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Cardiovascular and autonomic effects of fenfluramine hydrochloride*

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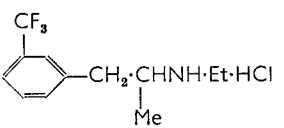
Fenfluramine hydrochloride (*N*-ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride; AHR-965) administered orally or intravenously to anaesthetised or unanaesthetised dogs, caused a predominant rise in arterial blood pressure, tachycardia, an increase in myocardial contractile force and cardiac output, and an enhanced total peripheral resistance. Fenfluramine was qualitatively like dexamphetamine in its cardiovascular effects; however dexamphetamine was 10 to 20 times more potent as a pressor agent.

THE effects of sympathomimetic amines on the cardiovascular and the central nervous systems are major deterrents to their use as appetite suppressants. Numerous variations have been made on the phenethylamine moiety in attempts to overcome these liabilities. One such compound, fenfluramine hydrochloride (I; *N*-ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride; AHR-965), has been reported by Alphin, Funderburk & Ward (1964) to reduce appetite in several laboratory species in doses that do not cause overt stimulation of the central nervous system. These findings led to the investigation of the cardiovascular and autonomic effects of this compound, the results of which are the subject of this report.



(I)

Methods

Adult mongrel dogs (either sex; 8·2 to 14·1 kg) were anaesthetised with intravenous phenobarbitone sodium, 125 mg/kg. A polygraph[1] and accessory equipment were used for recording blood pressure from a carotid artery and respiration from a tracheal cannula (24 animals); in addition, the electrocardiogram (lead II) was recorded in most of these experiments. Single doses of the drug were administered intravenously (1 to 16 mg/kg) and orally (5 and 10 mg/kg).

Alteration of cardiac dynamics was further investigated in other experiments. Cardiac rate was measured with a tachograph[2] and a myocardial force transducer[3] was sutured to the left ventricle for measuring contractile force (7 experiments); an electromagnetic flowmeter[4] was used for measuring cardiac output (flow probe placed on the ascending aorta) in two dogs.

The effect on the arterial blood pressure of trained, unanaesthetised dogs was investigated using essentially the technique of Prioli & Winbury

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[1] Model 5. Grass. [2] Grass. [3] Honeywell. [4] Medicon.

(1960). The occluding cuff was placed at the base of the tail. A microphone pickup, signal divider and electrical manometer[1] were used for detecting and measuring pressure; the signal was monitored on an oscilloscope and recorded.

A reference drug, dexamphetamine sulphate, was studied under similar conditions in each experimental procedure. Various autonomic agents and histamine acid phosphate were used in an effort to determine the mechanism by which the new drug exerted its effects. The doses of all the drugs are expressed in terms of the specified salts.

Results

ANAESTHETISED DOGS

Blood pressure. Fenfluramine usually elicited a biphasic change in arterial blood pressure, a brief decrease being followed by a more prolonged and pronounced pressor response (left panel of Fig. 1). With intravenous

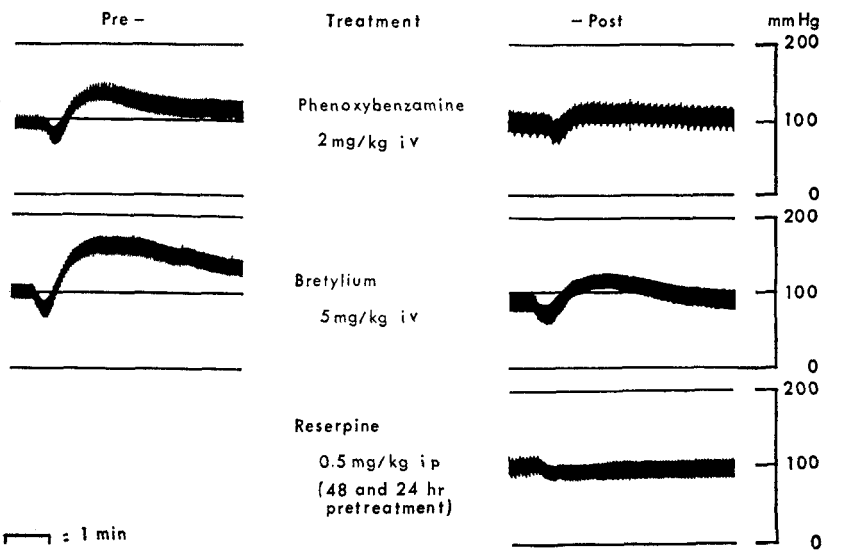

FIG. 1. Anaesthetised dogs (phenobarbitone sodium, 125 mg/kg, i.v.): effects of intravenous 4 mg/kg on carotid blood pressure; alteration of the pressor effect by adrenergic blocking agents.

doses of 1, 2 or 4 mg/kg, the pressor component was decidedly predominant; with higher doses, the depressor phase was more evident (but still not predominant) and the secondary pressor phase was much prolonged. The changes elicited by intravenous dexamphetamine (0·05 to 0·2 mg/kg) were similar to those produced by fenfluramine with the possible exception that the depressor component was seen less frequently. After fenfluramine 10 mg/kg orally, the depressor response was negligible and the pressor response reached a peak in 10 min from where it declined slowly to the control level over a period of 3 to 4 hr. An oral dose of 5 mg/kg did not alter blood pressure in the following 90 min.

[1] Beckman.

Repeated intravenous administration of fenfluramine (2 mg/kg every 6 min for 8 doses) had no apparent effect on the depressor phase of the arterial pressure response, but the pressor component became progressively less with each dose. Although the point was not investigated specifically, tachyphylaxis seemed to be more readily demonstrable with dexamphetamine than with fenfluramine.

Cardiac effects. In general, a bradycardia coincided with the hypotensive period and cardiac rate increased during the hypertensive phase. In one animal, for example, cardiac rate showed a slight decrease to 96% of the control and then was increased to 116% of the control after intravenous fenfluramine, 8 mg/kg. A comparable tachycardia was produced with dexamphetamine, 0·02 mg/kg, given by the same route. Heart rate was not altered by fenfluramine orally, 5 mg/kg; 10 mg/kg caused a maximum increase of 23% over the control rate in another experiment.

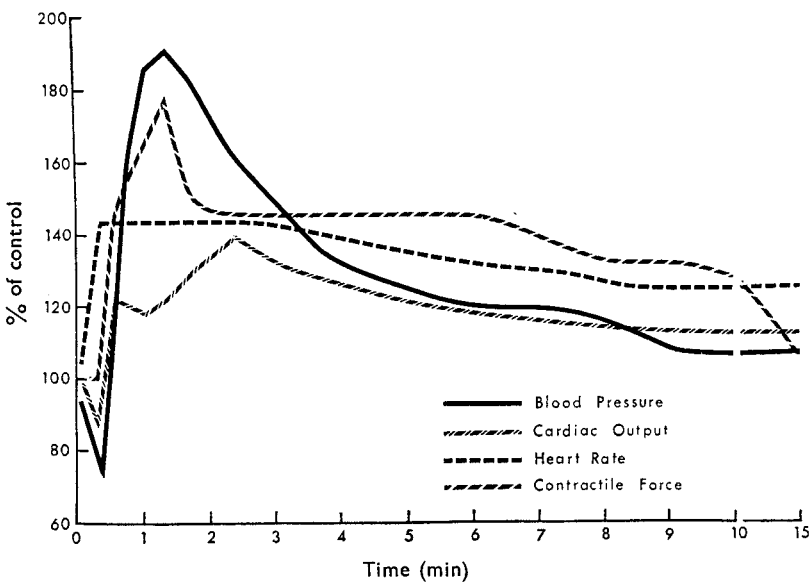

FIG. 2. Anaesthetised dogs (phenobarbitone sodium, 125 mg/kg, i.v.): effects of fenfluramine 4 mg/kg, i.v. (at ordinate) on carotid blood pressure and on cardiodynamics.

The contour of the electrocardiogram was not altered by the drug in intravenous doses below 4 mg/kg. The most distinct and frequent change after 4 or 8 mg/kg was a shortened TP interval that coincided with the tachycardia. In about 50% of the experiments, the administration of adrenaline, after treatment with fenfluramine or dexamphetamine, evoked extrasystoles throughout the adrenaline hypertension.

Force of ventricular contraction and aortic flow varied directly with arterial blood pressure alterations. These effects varied in degree among experiments, but in an individual animal there was usually a direct relationship between intensity of the response and the dose of fenfluramine. Fig. 2 illustrates these changes after intravenous fenfluramine, 4 mg/kg.

Similar changes were seen after the intravenous administration of dexamphetamine, 0·4 mg/kg.

Total peripheral resistance. Fenfluramine had the primary effect of increasing total peripheral resistance. The change was regular in occurrence and its intensity was related to dose.

Autonomic agents (and histamine). Fenfluramine had no significant effect on the arterial blood pressure responses to (−)-adrenaline hydrochloride, (−)-noradrenaline bitartrate, acetylcholine chloride, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP), or histamine. Phentolamine hydrochloride, phenoxybenzamine hydrochloride, guanethidine sulphate, reserpine and bretylium tosylate reduced or eliminated the pressor phase. Some of these effects are illustrated in Fig. 1. Hexamethonium chloride had little, if any, inhibiting effect. Atropine sulphate did not prevent the depressor response after the pressor phase had been eliminated with guanethidine. Dichloroisoprenaline hydrochloride antagonised only slightly the depressor component and diphenhydramine hydrochloride had no effect on it.

UNANAESTHETISED DOGS

The effect of fenfluramine on the arterial blood pressure of unanaesthetised dogs was not unlike that in the anaesthetised preparations. As indicated in Table 1, intravenous administration caused a pressor response.

TABLE 1. EFFECT ON MEAN ARTERIAL BLOOD PRESSURE IN UNANAESTHETISED DOGS

Compound	Dose mg/kg	No. expts	Mean % increase	Post-drug time (min)	
				Max. effect	Duration*
Fenfluramine i.v.	1	4	9	10	21
	2	2	21	12	52
	4	2	28	6	60
dexamphetamine i.v.	0·05	2	0	—	—
	0·1	2	22	4	13
	0·2	2	31	3	>300

* Approximate time required to return to pretreatment level.

These data also illustrate the greater potency of dexamphetamine in producing a rise in blood pressure. Oral administration of either fenfluramine or dexamphetamine likewise produced a hypertensive effect. The method of measuring blood pressure did not permit detection of a depressor component in the intravenously-treated animals.

Discussion

The results of this study show fenfluramine to qualitatively resemble dexamphetamine on the cardiovascular system. Both compounds were pressor, caused a tachycardia, increased myocardial contractile force and cardiac output, and enhanced total peripheral resistance. Quantitatively, dexamphetamine was 10 to 20 times more potent than fenfluramine on a mg/kg basis of the respective salts. In appetite-suppressant doses, dexamphetamine caused observable central nervous system stimulation whereas fenfluramine did not. Structurally these compounds differ in that fenfluramine contains a trifluoromethyl substituent in the

aryl nucleus and an ethyl group on the nitrogen atom. Thus the question arises as to which structural difference caused the slight decrease in anorexigenic potency and the greater quantitative change in cardiovascular and central nervous system effects.

In recent years there have been several reports (Emele, Shanaman & Warren, 1961; Leonard, Fujita, Tedeschi & Fellows, 1961; Boxill, Ben, Hillyard & Warren, 1962; Holland, Buck & Weissman, 1963; Witoslowski, Campbell & Hanson, 1963) on primary ethylamines, having a halogen- or a haloalkyl-substituted phenyl group, that share common pharmacological characteristics with fenfluramine, a secondary amine. Thus it is suggested that the substituent on the amino-group in fenfluramine is not responsible for the reduction in pharmacologic potency. But evidence to the contrary is seen in the diminishing of effects by the *N*-ethylation of dexamphetamine (van der Schoot, Ariens, van Rossum & Hurkmans, 1962; Le Douarec, 1963). As with fenfluramine, the anorectic property of *N*-ethylamphetamine was the least affected; these compounds differ only in that fenfluramine contains a trifluoromethyl substituent in the phenyl ring.

The halo- or haloalkyl-aryl group does not seem vital for the alterations in pharmacologic effects. 2-Amino-1-cyclohexylpropan-1-one is reported to be useful in curbing the appetite without having pronounced affects on the central nervous system (Boehringer, 1963) and 1-phenoxyprop-2-ylamine is described as having anorexigenic activity free from side-effects (Zeile & Thoma, 1963). The consensus of these reports would be that among 1-arylprop-2-ylamines, cardiovascular or central nervous system effects, or both, can be eliminated or reduced without seriously sacrificing anorexigenic activity by an appropriate structure at the aryl end of the molecule or the proper substituent on the amino-group. It appears then, that both the haloalkyl-substituted aryl moiety and the *N*-ethyl group of fenfluramine contribute to the quantitative pharmacologic difference between this compound and dexamphetamine.

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