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H_1- and H_2-Histamine Receptor Antagonists and Protection against Traumatic Shock[1] (39692)

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Ever since the classic work of Sir Henry Dale and Sir Thomas Lewis, histamine has been implicated by many workers in lethality from circulatory shock and trauma (1-6). More recently, it has been proposed that a newly formed "intrinsic histamine" synthesized by endothelial and/or vascular smooth muscle cells may contribute to lethality in shock syndromes (7, 8). In contrast to these ideas, there is evidence which indicates that pretreatment of animals with histamine prior to shock may actually protect animals rather than exacerbate mortality (9, 10).

Although H_1-receptor antihistamines have been utilized from time to time to explore the possible contribution of histamine in different forms of circulatory shock (2, 5, 11), there is not to our knowledge any comprehensive study available which has utilized several different forms of these antihistamines over a wide dose range in a controlled shock model, nor have any studies been done with H_2-receptor antagonists in whole-body traumatic shock. It would be necessary to examine both kinds of histamine antagonists since information is accumulating which suggests that both kinds of histamine receptors may be important in regulation of the cardiovascular system (12, 13). Furthermore, it is distinctly possible that histamine exerts differential receptor actions in shock. The studies herein explore the use of both H_1- and H_2-receptor blockers and suggest that histamine may be involved in more than one way in traumatic shock.

Methods. Adult male mice of the ICR strain (Royalhart Laboratory Animals, Inc., New Hampton, N.Y.), weighing 26-28 g and lightly anesthesized with pentobarbital sodium (Nembutal, 2 mg/100 g, ip), were subjected to 350 revolutions of Noble-Collip drum trauma (NCDT) at 40 rpm (14). NCDT was chosen since it has been shown to be readily amenable to quantitation of the imposed stress in mice (14). In other terms, by varying the number of revolutions of the drum, a specific degree of hypotension and survival can be produced. ICR mice were specifically utilized because they are known to be sensitive to the toxic effects of histamine (15). Different groups of mice were pretreated ip 50 min prior to NCDT with various doses (i.e., 1, 10, and 25 mg/kg) of an antihistamine. Each antihistamine was dissolved in normal isotonic saline solution. The volume injected in all cases was 1 ml/100 g. Unpretreated controls were always subjected to NCDT simultaneously with the experimentals. Two groups of untraumatized mice were pretreated with high doses of antihistamines (e.g., 25 or 100 mg/kg). The H_1-receptor blockers utilized in this study were: diphenhydramine hydrochloride (Parke Davis and Co.), chlorpheniramine maleate (Schering Corp.), promethazine hydrochloride (Wyeth Laboratories), pyrilamine maleate (K & K Laboratories), and pyribenzamine hydrochloride (Ciba Pharmaceuticals). The H_2-receptor antagonist, burimamide hydrochloride, was a gift from Dr. J. W. Black (Smith, Kline and French Laboratories). Cumulative mortality was monitored for 120 hr. All animals were grossly autopsied at death for characteristic signs of shock (14, 16, 17). Mice showing fractured skulls, subdural hematoma, lacerated viscera, or torn vessels in the thoracic or abdominal cavities were not included; less than 3% of the animals exhibited such injuries. The data were analyzed for statisti-

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TABLE I. INFLUENCE OF ANTIHISTAMINES ON DRUM TRAUMA MORTALITY.

Therapy	Dose (mg/kg)	N	Cumulative mortality (%) 2 hr	72 hr	120 hr
Controls	–	34	38	38	38
Diphenhydramine	1	20	5[a]	5[a]	5[a]
	10	20	5[a]	15	15
	25	20	15	15	15
Promethazine	1	23	4[a]	13[c]	13[c]
	10	20	10[c]	10[c]	10[c]
	25	25	4[a]	4[a]	4[a]
Pyrilamine	1	19	11[c]	32	32
	10	19	11[c]	26	37
	25	19	11[c]	11[c]	11[c]
Pyribenzamine	1	20	0[a]	10[c]	25
	10	19	11[c]	42	53
	25	19	11[c]	32	37
Chlorpheniramine	1	20	30	65	90[d]
	10	18	44	89[d]	89[d]
	25	18	78[a]	83[a]	94[d]
	(25)[b]	28	0[d]	0[d]	0[d]
Burimamide	1	18	44	61	67
	10	20	30	45	60
	100	18	94[d]	94[d]	94[d]
	(100)[b]	18	0[a]	0[a]	0[a]

[a] Significantly different from controls ($P < 0.01$).
[b] Animals in this group were not subjected to trauma.
[c] Significantly different from controls ($P < 0.05$).
[d] Significantly different from controls ($P < 0.001$).

cal significance by use of a one-way χ^2 test. A total of 550 mice was utilized for these studies.

Results. A scan of the data in Table I reveals that different antihistamines exerted a differential effect on mortality resulting from NCDT in mice.[3] Four of the five H_1-receptor antagonists exerted significant protection against death resulting from the trauma. All of the H_1-receptor antagonists except chlorpheniramine resulted in significant protection early after trauma, i.e., at 2 hr. Promethazine was the only H_1-receptor antagonist that resulted in significant protection beyond 72 hr at all dose levels. It should be noted that there appears to be a reverse dose-response relationship with diphenhydramine in contrast to the other antihistamines used.

[3] We are indebted to Dr. Patrick L. Ross, Department of Psychiatry and Psychology, Nassau County Medical Center (East Meadow, New York), for aiding us in the statistical calculations presented in this manuscript.

Pretreatment with the H_2-receptor antagonist, burimamide, as well as chlorpheniramine (an H_1-receptor blocker) was associated, at many dose levels, with an exacerbation of mortality. Mortality was, however, not seen in the two groups of untraumatized animals which were pretreated with high doses of chlorpheniramine (25 mg/kg) and burimamide (100 mg/kg).

Discussion. To our knowledge, this is the first report which demonstrates that at least four different H_1-receptor antagonists exert significant protection in a form of circulatory trauma other than anaphylaxis or endotoxemia. Since the early 1930s, plasma histamine levels have been shown to increase early after several different forms of circulatory stress, e.g., burns (1, 2, 6), anaphylaxis (2), endotoxemia (4, 5), hemorrhage (18), and NCDT (19). Tissue levels of histamine decarboxylase are also known to be increased in several forms of circulatory stress and trauma (7, 8, 19).

The response of the cardiovascular system to histamine depends upon the existence,

and proportion, of at least two different receptors for histamine, H_1- and H_2-receptors (12, 13). However, in most species so far investigated, the dilator responses of microcirculatory blood vessels as well as the inotropic and chronotropic responses to histamine are thought to be mediated primarily by H_2-receptors (12, 13). H_1-receptor antagonists are known to be capable of completely blocking the contractile responses of histamine on large arterial and venous vessels (20, 21) and to block partially the depressor actions of histamine on microcirculatory blood vessels (2, 12, 13, 20, 22). A possible mechanism for the protective actions of H_1-receptor antagonists in NCDT could, therefore, be attributed to the prevention of excessive vasoconstriction brought about by either released or newly formed histamine. It is thought that excessive vasoconstriction may be a major cause of lethality in many shock syndromes (23). One must also entertain the possibilities that H_1-receptor antagonists could: (i) indirectly block the histamine mediated release of catecholamines from the adrenal medulla (2), thereby preventing excessive vasoconstriction, and/or (ii) prevent the histamine-induced increases in capillary permeability (2). NCDT is known to be associated with a frank loss of plasma from the intestinal capillary walls into the interstitial fluid spaces and hemoconcentration (14, 16, 24). Rodents dying from NCDT also exhibit microcirculatory failure (24).

Other data in this report indicate that administration of either chlorpheniramine or burimamide exacerbate mortality following NCDT. It is of interest to note that chlorpheniramine, of all antihistamines so far investigated in the mouse skin microcirculation, produces potent vasoconstriction of all microvessels (i.e., precapillary sphincters, metarterioles, arterioles, and venules) (25). In addition, chlorpheniramine is the only antihistamine of those used here known to induce venular stasis and rhexis of the postcapillary venular walls in the mouse microcirculation (25). These specific pharmacologic actions of chlorpheniramine could be important contributing factors accounting for the increased mortality seen after trauma in our experiments. It is noteworthy that chlorpheniramine can antagonize the coronary dilatating action of histamine (26), as do H_2-receptor antagonists (27). Such data could be used to suggest that chlorpheniramine may have H_2-receptor blocking properties.

The action of released (or newly formed histamine) on H_2-receptors in NCDT may be important for survival since the specific H_2-receptor blocker, burimamide, enhances mortality at the highest dose level studied. Histamine induced vasodilatation via H_2-receptors may thus be a beneficial effect in NCDT. In this context, it is interesting to note that histidine decarboxylase activity is activated in NCDT, presumably at the microcirculatory level rather than in large blood vessels (19). Although our data could therefore indirectly be used as support for the contention that activation of histidine decarboxylase may be beneficial in certain shock syndromes (7, 8, 19), this will have to await further investigation. Other factors that will have to be contended with in future investigations are the inverse dose–response relationships observed with diphenhydramine, the possibility of H_2-receptor antagonism by H_1-receptor blockers at higher doses, and the possibility of local anesthesia induced by high doses of antihistamines (20).

Summary. Pretreatment of mice with four different H_1-receptor antagonists (i.e., diphenhydramine, promethazine, pyrilamine, and pyribenzamine) exerted significant protection against Noble–Collip drum trauma (NCDT). Blockage of H_2-receptors, however, was associated with an exacerbation of mortality after NCDT. These results suggest that certain actions of histamine on H_2-receptors could be beneficial in NCDT in mice, while actions on H_1-receptors may be detrimental.

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