initiating an auto-immune response in the thymus.

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Hypotensive Activity of 3-(N-methyl-t-butyl-amino)-1-bromo-3-methyl-1-butyne Hydrochloride. (29038)

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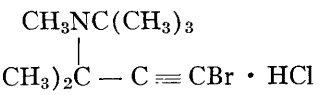
In searching for agents that lower blood pressure, much attention has been given to substances whose principal action is ganglionic blockade. Since these agents block all autonomic ganglia to a varying degree, search continues for a compound having more specific blood pressure lowering action, but with a minimum of ganglionic block.

A series of haloethynyl derivatives has been prepared(1), of which 3-(N-methyl-t-butyl-amino)-1-bromo-3-methyl-l-butyne hydrochloride (Lilly no. 37157) has exhibited good hypotensive activity with minimum ganglionic blockade in animals. This paper presents data obtained in the pharmacologic evaluation of this compound.



37157

Methods. Hypertension was produced in male Long-Evans rats by a modification of the Goldblatt procedure(2). Control blood pressures were taken by a microphonic manometric technique(3) before oral administration of 20 mg/kg of the drug or an equivalent volume of 0.9% saline. Following drug administration, blood pressure was determined every hour for 7 hours and the mean change over the 7-hour period was calculated for 3 hypertensive rats. The average maximum depression of blood pressure was also recorded.

TABLE I. Blood Pressure Response in Renal Hypertensive Rats.

	B.P.	%	B.P.	%	B.P.	%	B.P.	%	B.P.	%
					Control—.9% Saline—Oral					
$\bar{X}$	215	2.12	217	3.25	222	4.73	223	5.59	219	6.55
M		3.72		5.53		8.56		7.17		10.05
$\bar{X}$	226	2.51	229	1.02	223	1.96	227	5.93	234	4.03
M		4.42		2.55		5.83		7.93		6.84
					37157—20 mg/kg—Oral					
$\bar{X}$	223	11.28	218	10.55	219	10.69	220	11.32	216	9.56
M		12.56		13.30		11.87		12.73		12.04
$\bar{X}$	229	12.34	220	9.42	221	12.35	217	11.36	215	11.06
M		12.23		13.14		13.12		13.36		12.56

$\bar{X}$ Mean value for control blood pressure and % decrease of blood pressure over 7-hour period for 3 hypertensive rats.
M Maximum depression of blood pressure during 7-hour period.

Hypertension was produced in mongrel dogs by the method of Page(4). Blood pressures were determined by the arterial puncture technique 1, 2, 3, and 6 hours following oral drug administration.

Normotensive dogs were anesthetized with sodium phenobarbital (150 mg/kg, i.v.) and either 37157 (5 mg/kg) or an equivalent volume of 0.9% NaCl solution alone was administered intravenously. Changes in blood pressure, respiration, and electrocardiogram were monitored for 5 hours. A similar experimental preparation was used to study alterations in blood pressure responses to bilateral carotid occlusion.

In 2 decerebrate-pithed male dogs and female cats the drug was administered intravenously (5 mg/kg) and subsequent blood pressure changes were recorded.

Normotensive cats anesthetized with chloralose (50 mg/kg, i.v.) were prepared for kymographic recording of blood pressure and contractions of the nictitating membrane. The cervical sympathetic trunk was exposed so that it could be stimulated with platinum electrodes. A dose-response curve was obtained for blood pressure and blockade of the cervical sympathetic ganglion with supramaximal stimulation at 2 and 20 cycles per second 4 minutes following injection of 37157 into the femoral vein. Four minutes were allowed for recovery of the nictitating membrane before administration of succeeding doses. A similar study was made using hexamethonium.

Strips of aorta from 9 female rabbits were suspended in a 25-ml muscle chamber containing Krebs-Henseleit solution as described by Furchgott and Bhadrakon(5). Muscle response following drug administration was recorded by means of ink writing levers with a 1-12 magnification and 4-g tension.

Isolated rabbit and guinea pig ileum and rabbit uterus were suspended in Tyrode solution at 37.5°C and gassed with a mixture of 95% O_2 and 5% CO_2. Muscle responses were recorded from an ink writing lever with a 1-7 magnification.

Isolated rabbit hearts were suspended in an Anderson-Carver apparatus(6) using Chenoweth's perfusion fluid(7) maintained at 37.5°C. The heart contractile force was recorded electronically by a myograph attached to the apex of the heart. Coronary flow and electrocardiogram were also recorded.

Results and discussion. Compound 37157 was administered daily to 3 hypertensive rats for two 5-day periods (Table I). During the first 5-day period the mean fall in blood pressure for 7 hours ranged from 9.6 to 11.3%. During the second 5-day period the mean fall varied from 9.4 to 12.4%. The maximum fall was 12 to 14%.

An oral dose of 10 mg/kg, given to a hypertensive dog, caused the blood pressure to fall from a control value of 210 mm Hg to 165 mm HG at 3 hours (Fig. 1). At the end of 6 hours, pressure had returned to 200 mm Hg. Another hypertensive dog re-

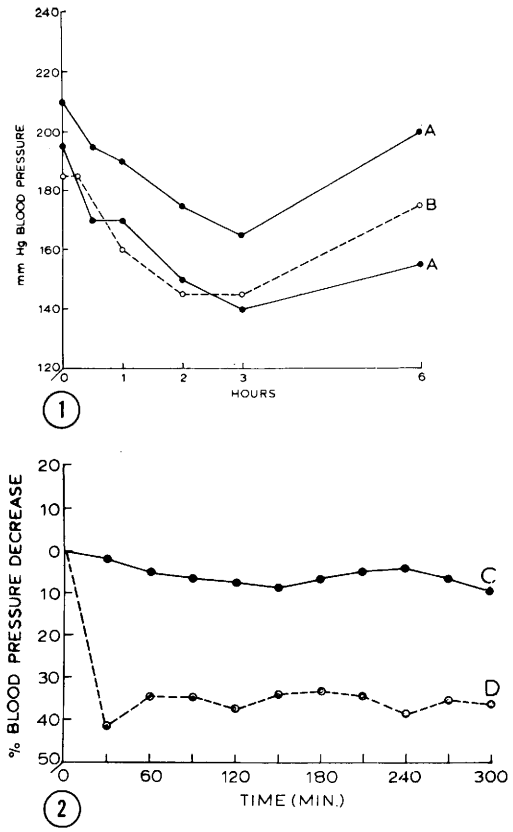


FIG. 1. A. Two renal hypertensive unanesthetized dogs 10 mg/kg 37157. B. One renal hypertensive dog 5 mg/kg 37157 orally.

FIG. 2. C. Two control normotensive anesthetized dogs. D. Three normotensive anesthetized dogs 37157 (5 mg/kg) intravenously.

ceived both 5 and 10 mg/kg by mouth. Following a dose of 5 mg/kg, the pressure decreased from 185 mm Hg to 145 mm Hg in 2 hours and returned to 175 mm Hg at 6 hours. Ten mg/kg produced a decrease in blood pressure from 195 mm Hg to 140 mm Hg at 3 hours. A prolonged hypotensive effect was obtained, and at 6 hours the blood pressure remained at 155 mm Hg.

Various doses (1-5 mg/kg) of the compound, when given intravenously to anesthetized normotensive dogs, caused decreases in blood pressure which corresponded to the amount administered (Fig. 2). Doses of 5 mg/kg produced a 35-40% reduction in blood pressure with no apparent alteration in electrocardiogram and respiratory pattern.

Pressor response to bilateral carotid occlusion in anesthetized dogs was completely inhibited by doses as low as 1 mg/kg, i.v. Since some ganglionic blocking activity was present, it is difficult to ascertain the degree of central block. Some central block is apparent, however, since total ganglionic block was not obtained with large doses (10 mg/kg) with the cat nictitating membrane preparation.

Blood pressures of decerebrate cats and dogs were not altered by 5 mg/kg of compound 37157 by vein. This would again indicate central activity of this compound. In decerebrate cats and dogs, pressor response to 10 μg of levarterenol was slightly higher following compound 37157.

Four normotensive cats received graded doses of 0.1, 0.25, 0.50, 1, 2, 5, and 10 mg/kg of 37157. A 28% maximum decrease in blood pressure was obtained with the 5 mg/kg dose (accumulative dose of 8.85 mg/kg). The greatest degree of ganglionic block obtained was 55% (2 cycles per second stimulation) following the 5 mg/kg dose. These responses were compared with results obtained from cats given hexamethonium, which were treated and observed similar to those receiving 37157. The nictitating membrane response was not blocked in the same manner as with hexamethonium in that the 20 cycles per second stimulation did not show a predominantly larger block of the ganglia than the 2 cycles per second stimulation.

Doses of 1, 2, and 4 mg of the compound produced a slight contraction of the rabbit aortic strip. The addition of angiotensin amide (0.1 or 0.2 μg) to the treated muscle slightly increased muscle contraction over the untreated muscle strip. However, following a washing of the treated muscle the contraction in response to angiotensin amide was decreased by 30%, indicating a delayed or slow blocking effect by the compound. Doses of 0.1 and 0.2 μg of levarterenol were also inhibited by 30% following pretreatment with this material.

Spastic contraction of the guinea pig ileum produced by 1 μg of angiotensin amide was relaxed with 1 mg doses of compound 37157. When the compound was administered one

minute prior to treatment with angiotensin amide, contraction was reduced by 50%. Doses of 0.2 and 0.4 mg of 37157 also blocked by 50% the spasm induced by 15 μg of serotonin and doses of one mg completely blocked the serotonin response.

Doses of 5 mg of the compound briefly relaxed the rabbit ileum, followed by a slight decrease in tone. The relaxing action of 0.5 μg of levarterenol was not altered.

The rabbit uterus was contracted with 1, 3, and 5 mg doses of 37157. No alteration of the uterine response to 3 μg doses of levarterenol was noted.

Contractile force, rate, and coronary blood flow of the rabbit heart were decreased by 2 mg of compound 37157. Complete recovery occurred in 8 minutes. A dose of 5 mg stopped the heart for 20 minutes. The voltage of the R wave of the electrocardiogram was decreased.

Summary. It has been shown that haloethynyl derivatives have a hypotensive action in animals with a minimum of ganglionic blockade. Oral administration of compound 37157 resulted in a significant fall in blood pressure in renal hypertensive rats and dogs. In the anesthetized cat, compound 37157 lowered blood pressure and only partially blocked the contraction of the electrically stimulated nictitating membrane. The anesthetized normotensive dog responded with a fall in blood pressure, persisting for 5 hours. Respiration and electrocardiogram were not altered. The pressor response to carotid occlusion was completely abolished. Hypotensive activity could not be elicited in decerebrate cats and dogs, indicating partial central activity. In this preparation the pressor response to levarterenol was augmented. Compound 37157 stimulated the rabbit aortic strip and produced a delayed block of the response to angiotensin amide and levarterenol. The spastic action of angiotensin amide and serotonin on isolated ileum preparations was inhibited by 37157. The isolated rabbit uterus was stimulated. In the perfused isolated rabbit heart, there was a decrease in cardiac contractility, heart rate, and coronary flow.

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New Effects of Sodium Chloride and Protamine on Human Postheparin Plasma 'lipoprotein' Lipase Activity.* (29039)

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Sodium chloride and protamine have long been thought to be inhibitors of postheparin plasma 'lipoprotein' lipase(1-10). The mechanism of their action is not known. The described inhibition by sodium chloride was not reversed by heparin nor by addition of whole serum or boiled extract of lipoprotein lipase(1). The protamine inhibition was thought to indicate the presence of enzyme bound heparin which is apparently an essential component of the system(1).

The present study reports the effect of sodium chloride and protamine on posthep-

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