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A comparison of the haemodynamic effects of propranolol, 4-hydroxypropranolol and practolol in anaesthetized dogs

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Summary

1. The haemodynamic effects of propranolol, practolol and 4-hydroxypropranolol have been compared in anaesthetized dogs both at free heart rates and at heart rates fixed by electrical pacing. All three drugs produced a fall in heart rate at the lowest dose of 0·09 mg/kg.

2. Practolol caused less change in dP/dt, cardiac output and blood pressure than did propranolol. 4-Hydroxypropranolol had intermediate effects. Since the changes in dP/dt caused by these three drugs were still present when the heart rate was fixed by pacing, it is concluded that these were independent of changes in heart rate.

3. The fact that practolol and 4-hydroxypropranolol cause less change in haemodynamic function than propranolol may be associated with the intrinsic sympathomimetic activity possessed by the first two of these drugs.

Introduction

Propranolol has been shown to possess negative chronotropic, inotropic and dromotropic properties in animals and man (Black, Duncan & Shanks, 1965; Nakano & Kusakari, 1966; Murray, Escobar, Jones & Rapaport, 1966; Hamer & Fleming, 1967; Sowton & Hamer, 1966). These effects are due to blockade of cardiac β-adrenoceptors (Flacke, Osgood & Bendixen, 1966) except after administration of very high doses when the membrane stabilizing actions of propranolol contribute to the effects seen (Fitzgerald, Wale & Austin, 1972). The β-adrenoceptor blocking drug, practolol, differs from propranolol in that it is relatively cardioselective, possesses intrinsic sympathomimetic activity and is without membrane stabilizing activity (Dunlop & Shanks, 1968). Haemodynamic studies with practolol in animals and man (Bussman, Rauh & Krayenbuehl, 1970; Sowton, Balcon, Cross & Frick, 1968; Gibson, 1970; Jewitt, Burgess & Shillingford, 1970) suggest that it has less negative chronotropic and inotropic activity than propranolol.

The experiments described in this paper were carried out for three reasons. Firstly, to determine whether or not there is a quantitative difference between the

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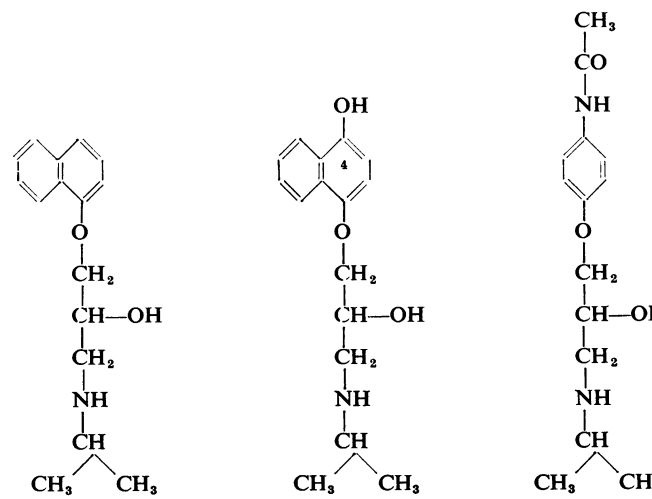
haemodynamic effects of propranolol and practolol. Secondly, to examine the influence of the changes in heart rate produced by these drugs on their negative inotropic action. Thirdly, to try and determine the relevance of intrinsic sympathomimetic activity in these compounds. Their haemodynamic properties have been compared with those of 4-hydroxypropranolol (Fig. 1). This is a β-adrenoceptor blocking drug which, like propranolol, but unlike practolol, is thought to possess membrane stabilizing activity. However, unlike propranolol but like practolol, it also has significant intrinsic sympathomimetic properties (Fitzgerald & O'Donnell, 1971). By comparing these three closely related β-adrenoceptor blocking drugs, each with a different spectrum of pharmacological activity, it was hoped to obtain some information on the role of heart rate changes, membrane stabilizing properties, intrinsic sympathomimetic activity and possibly also of cardio-selectivity in the haemodynamic changes observed following β-adrenoceptor blockade.

Methods

Eighteen male beagle dogs (12–16 kg) were used. The animals were anaesthetized with 30 mg/kg pentobarbitone sodium intravenously, and maintained on artificial respiration with a mixture of 60% air and 40% oxygen. Systemic blood pressure, heart rate, aortic flow, atrioventricular conduction time and the rate of rise of pressure in the left ventricle (dP/dt) were recorded and measured as described by Fitzgerald & O'Donnell (1971). An atrial electrode was sutured to the right atrium for electrical pacing of the heart. The vagus nerves were sectioned in the neck and the animals left for 30 min before starting the control readings.

Eight recordings of resting values were taken over 15 minutes. A record was made every 5 min at the intrinsic heart rate of the animal and 2 min later at a constant paced heart rate. The control values are the mean of these 4 readings. In 16 of the dogs the paced rate was between 150 and 170 beats/minute. In the other two it was 132 and 197 beats/minute. Propranolol, 4-hydroxypropranolol



Propranolol 4-hydroxypropranolol Practolol

FIG. 1. Chemical structures of β-adrenoceptor blocking drugs.

and practolol were administered intravenously at 0, 15, 30, 45 and 60 min in fixed doses of 0·09, 0·16, 1·0, 4·0 and 8·0 mg/kg resulting in cumulative doses of 0·09, 0·25, 1·25, 5·25 and 13·25 mg/kg. Recordings were taken at 5 and 10 min (unpaced) and 7 and 12 min (paced) after each injection and values of each parameter were measured as the mean of at least 10 complete cardiac cycles. The effects of each dose of drug on each parameter were determined by comparing the average value of the two recordings taken at 5 and 10 min (unpaced) and 7 and 12 min (paced) with the value obtained in the control recording. Changes are expressed as percentage change from the mean control value. The mean values of per cent change from control ± standard error from a number of animals were then calculated and plotted against cumulative dose of drug. The significance of the difference of these values from zero or of the difference between two values was assessed by Student's *t* test.

The drugs used were 4-hydroxypropranolol hydrochloride; (±)-propranolol hydrochloride; practolol free base. The doses of drug refer to the base. The 4-hydroxypropranolol hydrochloride was dissolved in normal saline containing citric acid (half the weight of 4-hydroxypropranolol). The solution was prepared immediately before use and was kept in ice during experiments.

Results

The mean resting values of the various parameters measured in the 18 dogs are summarized in Table 1. In the three groups of dogs used, they were reasonably comparable. The main differences observed were the spontaneously lower resting heart rate in the 4-hydroxypropranolol-treated group, and the higher mean blood pressure of the propranolol-treated group. These differences were not great enough to invalidate comparisons of haemodynamic data after drug treatment. The pacing of the heart at constant rate had very little effect on the resting dP/dt, aortic flow, or mean blood pressure. It did produce a highly significant increase in atrioventricular conduction time in all three groups of dogs. The extent of this increase was similar (32, 34 and 37 msec) for all three groups, even though the paced heart

TABLE 1. *Control haemodynamic values in anaesthetized dogs*

Unpaced	4-Hydroxy propranolol* (*n*=7)†	Propranolol (*n*=6)	Practolol (*n*=5)
Heart rate (beats/min)	137·7± 8·8‡	152·2± 7·8	154·4± 7·4
dP/dt (mmHg/s)	1956·2±134·3	3248·0±510·3	2417·0±136·0
Atrioventricular conduction time (msec)	107·8± 5·0	106·4± 4·8	108·3± 8·6
Aortic flow (ml/min)	989·0±174·9	1211·3±213·4	1366·4±241·5
Mean blood pressure (mmHg)	76·5± 4·1	104·2± 7·7	82·6± 7·2
Paced			
Heart pacing	161·0± 7·3	169·0± 7·2	164·2± 4·9
dP/dt (mmHg/s)	2152·8±148·3	3363·0±484·9	2459·2±110·8
Atrioventricular conduction time (msec)	144·8± 5·0§	138·4± 6·7§	142·2± 11·5§
Aortic flow (ml/min)	1003·0±164·4	1251·2±221·2	1362·0±214·6
Mean blood pressure (mmHg)	78·7± 3·8	104·5± 7·7	83·6± 7·2

* Data from Fitzgerald & O'Donnell (1971)
† Number of animals
‡ Mean ± standard error of mean
§ Sig. difference from unpaced control value
Summary of mean control values (±S.E.M.)

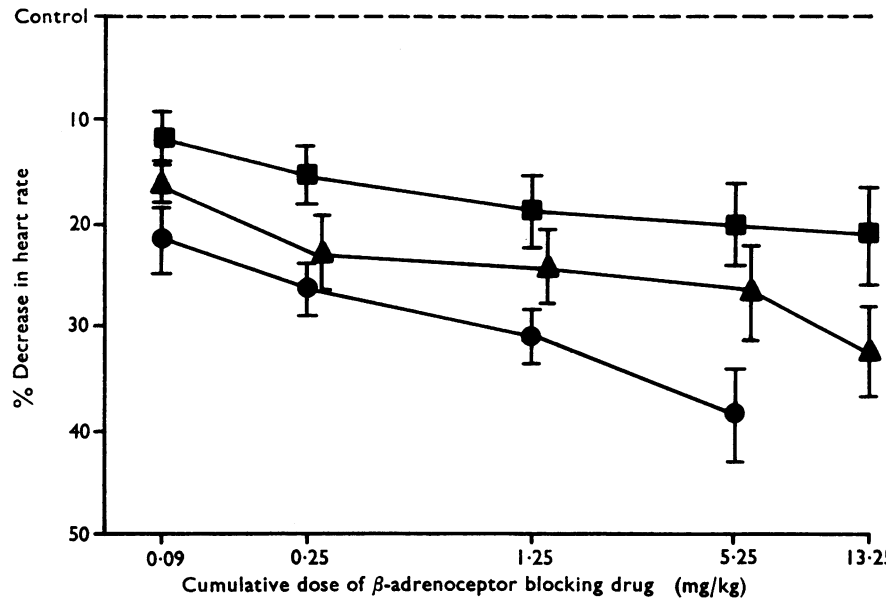


FIG. 2. Mean change in heart rate, expressed as % change from control values, to cumulative doses of propranolol (●) in six dogs, 4-hydroxypropranolol in seven dogs (▲) and practolol (■) in five dogs. Each point represents the mean; one standard error is shown. The data for 4-hydroxypropranolol are from Fitzgerald & O'Donnell (1971).

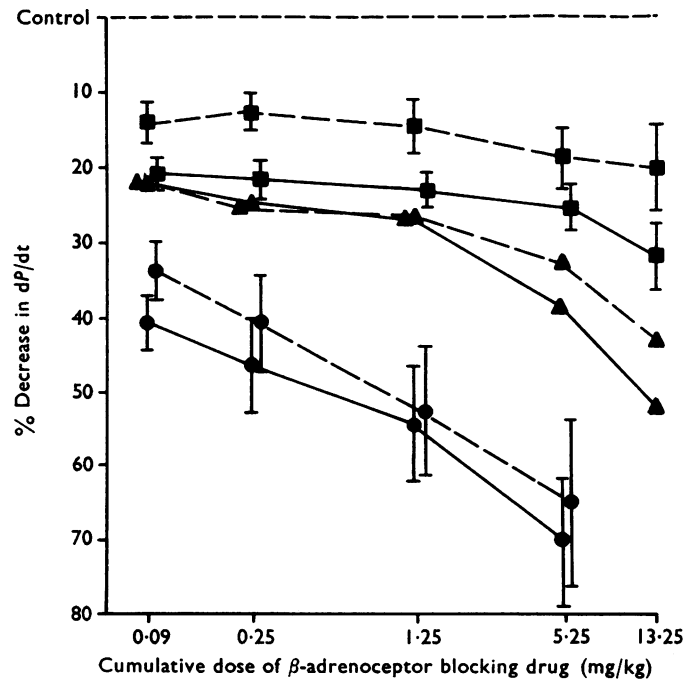


FIG. 3. Mean change in dP/dt, expressed as % change from control values, to cumulative doses of propranolol (●), in six dogs, 4-hydroxypropranolol (▲) in seven dogs and practolol (■) in five dogs. Values were obtained before (full lines) and after (dotted lines) electrical pacing of the heart at a constant rate. Each point represents the mean and brackets, where shown, represent one standard error. The data for 4-hydroxypropranolol are from Fitzgerald & O'Donnell (1971).

rate was increased by 23·0 ± 3·1 beats/min in the 4-hydroxypropranolol-treated group and by only 9·8 ± 2·6 beats/min in the practolol-treated group.

Heart rate

Administration of 0·09 mg/kg of all three β-adrenoceptor blocking drugs caused a significant reduction in the resting heart rate. Administration of further doses of propranolol produced a clearly dose-dependent fall in rate and no animal survived a total of 13·25 mg/kg (Fig. 2). Propranolol caused a significantly greater fall in heart rate than did practolol. The fall in heart rate after 13·25 mg/kg practolol was no greater than after 0·25 mg/kg ($P=0·1$). The effect of 4-hydroxypropranolol on heart rate was intermediate between propranolol and practolol at all doses. The highest dose of 4-hydroxypropranolol (13·25 mg/kg) reduced the mean resting heart rate less than a lower dose (5·25 mg/kg) of propranolol, even though the drugs are equipotent β-adrenoceptor blocking drugs (Fitzgerald & O'Donnell, 1971).

Contractility (dP/dt)

Propranolol caused a dose-dependent decrease in dP/dt which was still present if changes in heart rate, resulting from administration of the drug, were prevented by atrial pacing. There was no statistical difference between the dose-response lines in unpaced and paced conditions (Fig. 3). Administration of practolol (0·09 mg/kg) caused a 20% decrease in dP/dt, compared with the 40% decrease produced by the same dose of propranolol. However, subsequent doses of practolol caused no further decrease in dP/dt until after the highest dose used (13·25 mg/kg) when dP/dt was reduced by 32% from control values. When the heart rate was maintained at a constant rate by atrial pacing, practolol still produced a significant reduction in dP/dt. However, although the differences were not statistically significant, there was a tendency for the reduction in dP/dt to be less than that occurring when the heart rate was allowed to change. The effects of 4-hydroxypropranolol on dP/dt were intermediate between those of practolol and propranolol and showed the same trend even when changes in heart rate were prevented by atrial pacing.

Cardiac output (aortic flow)

Propranolol (0·09 mg/kg) reduced the cardiac output by 18% and this reduction increased in a dose-dependent manner with increasing doses of drug to a value of 48% decrease after 5·25 mg/kg. The reduction was only slightly less during atrial pacing (Fig. 4a). Practolol (0·09 mg/kg) reduced the cardiac output by only 10% and after 13·25 mg/kg it was still only decreased 15% from control values. The reduction in cardiac output after 4-hydroxypropranolol (0·09 mg/kg) was not significantly different from that caused by practolol, but it was significantly less than that due to propranolol. On continuing administration of 4-hydroxypropranolol, cardiac output was not reduced further until 5·25 mg/kg had been given. When the heart was paced at constant rate there was a tendency for cardiac output to be slightly less depressed by all three drugs, but in particular by practolol.

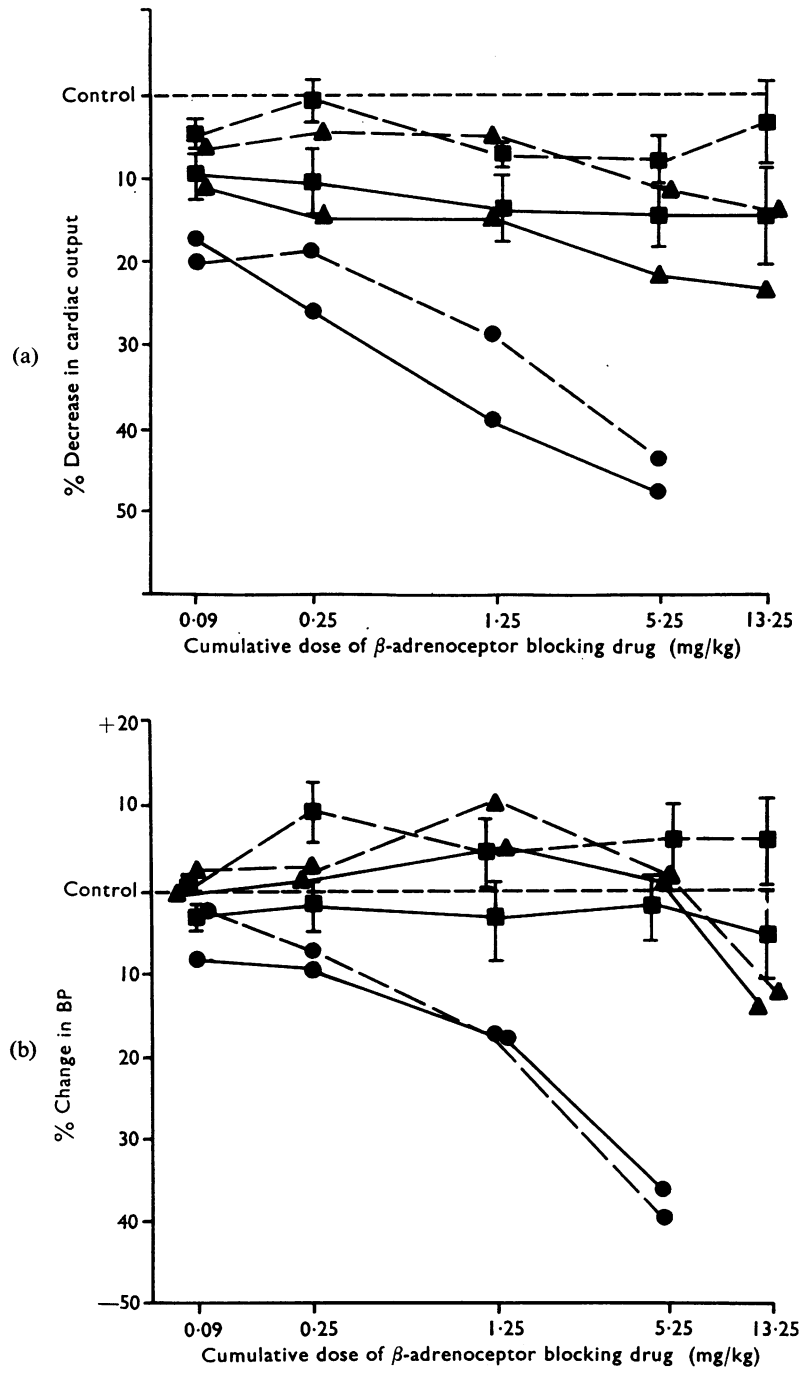


FIG. 4. Mean change in (a) cardiac output and (b) mean blood pressure, expressed as % change from control values, after cumulative doses of propranolol (●) in six dogs, 4-hydroxypropranolol (▲) in seven dogs and practolol (■) in five dogs. Values were obtained before (full lines) and after (dotted lines) electrical pacing of the heart at a constant rate.
Standard errors of the mean are not shown for propranolol and 4-hydroxypropranolol as there were no significant differences between unpaced and paced values. One standard error of the mean is shown for the practolol values. The data for 4-hydroxypropranolol are from Fitzgerald & O'Donnell (1971).

Mean blood pressure

Whereas propranolol in doses of 1·25 mg/kg or greater caused a sharp fall in mean blood pressure, neither practolol nor 4-hydroxypropranolol significantly affected blood pressure at any dose level (Fig. 4b). Pacing the atria at constant rate had no significant effect on the responses to propranolol or 4-hydroxypropranolol. During treatment with practolol, however, the blood pressure was higher than in the absence of pacing.

Atrioventricular conduction time

All three β-blocking drugs increased atrioventricular conduction time above control values (Fig. 5). Propranolol produced a progressive increase with increasing dose, whereas after the initial increase conduction time remained fairly constant with practolol. The initial dose of 4-hydroxypropranolol caused an increase in A.V. conduction time which remained constant until doses above 1·25 mg/kg were reached, when it increased further with increasing dose of drug. With all three drugs there was a tendency for the increase in conduction time to be greater when the atria were being paced than at the free heart rate. The difference between unpaced and paced values only reached statistical significance with 4-hydroxypropranolol.

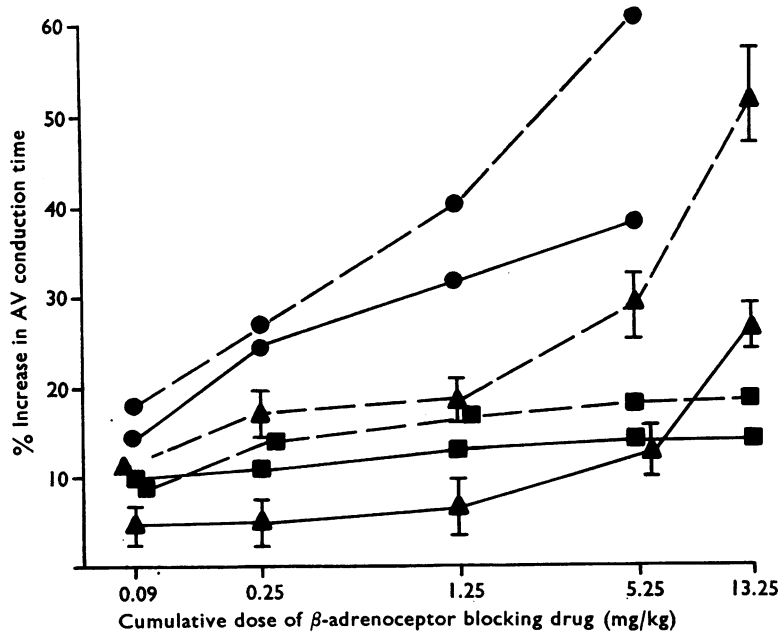


FIG. 5. Mean change in atrioventricular conduction time, expressed as percentage change from control values after cumulative doses of propranolol (●) in six dogs, 4-hydroxypropranolol in seven dogs (▲) and practolol (■) in five dogs. Values were obtained before (full lines) and after (dotted lines) electrical pacing of the heart at a constant rate. Standard errors of the mean are not plotted for propranolol and practolol as there was no significant difference between unpaced and paced values. One standard error of the mean is shown for the 4-hydroxypropranolol values and these data are from Fitzgerald & O'Donnell (1971).

Discussion

The reduction in heart rate and cardiac output observed after administration of β-adrenoceptor blocking drugs in vagotomized dogs is believed to be due to antagonism of endogenous catecholamines. Thus the extent of the changes observed will depend partly on the amount of catecholamine activity present prior to the administration of the drug. Because the experiments described were designed not only to study the haemodynamic effects of β-adrenoceptor blockade but also the possible implications of membrane stabilizing activity and intrinsic sympathomimetic activity, the experiments were carried out in animals anaesthetized with pentobarbitone. Under this anaesthetic, sympathetic tone is lower than in animals anaesthetized with chloralose or halothane (Price, 1960). It was felt that the effects of intrinsic sympathomimetic activity of the drugs may be more obvious in animals with a lower level of sympathetic activity. The range of doses of β-adrenoceptor blocking drugs used in this study was such that maximal block of endogenous catecholamine activity could be expected after administration of the first three doses (totalling 1·25 mg/kg) (Fitzgerald, Wale & Austin, 1972; Flack *et al.*, 1967). Thus alterations in cardiovascular function observed with doses greater than 1·25 mg/kg might be expected to result from actions other than β-adrenoceptor blockade.

Propranolol caused a dose-dependent reduction in all the haemodynamic parameters measured, its effect being greater than equivalent doses of either 4-hydroxypropranolol or practolol. In contrast to propranolol, the haemodynamic changes resulting from administration of practolol were not dose-dependent but tended to remain constant after doses greater than 0·25 mg/kg. 4-Hydroxypropranolol resembled practolol in its effects on cardiac output, heart rate and mean blood pressure, though the magnitude of the reductions was slightly greater. After doses greater than 5·25 mg/kg of 4-hydroxypropranolol a dose-dependent reduction in dP/dt was observed. Although differences in response to the three drugs in the dose range 0·09–1·25 mg/kg could be explained by differences in their β-receptor blocking potency, this seems an unlikely explanation since 4-hydroxypropranolol has a similar potency to propranolol in terms of the antagonism of isoprenaline tachycardia in cats (Fitzgerald & O'Donnell, 1971). Although practolol is only one-third as potent as propranolol against isoprenaline-induced tachycardia in cats, it has a potency equivalent to propranolol in preventing the rise in heart rate following stellate stimulation in the dog and cat (Barrett, 1970). Thus factors other than β-adrenoceptor blocking potency must be considered to account for the differences in haemodynamic changes observed after administration of propranolol, 4-hydroxypropranolol and practolol.

Of the three drugs studied, propranolol caused the greatest reduction in heart rate after each dose. It is possible that the concomitant reductions in cardiac output, dP/dt, and blood pressure are secondary to the marked falls in heart rate. However, when these changes in heart rate were prevented by pacing the atria electrically at a constant rate, cardiac output, dP/dt and blood pressure were still reduced. Although there was a tendency for the reduction to be less with the heart being paced the difference between the unpaced and paced result was never statistically significant (i.e. at $P<0·05$). The rate-independent negative inotropic action of propranolol has previously been described in animals (Fitzgerald, *et al.*,

1972) and in man (Bloomfield & Sowton, 1966; Donoso, Cohn, Newman, Bloom, Stein & Friedberg, 1967).

Practolol reduced the resting heart rate much less than propranolol, and, after the initial reduction, there was no further decrease with increasing dose of drug. Since practolol is a potent β-adrenoceptor blocking drug (see above) this lesser effect on heart rate might be due to one or more of its other properties, e.g., sympathomimetic activity or lack of membrane stabilizing properties. Presence or absence of membrane stabilizing properties seems unlikely to be the explanation for the differences between these drugs observed after doses up to 1·25 mg/kg for two reasons. Firstly, Fitzgerald *et al.* (1972) have shown that the membrane stabilizing properties of propranolol can only be detected in anaesthetized dogs when doses greater than 2·56 mg/kg are used. Secondly, 4-hydroxypropranolol, a β-adrenoceptor blocking drug equipotent with propranolol and which possesses membrane stabilizing properties (as well as intrinsic sympathomimetic activity), did not reduce the heart rate as much as propranolol and there was no dose-dependent decrease in heart rate with 4-hydroxypropranolol until after administration of 5·25 mg/kg. The effects observed after these higher doses of 4-hydroxypropranolol are probably the result of its membrane stabilizing activity.

It thus seems possible that the more marked reduction in heart rate after propranolol than after practolol or 4-hydroxypropranolol might be accounted for by the lack of sympathomimetic activity of propranolol. The intrinsic sympathomimetic activity of practolol and 4-hydroxypropranolol may counteract their β-receptor blocking activity. Practolol was less effective than propranolol, not only in reducing heart rate but also in reducing cardiac output, dP/dt and blood pressure—4-hydroxypropranolol being intermediate in its effects. The observation that this pattern occurred at all dose levels studied would suggest that, in the case of 4-hydroxypropranolol, intrinsic sympathomimetic activity can counteract not only β-receptor blocking activity (the low dose effects of 4-hydroxypropranolol) but also membrane stabilizing activity (high dose effects). Some support for the view that β-receptor stimulant activity can effectively counteract cardio-depressant properties has been obtained by Fitzgerald, Wale & Austin (unpublished observations). These authors studied the effect of quinidine on the response to isoprenaline in anaesthetized dogs with fixed heart rate. Whereas quinidine itself (10–40 mg/kg intravenously) depressed dP/dt and atrioventricular conduction, there was still a rise in dP/dt and a decrease in atrioventricular conduction time after administration of isoprenaline even in the presence of quinidine.

Direct evidence for membrane stabilizing activity in 4-hydroxypropranolol is lacking because of the instability of the compound in oxygenated physiological solutions. Hence it has not been possible to use tests such as depression of the spike potential in the frog sciatic nerve or depression of the rate of rise and overshoot of the action potential in isolated atria, as described by Singh & Vaughan Williams (1969), to demonstrate membrane stabilizing properties. The only evidence currently available to suggest that 4-hydroxypropranolol has membrane stabilizing properties is its capacity to increase atrioventricular conduction time in dogs depleted of catecholamines. This increase occurs with doses of 4-hydroxypropranolol in excess of 5·25 mg/kg and is dose-dependent. This effect is in marked contrast to that obtained with doses below 5·25 mg/kg when the drug causes a decrease in the atrioventricular conduction time (Fitzgerald & O'Donnell, 1971). Fitzgerald &

O'Donnell interpreted these findings as indicating (a) that 4-hydroxypropranolol has intrinsic sympathomimetic activity, and in low doses facilitates atrioventricular conduction in the same way as does practolol on the identical preparation (Fitzgerald *et al.*, 1972); (b) that, at higher doses, the drug probably possesses membrane stabilizing activity. An increase in conduction time after high doses of 4-hydroxypropranolol (13·25 mg/kg) but not after the equivalent dose of practolol (see Fig. 5), would support the hypothesis that 4-hydroxypropranolol has membrane stabilizing properties whereas practolol does not.

The effects of 4-hydroxypropranolol on atrioventricular conduction time have been described previously (Fitzgerald & O'Donnell, 1971). Fitzgerald *et al.* (1972) have also previously reported on the changes in conduction time after propranolol and practolol in dogs with fixed heart rates. However, with the experimental design used in the present study, additional data are available enabling comparison to be made of the effects of these 3 drugs on atrioventricular conduction time at free heart rate as well as at fixed heart rate. In all experiments, conduction time increased less when the heart rate was not fixed by pacing. The possible reason for this has been discussed by Fitzgerald & O'Donnell (1971) for 4-hydroxypropranolol. However, the difference between unpaced and paced values after 4-hydroxypropranolol was greater than that observed after propranolol or practolol. This might reflect the lower resting heart rate of the animals used for 4-hydroxypropranolol which therefore required a greater mean increase in the number of beats/min (23 beats/min) to equalize the mean pacing rate in the three groups of dogs.

In conclusion practolol caused quantitatively less change in haemodynamic function in anaesthetized dogs with free heart rate than did propranolol. 4-Hydroxypropranolol had intermediate effects. This trend was seen even if the heart was paced electrically at a fixed rate and thus changes in dP/dt, cardiac output and blood pressure are not solely due to the changes in heart rate which occur after administration of all three β-adrenoceptor blocking drugs. The difference in magnitude of the haemodynamic changes observed with propranolol and practolol are believed to result from the fact that practolol possesses intrinsic sympathomimetic activity. 4-Hydroxypropranolol also possesses intrinsic sympathomimetic activity and is closely related chemically to propranolol and a comparison of the effects of this drug with those of propranolol further demonstrated that differences in the effects which were observed could be due to the sympathomimetic activity of 4-hydroxypropranolol.

This view receives support from a recent study in which the haemodynamic effects of four beta-blocking drugs were compared in conscious dogs (Bergamaschi, Shanks, Caravaggi & Mandelli, 1971). It was shown that propranolol and sotalol, which do not have intrinsic sympathomimetic activity, reduce cardiac output. In contrast, alprenolol and practolol, which do possess intrinsic activity, do not have this effect.

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