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DEPARTMENT OF PHARMACOLOGY, WEST VIRGINIA UNIVERSITY SCHOOL OF MEDICINE. MORGANTOWN, WEST VIRGINIA

THE COMPARATIVE PHARMACOLOGY OF THE N-ALKYL-1-(p-HYDROXYPHENYL)-2-AMINOETHANOLS

BY

DAVID F. MARSH AND D. A. HERRING

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Since the fundamental study of BARGER and DALE (1) of the relationship between the chemical constitution and physiological action of the sympathomimetic amines, numerous investigations have been made of many structurally and pharmacologically related compounds. Although many studies (2-11) have been concerned with *dl*-1-(*p*-hydroxyphenyl)-2-methylaminoethanol, or "Sympatol," only LANDS, RICKARDS, NASH and HOOPER (12) have investigated any of the higher N-alkyl homologs of this material. We have compared the N-ethyl, N-isopropyl, N-*n*-butyl, and N-*t*-butyl-1-(*p*-hydroxyphenyl)-2-aminoethanol and the N-methyl homolog, 'Sympatol' (1).

1. — BLOOD PRESSURE EFFECTS IN DOGS

Experimental Procedure. Twenty-six apparently healthy, adult mongrel dogs (4.5-22 kgm.) were anesthetized by the intraperitoneal injection of 330 mgm. of sodium barbital per kgm. (10 per cent solution) 90 minutes prior to operation. Twenty of these (14 received 1 mgm. of atropine sulfate per kgm.) had the carotid artery cannulated and connected to the usual mercury manometer recording on a soot kymo-

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graph. Blood pressure in the remaining 6 anesthetized dogs was measured with a 20-gauge needle introduced into an unobstructed carotid artery and connected to a HAMILTON (13) manometer. This technic was also used for 8 trained dogs (4 had hypertension as a result of old age or kidney damage) which had received no premedication except 1 cc. of 1 per cent procaine hydrochloride solution intradermally at the site of insertion of the hypodermic needle cannula.

Results. It is possible to give repeated injections of 'Sympatol' or 1-(*p*-hydroxyphenyl)-2-aminoethanol in barbitalized dogs and obtain virtually the same response in blood pressure effect if the cardiovascular system is allowed to return to normal and if excessive doses (over 500 micrograms/kgm.) are avoided. The administration of graded doses of these agents yields typical response curves such as HJORT, DE BEER and RANDALL (14) obtained with *l*-epinephrine and 3,4-dihydroxyphenyl-ethylmethylamine, and the ratio of pressor activity to epinephrine can be determined. The epinephrine equivalence of these compounds is given in table I. Most of the comparisons of the pressor potency of 'Sympatol' with epinephrine have been done in the cat, and the ratios published are extremely variable (2-5, 8). Our results for the barbitalized dog are in fair agreement with those of LANDS et al. (12).

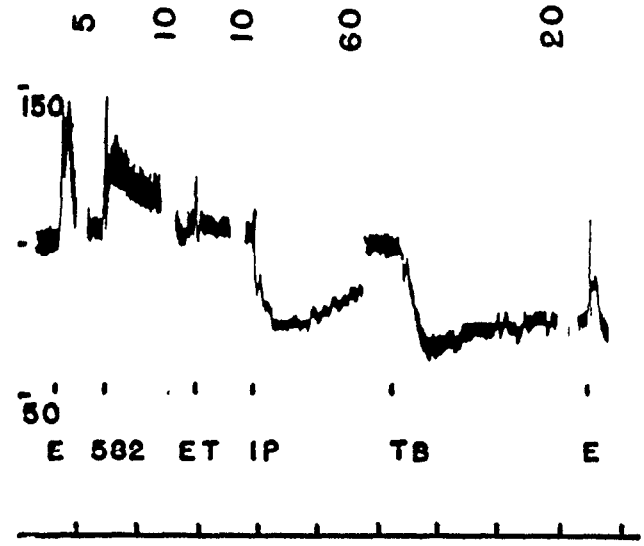


FIG. 1

Dog (Female : 7 kgm.). 330 mgm. of Na Barbital per kgm. Blood pressure in mm. Hg, ordinate; time in 5 minute intervals, abscissa.

Time interval in minutes between injections given by upper figures. Two micrograms of epinephrine base per kgm. at E, 200 μgm. 1-(*p*-hydroxyphenyl)-2-aminoethanol hydrochloride per kgm. at 582, 200 μgm. of the N-ethyl homolog per kgm. at ET, of the N-isopropyl at IP, and of the N-*t*-butyl at TB.

Small doses (25-200 micrograms/kgm.) of 1-(*p*-hydroxyphenyl)-2-ethylaminoethanol usually give only a slight, transient rise in blood pressure (FIG. 1). As the dose is increased, this transient rise increases slightly, but is followed by a prolonged fall in blood pressure.

The N-isopropyl homolog does not produce much pressor response, but it is a potent depressor agent. Typical examples of its action are given in figures 1 and 2. The quantitative relationships between

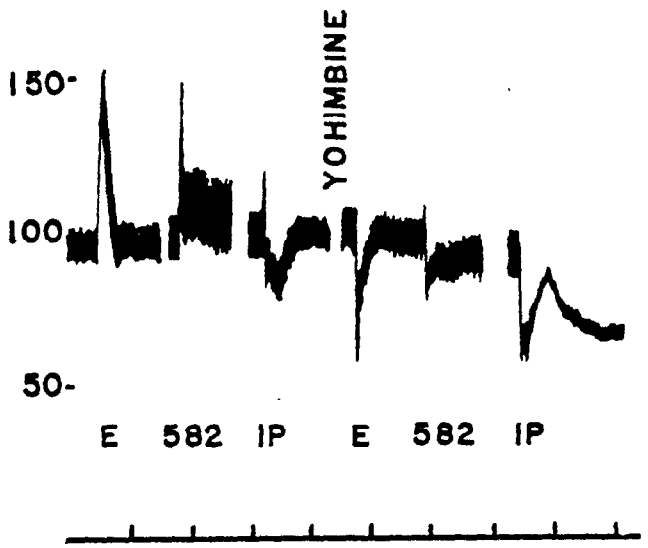
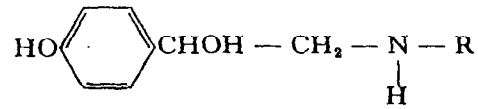


FIG. 2

Dog (Male: 10 kgm.). 330 mgm. of Na Barbital per kgm. Blood pressure in mm. Hg, ordinate; time in 5 minute intervals abscissa. Eight — 15 minute intervals between injections of agents. Two micrograms of epinephrine base per kgm. at E, 200 μgm. 1-(*p*-hydroxyphenyl)-2-aminoethanol HCl per kgm. at 582, 200 μgm. 1-(*p*-hydroxyphenyl)-2-isopropylaminoethanol HCl per kgm. at IP, and 1 mg. yohimbine HCl per kgm. given during rest period at point indicated.

dose and the amount of fall in mean blood pressure are apparently dependent in part on the condition of the animal. In animals with high normal blood pressure, small doses (100-200 micrograms/kgm.) are appreciably depressor, and the result is quantitatively reproducible after the blood pressure has returned to normal. In animals with low blood pressure (less than 80 mm. Hg. mean pressure), considerably larger doses of agent are required to produce an equivalent depressor effect and the return to normal is often incomplete. In this respect the agent is similar to histamine, which in small doses produces reproducible falls in blood pressure in animals in good condition (15). It was found that animals which were abnormally sensitive to histamine were very sensitive to this compound and that the reverse relationship

TABLE I



Agent (*a*)	R	Anesthetized Dogs			Perfused Cat Heart			Rabbit Jejunum
		Dose μ gm. per kgm.	Micrograms of epinephrine (*b*) per kgm. equivalent pressor effect	Micrograms of histamine (*c*) per kgm. equivalent depressor effect	Per cent increase by addition of 1 mgm. to perfusion fluid			Per cent inhibition by 10 mgm./liter
					Rate	Force	Flow	
1-(*p*-Hydroxyphenyl)-2-aminoethanol	— H	200	2 (*d*)		15 (*e*)	25	10	80 (*f*)
		500	5					
1-(*p*-Hydroxyphenyl)-2-methylaminoethanol	— CH_3	500	2		25	40	15	50
		1000	4					
1-(*p*-Hydroxyphenyl)-2-ethylaminoethanol	— CH_2CH_3	200		0.25 (*d*)	40	50	30	60
		500		1				
		1000	0.75	2 (*g*)				
1-(*p*-Hydroxyphenyl)-2-isopropylaminoethanol	— $CH(CH_3)_2$	200		2	100 (*h*)	200 (*h*)	80 (*h*)	40
		500	0.5	6				
1-(*p*-Hydroxyphenyl)-2-*n*-butylaminoethanol	— $CH_2CH_2CH_2CH_3$	500		0.75	50	80	40	50
1-(*p*-Hydroxyphenyl)-2-*t*-butylaminoethanol	— $C(CH_3)_3$	100		1.75	105	215	80	30
		200		3.5				
		500	0.5	9.5				

(*a*) All compounds used as the *dl*-base-hydrochlorides. (*b*) As base. (*c*) As histamine acid phosphate. (*d*) All equivalence data average of determinations in at least five animals and rounded off to nearest 0.25 μgm. (*e*) Average of at least five determinations and rounded off to nearest 5%. (*f*) Similar effect by 18.5 μgm. epinephrine base/liter. (*g*) Two μgm. histamine acid phosphate per kgm. gave an average depressor response of

was also true. Consequently, we used small doses of histamine to produce reference falls in blood pressure for comparing the N-isopropyl homolog with the other agents. The histamine equivalence data is given in table I.

The N-*n*-butyl compound is not very active, but the tertiary butyl homolog is the most potent depressor agent of the group, being 50 to 75 per cent more active than the isopropyl compound (FIG. 1).

Measurements of the optical manometer records from 6 anesthetized dogs by the method of REMINGTON and HAMILTON (16) indicate that all these agents produce an increase in cardiac output. This increase is large enough to account for much of the rise in blood pressure following the administration of 1-(*p*-hydroxyphenyl)-2-aminoethanol and 'Sympatol,' and for all the transient rise seen with the N-ethyl, isopropyl and *t*-butyl homologs. In the case of these latter agents, the peripheral vasodilation (12) produced is sufficient to cause the blood pressure to fall more than the increased cardiac output can overcome. Other workers (6, 9) have shown that 'Sympatol' increases cardiac output.

The effects of these agents in unanesthetized dogs are similar but not so pronounced. 1-(*p*-Hydroxyphenyl)-2-aminoethanol and 'Sympatol' produce small rises in both systolic and diastolic blood pressure until doses of 0.5 mgm. per kgm. are exceeded and then the cardiac rate decreases so that greater rises are not obtained. The N-ethyl and N-*n*-butyl homologs have little effect other than to produce some cardiac acceleration. One-tenth to 0.5 mgm. of the N-isopropyl and N-*t*-butyl homologs produce marked falls in diastolic pressure, but the systolic pressure stays very nearly the same, and there is considerable accompanying cardiac acceleration. Larger doses of these agents in the unanesthetized dog produce records that are very difficult to interpret inasmuch as the dogs howl and struggle vigorously at these higher dose levels. Other than the higher control pressures involved, there was no difference in response by the hypertensive dogs.

Effect of prior administration of other drugs. The administration of 1 mgm. of atropine sulfate per kgm. in barbitalized dogs had little effect on the actions of these drugs, other than a slight potentiation of the blood pressure rise in some cases. Diphenhydramine hydrochloride ('Benadryl,' 2.9 mgm./kgm.) similarly produced only slight potentiation of pressor effect and had no effect on depressor response. Yohimbine hydrochloride (1-2 mgm./kgm.), in doses that antagonize the pressor rise of epinephrine and allow the vasodepressor action of

(*a*) All compounds used as the *dl*-base-hydrochlorides. (*b*) As base. (*c*) As histamine acid phosphate. (*d*) All equivalence data ave... determinations in at least five animals and rounded off to nearest 0.25 μgm. (*e*) Average of at least five determinations and rounded off to nearest... (*f*) Similar effect by 18.5 μgm. epinephrine base/liter. (*g*) Two μgm. histamine acid phosphate per kgm. gave an average depressor response... 33.4 ± 5.1 mm. Hg. in 16 dogs. (*h*) Similar effect by addition of 10 μgm. epinephrine base.

epinephrine to become apparent, has a similar effect with these agents. As illustrated in figure 2, even the pressor rise of 1-(*p*-hydroxyphenyl)-2-aminoethanol is converted to a slight depressor fall, and the N-isopropyl homolog is considerably potentiated in depressor activity. Similar results were obtained with the other members of the series.

2. — Action on isolated tissue segments

Standard technics (17) were used to study the effects of these agents on various isolated organs. Quantitative results of effects on isolated rabbit jejunum are given in table I. Effects on isolated uteri of rabbits and guinea pigs similar to those of Lands et al. (11) were observed. None of the agents had any certain reproducible bronchodilator action as determined by the method of Tainter, Pedden, and James (18) although Lands et al. (12) found some of the members of the series to have activity by this method and Kuschinsky (5) found 'Sympatol' active against pilocarpine bronchospasm.

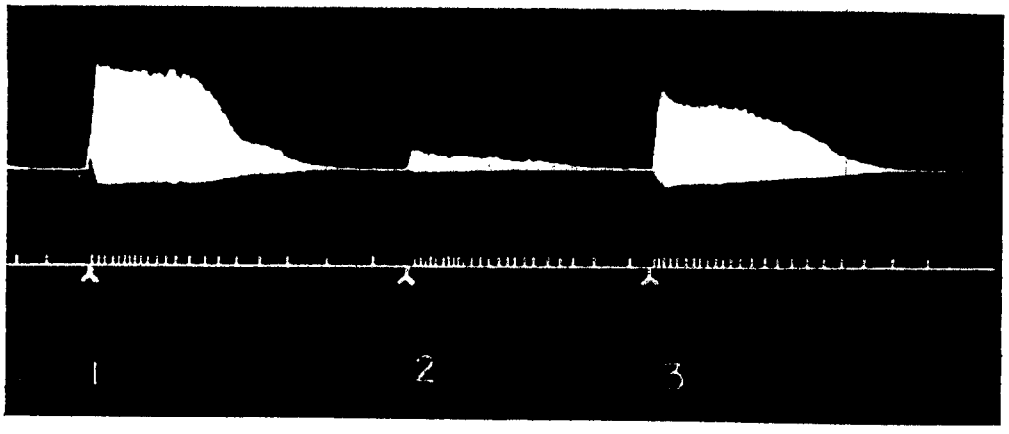


Fig. 3

Cat Heart. Low level perfusion with Ringer-Locke solution.

Rate and force of contraction above and perfusion rate in 0.5 cc. units below. Final bath concentrations calculated to be 5×10^{-6} Molar epinephrine at 1, 5×10^{-5} Molar N-isopropyl-1-(*p*-hydroxyphenyl)-2-amino-ethanol at 2, and 1.2×10^{-6} Molar N-isopropylarterenol (Isuprel) at 3.

The action in the Langendorff perfused heart of the cat or rabbit is more pronounced. Data from the cat hearts, which were more uniform, are summarized in table I. These results were obtained with hearts perfused with a 50 cm. water pressure head. Since the increase in coronary flow in this preparation might have been a reflection of

the increased heart action, experiments with hearts perfused under a low perfusion pressure (13 cm. water) were carried out. Such hearts show very little flow and often almost no contraction. As illustrated in figure 3, these agents can produce a marked increase in coronary flow with slight changes in rate and force of contraction. In two hearts (of five successfully prepared), it was possible to obtain doubling and tripling of flow rates with no measurable augmentation of beat. Contrariwise, concentrations of epinephrine and N-isopropylarterenol that produce similar increases in flow always produce large increases in force of contraction (FIG. 3). With low level perfusion, the derivatives of 'Sympatol' are about 5 to 10 times as active as at the standard 50 cm. perfusion pressure.

3. — EFFECTS IN MAN

A series of 16 experiments on normal human male adults (age 29-34 yrs., weight 66-80 kgm.) was performed. Systolic and diastolic blood pressure and pulse rate were determined by the common sphygmomanometer cuff procedure in upright individuals. Experiments were started not less than 2 hours after a light morning meal, and repeated once each week. After controls had been established, the drugs were administered orally in 200 ml. warm water.

Doses as high as 6 mgm. of 1-(*p*-hydroxyphenyl)-2-aminoethanol and 'Sympatol' per kgm. had only slight effects. There was usually a slight rise in systolic and diastolic blood pressure with no change or a slight diminution in pulse rate. There were no particular subjective symptoms. The results with 'Sympatol' are similar to those obtained by FLECKEN (9). This dose of the N-ethyl and N-*n*-butyl homologs had no observable effects. However, as little as 1 mgm. of the N-isopropyl or N-*t*-butyl homologs per kgm. had some demonstrable vasodepressor effect. Two and 3 mgm. of these agents per kgm. produced marked effects (FIG. 4). Flushing and tingling of extremities and face occurred. As the diastolic blood pressure fell, the pulse rate increased. The individual usually became apprehensive and this may have contributed to the cardiac rate although the predominant effect is presumably a direct one on the myocardium, if the perfused heart results are transferrable to man. The increase in pulse pressure concurrent with the increase in rate is evidence of direct myocardial stimulation and increased cardiac output.

Vomiting usually occurred after higher doses (5 mgm./kgm.) of either agent at the time the diastolic blood pressure fell below 40 mm. Hg. At this point the individual was no longer able to sit erect and complained of dizziness, blurring of vision, pounding heart, weakness and respiratory distress. No apparent effects persisted more than 5 hours after a single dose.

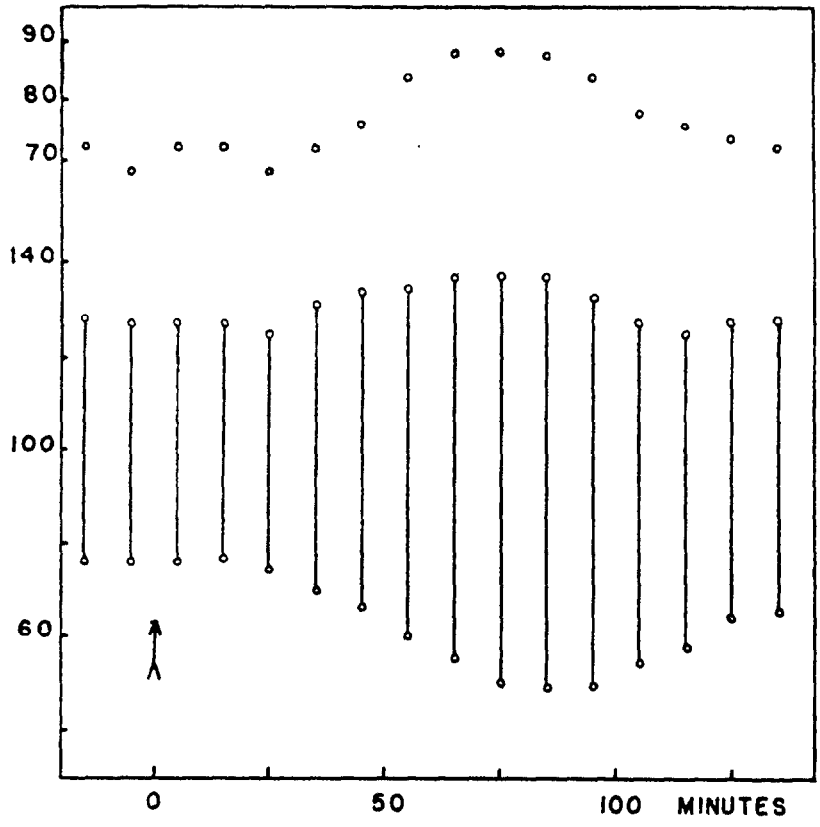


FIG. 4

Human male (77 kgm., 33 yrs.). Pulse rate in beats per minute, above; systolic and diastolic blood pressure in mm. Hg, below. Blood pressure determined sphygmomanometrically from left arm. Two milligrams of N-isopropyl-1-(*p*-hydroxyphenyl)-2-aminoethanol hydrochloride per kgm. swallowed in water solution at time indicated by arrow.

DISCUSSION

Slight modifications in the structure of the epinephrine molecule usually lead to compounds with less activity, although some of the typical epinephrine-like effects may be more diminished than others. Such is the case with this series of compounds. Although the relative vasopressor activity of the most pressor members of the series is very low and the compounds are poor bronchodilators, the agents still possess potent coronary dilator, myocardial stimulant, and peripheral vasodilator

actions. As observed (17) with the corresponding 1-(3,4-dihydroxyphenyl)-2-aminoethanol, or Arterenol, series, increasing the number of carbon atoms in the alkyl substituent on the nitrogen atom, but still retaining a minimum molecular size, leads to compounds with enhanced cardiac and vasodepressor activity; i.e., the N-isopropyl and N-tertiary-butyl compounds are most depressor while the N-ethyl and N-normal-butyl homologs are not particularly active, and the N-methyl compound is a pressor agent.

Since the depressor compounds are not particularly toxic in man and do have oral activity in adequate dosage, they may be found to be of clinical usefulness in conditions in which augmented coronary flow or peripheral sympathetic vasodilation are needed.

Summary

N-Ethyl, N-isopropyl, N-*n*-butyl, and N-*t*-butyl-1-(*p*-hydroxyphenyl)-2-aminoethanol have been compared with the parent compounds, 1-(*p*-hydroxyphenyl)-2-aminoethanol and the N-methyl homolog, 'Sympatol,' in anesthetized and unanesthetized dogs, on isolated tissue segments, and orally in man. Only 1-(*p*-hydroxyphenyl)-2-aminoethanol and 'Sympatol' are active vasopressor agents, being 1/100 to 1/250 as active as epinephrine. All these agents are potent coronary dilators and myocardial stimulants, with the N-isopropyl and N-*t*-butyl homologs being 1/25 to 1/100 as active as epinephrine. Although oral doses of 400-500 milligrams of 1-(*p*-hydroxyphenyl)-2-aminoethanol and 'Sympatol' produce only slight rises of blood pressure in man, as little as 100 to 200 milligrams of N-isopropyl-1-(*p*-hydroxyphenyl)-2-aminoethanol and the N-tertiary butyl analog produce peripheral vasodilation and myocardial stimulation.

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