Proc. Natl. Acad. Sci. USA
Vol. 75, No. 6, pp. 2941–2944, June 1978
Medical Sciences

Beneficial and detrimental actions of histamine H_1- and H_2-receptor antagonists in circulatory shock

(hemorrhage/trauma/antihistamines/pathophysiology of shock)

BURTON M. ALTURA* AND SIMON HALEVY†

* Department of Physiology, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203; and † Department of Anesthesiology, Nassau County Medical Center, East Meadow, New York 11554

Communicated by Chandler McC. Brooks, March 29, 1978

ABSTRACT **This study explores the use of both histamine H_1- and H_2-receptor antagonists in two different forms of circulatory shock and suggests that histamine may be involved in more than one way in the pathophysiology of circulatory shock. Various single doses of diphenhydramine, chlorpheniramine, promethazine, and burimamide were administered intravenously to Wistar rats subjected to hemorrhagic or bowel ischemia shock. Cumulative survival and mortality, as well as arterial blood pressures and microhematocrits, were monitored. Pretreatment of the animals with the three different H_1-receptor antagonists exerted significant protection against both forms of shock. Rats pretreated with the H_2-receptor antagonist, burimamide, demonstrated an exacerbated mortality after induction of shock. Animals pretreated with H_1-receptor antagonists showed significantly higher mean arterial blood pressure, greater compensatory rebound of blood pressure after induction of shock, and greater responses to transfusion after hemorrhage than control, shocked animals. Similarly, rats pretreated with the H_1-receptor blockers demonstrated significantly greater compensatory hemodilution which continued late in shock. In marked contrast, rats pretreated with burimamide exhibited opposite effects after hemorrhage and bowel ischemia, i.e., significant falls in blood pressure, lack of compensatory rebound and response to transfusion of shed blood, and a progressive hemoconcentration. This report clearly demonstrates beneficial actions of histamine H_1-receptor antagonists and detrimental effects of H_2-receptor antagonists on survival and other parameters in these forms of circulatory shock.**

For more than 75 years, numerous investigators have suggested that various blood-borne substances are involved in the pathophysiology of circulatory shock syndromes. The release into the blood stream of several vasoactive agents has, from time to time, been implicated as both etiologic and sustaining factors in many shock syndromes (1–5). In order to gain insight into this area, specific pharmacologic antagonists to several of these vasoactive substances have been used by various workers over the past 40 years (6–9).

Although histamine H_1-receptor antagonists have been used previously to explore the possible contribution of histamine in some forms of circulatory shock (10–12), no previous study used several different antihistamines over a wide dose range in controlled sublethal shock models (see review, ref. 13). Nor have studies been done with histamine H_2-receptor antagonists in hermorrhagic or intestinal ischemic shock. The studies presented herein explore the use of both H_1- and H_2-receptor blockers in rats and indicate that histamine may be involved in more than one way in the pathophysiology of different forms of circulatory shock.

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MATERIALS AND METHODS

Animals. Young, adult male rats (Wistar strain, 150 ± 30 g), lightly anesthetized with pentobarbital sodium (Nembutal, 3.5 mg/100 g), were used.

Acute Hemorrhage and Blood Pressure. The technique used here was similar to that described previously (14). Femoral arteries and veins were cannulated and connected to calibrated bleed-out reinfusion devices containing heparin-treated Ringer's solution and in tandem with conventional mercury manometers. The animals were then administered, intravenously, 1.0 ml of Ringer's solution alone or containing various doses of H_1- or H_2-receptor antihistamines (1, 10 or 25 mg/kg). Sixty minutes later, the animals were bled via femoral arteries over a 30-min period to a fixed 3% by body weight. The blood was withheld from the latter animals for 110 min. At the conclusion of this hypotensive period, the shed blood was reinfused (intra-arterially) over a 30-min period. Blood pressure monitoring was continued after transfusion for 20–30 min. The cannulas were then removed and the wounds sutured. The animals were then carefully monitored for survival for 7 days. Unpretreated controls were always subjected to hemorrhage simultaneously with the experimental animals.

Bowel Ischemia Shock, Blood Pressure, and Hematocrit. The technique used here, as well as the procedure of assessing the presence of circulatory shock, was similar to that described previously (14). Femoral arteries and veins were cannulated in these anesthetized animals as in the hemorrhage experiments. The animals were then administered, intravenously, 1.0 ml of Ringer's solution alone or containing various doses of antihistamines, as in the hemorrhage experiments. Sixty minutes later, bowel ischemia was induced by a 45-min temporary occlusion of the superior mesenteric artery. Serial arterial microhematocrits (i.e., every 15 min) and mean arterial blood pressures were determined in selected animals. These cardiovascular parameters were monitored for at least 130 min after release of the temporary superior mesenteric arterial occlusion. The cannulas were then removed and the wounds were sutured. These animals were also observed for 7 days for survival. The statistical validity of the survival data was assessed by means of the chi-square test. Mean blood pressures (±SEM) and hematocrits (±SEM) were compared for statistical significance by means of Student's *t* test.

Antihistaminics. Three H_1-receptor blockers were used: diphenhydramine hydrochloride (Parke Davis and Company), chlorpheniramine maleate (Schering Corporation), and promethazine hydrochloride (Wyeth Laboratories). The H_2-receptor antagonist, burimamide hydrochloride, was a gift from J. W. Black (Smith, Kline and French Laboratories). Each antihistamine, after appropriate buffering to pH 7, was dissolved in normal isotonic Ringer's solution.

RESULTS

Influence of Antihistamines on Mortality after Bowel Ischemia Shock and Acute Hemorrhage. Table 1 indicates that three different types of H_1-receptor blockers, when given as single doses over a wide dose range prior to production of bowel ischemia shock, enhance survival in rats. The following relative descending order of potency can be noted: chlorpheniramine > diphenhydramine > promethazine. Although pretreatment with all three H_1-receptor antagonists produce significant increases in survival, the best results are seen within 48 hr after release of the superior mesenteric arterial occlusion. In hemorrhagic shock, pretreatment with 1 mg of diphenhydramine per kg yields a 100% permanent survival (Table 2). Although chlorpheniramine pretreatment also confers protection against death from hemorrhage, it is less potent than diphenhydramine (Table 2). There appears to be a reverse dose-response relationship with the three antihistamines with respect to protection against shock.

Pretreatment with the H_2-receptor blocker is associated with a progressive, dose-dependent exacerbation of mortality after both types of shock (Tables 1 and 2). Burimamide administration to nonshocked control animals was not associated with any mortality at a dose level of 15 mg/kg and only 1 out of 25 animals died at a dose level of 30 mg/kg (Table 1).

Influence of Antihistamines on Blood Pressure Patterns in Shock. Pretreatment with any of the antihistamines did not significantly influence mean arterial blood pressure from control levels prior to shock (Figs. 1 and 2). In general, the expected drop in mean blood pressure with both hemorrhage and release of superior mesenteric arterial occlusion is significantly less ($P < 0.02$) in animals pretreated with all three H_1-receptor antagonists (Figs. 1 and 2). The compensatory response of the blood pressure, seen after shock in animals pretreated with H_1-receptor blockers, is significantly greater and better maintained than untreated controls. In addition, in hemorrhagic shock the magnitude of the blood pressure response to transfusion was significantly greater in animals pretreated with H_1-receptor antagonists when compared to controls ($P < 0.001$) (Fig. 2).

Animals pretreated with burimamide exhibit the greatest drop in mean arterial blood pressure after hemorrhage or release of the superior mesenteric arterial occlusion (Figs. 1 and 2). After hemorrhagic shock, the arterial blood pressure in these pretreated animals was maintained at a significantly lower level than in controls ($P < 0.02$) and almost failed to respond to transfusion. With intestinal ischemia shock, the mean arterial blood pressure was maintained at a low level for about 45% of the observed time and dropped precipitously shortly thereafter.

During occlusion of the superior mesenteric artery, the expected rise in mean arterial blood pressure (15) occurred in both controls and with animals pretreated with antihistamines. However, burimamide significantly ($P < 0.03$) potentiated this pressor response when compared to untreated control animals.

Influences of Antihistamines on Hematocrit Patterns in Bowel Ischemia Shock. With the exception of the group pretreated with burimamide, all animals exhibit a fall in arterial hematocrit upon release of the arterial occlusion (Fig. 3). Rats pretreated with the H_1-receptor antagonists exhibit the greatest compensatory hemodilution, which continues late in shock. Animals pretreated with the H_2-receptor blocker exhibit very little early compensatory hemodilution, and late in shock they exhibit a progressive hemoconcentration that is significantly greater than in the untreated control group ($P < 0.02$). Although the normal response to occlusion of the superior mesenteric artery is a significant rise in arterial hematocrit (15), rats pretreated with burimamide fail to demonstrate this elevation.

Table 1. Influence of antihistamines on mortality after bowel ischemia

Therapy	Dose, mg/kg	n	Cumulative mortality, % 48 hr	96 hr	168 hr
Controls	—	78	65	67	67
Chlorpheniramine	1	25	8*	12*	12*
	10	24	12*	12*	12*
	25	23	17†	26†	26†
Diphenhydramine	1	24	8*	25†	29†
	10	23	17†	39‡	39‡
	25	23	43	57	57
Promethazine	1	25	36‡	40‡	40‡
	10	24	12*	29†	29†
	25	24	17†	33‡	42‡
Burimamide	15	30	73	80	87§
	30	34	85§	91‡	91‡
	(30)¶	25	4	4	4

* Significantly different from untreated controls ($P < 0.001$).
† Significantly different from untreated controls ($P < 0.01$).
‡ Significantly different from untreated controls ($P < 0.02$).
§ Significantly different from untreated controls ($P < 0.03$).
¶ Animals in this group were not subjected to bowel ischemia shock.

Table 2. Influence of antihistamines on mortality after acute hemorrhage

Therapy	Dose, mg/kg	n	Cumulative mortality, % 24 hr	96 hr	168 hr
Controls	—	22	50	55	55
Chlorpheniramine	1	10	10*	10*	10*
	10	10	10*	20	20
	25	9	22	33	33
Diphenhydramine	1	7	0*	0*	0*
	10	9	0*	11*	33
	25	9	0*	11*	33
Burimamide	30	12	92*	100*	100*

* Significantly different from untreated controls ($P < 0.03$).

DISCUSSION

In this report we demonstrate that at least three different histamine H_1-receptor antagonists exert significant protection, over wide dose ranges, in forms of circulatory shock other than anaphylaxis. In addition, we show that an H_2-receptor antagonist exacerbates mortality in at least two different forms of circulatory shock.

The clinical counterpart of bowel ischemia shock, used here as a shock model, carries a discouragingly high mortality rate (16, 17). Acute occlusion of the superior mesenteric artery is all too frequently completely refractory to corrective surgical and supportive therapy (16–18). It is of interest, therefore, that experimental bowel ischemia shock with very low survival

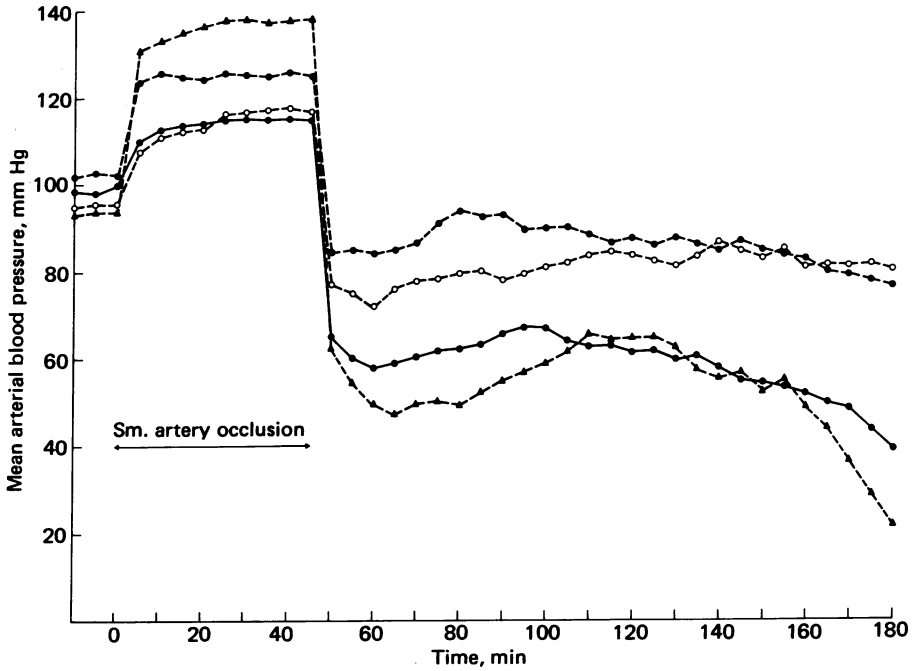

FIG. 1. Influence of pretreatment with H_1- and H_2-receptor blockers on mean arterial blood pressure in rats subjected to bowel ischemia shock. (●—●) Untreated controls (n = 32); (●- - -●) chlorpheniramine (1 mg/kg) pretreatment (n = 8); (○- - -○) diphenhydramine (1 mg/kg) pretreatment (n = 8); (▲- - -▲) burimamide (30 mg/kg) pretreatment (n = 12). Each point represents the mean value derived from the number of different experimental animals indicated in parentheses. The SEMs for each mean value were between 1.2 and 4.2 mm Hg.

(33%) in untreated animals yields significantly improved survival (>80%) when animals are pretreated shortly before induction of shock; however, survival is not particularly affected by other pharmacologic agents (16–18).

Several of the effects induced by the H_1- and H_2-receptor blockers on blood pressure and hematocrit patterns in shocked animals suggest possible mechanisms of action whereby these antagonists protect and exacerbate mortality, respectively. With respect to blood pressure, shocked rats pretreated with H_1-receptor blockers, when compared to untreated controls, clearly demonstrated three important responses: (*a*) significantly higher mean levels; (*b*) greater compensatory rebound; and (*c*) greater

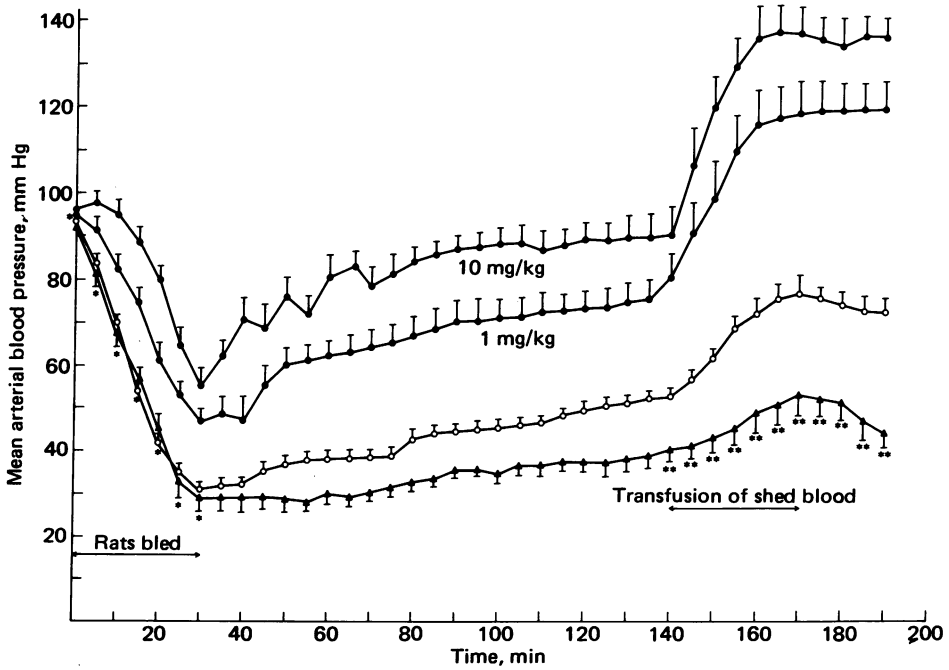

FIG. 2. Mean arterial blood pressure responses of untreated controls (n = 22) (○—○) and of rats pretreated with diphenhydramine (1 and 10 mg/kg; n = 7 and 9, respectively) (●—●) and burimamide (30 mg/kg; n = 12) (▲—▲) subjected to a 3% hemorrhage by body weight. Each point represents the mean value (±SEM) derived from the number of different experimental values indicated in parentheses. *, Bleedings; **, transfusions.

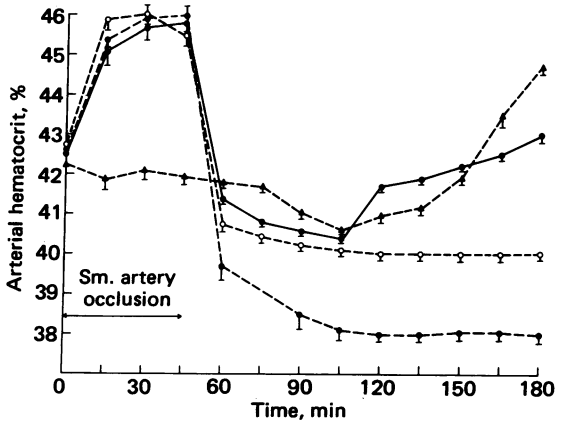

FIG. 3. Influence of pretreatment with H_1- and H_2-receptor blockers on serial arterial hematocrits in rats subjected to bowel ischemia shock. For symbols and doses, see legend to Fig. 1. Control (n = 20); chlorpheniramine, diphenhydramine, and burimamide (n = 7). Each point represents the mean value (±SEM) derived from the number of different experimental values indicated in parentheses.

responses to transfusion of blood after hemorrhage. In order to relate these striking phenomena, observed on arterial blood pressure, to the improvement in survival, one has to consider the actions that histamine has on different components of the peripheral vasculature. Data have accumulated to indicate that histamine, acting via H_1-receptors, constricts most arteries and veins (19–22) and partially dilates arterioles, metarterioles, precapillary sphincters, and venules, in this order of relative sensitivity. Our data on blood pressure and survival would be compatible with the concept of an interaction between histamine acting via H_1-receptors, in the above manner in shock and H_1-antihistaminics counteracting these segmental and differential actions on the vasculature. As a result, one could envision that blood pressure would be better maintained in shock with H_1-receptor antagonists by restoring microvascular tone towards normal and inhibiting released histamine-induced constriction of small veins, thereby restoring a *vis-a-tergo*, i.e., increasing venous return. Thus, H_1-receptor blockers would result in: (*a*) improvement in perfusion of critical, including target (e.g., splanchnic vasculature), organs; (*b*) maintenance of blood pressure; and (*c*) markedly enhanced survival. In marked contrast, shocked animals pretreated with the H_2-receptor antagonist failed to demonstrate compensatory responses in blood pressure or responses to transfusion of shed blood in hemorrhage. Since histamine action on H_2-receptors in the peripheral vasculature is exclusively as a dilator (19, 21, 22), which can be effectively antagonized by H_2-receptor antihistamines (13, 19, 22), one could expect that both inflow arterioles, as well as outflow venules across numerous vascular beds, would constrict in the presence of burimamide in circulatory shock. As a consequence, venous return, cardiac output, and blood pressure could be expected to fall. Our data with burimamide are compatible with this thesis. In addition to the peripheral vascular actions of histamine, one should also consider the possible stimulatory actions of histamine on the heart (e.g., increases in coronary flow, heart rate, and force of contraction), which are thought to be mediated exclusively by H_2-receptors (23–26). It is, therefore, probable that use of H_2-receptor antagonists in shock, such as burimamide, would prevent these beneficial compensatory responses.

The hematocrit patterns noted here in shocked animals pretreated with the H_1- and H_2-receptor antagonists seem to closely parallel the observed blood pressure changes and would be compatible with the above suggested explanations concerning microcirculatory hemodynamics. As a consequence, hemodilution is pronounced and maintained in animals pretreated with H_1-receptor blockers, whereas hemoconcentration is exacerbated late in shock in animals that received burimamide.

Histamine-induced vasodilatation via H_2-receptors may thus be a beneficial effect in cardiovascular compensation in circulatory shock and trauma. In conclusion, our results suggest that certain actions of histamine on H_2-receptors could be beneficial in circulatory shock, while actions on H_1-receptors may be detrimental. In view of the data presented herein, one must think seriously about the potential value of antihistamines as adjuvant drugs in the treatment of low-flow states and as pre-operative medication.

We thank Janet Ficcara and William Cannon for their excellent technical assistance in these studies. The work reported herein was supported by Research Grants HLBI-18002 and HLBI-18015 from the U.S. Public Health Service.

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