocurarine is increased, there is an increased likelihood that the patient will release histamine. Similar dose–response relationships and similar variability for histamine release have been described with the administration of experimental neuromuscular blocking agents BW785 and BW444. In contrast to d-tubocurarine, the bolus administration of metocurine (0.25 mg/kg) appears to be devoid of histamine release and hemodynamic sequelae. The ability to generate dose–response relationships and the absence of prior sensitization in most cases suggests a direct histamine release rather than an immunologically mediated response.

The classic descriptions of morphine-induced histamine release emphasize cutaneous signs (e.g., urticaria, flushing, redness, etc.). The cutaneous manifestations may not correlate with plasma histamine or with hemodynamic changes. Despite intensive investigation by physiologists and pharmacologists, it has been only recently that we have been able to demonstrate directly that administration of intravenous morphine causes an elevation in plasma histamine in humans. Rosow et al. administered morphine intravenously (1 mg/kg) to cardiac surgical patients undergoing elective coronary artery bypass procedures. Peak histamine levels following the administration of morphine range from unchanged to over 19 ng/ml. This interpatient variability is similar to that previously described following the administration of d-tubocurarine. (fig. 2) Patients who received fentanyl as their primary anesthetic agent in doses of 50 μg/kg failed to show any elevation in plasma histamine. Only one dose of morphine was studied, although samples taken after one-third of the morphine dose had been given indicated that those patients who released histamine showed significant elevations with only one-third of the total morphine dose. Recent studies with the narcotics sufentanil, butorphanol, and methadone suggest that little or no histamine is released after intravenous administration.2,4

**Cardiovascular Sequelae of Histamine Release**

Histamine can exert multiple effects on the human cardiovascular system. In the human heart, inotropic, chronotropic, antidromic, and coronary artery flow effects have been documented. Recent experiments on transplanted human hearts have confirmed many of the earlier findings in guinea pig preparations. In the animal model and in isolated perfused human heart tissue, significant changes in the threshold for ventricular fibrillation may be caused by the liberation of small amounts of histamine that may not be detectable in plasma. The extent to which regional tissue release of histamine contributes to malignant arrhythmias occurring in clinical practice is undetermined. The results of in vitro studies suggest that special caution should be exercised using potential histamine releasing drugs in patients with unstable rhythm.

The effects of exogenous histamine administration have been well documented, however studies with exogenous administration of hormones must be viewed with caution. In studies of the sympathetic nervous system, Yamaguchi and Kopin have demonstrated that the release of endogenous norepinephrine produces tachycardia. On the other hand, infused norepinephrine may elicit a bradycardia. Lorenz and his associates infused histamine into human volunteers and noted that when elevated plasma levels (to 5 ng/ml) were achieved, three-quarters of the subjects developed tachycardia. In a recent study, histamine was infused in 12 subjects in order to increase plasma levels from resting (0.62 ng/ml) to levels at which flush, tachycardia (30% increase in heart rate), and blood pressure changes (30% increase in pulse pressure) occurred. In these subjects, tachycardia occurred at a lower mean level of plasma histamine (1.61 ng/ml) than flush (2.99 ng/ml) or blood pressure changes (2.45 ng/ml). It appears that the plasma levels at which tachycardia occurs are the same whether the histamine is administered exogenously or released by histamine-liberating drugs. Even small elevations in plasma histamine may reflect the release of massive quantities of histamine. Kaliner et al. demonstrated that 210,000 ng of histamine infused into a 70-kg man over 30 min resulted in an elevation of only 1 ng/ml in plasma histamine levels.

While histamine itself is chronotropic, there is some evidence that its chronotropic effect may result in part from the liberation of catecholamines. Elegant animal experiments on morphine-induced vasodilatation have suggested that there may be both centrally and locally mediated causes for the vasodilatation, the latter possibly resulting from the histamine release. This may explain the fact that very high doses of morphine produce a profound paralysis of capacitance beds, while very high doses of fentanyl do not. Philbin et al. have provided more data on the relationship between morphine-induced histamine release and hemodynamics in humans. Patients receiving one mg/kg of morphine for coronary artery bypass surgery were monitored with systemic and pul-
monary artery catheters. Calculation of systemic vascular resistance using thermodilution cardiac outputs avoided the problems associated with plethysmography and dye dilution method, i.e., artifacts resulting from histamine-induced increases in vascular permeability. In this study, it was found that histamine release correlated with increased cardiac index and decreased blood pressure and systemic vascular resistance (table 1) In a similar study, Rosow et al. have demonstrated that systemic vascular resistance correlates well with the log of plasma histamine ($r = -0.81, P < 0.03$).57

Although systemic vascular resistance may be the most direct measure of the hemodynamic effects of histamine, it should be remembered that hypotension and tachycardia are the most frequently observed clinical signs of histamine release. The increased levels of plasma histamine observed 2 min after the d-tubocurarine administration correlated well with the observed hypotension in our series of patients ($r = 0.61, P < 0.005)\textsuperscript{48}$ (fig. 3). We found a similar correlation between the dose of d-tubocurarine and the peak plasma histamine and a somewhat weaker correlation between the dose of d-tubocurarine and the extent of hypotension. While d-tubocurarine has been shown to have ganglionic blocking activity in animals, this effect lasts more than 20 to 30 min. This restoration of hemodynamic variables and plasma histamine within 5 min of curare administration suggests that ganglionic blockade does not play a major role. Further, recent experiments in humans in which BW444U, a drug devoid of ganglionic blocking activity, was administered demonstrated a similar relationship between hypotension and plasma histamine.\textsuperscript{2} Thus, neuromuscular blocking agents of different chemical classes can cause increases in plasma

<table>
<thead>
<tr>
<th>Period</th>
<th>BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>CI (l/min·m$^{-2}$)</th>
<th>HR (beats·min$^{-1}$)</th>
<th>SVR (mmHg·l/min·m$^{-2}$)</th>
<th>Venous Histamine (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Control</td>
<td>88 ± 4</td>
<td>71 ± 3</td>
<td>2.4 ± 0.2</td>
<td>57 ± 2</td>
<td>15.5 ± 1</td>
<td>880 ± 163</td>
</tr>
<tr>
<td>II Placebo</td>
<td>85 ± 3</td>
<td>67 ± 2</td>
<td>2.6 ± 0.1</td>
<td>57 ± 2</td>
<td>14.8 ± 1</td>
<td>657 ± 98</td>
</tr>
<tr>
<td>III One-third in</td>
<td>79 ± 5</td>
<td>61 ± 4$\dagger$</td>
<td>2.8 ± 0.1$\dagger$</td>
<td>58 ± 2</td>
<td>12.2 ± 1$\dagger$</td>
<td>2467 ± 1208$\dagger$</td>
</tr>
<tr>
<td>IV 2 min after</td>
<td>61 ± 4$\dagger$</td>
<td>45 ± 4$\dagger$</td>
<td>3.0 ± 0.2$\dagger$</td>
<td>59 ± 3</td>
<td>9.0 ± 1$\dagger$</td>
<td>7437 ± 2684$\dagger$</td>
</tr>
<tr>
<td>V 5 min after</td>
<td>73 ± 8</td>
<td>50 ± 7$\dagger$</td>
<td>2.9 ± 0.3</td>
<td>64 ± 4</td>
<td>11.5 ± 1$\dagger$</td>
<td>4980 ± 1681$\dagger$</td>
</tr>
<tr>
<td>VI 10 min after</td>
<td>74 ± 5</td>
<td>57 ± 5$\dagger$</td>
<td>2.7 ± 0.2</td>
<td>59 ± 4</td>
<td>12.7 ± 1$\dagger$</td>
<td>3307 ± 1090$\dagger$</td>
</tr>
</tbody>
</table>

* Values are means ± SE.
$\dagger P < 0.05$ compared with control.

\[ P < 0.01 \text{ compared with control.} \]

\[ 0.25 \text{ mg/kg DTC} \]
\[ 0.5 \text{ mg/kg DTC} \]
\[ 0.6 \text{ mg/kg DTC} \]
\[ 0.75 \text{ mg/kg DTC} \]

\[ BP (2' \log \text{ DTC}) \]

\[ \text{Log [Plasma Histamine]} \]

\[ 2' \log \text{ DTC} \]

\[ (Reproduced by permission of the authors and the Anesthesiology. Moss J, Rosow CE, Savaresi JJ: Role of histamine in the hypotensive action of d-tubocurarine in man. Anesthesiology 55:19–25, 1981.) \]
histamine that are correlated with the degree of hypotension in humans.\textsuperscript{46}

Strategies for the Attenuation of Histamine-mediated Hemodynamic Changes

While it is clear that the administration of a neuromuscular blocking agent or narcotic rapidly can evoke hemodynamically significant histamine release, it is also clear that a variety of clinical strategies can be employed that may attenuate the adverse reactions (table 2).

Alteration of the rate of administration may be very effective. A comparison of the alteration in hemodynamics and histamine release for the investigational neuromuscular blocking agent BW785U is demonstrated in figure 4.\textsuperscript{54,55} The dose–response relationship was derived when this drug was administered as a bolus or as a continuous infusion over a 1-min period. It can be seen that the same quantity of drug administered in a 1-min infusion has significantly less hemodynamic effect than when administered as a bolus. The fact that plasma histamine levels after the highest dose (0.5 mg/kg) are equivalent during both infusion and bolus suggest that the peak release of histamine after the bolus may have occurred before the 2-min point at which the sample was taken. In a recent study, the administration of BW444U (1.2 mg/kg) as a 5-s bolus caused significant plasma histamine release in several patients, while no detectable change was seen in patients receiving the same dose as a 15–30-s slow bolus.\textsuperscript{46} It thus appears that even small time differences in the rate of administration of intravenous drugs can lead to significant changes in the likelihood of generating clinically significant histamine release.

Abundant data now demonstrates that the prophylactic use of H1 and H2 antagonists can attenuate the histamine-mediated cardiovascular responses caused by administration of several anesthetic drugs.\textsuperscript{35,58} H1 and H2 receptors mediate separate hemodynamic responses. Thus, older studies in which H1 antagonists alone were employed are difficult to interpret.

It is apparent from animal experiments that the initial phase of hypotension during histamine release is mediated primarily by an H1 response, while the prolonged hypotension may result from an H2-mediated response.\textsuperscript{11,59,46} Data from human heart transplant material demonstrate that coronary artery vasoconstriction is mediated by H1 receptors, while coronary artery vasodilation is mediated by H2 receptors.\textsuperscript{11,12} H2 receptor mechanisms mediate positive inotropic responses in atrial and ventricular muscle. There appear to be no positive H1 effects on human ventricular muscle, although negative inotropic effects have been described.

**TABLE 2. Clinical Strategies for Attenuation of Histamine Mediated Hemodynamic Effects**

<table>
<thead>
<tr>
<th>A.</th>
<th>Rate of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.</td>
<td>Use of antihistamines</td>
</tr>
<tr>
<td>C.</td>
<td>Drug design</td>
</tr>
</tbody>
</table>

FIG. 4. Effect of method of administration on hemodynamics and plasma histamine. Patients received BW785U as a bolus or as an infusion over 1 min. The dose–response relationship for BP, HR, and histamine are significant (P < 0.05). Slopes for bolus versus infusion are significantly different for plasma histamine (P < 0.01). Data are given as mean ± SEM. (Data are reproduced by permission of authors and *Anesthesiology*. Rosow CE, Basta SJ, Sivarese JJ, et al: BW785U: Correlation of cardiovascular effects with increases in plasma histamine. *Anesthesiology* 53:5270, 1980.)
The H2 receptor is analogous to the beta-adrenergic receptor both in its physiologic role in mediating relaxation responses and in its linkage to adenylate cyclase. The H1 receptor is analogous to the alpha-adrenergic receptor in many of its physiologic roles (table 3).11 Several groups of investigators have utilized combined H1 and H2 prophylactic regimens to prevent the cardiovascular sequelae of anaphylactoid reactions that accompany the administration of dextran or propanidid.12,35,36,52 Their experience suggests that both H1 and H2 blockers must be administered in order to achieve significant attenuation of the cardiovascular response. Recent data suggest that combined receptor blockade is effective in blunting the cardiovascular effects of narcotics and muscle relaxants. The hemodynamic effects of muscle-relaxant–induced histamine release can be attenuated by the administration of H1 and H2 receptor antagonists. When cimetidine (4 mg/kg) and diphenhydramine (1 mg/kg) were administered intravenously 15 min before the rapid administration of BW7585U, significant protection from the released histamine could be achieved.55 In a more recent study, Philbin et al. examined the effectiveness of H1 and H2 receptor antagonists in preventing morphine-induced hemodynamic changes in 40 patients undergoing coronary artery bypass surgery.50,53 In this double-blind study, patients randomly were assigned to receive a placebo, an H1 antagonist (diphenhydramine), an H2 antagonist (cimetidine), or a combination of H1 and H2 antagonists administered intravenously before surgery. All patients then received morphine (1 mg/kg) over a prescribed time interval. Morphine-induced elevations in plasma histamine were the same in all four treatment groups. While neither an H1 or an H2 blocker alone prevented the hemodynamic changes following morphine administration, the use of H1 and H2 antagonists in combination completely prevented the change in systemic vascular resistance (fig. 5).52 Combination treatment completely eliminated the need for pressor support during induction, a major problem in the three groups (table 4). When the data were analyzed by analysis of covariance, it was demonstrated that there was no apparent interaction between H1 and H2 receptors in the cardiovascular system, i.e., they appear to mediate the cardiovascular effects independently (table 5). These data are in agreement with studies that have been performed on plasma expanders and intravenous induction agents, in which neither H1 nor H2 receptor blockade was effective, but the combination did work. The importance of combined H1 and H2 receptor blockade is confirmed in a recent study in which histamine was infused in volunteers to elicit the clinical end points of flush, tachycardia, or widened pulse pressure.24 The

<table>
<thead>
<tr>
<th>Response</th>
<th>Histamine Receptor</th>
<th>Catecholamine Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive chronotropic, atria</td>
<td>H2</td>
<td>Beta</td>
</tr>
<tr>
<td>Positive inotropic, atria, and</td>
<td>H2</td>
<td>Beta</td>
</tr>
<tr>
<td>ventricles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenylate cyclase stimulation,</td>
<td>H2</td>
<td>Beta</td>
</tr>
<tr>
<td>ventricles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary vasodilation</td>
<td>H2</td>
<td>Beta</td>
</tr>
<tr>
<td>Coronary vasconstriction</td>
<td>H1</td>
<td>Alpha</td>
</tr>
</tbody>
</table>


Fig. 5. The relationship between plasma histamine levels, SVR, and diastolic blood pressure for patients receiving placebo and patients receiving both cimetidine and diphenhydramine. The decreases in diastolic blood pressure and systemic vascular resistance are significantly different (P<0.05, P<0.01), although comparable histamine release is achieved. Data are given as mean ± SD. (Data are reproduced by permission of authors and Anesthesiology. Philbin DM, Moss J, Akins CW, et al: The use of H1 and H2 histamine blockers with high dose morphine anesthesia: A double blind study. Anesthesiology 55:292–296, 1981.)

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administration of cimetidine did not alter the plasma levels at which these end points occurred. The levels at which systemic flush and blood pressure changes occurred were not attenuated by the administration of the H1 antagonist hydroxyzine. However, when cimetidine and hydroxyzine were both administered, significantly higher plasma histamine levels were required to elicit these clinical symptoms. These studies demonstrating the importance of using both H1 and H2 antagonists to attenuate the effects of exogenously administered histamine confirm the experiments in which endogenous (drug-induced) histamine release was evaluated.

The third strategy to attenuate clinically important histamine release involves alteration of molecular structure. Minor chemical modification significantly may alter the hemodynamic effects of the complex alkaloids used as neuromuscular blockers. For example, metocurine has been shown to cause less hypotension than its parent molecule, d-tubocurarine.1,59,78 Recent studies suggest that this results from a reduction in histamine release.3 Recent clinical experience with atracurium, another investigational neuromuscular blocker, suggests that at a dose twice the ED95 for neuromuscular blockade, there are no changes in the level of plasma histamine in human volunteers.22,46,51 More potent muscle relaxants and narcotics are less likely to release histamine at usual clinically administered doses. Given the relatively wide choice of compounds that are active as neuromuscular blocking agents and narcotics, it may be possible to select or design drugs that will be devoid of histamine release.

Strategies such as those outlined above are often not necessary, because histamine release is not a factor in most clinical situations. Recent epidemiologic studies suggest that a history of atopy may predispose to histamine-mediated adverse reactions during anesthesia.25 In these patients and in patients with significant cardiovascular compromise, antihistamine pretreatment should be considered. Possibly drugs with a lower potential for histamine release should be selected.

While this review has concentrated on the histamine release that is detectable in plasma, evidence is accumulating that significant changes may be present within the intact tissue, which may be even more important in the clinical practice of anesthesia. While plasma levels can give an indication of tissue levels, physiologically

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**TABLE 4. Requirement for Pressor Support during Morphine Induction**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients Requiring Neosynephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>6</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>5</td>
</tr>
<tr>
<td>Cimetidine + diphenhydramine</td>
<td>0</td>
</tr>
</tbody>
</table>

Four groups of 10 cardiac surgical patients received either placebo, cimetidine (4 mg/kg), diphenhydramine (1 mg/kg), or a combination of cimetidine (4 mg/kg) and diphenhydramine (1 mg/kg) before administration of morphine (1 mg/kg). The number of patients requiring neosynephrine in each group suggests the extent to which H1 and H2 receptor antagonists provide cardiovascular protection.

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**TABLE 5. Summary of Significant Comparisons among Treatments by ANCOVA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Slope</th>
<th>C</th>
<th>D</th>
<th>C x D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>0.19</td>
<td>0.02</td>
<td>0.62</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.51</td>
<td>0.18</td>
<td>0.001</td>
<td>0.95</td>
</tr>
<tr>
<td>BP</td>
<td>0.32</td>
<td>0.09</td>
<td>0.005</td>
<td>0.83</td>
</tr>
<tr>
<td>HR</td>
<td>0.67</td>
<td>0.08</td>
<td>0.18</td>
<td>0.98</td>
</tr>
<tr>
<td>SVR</td>
<td>0.07</td>
<td>0.0005</td>
<td>0.04</td>
<td>0.26</td>
</tr>
</tbody>
</table>

C = Cimetidine; D = Diphenhydramine.

* Analysis of covariance (ANCOVA). The data from Philbin et al. were analyzed by ANCOVA. The C designation represents patients receiving cimetidine; the D designation represents patients receiving diphenhydramine. The lack of significance in the C x D term indicates that cimetidine and diphenhydramine confer protection independently and without interaction for any given cardiovascular variable. The significance level of cimetidine (C) and diphenhydramine (D) in providing protection for each variable is given in the "C" and "D" terms.

† P-values that are not significant indicate the model assumption of equal slopes holds.

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**Fig. 6. Relationship between fibrillation threshold and exogenously applied histamine.** Administration of exogenous histamine to isolated human arterial appendage achieved the above relationship. Note that the change in fibrillation threshold occurs with as little as 1 pg/ml of histamine in the perfusate. Data are given as mean ± SD. Data are reproduced by permission of authors and Klinische Wochenschrift. Levi R., Chenouda AA, Luskind RD, et al: Dysrhythmias caused by histamine release in guinea pig and human hearts. Klin Wochen 60:965–971, 1982.
significant events can occur as the result of histamine release, which may not be detectable in plasma. The changes in ventricular fibrillation threshold that have been demonstrated in vitro may be clinically important (fig. 6). The amount of histamine needed to cause such changes may not be detectable in plasma. Knowledge of the relative histamine-releasing potential of various narcotics and neuromuscular blocking agents may provide a rational basis for selection of anesthetic agents and the use of receptor antagonists. In addition, the possible clinical introduction of newer histamine antagonists (astemizole, ranitidine, terfenidine, etc.) should provide a valuable tool in anesthesia and intensive care.

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