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Pharmacology of AH 5158; a drug which blocks both α- and β-adrenoceptors

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Summary

1. AH 5158 differs from conventional adrenoceptor blocking drugs in producing competitive blockade of both α- and β-adrenoceptors.

2. AH 5158 is 5–18 times less potent than propranolol in blocking β-adrenoceptors. It resembles propranolol in its non-selective blockade of β_1-cardiac and β_2-vascular and tracheal adrenoceptors and in its lack of intrinsic sympathomimetic activity.

3. AH 5158 is 2–7 times less potent than phentolamine in blocking α-adrenoceptors. AH 5158 itself is more active on β- than α-adrenoceptors.

4. Blockade of noradrenaline vasopressor responses by AH 5158 in anaesthetized dogs was dose-dependent up to 1 mg/kg but no further blockade was obtained with larger doses of AH 5158. 'Self-limiting' blockade was not observed in dogs pretreated with cocaine, or in untreated dogs if the vasopressor agent was oxymetazoline instead of noradrenaline. A possible cause of 'self-limiting' blockade is discussed.

5. In doses higher than those required for either α- or β-adrenoceptor blockade, AH 5158 produced effects on cardiac muscle that are attributable to membrane-stabilizing activity. This was manifested as a negative inotropic action in spinal dogs and in guinea-pig left atrial strips, as a negative chronotropic action in syrosingopine pre-treated dogs, and as an increase in the effective refractory period of guinea-pig left atrial strips. AH 5158 was 3–11 times less potent than propranolol in these tests.

6. In open chest dogs AH 5158 resembled propranolol in reducing cardiac output, rate and contractility, effects which are attributable to β-adrenoceptor blockade. The drug differed from propranolol in decreasing rather than increasing total peripheral resistance and in causing larger decreases in arterial blood pressure at equipotent β-adrenoceptor blocking doses. These differences are attributable to the α-adrenoceptor blocking actions of AH 5158.

7. In anaesthetized dogs, intravenously administered AH 5158 antagonized both catecholamine and ouabain-induced arrhythmias. Orally administered AH 5158 lowered systolic arterial pressure in conscious renal hypertensive dogs.

8. These results show AH 5158 to possess a novel profile of activity. Possible uses of the drug in cardiovascular disorders such as hypertension, angina pectoris and cardiac arrhythmias are discussed.

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Introduction

This paper describes the properties of AH 5158, 5-{1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl} salicylamide, a drug which differs from currently available adrenoceptor blocking drugs in blocking both α- and β-adrenoceptors. AH 5158 is related chemically to the previously reported β-adrenoceptor blocking drug, AH 3474, 5-(2-*t*-butylamino-1-hydroxyethyl) salicylamide (Blackburn, Byrne, Cullum, Farmer & Levy, 1969) (Fig. 1).

Preliminary results with AH 5158 were communicated to a joint meeting of the British and French Pharmacological Societies (Farmer, Kennedy & Levy, 1971).

Methods

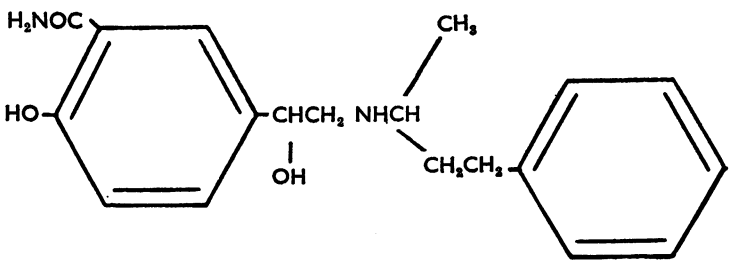
In the methods described below, tension was measured with Dynamometer UF1 or Statham force displacement transducers, and pressure measured with Bell & Howell physiological pressure transducers. All recordings were made on Devices M4 or M8 polygraphs.

Isolated tissues

Guinea-pig atrial strips

Left and right atrial strips obtained from guinea-pigs of either sex weighing 350–450 g were mounted on an electrode block of the type described by Blinks (1966). The preparations were set up in McEwen's solution (1956) maintained at 32° C and bubbled with 5% carbon dioxide in oxygen. Cardiac rate was recorded from spontaneously beating right atrial strips and force of contraction from electrically driven left atrial strips. Electrical stimulation consisted of square wave pulses of 5 ms duration and voltage just sufficient to elicit contractions delivered at a frequency of 1 Hz.

AH 5158



AH 3474

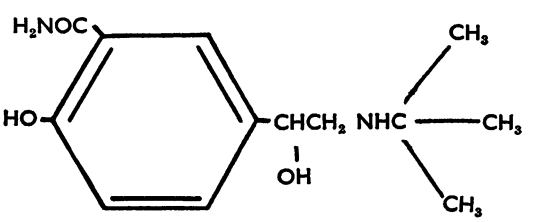


FIG. 1. Chemical structures of AH 5158 and AH 3474.

For assessment of β-adrenoceptor blocking potency, cumulative concentration-effect curves were obtained for isoprenaline before and after exposure to three graded concentrations of antagonist. pA_2 values were calculated by the method of Arunlakshana & Schild (1959). A contact time of 45 min was used for antagonists in these and all other experiments in which pA_2 was determined.

Negative inotropic effects of AH 5158 and propranolol were determined on electrically driven left atrial strips. Preparations were allowed to stabilize for 1 h, after which graded concentrations of antagonist were added until contractions were abolished. Each concentration of drug was left in contact with the tissue for 30 min, or until an equilibrium response was achieved. In each experiment the concentration which caused a 50% reduction in force of contraction was obtained from the plot of % reduction in force against log concentration of antagonist.

The effects of AH 5158 and propranolol on the relative refractory period of left atrial strips were investigated by the method of Dawes (1946). Determinations of maximal driving frequency were made before and 30 min after exposure to graded concentrations of antagonist. In each experiment the concentration which reduced maximal driving frequency by 50% was obtained from the plot of % reduction in maximal driving frequency against log concentration of antagonist.

Guinea-pig intact tracheal tube

The preparation was set up as described by Coleman & Farmer (1971). Intraluminal pressure was increased by adding bethanechol, 5 μg/ml, to the tissue bath 5 min before obtaining an isoprenaline concentration-effect curve. Cumulative concentration-effect curves for decrease in intraluminal pressure were obtained for isoprenaline before and after exposure to graded concentrations of antagonist.

Guinea-pig mesenteric vein

The preparation described by Sutter (1965) was set up in McEwen's solution maintained at 32° C and bubbled with 5% carbon dioxide in oxygen. Cumulative concentration-effect curves were obtained for noradrenaline-induced contractions before and after exposure to graded concentrations of antagonist.

Rat vas deferens

Vasa deferentia were removed from albino rats weighing 250–400 g. The serous coat and mesenteric attachments were stripped away, and the vasa suspended in McEwen's solution maintained at 32° C and bubbled with 5% carbon dioxide in oxygen. Cumulative concentration-effect curves were obtained for noradrenaline-induced contractions before and after exposure to graded concentrations of antagonist.

Anaesthetized dogs

Beagles of either sex weighing 7–13 kg were used. Anaesthesia was induced with thiopentone, 25 mg/kg intravenously, and maintained with barbitone, 250 mg/kg intraperitoneally. Animals were artificially respired with room air through a cuffed endotracheal tube, using a stroke-volume of 13 ml/kg and a rate of 30/minute.

Arterial blood pressure (1 mmHg≡1·333 mbar) was measured from a cannula in a femoral artery and heart rate obtained from a cardiotachometer triggered by the arterial pressure signal. Drugs were injected through a cannula in a femoral vein.

Adrenoceptor blocking activity

One agonist-antagonist combination was tested in each dog. Dose-response curves were obtained by the sequential intravenous injection of increasing doses of agonist before and 15 min after administration of graded doses of antagonist. Antagonists were tested at three or more dose-levels in each experiment.

Sympathomimetic activity

Sympathomimetic activity was investigated in dogs depleted of noradrenaline by treatment with syrosingopine, 5 mg/kg intraperitoneally, 24 h before use. A control isoprenaline dose-response curve for increase in heart rate was obtained initially, and graded doses of AH 5158 injected intravenously at intervals of 30 min thereafter.

Haemodynamic function

Haemodynamic actions of AH 5158 were determined in open chest dogs. Aortic flow, which is equivalent to cardiac output minus the blood flow through the coronary vessels, was measured with a probe of an electromagnetic flowmeter (M4000, Statham Instruments Inc.) placed around the ascending aorta. Myocardial contractility was measured from a strain-gauge arch sutured to the surface of the left ventricle. Aortic blood pressure was recorded from a cannula inserted into a carotid artery and passed retrogradely into the aorta. Heart rate was obtained from the aortic pressure signal. Ejection time, from the onset of systole to the dicrotic notch, was estimated from the aortic pressure trace, using a chart speed of 10 cm/second. Stroke volume was calculated as mean aortic flow/heart rate, ejection rate as stroke volume/ejection time and total peripheral resistance as mean arterial blood pressure/aortic flow. After control levels had stabilized, each dog received two intravenous doses of AH 5158 separated by an interval of 1 hour. Changes in haemodynamic function were measured 15 min after injection of each dose.

Ouabain-induced arrhythmias

Ventricular tachycardia was induced by the method of Somani & Lum (1965). An initial intravenous dose of ouabain, 40 μg/kg, was followed 30 min later by an additional dose of 20 μg/kg, and at 15 min intervals thereafter by additional doses of 10 μg/kg until a persistent ventricular tachycardia was established. An infusion of either AH 5158 or propranolol was started 10 min later and maintained until the arrhythmias were abolished.

Noradrenaline-induced arrhythmias

Arrhythmias were elicited by intravenous injections of 50 μg/kg noradrenaline. The method is similar to that described by Somani & Lum (1965) for inducing

arrhythmias with adrenaline. The results were analysed by determining the proportion of ectopic beats during a 5 s period in each 30 s during the response, which usually lasted 3–5 minutes. Noradrenaline was administered every 45 min, since tachyphylaxis occurred when shorter intervals were used. Reproducible control responses to noradrenaline were established, and either AH 5158 or propranolol, 1 mg/kg intravenously, was administered 10 min before the subsequent dose of noradrenaline. Dosing with noradrenaline was continued at 45 min intervals until the protective effect of the test drug showed signs of diminishing.

Spinal dogs

Anaesthesia was induced with thiopentone, 25 mg/kg intravenously, and maintained with 3% halothane in a $N_2O:O_2$ mixture (3:1). Dogs were spinalized by the method of Burn (1952) and artificially respired with room air through a cuffed endotracheal tube, using a stroke volume of 13 ml/kg and a rate of 30/minute. Myocardial contractility was measured from a strain-gauge arch sutured to the surface of the left ventricle. An equilibrium period of 30 min was interposed between the spinalization procedure and the start of the experiment. Increasing doses of AH 5158 or propranolol were given by intravenous infusion. Each dose was administered over a period of 30 min and a further 20 min was allowed to elapse between the end of one infusion and the start of the next. In each experiment the dose causing a 40% reduction in force of contraction was obtained from the plot of % reduction in force of contraction against log dose of antagonist.

Conscious dogs

Male beagle dogs, equipped with carotid loops, were made hypertensive as described by Cullum, Farmer & Handley (1967). Systolic blood pressure was measured from the exteriorized carotid artery using a sphygmomanometer. Heart rate was obtained from the arterial pulse. Measurements were taken each day at 10.00, 12.00, 14.00 and 16.00 hours. Drugs were given orally in gelatin capsules at 11.00 hours.

Quantitative analysis

The mean values quoted in the text and tables are accompanied by 95% confidence intervals (C.I.) in parentheses. In Fig. 3 comparison of antagonist potency was made at an agonist dose-ratio of 10.

Drugs

AH 5158, 5-{1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl} salicylamide, either as the base or the hydrochloride AH 5158 has two asymmetric centres (see Fig. 1) and therefore exists as two racemic diastereoisomers. The unseparated mixture of diastereoisomers was used in the present work. The drug was synthesized by Dr. L. H. C. Lunts of the Chemical Research Department, Allen & Hanburys; angiotensin amide (CIBA); barium chloride (May & Baker); calcium chloride (BDH); (−)-isoprenaline sulphate (Burroughs Wellcome); (−)-nor-

adrenaline acid tartrate (Winthrop); ouabain (BDH); oxymetazoline hydrochloride (Merck); phentolamine methanesulphonate (CIBA); phenoxybenzamine hydrochloride (S.K.F.); (±)-propranolol hydrochloride (I.C.I.); syrosingopine (CIBA).

Results

α- and β-Adrenoceptor blocking actions of AH 5158, phentolamine and propranolol

Isolated tissues

The blocking potencies of AH 5158, phentolamine and propranolol are compared in Table 1. The blockade of both α- and β-adrenoceptors produced by AH 5158 satisfied accepted criteria for competitive antagonism (Arunlakshana & Schild, 1959). In contrast, the blockade produced by phentolamine was competitive for α-adrenoceptors only and that produced by propranolol competitive for β-adrenoceptors only. The results of typical experiments with the three antagonists are illustrated in Figure 2.

AH 5158 was 7 times less potent than phentolamine in blocking α-adrenoceptors in guinea-pig mesenteric vein and 11 and 18 times less potent than propranolol in blocking β-adrenoceptors in guinea-pig left and right atrial strips respectively. The blocking potency of AH 5158 was similar for atrial β_1- and tracheal β_2-adrenoceptors (Table 1).

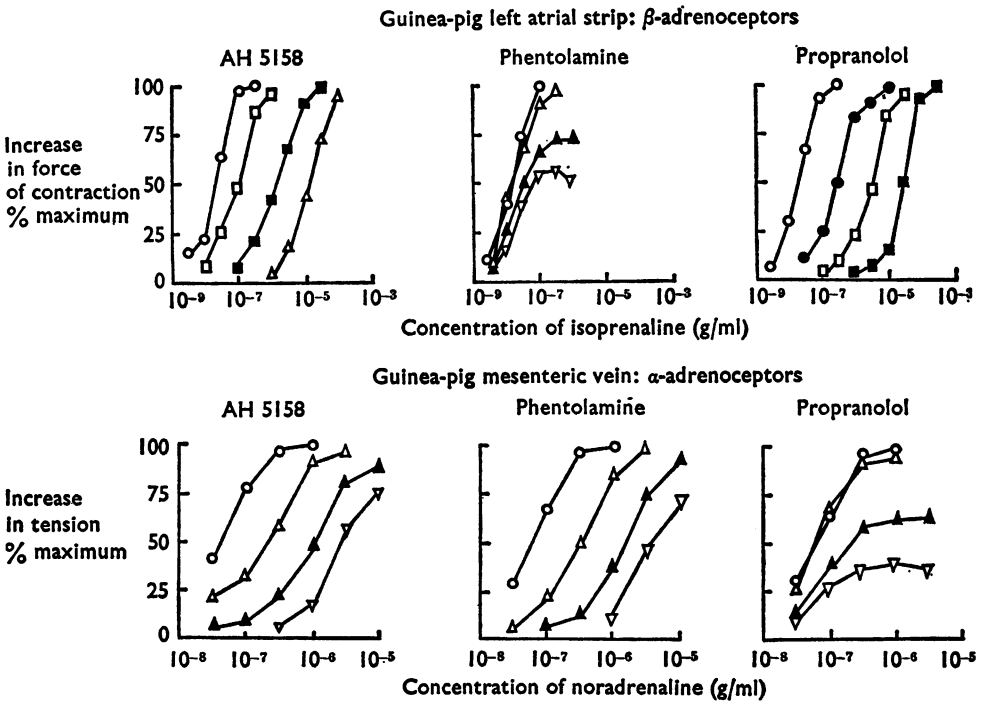


FIG. 2. Comparison of the α- and β-adrenoceptor blocking actions of AH 5158, phentolamine and propranolol in isolated tissues. Typical experiments are illustrated for each interaction. ○——○, control; after 45 min exposure to ●——●, 0·03 μg/ml; □——□, 0·1 μg/ml; ■——■, 0·3 μg/ml; △——△, 1·0 μg/ml; ▲——▲ 3·0 μg/ml; ▽——▽, 10·0 μg/ml of antagonist. AH 5158 causes parallel shifts to the right of the agonist concentration-effect curve in both mesenteric vein and left atrial strip, but phentolamine does so only in mesenteric vein and propranolol only in left atrial strip.

TABLE 1. *Comparison of adrenoceptor blocking activities of AH 5158, phentolamine and propranolol in isolated tissues*

Preparation	Receptor type	Agonist and response	Antagonist	No. of determinations	pA_2 (45 min) (95% C.I.)	Slope* (95% C.I.)
Guinea-pig mesenteric vein	α	Noradrenaline. Contraction	AH 5158	8	6·00 (5·8–6·6)	1·02 (0·91–1·20)
			Phentolamine	7	6·86 (6·2–7·01)	1·08 (0·92–1·22)
			Propranolol	3	Non-competitive antagonist in dose-range 3–30 μg/ml	
Rat vas deferens	α	Noradrenaline. Contraction	AH 5158	12	6·13 (5·91–6·65)	1·13 (0·98–1·29)
Guinea-pig left atrial strip	β_1	Isoprenaline. Increase in force of contraction	AH 5158	9	7·35 (7·09–7·62)	1·25 (1·00–1·37)
			Phentolamine	2	Non-competitive antagonist in dose-range 1–20 μg/ml	
			Propranolol	8	8·40 (8·29–8·61)	1·3 (1·10–1·44)
Guinea-pig right atrial strip	β_1	Isoprenaline. Increase in rate	AH 5158	9	7·24 (7·01–7·44)	1·31 (1·07–1·50)
			Propranolol	8	8·51 (8·29–8·71)	1·33 (1·05–1·53)
Guinea-pig intact trachea	β_2	Isoprenaline. Relaxation	AH 5158	4	7·05 (6·88–7·09)	1·26 (1·20–1·38)

* For plot of log (agonist dose-ratio-1) *v* log molar concentration of antagonist.

Anaesthetized dogs

α-Adrenoceptor blocking potency was assessed with oxymetazoline as the agonist. Mujić & van Rossum (1965) have shown that oxymetazoline is an α-adrenoceptor agonist with no action on β-adrenoceptors. AH 5158 and phentolamine produced dose-dependent, parallel shifts to the right in the vasopressor dose-response curve to oxymetazoline. The degree of blockade, expressed as the log dose-ratio of oxymetazoline, was plotted against log dose of antagonist (Fig. 3). Comparison of the regression lines shows AH 5158 to be 1·77 (1·15–2·71) times less potent than phentolamine in blocking vascular α-adrenoceptors. In contrast, propranolol, in intravenous doses of up to 10 mg/kg, failed to block vasopressor responses to oxymetazoline.

The effects of AH 5158 and phentolamine on noradrenaline vasopressor responses were also investigated. The results with phentolamine were similar to those obtained with oxymetazoline as the agonist, but the results with AH 5158 differed. Thus AH 5158 produced progressive shifts to the right of the noradrenaline dose-response curve in doses up to 1 mg/kg, but doses of 1–10 mg/kg produced no further blockade and in some experiments even less. However, in two subsequent experiments in which dogs were pretreated with cocaine, 5 mg/kg intravenously, blockade of noradrenaline vasopressor responses by AH 5158 was progressive over the complete dose-range examined, that is from 0·1 to 10 mg/kg. Representative experiments in an untreated dog and in a dog pretreated with cocaine are illustrated in Fig. 4.

β-Adrenoceptor blocking activity was assessed with isoprenaline as the agonist. AH 5158 and propranolol blocked both the positive chronotropic and vasodepressor responses to isoprenaline; the former were used to assess blocking potency because AH 5158 itself produced large, long-lasting falls in blood pressure (see below). Both drugs produced dose-dependent, parallel shifts to the right of the positive chronotropic dose-response curve to isoprenaline. The results showed AH 5158 to be 4·73 (3·14–7·11) times less potent than propranolol.

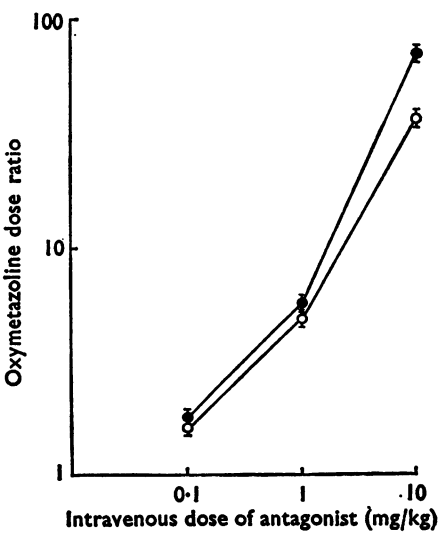


FIG. 3. Comparison of the blockade of vasopressor responses to oxymetazoline by AH 5158 (○——○, $n=3$) and phentolamine (●——●, $n=4$) in the anaesthetized dog. Each point is the mean ± S.E.M.

Phentolamine, 0·1–10 mg/kg, increased heart rate by 50–70 beats/min for several hours; thus, effects on isoprenaline-induced positive chronotropic responses could not be determined. However in this dose-range, phentolamine had no effect on vasodepressor responses to isoprenaline.

Comparison of blocking potencies for AH 5158 showed that the drug was 4·06 (2·65–6·24) times more active in blocking β- than α-adrenoceptors in anaesthetized dogs.

Sympathomimetic activity in syrosingopine-pretreated dogs

In dogs pretreated with syrosingopine, AH 5158 0·01–1 mg/kg, had no effect on blood pressure or heart rate but doses of 3 and 10 mg/kg caused falls in blood pressure of 10–25 mmHg and in heart rate of 10–20 beats/minute.

Specificity of the adrenoceptor blocking actions of AH 5158

Isolated tissues

AH 5158 had no effect on positive inotropic responses of guinea-pig left atrial strips to calcium chloride, or on contractile responses of guinea-pig mesenteric vein to barium chloride in concentrations of up to 30 μg/ml.

Anaesthetized dogs

AH 5158 had no effect on vasopressor responses to angiotensin in doses up to 10 mg/kg, or on the positive inotropic responses to calcium chloride in doses up to 3 mg/kg.

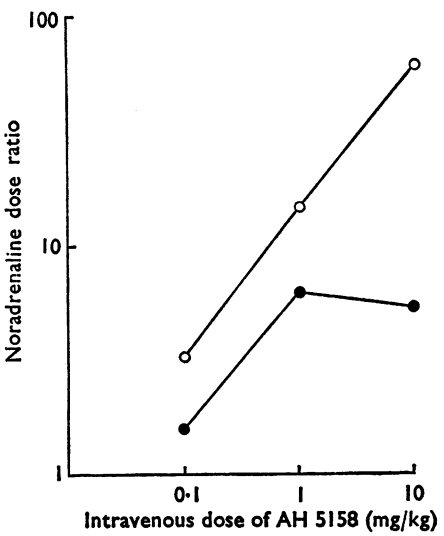


FIG. 4. Effect of cocaine on the blockade of noradrenaline vasopressor responses by AH 5158 in the anaesthetized dog. Control animal (●——●) and animal pretreated with cocaine 5 mg/kg intravenously (○——○).

Membrane-stabilizing activity on cardiac muscle

A number of β-adrenoceptor blocking drugs possess other actions unrelated to β-adrenoceptor blockade, which are probably manifestations of membrane-stabilizing activity (Fitzgerald, 1969; Langslet, 1970). These actions include local anaesthesia (Morales-Aguilera & Vaughan Williams, 1965; Murmann, Saccani-Guelfi & Gamba, 1966; Davis, 1970) and 'quinidine-like' activity on cardiac muscle as represented, for example, by characteristic alterations in the cardiac action potential (Vaughan Williams, 1966), a reduction in maximal driving frequency (Dawes, 1946; Sekiya & Vaughan Williams, 1963) and direct negative inotropic activity (Blinks, 1967; Nayler, Chipperfield & Lowe, 1969). Some properties of propranolol and AH 5158 arising from membrane stabilization were measured in the following experiments:

Isolated atria

AH 5158 and propranolol decreased the force of contraction and the maximal driving frequency of guinea-pig left atria in a dose-dependent manner (Table 2). AH 5158 was 3–11 times less potent than propranolol in these tests.

Spinal dogs

Intravenous infusions of AH 5158 or propranolol produced dose-dependent decreases in myocardial contractility, as measured from a strain-gauge arch. The minimal effective dose for propranolol was 1–3 mg/kg, and for AH 5158, 3–10 mg/kg. Estimates of relative potency were obtained by comparing the doses of each drug required to produce a 40% reduction in force of contraction, since reductions in contractility of 50% or greater were only occasionally obtained. In three experiments with each drug, AH 5158 was 4·5 (3·9–4·8) times less active than propranolol (Table 2).

TABLE 2. *Comparison of the membrane-stabilizing activities of AH* 5158 *and propranolol in guinea-pig isolated left atrial strips and spinal dogs*

Guinea-pig left atrial strip

Drug	No. of determinations	Concentration μg/ml (95% C.I.) causing a 50% reduction of		Dose ratio (95% C.I.)	
		Contractile force	Decrease in maximum driving frequency	Negative inotropic effect	Decrease in maximum driving frequency
Propranolol	4	6·2 (5·6–6·7)	4·1 (3·7–4·8)	1	1
AH 5158	4	19·3 (17·9–20·9)	45·5 (41·4–50·1)	3·1 (2·8–3·7)	11·1 (8·8–13·4)

Spinal dog

Drug	No. of determinations	Negative inotropic effect	
		Dose (mg/kg) (95% C.I.) causing 40% reduction	Dose ratio (95% C.I.)
Propranolol	3	9·1 (8·1–10·3)	1
AH 5158	3	40·9 (36·9–42·2)	4·5 (3·9–4·8)

TABLE 3. *Haemodynamic actions of AH* 5158 *in anaesthetized dogs*

Dose mg/kg (n=3)	% Change from control ± S.E.M.							
	Blood pressure	Heart rate	Aortic flow	Stroke volume	Total peripheral resistance	Ejection		Contractility
						Time	Rate	
0·1	−11·0± 2·5	−16·75±3·1	−10·0±1·9	−4·6±5·1	+4·1±3·1	+3·7±2·9	+8±4·8	−9±2·7
0·3	−14·7± 4·1	−15·8±4·1	−16·2±3·1	+2·1±4·3	−2·1±2·7	−2·0±2·7	−21±5·9	−28·4±3·1
1·0	−45·6± 8·8	−26·9±2·8	−27·3±3·3	+4·1±4·8	−42·4±5·3	+23·6±5·3	−1±4·6	−37·1±2·8
3·0	−67·3±11·8	−24·5±5·7	−38·3±4·9	−21·4±3·7	−53·9±9·1	+58·2±6·9	−31±4·1	−51·6±4·1

Haemodynamic actions of AH 5158 in anaesthetized dogs

AH 5158 was tested at 0·1 and 1 mg/kg intravenously in three dogs and at 0·3 and 3 mg/kg in a further three dogs. The results obtained are summarized in Table 3.

AH 5158, 0·1–3 mg/kg intravenously, caused dose-dependent reductions in arterial blood pressure, heart rate, aortic flow and contractility. These effects lasted for more than 1 hour. Effects on stroke volume were slight with doses of 1 mg/kg or less but a consistent reduction was seen with 3 mg/kg. Total peripheral resistance was little altered after doses of 0·1 and 0·3 mg/kg, but was consistently reduced after 1 and 3 mg/kg. Ejection time was usually increased and ejection rate usually decreased.

Antiarrhythmic actions of AH 5158 and propranolol in anaesthetized dogs

Noradrenaline-induced arrhythmias

Arrhythmias caused by noradrenaline, 50 μg/kg intravenously, resembled those caused by adrenaline (Somani & Lum, 1965) and consisted of periods of ventricular tachycardia and occasional extrasystoles. In each of three experiments, AH 5158 or propranolol, 1 mg/kg intravenously, abolished these cardiac irregularities. Subsequent doses of noradrenaline increased ectopic activity but partial blockade was still evident with both compounds 3–4 h after their administration.

Ouabain-induced arrhythmias

Both AH 5158 and propranolol abolished ventricular tachycardia induced by ouabain, and restored sinus rhythm. AH 5158 was 1·9 (1·7–2·2) times less active than propranolol, the mean intravenous doses necessary to abolish the arrhythmias being 8·0 mg/kg (7·2–8·8 mg/kg) for AH 5158 (four experiments) and 4·2 mg/kg (3·5–5·0 mg/kg) for propranolol (three experiments).

Hypotensive activity of AH 5158, propranolol and phenoxybenzamine in conscious renal hypertensive dogs

AH 5158, 0·25–5 mg/kg orally, lowered systolic arterial pressure by 10–35 mmHg for approximately 5 h without causing any consistent change in heart rate. No sign of tolerance to the hypotensive effect was observed in dogs given 1 mg/kg orally once a day for 19 days. Propranolol, 0·3–3 mg/kg orally, either had no effect or reduced systolic pressure by 5–10 mmHg. The effects on systolic pressure of the α-adrenoceptor blocking drug phenoxybenzamine, 10–40 mg/kg orally, were unpredictable. When falls in systolic pressure occurred, they were usually accompanied by increases in heart rate of up to 50 beats/minute.

Discussion

AH 5158 differs from conventional adrenoceptor blocking drugs in producing competitive blockade of both α- and β-adrenoceptors. This action is specific for adrenoceptors since responses to 'non-adrenergic' agonists such as angiotensin, calcium chloride or barium chloride were unaffected by AH 5158.

The present experiments showed that AH 5158 is 5–18 times less potent than propranolol in blocking β-adrenoceptors. The potency difference is somewhat

less pronounced in anaesthetized dogs than in isolated tissues, possibly because propranolol is inactivated in the blood by binding to serum protein (Barrett, Jackson, Lowe & Shakespear, 1970, quoted by Wale, 1970). AH 5158 resembles propranolol in its non-selective blockade of β_1-cardiac and β_2-vascular and tracheal receptors and in its lack of intrinsic sympathomimetic activity.

AH 5158 is 2–7 times less potent than phentolamine in blocking α-adrenoceptors. Comparison of blocking potencies shows that AH 5158 is more active on β- than on α-adrenoceptors. For example, in the anaesthetized dog the ratio of β- to α-adrenoceptor blocking potency is approximately four, which corresponds closely to the ratio obtained after intravenous administration in man (Boakes, Knight & Prichard, 1971). The greater β-adrenoceptor blocking potency is important in any possible clinical use of AH 5158 because it should prevent the reflexly induced cardiac stimulant effects which usually accompany α-adrenoceptor blockade.

Blockade of noradrenaline vasopressor responses by AH 5158 in the anaesthetized dog was 'self-limiting' (maximum 4–5 fold shift obtainable) in intravenous doses above 1 mg/kg, but was progressive in dogs treated with cocaine. Since cocaine is known to block the Uptake$_1$ process (Iversen, 1965) which is, in part, responsible for the removal of circulating noradrenaline (Gryglewski & Vane, 1970), a possible explanation of these results is that AH 5158, in common with several β-adrenoceptor blocking drugs (Foo, Jowett & Stafford, 1968), progressively blocks uptake of noradrenaline in doses above 1 mg/kg. A larger proportion of the injected dose of noradrenaline would then be available to compete with AH 5158 at α-adrenoceptors, thereby reducing the degree of the observed antagonism. Two other observations are in accord with this suggestion; first, the blockade by AH 5158 of vasopressor responses to oxymetazoline, which is not a substrate for Uptake$_1$ (Birmingham, Paterson & Wójcicki, 1970), was not 'self-limiting'; and second, the interaction between noradrenaline and AH 5158 on α-adrenoceptors in isolated tissues was also not 'self-limiting' but was a simple competitive antagonism.

In doses higher than those required for α- and β-adrenoceptor blockade, AH 5158 exerted a membrane-stabilizing action on cardiac muscle. This was manifested as a negative inotropic action in spinal dogs and in electrically-driven left atrial strips, as a negative chronotropic action in syrosingopine pretreated dogs and as an increase in the effective refractory period of guinea-pig left atrial strips. In this respect, AH 5158 resembles several β-adrenoceptor blocking drugs, including propranolol (Fitzgerald, 1969; Fitzgerald & O'Donnell, 1971; Fitzgerald, Wale & Austin, 1972; Vaughan Williams, 1970). The ratio of β-adrenoceptor blocking to membrane-stabilizing activity was similar for propranolol and AH 5158; AH 5158 also resembled propranolol in possessing potent local anaesthetic activity (unpublished experiments).

The effects of AH 5158 on haemodynamic function in the anaesthetized dog are attributable to adrenoceptor blockade. Thus, like propranolol (Barrett, 1969), AH 5158 reduced heart rate, cardiac output and myocardial contractility by blocking β-adrenoceptors. AH 5158 differed from propranolol in decreasing rather than increasing total peripheral resistance and in causing larger falls in arterial blood pressure in equipotent β-adrenoceptor blocking doses (compare Table 3 in present paper with Table 3, Barrett, 1969). It seems reasonable to

attribute these differences to vasodilatation resulting from the vascular α-adrenoceptor blocking action of AH 5158. The membrane-stabilizing action of the drug is unlikely to have contributed to the observed haemodynamic changes in the dose-range used.

The profile of action described for AH 5158 is novel. Other drugs which have been claimed to block both α- and β-adrenoceptors include WR 4809 (Cambar & Aviado, 1970), but without adequate evidence of specific and competitive antagonism, and the α-adrenoceptor blocking drug, dihydroergotamine, whose effect at β-adrenoceptors is probably non-specific (Hornbrook, 1967). The anti-anginal drug, amiodarone has been shown to reduce effects mediated through both α- and β-adrenoceptors, but by non-competitive mechanisms (Charlier, Deltour, Baudine & Chaillet, 1968; Charlier, 1970). Indoramin resembles AH 5158 in possessing α-adrenoceptor blocking and membrane-stabilizing actions but differs in its lack of β-adrenoceptor blocking activity (Alps, Hill, Johnson & Wilson, 1970).

AH 5158 may find application in a number of cardiovascular disorders, notably hypertension, ischaemic heart disease and cardiac arrhythmias. The demonstration of hypotensive activity in conscious hypertensive and anaesthetized normotensive dogs suggested that the drug could be useful in the treatment of hypertension in man. In a pilot trial, AH 5158 effectively lowered arterial blood pressure in hypertensive patients and the studies are being extended (Boakes & Prichard, personal communication).

β-Adrenoceptor blocking drugs, such as propranolol, have proved effective in the treatment of angina pectoris (Epstein & Braunwald, 1966a; Dollery, Paterson & Conolly, 1969). The additional α-adrenoceptor blocking action of AH 5158 may provide advantages over conventional β-adrenoceptor blocking drugs since, in doses equipotent in reducing heart rate, the drug should produce greater falls in blood pressure and, therefore, in cardiac work.

β-Adrenoceptor blocking drugs are effective antiarrhythmic agents in animals and man (Sekiya & Vaughan Williams, 1963; Somani & Lum, 1965; Epstein & Braunwald, 1966b). The mechanism of the antiarrhythmic action of propranolol in animals appears to differ with different types of experimental arrhythmia. Thus Barrett & Cullum (1968) found in anaesthetized cats and dogs that membrane-stabilizing activity was essential to control ouabain-induced arrhythmias, but that a combination of membrane-stabilizing and β-adrenoceptor blocking activity was more effective. In contrast, arrhythmias produced by adrenaline could be reversed by β-adrenoceptor blockade alone (Barrett & Cullum, 1968). Recent work with indoramin has shown that the drug abolishes ouabain arrhythmias by membrane-stabilization, and adrenaline arrhythmias by a combination of membrane-stabilization and α-adrenoceptor blockade (Alps, Hill, Fidler, Johnson & Wilson, 1971). In view of these results it was not surprising to find that AH 5158 effectively controlled both ouabain and catecholamine-induced arrhythmias in anaesthetized dogs, and might reasonably be tested in various types of arrhythmia in man. Indeed the unique combination of α- and β-adrenoceptor blocking the membrane-stabilizing properties in AH 5158 may provide advantages over currently available antiarrhythmic agents.

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