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A comparison of the effects of (±)-propranolol and (+)-propranolol in anaesthetized dogs; β-receptor blocking and haemodynamic action

A. M. BARRETT

Pharmacological Research Department, Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England

The adrenergic β-receptor blocking activities of (±)-propranolol and (+)-propranolol have been compared in anaesthetized dogs, using isoprenaline as the agonist. (+)-Propranolol possessed less than one fiftieth the potency of (±)-propranolol. Intravenous (±)-propranolol (0·25 mg/kg) produced a six-fold increase in the isoprenaline dose ratio and significantly lowered heart rate, cardiac contractile force, ejection rate and tension time index. The same dose of (+)-propranolol had no effect on the isoprenaline dose ratio nor did it significantly alter these haemodynamic variables. Since both isomers of propranolol have equivalent membrane stabilizing properties it was concluded that the haemodynamic effects of (±)-propranolol at this dose level were due to specific β-blockade and not to any "quinidine-like" properties. Higher doses of (+)-propranolol (1·25 mg/kg) significantly reduced heart rate and cardiac contractile force whilst increasing atrio-ventricular conduction time without raising the threshold to isoprenaline. There was no effect on ejection time, mean ejection rate or tension time index. Extremely high doses of (+)-propranolol slightly raised the isoprenaline dose ratio in intact dogs but not after vagal section. The arithmetic difference between the effects of equivalent doses of (±)-propranolol and (+)-propranolol was approximately constant. The findings suggest that (±)-propranolol reduces cardiac work by blocking the sympathetic drive to the heart at doses up to 0·2 mg/kg (the usual clinical dose range) and that direct depression of the mycardium only occurs at doses well above this.

Many clinical reports demonstrate the utility of (±)-propranolol in correcting or ameliorating a wide range of cardiac arrhythmias (Bath, 1966). The precise mechanism of action of (±)-propranolol in these conditions is not fully understood for two principal reasons. First the aetiology of most arrhythmias is obscure and second (±)-propranolol not only possesses specific competitive blocking properties at adrenergic β-receptors but also marked local anaesthetic activity. Chemical separation of the isomers of propranolol facilitated a detailed study of their respective pharmacological actions (Barrett & Cullum, 1968). The authors concluded that only the (−)-isomer exhibited significant β-receptor blocking activity whereas both isomers possessed equivalent local anaesthetic potency. In arrhythmias associated with adrenergic stimulation, (−)-propranolol was effective in the dose range of 60–100 μg/kg. The (+)-isomer was also effective against these arrhythmias but only at dose levels which also depressed conduction in the myocardium (2–6 mg/kg). Both isomers were effective in reversing arrhythmias produced by ouabain overdosage but only at higher dose levels (2–6 mg/kg). In view of the risk of inducing heart failure with (±)-propranolol many clinicians are reluctant to use this agent for the correction of

arrhythmias where there is evidence of damage to the myocardium. It seemed logical therefore to assess the value of (+)-propranolol as an anti-arrhythmic agent in its own right. This paper compares the degree of β-receptor blockade produced by incremental doses of (±)-propranolol and its (+)-isomer and assesses the haemodynamic effects of those doses to provide background information on the expected effects of (+)-propranolol following intravenous injection in man.

EXPERIMENTAL

Animals and methods

Mongrel dogs (11–16 kg) of either sex were used in these experiments. Anaesthesia was induced with thiopentone and maintained with chloralose in order to maintain a relatively high degree of sympathetic tone. All dogs were artificially ventilated via a cuffed endotracheal tube and in some, bilateral vagotomy was performed. Following thoracotomy through a midsternal incision, a strain-gauge arch was sutured to the epicardial surface of the left ventricle. Heart rate was recorded with a cardiotachometer (Horsfall, 1965) and arterial blood pressure from the left carotid artery using pressure transducer. In some experiments we also recorded Lead II electrocardiogram and aortic flow by placing a probe for an electromagnetic flow-meter (Medicon K 2000) around the root of the aorta.

All responses were monitored on a four channel oscilloscope (Airmec) and recorded continuously on a multi-channel tape-recorder (Ampex SP 300). Permanent records were obtained from the tape on an ink-writing recorder (Minograph 81 B) at the end of each experiment. Accurate measurements of cardiac functions were made from records obtained at a paper speed of 100 mm/s.

Calculations

The following calculations were employed to determine haemodynamic functions:

(1) Cardiac output = aortic flow (ml/min)/body wt (kg). (2) Stroke volume = aortic flow (ml/min)/heart rate (bts/min). (3) Mean blood pressure = Diastolic pressure + $\frac{1}{3}$ pulse pressure. (4) Mean systolic ejection pressure was determined by planimetric integration of the area under the systolic portion of the aortic pressure trace. (5) Ejection time was taken between the onset of systole and the dicrotic notch, from the aortic pressure trace. (6) Mean ejection rate = stroke volume/ejection time. (7) Total peripheral resistance = mean blood pressure/aortic flow. (8) Tension time index (pressure time/min) = mean systolic ejection pressure × heart rate × ejection time. Each measurement was taken as the mean for 10 complete cardiac cycles.

Dose-response curves for the positive chronotropic, positive inotropic and vasodilator actions of isoprenaline were obtained in eight dogs. Four dogs each received 0·25, 1·0 and 4·0 mg/kg consecutively of (±)-propranolol or (+)-propranolol intravenously. After each dose the amount of isoprenaline was increased until the maximum response seen before the administration of the drugs was obtained. The results were plotted graphically and the dose of isoprenaline required to produce 50% of the maximum response determined. The experiments were repeated in eight vagotomized dogs.

Eight further dogs received (±)-propranolol or (+)-propranolol only, in the above doses, at 15 min intervals. Changes in haemodynamic functions were measured 13 min after the injection of each dose.

Drugs

The drugs used were (±)-isoprenaline sulphate (Burroughs Wellcome), (±)-propranolol hydrochloride (Inderal, I.C.I.) and (+)-propranolol (prepared by Dr. T. Leigh of the Chemical Research Department at Alderley Park). The (+)-isomer contained less than 0·5% of (−)-isomer as determined by measuring optical rotations.

RESULTS

The effects of (±)-propranolol and (+)-propranolol on the responses to isoprenaline are summarized in Table 1. There was no reduction in the maximum response for the positive chronotropic and inotropic effects with either drug. However, with the highest dose level of (±)-propranolol (5·25 mg/kg) it was not possible to produce a dose-dependent vasodilator response and in some cases a pressor response was observed after higher doses of isoprenaline. Following the 5·25 mg/kg dose of (+)-propranolol the response of the blood pressure to isoprenaline became biphasic, there being an initial rise and a secondary fall. From the data given in Table 1, the dose

Table 1. *A comparison of the doses of isoprenaline necessary to produce 50% of the maximum response in heart rate, heart force and vasodilation before and after various doses of* (±)-*propranolol and its* (+)-*isomer*

		(±)-Propranolol		(+)-Propranolol	
Function	Dose (mg/kg)	Isoprenaline for 50% max. (ng/kg)	Dose ratio	Isoprenaline for 50% max. (ng/kg)	Dose ratio
Heart rate ..	0	150 ± 12	1·00	150 ± 9	1·00
	0·25	920 ± 29	6·13	130 ± 12	0·87
	1·25	5000 ± 104	33·4	260 ± 14	1·73
	5·25	20,500 ± 812	137	500 ± 17	3·33
Heart force ..	0	152 ± 14	1·00	89 ± 8	1·00
	0·25	1380 ± 61	9·06	110 ± 10	1·23
	1·25	7000 ± 104	47·0	180 ± 12	2·02
	5·25	28,800 ± 916	189	270 ± 17	3·03
Vasodilator ..	0	36 ± 4	1·00	36 ± 6	1·00
	0·25	520 ± 21	14·5	81 ± 6	2·25
	1·25	6150 ± 219	172	148 ± 14	4·11
	5·25	∞	∞	285 ± 12	7·92

ratio for (±)-propranolol at 0·25 mg/kg was twice that of (+)-propranolol at 5·25 mg/kg. Allowing for a 25-fold difference in dose-level, it could be said that (+)-propranolol was about 50 times less active than (±)-propranolol. However, the dose-response curves were not parallel and the validity of this conclusion is dubious.

Since the highest dose of (+)-propranolol altered the characteristic of the blood pressure response to isoprenaline, it was possible that the apparent degree of β-blockade resulted from the initiation of a reflex bradycardia via the vagal nerves. Accordingly the experiments were repeated in vagotomized dogs, the results being summarized in Table 2. Under these conditions (+)-propranolol did not significantly reduce the positive chronotropic or inotropic actions of isoprenaline but did significantly diminish the vasodilator responses. The results for (±)-propranolol were not significantly different in dogs with intact or sectioned vagi. From these experiments it was concluded that (+)-propranolol was devoid of cardiac β-blocking actions at the dose-levels tested.

Table 2. *A comparison of the doses of isoprenaline necessary to produce 50% of the maximum response in heart rate and heart force before and after various doses of (±)-propranolol and its (+)-isomer in vagotomized dogs*

Function	Dose (mg/kg)	(±)-Propranolol: Isoprenaline for 50% max. (ng/kg)	(±)-Propranolol: Dose ratio	(+)-Propranolol: Isoprenaline for 50% max. (ng/kg)	(+)-Propranolol: Dose ratio
Heart rate ..	0	100 ± 16	1·00	185 ± 17	1·00
	0·25	670 ± 21	6·70	198 ± 21	1·07
	1·25	3200 ± 161	32·0	244 ± 41	1·32
	5·25	15,800 ± 914	158	215 ± 31	1·16
Heart force ..	0	105 ± 46	1·00	142 ± 21	1·00
	0·25	721 ± 60	6·87	131 ± 18	0·92
	1·25	4000 ± 120	38·0	157 ± 20	1·10
	5·25	17,500 ± 600	166	160 ± 41	1·13

The effects of (±)-propranolol and its (+)-isomer on haemodynamic function are summarized in Table 3. Mean control values are given for 8 dogs together with percentage changes from control for the 4 dogs receiving each drug. Since the β-blocking potency of the (+)-isomer is virtually negligible and the local anaesthetic potency of both isomers is equivalent, the difference between the results obtained with (±)-propranolol and (+)-propranolol may be considered to approximate to the effect of β-blockade *per se*. These differences are also given in Table 3.

Table 3. *Haemodynamic effects of (±)-propranolol and (+)-propranolol in anaesthetized dogs*

Parameter	Control value (n = 8)	Dose (mg/kg)	(±)-Propranolol (n = 4)	P	(+)-Propranolol (n = 4)	P	Diff. (±)—(+)	P
Heart rate (bt/min)	167 ± 15	0·25	−23 ± 2·7	0·001	−2 ± 0·8	0·05	−21 ± 2·9	0·001
		1·25	−30 ± 3·1	0·001	−8 ± 1·0	0·001	−22 ± 3·3	0·001
		5·25	−37 ± 4·2	0·001	−20 ± 2·5	0·001	−17 ± 3·9	0·01
PR Interval (ms)	88 ± 4	0·25	+9 ± 3·0	0·05	+3 ± 1·6	N.S.	+6 ± 3·4	N.S.
		1·25	+11 ± 3·2	0·05	+9 ± 1·1	0·001	+2 ± 3·4	N.S.
		5·25	+23 ± 6·4	0·05	+39 ± 4·2	0·001	−'6 ± 7·6	N.S.
Cardiac contractile force (% control)	100 ± 0	0·25	−18 ± 3·9	0·01	−6 ± 2·5	N.S.	−12 ± 4·6	0·05
		1·25	−26 ± 4·0	0·001	−15 ± 5·5	0·05	−11 ± 6·8	N.S.
		5·25	−44 ± 3·3	0·001	−32 ± 8·0	0·01	−12 ± 8·7	N.S.
Aortic flow (ml/min)	1610 ± 340	0·25	−20 ± 2·3	0·001	−1 ± 1·8	N.S.	−19 ± 3·0	0·001
		1·25	−34 ± 2·3	0·001	−11 ± 3·1	0·05	−23 ± 3·9	0·01
		5·25	−56 ± 9·0	0·001	−34 ± 7·6	0·01	−22 ± 11·6	N.S.
Carotid blood press. (mean) (mm Hg)	115 ± 9	0·25	−7 ± 3·5	N.S.	+7 ± 3·0	N.S.	−14 ± 4·6	0·05
		1·25	−10 ± 2·3	0·01	+5 ± 4·0	N.S.	−15 ± 4·6	0·05
		5·25	−23 ± 10·5	N.S.	−14 ± 13·2	N.S.	−9 ± 16·8	N.S.
Total peripheral res. (units)	84·8 ± 12	0·25	+17 ± 3·0	0·01	+8 ± 2·4	0·05	+9 ± 3·8	N.S.
		1·25	+37 ± 5·4	0·01	+20 ± 4·0	0·01	+17 ± 6·7	0·05
		5·25	+87 ± 22	0·01	+30 ± 5·8	0·01	+57 ± 22·7	0·05
Stroke volume (ml)	8·2 ± 1·3	0·25	+4 ± 4·4	N.S.	+3 ± 2·8	N.S.	+1 ± 5·2	N.S.
		1·25	−7 ± 2·0	0·05	+2 ± 3·6	N.S.	−9 ± 4·1	N.S.
		5·25	−28 ± 11·4	0·05	−16 ± 9·0	N.S.	−12 ± 14·5	N.S.
Ejection time (ms)	143 ± 15	0·25	+11·0 ± 2·2	0·01	+2·5 ± 2·5	N.S.	+8·5 ± 3·3	0·05
		1·25	+13·5 ± 3·1	0·01	+4·5 ± 2·5	N.S.	+9·0 ± 4·0	N.S.
		5·25	+18·1 ± 3·3	0·01	+19·2 ± 2·0	0·001	−1·1 ± 3·8	N.S.
Ejection rate (ml/s)	70·8 ± 12·1	0·25	−6·7 ± 1·5	0·01	+2·2 ± 2·4	N.S.	+8·9 ± 2·8	0·05
		1·25	−17·7 ± 2·8	0·001	−3·0 ± 3·0	N.S.	+14·7 ± 4·1	0·02
		5·25	−38·2 ± 12·2	0·02	−29·3 ± 8·0	0·01	+8·9 ± 14·4	N.S.
Tension time index (mm Hg sec/min)	2968 ± 225	0·25	−14·8 ± 4·2	0·02	+6·2 ± 4·0	N.S.	+21·0 ± 5·7	0·02
		1·25	−22·1 ± 7·1	0·05	−0·9 ± 2·0	N.S.	+21·2 ± 8·1	0·05
		5·25	−38·3 ± 6·0	0·001	−17·2 ± 6·2	0·05	+21·1 ± 8·6	0·05

Heart rate

Both racemic and (+)-propranolol produced a dose-dependent bradycardia the effect of the former being much greater at equivalent dose levels. The arithmetic difference between the two sets of results was remarkably constant at about 20% and was statistically significant at all 3 doses. This suggests that β-blockade was already complete at 0·25 mg/kg of propranolol and that the greater bradycardia at higher doses resulted from some other action.

Conduction

As judged by effects on the PR interval of the electrocardiogram both drugs significantly increased conduction time between atria and ventricles. At no dose level was the arithmetic difference between the two sets of results statistically significant. However, since 0·25 mg/kg of (±)-propranolol produced a significant effect whereas the same dose of (+)-propranolol did not, the results suggest that conduction time is affected by both β-blockade and local anaesthetic effects. It was interesting to note that the top dose of (+)-propranolol had a greater effect than that of (±)-propranolol (though the difference was not significant) which may reflect the slightly greater potency of the isomer over the racemate in tests *in vitro* for local anaesthetic action (Barrett & Cullum, 1968).

Myocardial contractility

At 0·25 mg/kg (±)-propranolol significantly depressed contractility as reflected by measurements from a strain-gauge arch. Ejection rate, which may be considered as an indirect index of contractility was also significantly depressed. The same dose (0·25 mg/kg) of (+)-propranolol did not exert a significant effect. Higher doses of both drugs produced a progressive reduction of both the direct and indirect indices of contractility. The arithmetic difference between both drugs' responses was again consistent.

Aortic flow

(+)-Propranolol had a significantly smaller depressant action than (±)-propranolol on aortic flow. Again, the difference between the two drugs' action was constant at equivalent dosage. The aortic flow is equivalent to cardiac output minus that fraction going to the coronary vessels which may possibly rise at lower cardiac rates owing to an ncrease in the duration of diastole.

Blood pressure

Mean blood pressure tended to fall with (±)-propranolol but the effects were small and variable and not of statistical significance. The effects of (+)-propranolol were even less pronounced.

Total peripheral resistance

Since there was a marked fall in cardiac output without much change in mean blood pressure there was a marked rise in calculated peripheral resistance. In the case of (±)-propranolol the increase was proportionately greater than the drop in output. The arithmetic differences were not constant and showed a dose-dependent increase even after allowing for the effects of the local anaesthetic properties.

Stroke volume and ejection time

(+)-Propranolol had no effect on stroke volume whilst higher doses of (±)-propranolol depressed it. Ejection time increased significantly at all dose levels of (±)-propranolol but only at the highest dose of (+)-propranolol.

Myocardial oxygen consumption

No direct measurements of oxygen consumption by the heart were made in this study but it has been shown that oxygen consumption is proportional to the area under the systolic portion of the left ventricular pressure curve (Sarnoff, Braunwald & others, 1958). Calculation of the tension time index (pressure time/min) according to the method of Sarnoff & others (1958) showed that this function decreased in a dose-dependent fashion with (±)-propranolol. The changes correlated well with the changes in myocardial contractility. Only at the highest dose level (5·25 mg/kg) was there any decrease with (+)-propranolol. The arithmetic differences between the effects of the two drugs were again constant, being statistically significant at all doses.

The overall effects of (±)-propranolol (0·25 mg/kg) and (+)-propranolol (1·25 mg/kg) have been presented in histogram form in Fig. 1. The doses selected correspond

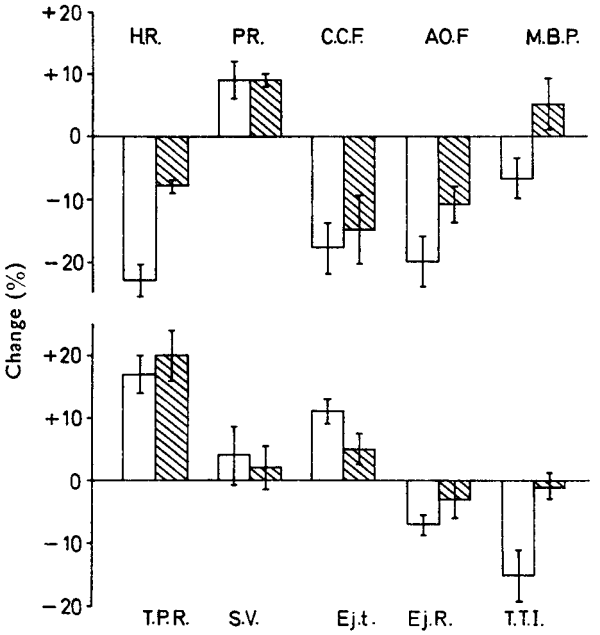

FIG. 1. Haemodynamic effects of (±)-propranolol (0·25 mg/kg) open columns and (+)-propranolol (1·25 mg/kg) hatched columns in anaesthetized dogs. Each bar represents the mean percentage difference from control values for 4 dogs. The vertical lines indicate the standard error of the means: H.R. = heart rate, C.C.F. = Cardiac contractile force, PR. = PR Interval of ECG AO.F = Aortic Flow, M.B.P. = Mean blood pressure, T.P.R. = total peripheral resistance, S.V. = stroke volume, Ej.t. = ejection time, Ej.R. = ejection rate, T.T.I. = tension time index.

approximately to the maximum doses likely to be used clinically on the basis of equivalent effects on conduction. After 1·25 mg/kg i.v.,(+)-propranolol produced a statistically significant lowering of heart rate, cardiac contractile force and aortic flow. The atrio-ventricular conduction time was significantly raised as was total peripheral resistance. Mean blood pressure, stroke volume, ejection time, ejection rate and tension time index were not significantly altered. In contrast (±)-propranolol, at 1/5th the dose, reduced heart rate significantly more than (+)-propranolol, raised ejection time and diminished ejection rate and tension time index. At 0·25 mg/kg (±)-propranolol raised the dose-ratio for isoprenaline to 6·13 ± 0·7 compared to

1·73 ± 0·7 (means ± s.e.; n = 4) for (+)-propranolol at 1·25 mg/kg. In vagotomized dogs the respective values were 6·7 ± 1·1 and 1·32 ± 0·3.

DISCUSSION

The functional capacity of the myocardium depends mainly on its intrinsic contractile properties but it is also re-inforced by the sympathetic outflow. Competitive inhibition of the sympathetic component by a specific adrenergic β-receptor antagonist will therefore automatically reduce both cardiac rate and contractile force. Whilst abolising the responsiveness of the myocardium to β-receptor agonists, the ability of the heart to respond to calcium, digitalis or xanthine derivatives is not impaired by β-receptor blockade. In contrast, drugs which produce a non-specific depression of the myocardium e.g. barbiturates or local anaesthetics, reduce sensitivity to all forms of cardiac stimulation. (±)-Propranolol possesses both specific β-receptor blocking and local anaesthetic properties. It is not possible to say therefore whether its effects are solely due to β-blockade or to a combination of both actions. Since (+)-propranolol has been shown to be devoid of significant β-blocking properties comparison of the two drugs at equivalent doses permits an evaluation of the two effects as they are equipotent as local anaesthetics. The results strongly support the view that (±)-propranolol at doses up to 0·25 mg/kg produces all its effects by means of β-receptor blockade since an equal dose of (+)-propranolol had no effect on haemodynamics apart from a minor rise in total peripheral resistance. For the effects on heart rate, cardiac contractile force, aortic flow and tension time index the arithmetic difference between the responses to (±)-propranolol and (+)-propranolol were remarkably constant which suggested that complete β-blockade of endogenous sympathetic activity was achieved with the lowest dose of (±)-propranolol (0·25 mg/kg). The additional effects at higher dose levels were therefore presumably due to the non-specific depressant actions of the compounds. Under certain clinical conditions these non-specific effects may be of therapeutic benefit particularly when the myocardium is sensitized to arrhythmogenic influences. The advantage of (+)-propranolol in this context is that it would not be expected to deprive the heart of sympathetic drive.

There are two important implications from these results. First, the observed anti-arrhythmic effects of (±)-propranolol in the clinic (usually at doses of 1–5 mg per 70 kg patient) are almost certainly due to β-blockade and not to any "quinidine-like" action. This is supported by the positive anti-arrhythmic actions of I.C.I. 50,172* which has no local anaesthetic properties whilst being an effective β-receptor antagonist (Gibson, Balcon & Sowton, 1968; Barrett, Crowther & others, 1968). Second, it may be noted that since (+)-propranolol had little effect on myocardial oxygen consumption as shown by estimates of tension time index it would not be anticipated that this isomer would relieve anginal pain due to oxygen deficit.

* 4(2-Hydroxy-3-isopropylaminopropoxy)acetanilide

REFERENCES

BARRETT, A. M., CROWTHER, A. F., DUNLOP, D., SHANKS, R. G. & SMITH, L. H. (1968), *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.*, **259**, 152–153.

BARRETT, A. M. & CULLUM, V. A. (1968). *Br. J. Pharmac.*, **34**, 43–55.

BATH, J. C. L. (1966). *Am. J. Cardiol.*, **18**, 415–25.

GIBSON, D. G., BALCON, R. & SOWTON, E. (1968). *Brit. med. J.*, **3**, 161–163.

HORSFALL, G. B. (1965), *J. Physiol. Lond.*, **180**, IP.

SARNOFF, S. J., BRAUNWALD, E., WELCH, G. H., CASE, R. B., STAINSBY, W. N. & MACRUZ, R. (1958). *Am. J. Physiol.*, **192**, 148–156.