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Histamine Receptor Control of Gastric Microvasculature in Shock

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Control of gastric mucosal blood flow in hemorrhagic shock was investigated, in an anesthetized miniature swine model, using H_1-receptor (diphenhydramine) and H_2-receptor (cimetidine) antagonisms. The animals were divided into two experimental groups: (i) diphenhydramine treatment; and (ii) diphenhydramine plus cimetidine treatment. Results were compared to previously reported untreated controls and animals who received cimetidine alone. Conclusions reached were: (1) Histamine receptors in the gastric microvasculature do play a role in the control of mucosal blood flow during shock. (2) H_2-Receptor antagonism, whether alone or in conjunction with H_1-receptor antagonism, results in significant protection against a shock-related decrease in gastric mucosal blood flow. (3) H_1-Receptor antagonism does not affect gastric mucosal blood flow in shock.

The interplay of changes in gastric acid production, mucosal blood flow, and mucosal integrity is believed to be the cause of stress-related gastric mucosal erosive disease. Prevention of these lesions has been based on the lowering of gastric acid secretion. The administration of H_2-receptor antagonists has been used to accomplish this end successfully in animals [9, 21, 23].

Gastric mucosal blood flow seems to play a central role in the genesis of erosive lesions. A decrease in this flow has been shown to be necessary, in animal models, before lesions can appear [20]. Prior work in our laboratory has demonstrated that treatment with H_2-receptor antagonists protects against the decrease in gastric mucosal blood flow seen in hypovolemic shock [10]. Both H_1 and H_2 histamine receptors are known to exert vascular effects in other organs of the body [19]. Therefore our prior studies were extended to include the investigation of H_1-receptor antagonism, alone and in conjunction with H_2-receptor antagonism, on control of gastric mucosal blood flow in shock.

MATERIALS AND METHODS

Fourteen miniature swine (Vita-Vet Laboratories, Marion, Ind.) weighing 9–12 kg each were fasted for 2 days (water allowed *ad lib*) prior to study. Each animal was anesthetized with intravenous chloralose (100 mg/kg) and mechanically ventilated with oxygen supplementation via a tracheostomy tube. Using a cervical incision, a 16-gauge polyethylene catheter was introduced into the right common carotid artery and advanced retrograde into the left ventricle. Through bilateral groin incisions two 16-gauge catheters were placed in the abdominal aorta retrograde from the femoral arteries. One of these arterial lines was coupled to a Statham P23Db transducer (Statham Instruments, Oxnard, Calif.) for measurement of systemic arterial blood pressure. The other was connected to a pressurized, heparinized reservoir to allow for controlled hemorrhage with maintenance of a designated systemic arterial pressure. Another 16-gauge catheter was placed in the left femoral vein for drug infusion. A No. 5

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Fr Swan–Ganz thermodilution catheter was floated, under continuous pressure monitoring, from the right femoral vein into the pulmonary artery. This catheter, coupled to a cardiac output computer (Instrument Laboratories, Chicago, Ill.) was used to determine cardiac output at 30-min intervals. Both the central venous and pulmonary artery channels of the catheter were connected to Statham P23Db transducers. All transducers were coupled to a multichannel monitoring system (Beckman Instruments, Schiller Park, Ill.) for continuous recording. Pa_{CO_2} was maintained between 30 and 40 Torr by adjusting tidal volume and/or respiratory rate.

Microspheres (3M Company, St. Paul, Minn.), 15 ± 5 μm in diameter, labeled with ^{125}I, ^{141}Ce, ^{85}Sr, or ^{46}Sc and suspended in 10% Dextran and Tween, were used to measure gastric mucosal blood flow. For each determination approximately 1.2×10^6 microspheres were mechanically agitated and injected as a bolus into the left ventricle. Immediately following this, the cannula was flushed with 5 ml of 5% dextrose in water at body temperature. Determinations of cardiac output were made immediately before and after each microsphere injection.

At the conclusion of each experiment, the animal was sacrificed by injection of potassium chloride. The stomach was surgically removed and divided into fundic, corpal, and antral sections. The mucosa and submucosa were dissected from the muscular and serosal layers, cut into equal-sized pieces, placed in preweighed tubes, and themselves weighed. Each specimen was then counted for 2 min in a Packard Auto gamma scintillation spectrometer (Packard Instruments, Downers Grove, Ill.). Energy window settings on the counter were ^{125}I, 30–115 keV; ^{141}Ce, 115–200 keV; ^{88}Sr, 420–590 keV; and ^{46}Sc, 790–1160 keV. Separation of the individual isotopic counts, with accommodation for interference by the other radioactive labels, was accomplished by the use of standard techniques. Gastric mucosal blood flows were then calculated by the formula:

Flow (ml/min/100 g of tissue)

$$= \frac{(\text{cardiac output})(\text{cpm}/100 \text{ g of tissue})}{\text{total counts injected}}.$$

Fourteen animals were divided into two equal groups: (1) treatment with the H_1-receptor antagonist, diphenhydramine; and (2) treatment with diphenhydramine + the H_2-receptor antagonist, cimetidine. All animals underwent a 45-min stabilization period after catheter placement, at the end of which an injection of microspheres was performed.

The two treatment groups each received their antihistaminics as a bolus intravenous injection after the stabilization period and subsequent first microsphere injection. The drug dosage for each compound, cimetidine and diphenhydramine (Benadryl, Parke–Davis, Detroit, Mich.), was 10 mg/kg. Thirty minutes after drug administration, each animal was hemorrhaged to a mean arterial pressure of 40 mm Hg. After 90 min of shock another microsphere injection was made and the animal sacrificed.

Changes in central hemodynamics (cardiac output and mean arterial pressure) among the experimental groups were compared by analysis of variance. Comparison of postshock gastric mucosal blood flows to baseline values within each group was done using Student's paired t test. Finally, changes in gastric mucosal blood flow, from stabilization to 90 min of shock, were compared among the experimental groups by the Kruskal–Wallis one-way analysis of variance [22].

RESULTS

Central hemodynamics. There was a significant decrease in both cardiac output and mean arterial pressure between baseline stabilization and shock periods (Figs. 1 and 2). This was seen in both groups. Cardiac output was reduced 63% with diphenhydr-
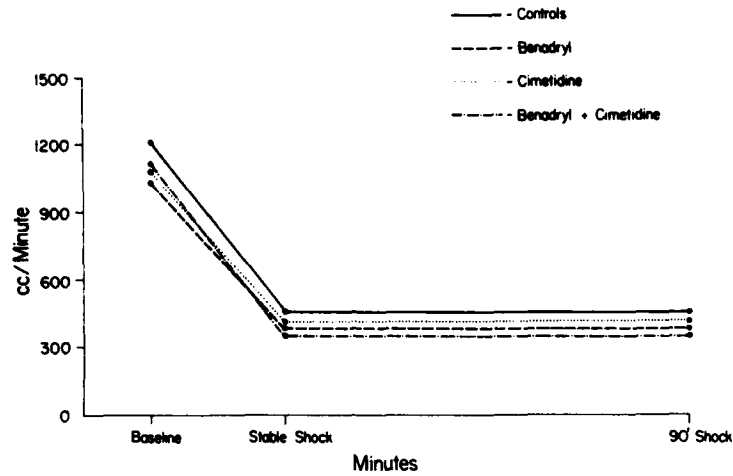
FIG. 1. Comparison of cardiac outputs in the two Benadryl-treated groups with those of the untreated control and cimetidine-alone groups.

amine and 69% with both antihistaminics. Mean arterial pressure was diminished by 60% with diphenhydramine and 57% with both drugs.

Diphenhydramine. Diphenhydramine administration caused a precipitous 60% decrease in mean arterial pressure, a 70% rise in heart rate, and a nonsignificant 8% decrease in cardiac output. These hemodynamic changes were transient, lasting 5 to 10 min before returning to pre-drug administration levels. All seven animals in this group showed decreases in gastric mucosal blood flow between baseline and 90-min shock periods (Table 1). This decrease was significant in each of the three anatomic areas (fundus, corpus, and antrum) and averaged 30%.

Diphenhydramine + cimetidine. Intravenous administration of diphenhydramine
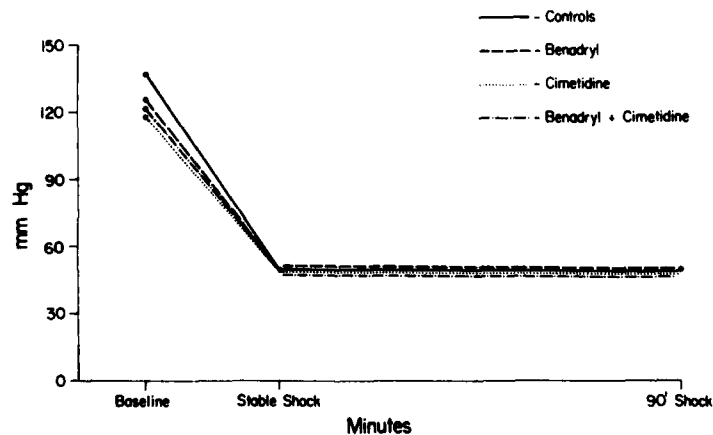

FIG. 2. Comparison of mean arterial pressures in the two Benadryl-treated groups with those of the untreated control and cimetidine-alone groups.

TABLE 1

Changes in Gastric Mucosal Blood Flow (GMBF), from Baseline to 90 min of Shock, in the Two Experimental Groups[a]

| | GMBF (ml/min/100 g tissue) | | | |
| | Benadryl | | Benadryl + Cimetidine | |
	Baseline	90-min Shock	Baseline	90-min Shock
Fundus	9.6 ± 0.6[a]	7.2 ± 0.7*	10.5 ± 1.2	8.7 ± 1.3
Corpus	13.0 ± 0.9	9.3 ± 0.9*	11.4 ± 1.4	9.4 ± 1.8
Antrum	10.7 ± 0.7	6.9 ± 0.9*	10.3 ± 1.3	8.0 ± 1.2*

[a] $\bar{X}$ ± SEM.
* Denotes $P < 0.05$ compared to the paired baseline value.

and cimetidine produced transient changes in central hemodynamic indices similar to those seen in the group receiving diphenhydramine alone. In the animals receiving both diphenhydramine and cimetidine, the shock-related decrease in gastric mucosal blood flow averaged 18% (Table 1). Only in the antral mucosa, however, was the shock-related fall in blood flow significant.

DISCUSSION

Diminution of gastric mucosal blood flow seems to be a necessary prerequisite for stress ulcer formation. Much has been written about the role of histamine in control of mucosal blood flow in normotensive states. However, little is known of its effect in states, such as hypovolemic shock, which result in decreased perfusion of the gastric mucosal circulation. These studies were undertaken in an effort to define that role.

Exogenous histamine administration has been shown to increase gastric mucosal blood flow in the normotensive state. Studies involving increasing doses of histamine in rats [11, 14] and feline [5] and canine models [7, 8, 24] have determined a linear relationship between the rise of both gastric acid secretion and mucosal blood flow. Once maximal acid secretion has been obtained, further administration of histamine results in

increases in mucosal blood flow which are disproportionate compared to the increase in acid secretion.

This latter finding leads to the hypothesis that there are two separate histaminic actions on the gastric mucosa. The first is on the parietal cell to secrete hydrochloric acid, which calls for a subsequent increase in blood flow to meet increased cellular metabolic demands. The second appears to be a direct and separate action on gastric mucosal blood flow independent of acid secretion.

Main and Whittle, in studies on normotensive, anesthetized rats, have investigated the actions of various H_1 and H_2 antagonists on mucosal blood flow and acid secretion [13]. Their findings suggest that H_1-receptor stimulation was responsible for histamine's control of independent mucosal blood flow while excitation of the H_2 receptor was associated with the musocal blood flow increases linked to rising gastric acid secretion. These findings may be species specific. Other investigators have found H_2-receptor antagonists in the cat to reduce histamine-stimulated gastric mucosal blood flow without affecting gastric acid secretion [6].

Variable results have been reported concerning the actions of histamine receptor antagonists on mucosal blood flow. This may be due to differences in both animal models and the drugs employed by dif-

ferent investigators. Thus the H_2-receptor antagonist burimamide has been noted to double blood flow in the resting rat gastric mucosa [13] while metamide, another H_2 blocker, has no effect on resting gastric mucosal blood flow in the normotensive rat model [18]. Finally cimetidine, the newest of the H_2-receptor antagonists has had no effect on mucosal circulation in unstimulated canine [3] and procine models [10].

However, all of these models may be inappropriate for extrapolation to the stress ulcer situation. First, all but one involve anesthetized animals whose gastric circulation is probably altered by that state. Second, the normotensive, resting animal is probably not akin to the pathophysiologic situation in stress ulcer formation. This is the experimental model in which Ritchie has demonstrated a decrease in mucosal blood flow to precede lesion appearance [20].

Studies of H_2-receptor antagonists have been carried out in models which do lead to stress ulcer formation. However, no unanimity exists as to their action on mucosal blood flow in this state either. McRae and Ritchie, using the canine ex vivo gastric chamber model has shown no effect by metamide on mucosal blood flow [15]. However, he used the aminopyrine clearance technique for mucosal blood flow determination. Archibald et al. have detailed the limitations of this method in accurately assessing blood flow by comparing it to the microsphere technique [1]. Furthermore, Cheung et al. have demonstrated that aminopyrine clearance most grossly underestimates blood flow when gastric mucosa is exposed to gastric mucosal barrier breakers [2] such as was done in the studies of McRae and Ritchie.

The miniature swine is a more applicable model than many of the others used because its physiology more closely resembles that of the human. Unlike the dog, it has both basal and histamine-stimulated gastric acid and pepsin secretion which are analogous to those seen in man [17]. In addition, these animals, like man, show spontaneous peptic ulcer disease [4].

Because of these advantages, the miniature swine has been the model of choice in our laboratory. Our initial studies, previously reported, evaluated the effect of H_2-receptor blockade on changes in gastric mucosal blood flow in animals receiving cimetidine versus untreated controls, following acute hemorrhage [10]. The present study similarly evaluates the effect of H_1- and H_1 + H_2-receptor blockade in the same model. To compare the effect of H_1- and H_2-receptor blockade, detailed comparisons among these four treatment groups were made.

Comparison of fundic mucosal blood flows in the four experimental groups is presented in Fig. 3. The flows during the baseline stabilization period represent the 100% standard of gastric mucosal blood flow against which the shock-related flows are compared. This format is also used in subsequent sections on corpal and antral flows. Both the untreated controls and the group receiving diphenhydramine alone showed significant drops in mucosal blood flow of 59 and 25%, respectively. The two groups receiving cimetidine, either alone or in combination with diphenhydramine, showed shock-related lowering of mucosal flows. However, this was not to a level which was significantly different from baseline values (11 and 16%, respectively). When the percentage decreases in mucosal blood flows were analyzed among the four groups, a significant difference ($P < 0.01$) was found between the two groups receiving cimetidine compared to those that did not. No significant differences were found between the cimetidine-treated groups or between the two noncimetidine groups.

Comparisons of corpal mucosal blood flows in the four groups are shown in Fig. 4. Gastric mucosal blood flow was significantly diminished by 53% in controls and 28% in the diphenhydramine-alone group. The postshock flow decreases seen
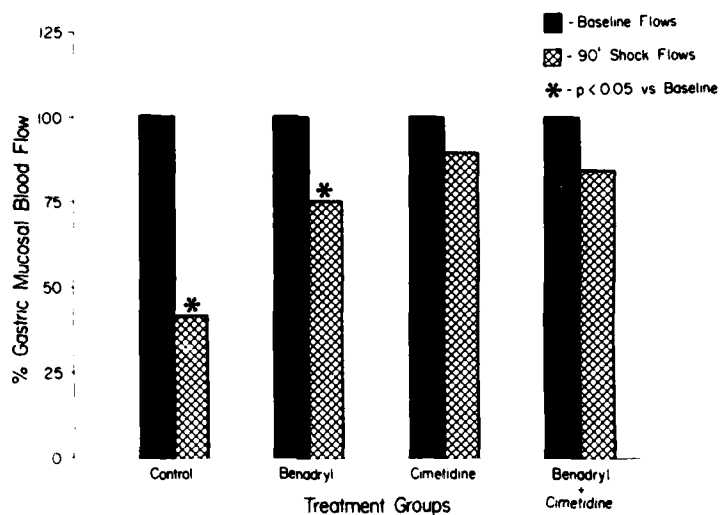
FIG. 3. Comparison of fundic mucosal blood flows, pre- and postshock, among the four groups.

in the cimetidine-alone ($\downarrow$11%) and the cimetidine plus diphenhydramine group ($\downarrow$17%) did not achieve statistical significance. When the shock-related falls in mucosal blood flow were compared among the four experimental groups, it was found that the two cimetidine-treated groups had significantly smaller decreases than the two other groups ($P < 0.01$). No significant difference in mucosal blood flow changes was observed either between the two cimetidine groups or the two groups without H_2-receptor blockade.

Comparisons of the antral mucosal blood flow changes are depicted in Fig. 5. Significant lowering of mucosal blood flow
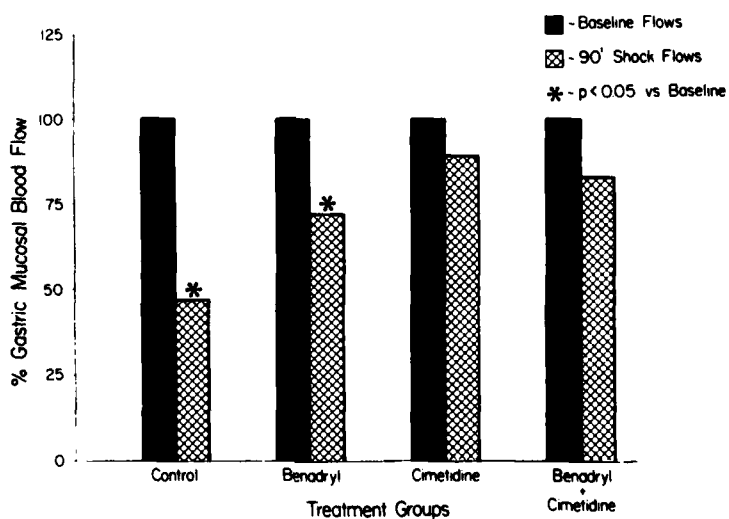

FIG. 4. Comparison of corpal mucosal blood flows, pre- and postshock, among the four groups.
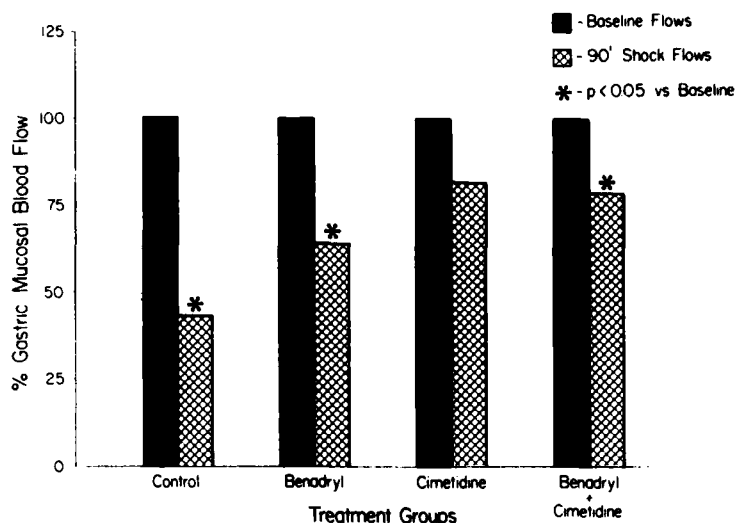
FIG. 5. Comparison of antral mucosal blood flows, pre- and postshock, among the four groups.

associated with hypotension was seen in the untreated controls (↓57%), diphenhydramine alone (↓36%), and cimetidine plus diphenhydramine (↓21%) groups. The flow changes in the cimetidine-alone group (↓19%) were not significant. Once more, when the shock-related changes in gastric mucosal blood flow were compared among the four groups, both cimetidine-treated groups differed significantly ($P < 0.01$) from the others. Also, as in the fundic and corpal areas, there was no significant difference between the two cimetidine groups or between those two groups not treated with cimetidine.

The normal vascular response to acute hemorrhage in this model is a 60% reduction in gastric mucosal blood flow. The results of the above comparisons show that protection from this normal vascular response is mediated by H_2-receptor blockade. In addition, blockade of the H_1 receptor does not appear to have significant effect on shock-related decreases in gastric mucosal blood flow. Therefore, the protective effect seen with combined H_1- and H_2-receptor blockade was due to the H_2 blockade alone.

The action of cimetidine in this model is probably local, or at least within the splanchnic bed. Evidence for this can be seen by examining the central hemodynamic indices following drug administration (Figs. 1 and 2). These were unchanged by cimetidine administration. Even when diphenhydramine was given with cimetidine, the effect of that drug on heart rate and arterial pressure had dissipated by the time the animal had undergone acute hemorrhage.

Cimetidine's mode of action in protecting gastric mucosal blood flow in shock is unclear. A possible explanation may be seen in work by Main and Whittle in which they found that burimamide caused an increase in histamine release from the gastric mucosa [12]. Therefore, the effect of an H_2-receptor antagonist on mucosal blood flow may actually be due to local histamine action on the mucosal vasculature. Whether or not cimetidine has a separate, more direct action on mucosal vessels in shock cannot be answered by these studies.

Finally, in the group of animals receiving both H_1- and H_2-receptor antagonists, there was a significant shock-related decrease in antral mucosal blood flow not seen in either

of the other two areas of the stomach. However, this group, along with the animals receiving cimetidine alone, still showed significant protection of shock-related mucosal blood flow compared to the groups whose H_2 receptors were not blocked. The antral mucosa has been shown to withstand greater levels of ischemia without ulcer formation. Menguy and Masters have linked this to an ability of the antrum to sustain its energy metabolism, better than the corpus or fundus, in the face of diminishing blood flow [16].

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