Blockade of cardiac and renal beta-receptors by low dose propranolol in normal subjects

Clues to its antihypertensive effect

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SUMMARY We studied the effects of oral propranolol administered in 2 low dose schedules (5 or 20 mg 8 hourly) and for a short term (30 to 36 hours) on heart rate, plasma renin activity, and arterial pressure, both at rest and after an isoprenaline challenge (8 mg i.v. over 2 min) in 6 normal subjects. Resting heart rate, plasma renin activity, and systolic pressure all fell significantly after the 5 mg dose and only small additional falls were observed when the dose was increased to 20 mg. The fall of diastolic pressure was not significant with 5 mg, but was significant with 20 mg. That beta-blockade occurred with these low doses was confirmed by diminished responses to isoprenaline. The isoprenaline-induced changes of heart rate, plasma renin activity, and diastolic pressure were reduced by 77, 80, and 65 per cent, respectively, by the 5 mg dose of propranolol, and by 89, 94, and 87 per cent by the 20 mg dose, suggesting that cardiac and renal receptors are equally sensitive to propranolol.

These data indicate a rapid blood pressure lowering action of low dose propranolol in normal subjects and suggest that this effect is in part at least a consequence of blockade of renal and/or cardiac beta-receptors. Our results also raise the possibility that much lower doses of propranolol than generally used may be clinically effective.

Despite the widespread use of beta-blockers in the treatment of hypertension, the exact mechanism by which they lower arterial pressure remains obscure. Some have argued that their action is attributable to the blockade of beta-receptors in the heart (Frohlich *et al.*, 1968; Pritchard, 1970) or in the kidneys (Bühler *et al.*, 1972; Casterfors *et al.*, 1973), while others have suggested that their action in hypertension results from effects not directly caused by beta-blockade, such as baroreceptor resetting (Pritchard and Gillam, 1969) or an action on the central nervous system (Offerhaus and Van Zweiten, 1974; Myers *et al.*, 1975). In support of the last two views are studies that indicate delay in the onset of the hypertensive relative to the beta-blocking effects (Pritchard, 1970) and studies suggesting that the hypotensive effect is only seen at doses considerably greater than those required to block peripheral beta-

receptors (Zacharias, 1969; Michelakis and McAllister, 1972). There is very little information as to whether administration of propranolol can lower blood pressure in normotensive individuals, though recent reports have indicated that it may (Le Winter *et al.*, 1975; Miller *et al.*, 1975). In this present study we have administered propranolol in low doses and for a short term to normal subjects, to examine the effects of blockade of peripheral beta-receptors on arterial pressure, and have assessed the degree of beta-blockade by a standardised isoprenaline test (Davies *et al.*, 1977).

Subjects and methods

Six normal subjects who gave their informed consent participated. They were aged 26 to 35 years, were in good physical health, and on no medication. They were studied supine on 4 occasions at approximately the same time in the afternoon; the order in which the first 3 studies were conducted was randomised, while in each subject in a fourth study resting heart

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rate and arterial pressure only were determined. At least 7 days elapsed between studies. The basic procedure was similar for each study; the subjects lay supine in a quiet environment; a slow intravenous infusion of 0.9 per cent saline was established in a left arm vein to facilitate blood sampling and the infusion of isoprenaline. The subjects rested for 30 minutes with the infusion *in situ*; during the last 5 to 10 minutes heart rate and sphygmomanometrically measured arterial pressure were determined at 1 to 2 minute intervals until a steady baseline was established. Korotkoff sounds I and IV were used to determine systolic and diastolic pressures, respectively, and the same mercury sphygmomanometer was used throughout. All measurements of heart rate and arterial pressure were made by the laboratory nurse who was unaware of the dosing sequence. A control sample for plasma renin activity was taken and then an infusion of 8 μ g isoprenaline diluted in 10 ml saline was administered slowly by hand over 2 minutes. Heart rate and arterial pressure were determined at 1 minute intervals for 6 minutes and at 2 to 3 minute intervals for a further 15 minutes. Further samples for plasma renin activity were taken 5, 10, 15, and 20 minutes after the beginning of the isoprenaline infusion. In the studies with propranolol, either 5 or 20 mg was administered beginning at 7 to 8 a.m. of the day before study; medication was taken 8-hourly for a total of 5 doses, the last dose being taken some 90 minutes before study. A 24-hourly urine collection was made from noon of the day before study until noon of the study day.

Plasma renin activity was determined as previously described (Sealey and Laragh, 1975) and urinary sodium was determined by flame photometry.

DETERMINATION OF RESTING HEART RATE AND BLOOD PRESSURE

The means of at least 4 determinations of heart rate, systolic and diastolic pressure observed in the first control study were used to determine the resting values. The values so obtained were then compared with similar values obtained in the fourth study. If these mean values differed by more than 4 beats/min or by more than 4 mmHg, then the mean of the mean values so determined was used in subsequent calculations.

STATISTICS

Results are expressed as mean $\pm$ SEM and are analysed by Student's *t* test for paired data, each subject providing his own control basal and isoprenaline response data. The percentage reduction of the isoprenaline response is calculated by com-

paring the responses of heart rate and plasma renin activity on propranolol with that subject's control response.

Results

Neither propranolol nor isoprenaline resulted in any untoward effect in any subject. In the control study the subjects experienced mild palpitation and throbbing of the trunk, symptoms which were diminished considerably by both doses of propranolol.

EFFECT OF PROPRANOLOL ON BASAL VALUES (Fig.)

The mean control systolic pressure of 120 ± 6.5 mmHg was significantly ($t = 7.01$, $P < 0.001$) reduced to 114 ± 6 mmHg by the 5 mg dose, and to 109 ± 7 mmHg by the 20 mg dose ($t = 3.42$, $P < 0.01$). The decrease of diastolic pressure from 71.5 ± 2 mmHg to 67 ± 4 mmHg with the 5 mg dose was not significant, but the fall to 61.5 mmHg with the 20 mg dose ($t = 4.24$, $P < 0.01$) was significant. Heart rate fell from 72.0 ± 1.5 beats/min to 61 ± 1.5 beats/min with the 5 mg dose ($t = 9.83$, $P < 0.001$) and to 58 ± 3.5 with 20 mg ($t = 4.17$, $P < 0.01$). Plasma renin activity fell from 3.1 ± 0.7^1 μ g/h per l to 1.8 ± 0.4 μ g/h per l with the 5 mg dose ($t = 2.17$, $P < 0.05$) and to 1.6 ± 0.7 μ g/h per l with the 20 mg dose ($t = 5.42$, $P < 0.001$). Urinary sodium excretion and serum potassium were unaffected by propranolol.

EFFECTS OF PROPRANOLOL ON RESPONSE TO ISOPRENALINE

In the control study, the mean increase in heart rate after isoprenaline was 43 ± 5 beats/min; after propranolol the mean increase was only 10 ± 2 beats/min for the 5 mg dose and 4.5 ± 1 beats/min for the 20 mg dose (5 mg and 20 mg vs control, $t = 6.47$ and 6.63 , respectively, $P < 0.001$ for each, 5 mg vs. 20 mg, $t = 2.69$, $P < 0.025$). The mean increase in plasma renin activity in the control study was 3.6 ± 1 μ g/h per l. This fell to 0.7 ± 0.1 μ g/h per l after the 5 mg dose ($t = 3.03$, $P < 0.025$) and to 0.2 ± 0.01 μ g/h per l after the 20 mg dose (control vs. 20 mg, $t = 3.61$, $P < 0.01$). The response after the 20 mg dose was significantly less than that after 5 mg ($t = 6.5$, $P < 0.001$). The mean isoprenaline-induced fall of diastolic pressure was 24 ± 4 mmHg in the control study; this was significantly attenuated to 8.5 ± 2 mmHg ($t = 3.1$, $P < 0.025$) by the 5 mg dose of propranolol, and further to 3 ± 1 mmHg by the 20 mg dose. The

¹ 1 μ g/h per l $\approx$ 0.77 nmol/h per l.

Fig. Effect of propranolol on resting heart rate (HR), blood pressure (BP), and plasma renin activity (PRA) (a, control; b, propranolol 5 mg; c, propranolol 20 mg). Note that the major fall in heart rate and plasma renin activity occurred with the 5 mg dose.

mean percentage reduction of the isoprenaline-induced changes of heart rate and plasma renin activity observed with the doses of propranolol employed amount to 77 ± 6 per cent and 89 ± 4 per cent, respectively, for heart rate (5 vs. 20, $t = 2.19$, $P < 0.05$) and to 80 ± 6 per cent and 94 ± 1 per cent, respectively for plasma renin activity (5 vs. 20, $t = 9$, $P < 0.025$). The corresponding values for the blockade of diastolic pressure were 65 ± 11 per cent and 87 ± 4 per cent, respectively.

Discussion

This study describes some interesting, heretofore unrecognised, effects of low dose propranolol in normal subjects. Of particular interest is the effect of propranolol in a dose of only 5 mg 8-hourly (15 mg daily) in lowering both resting heart rate and plasma renin activity. Indeed, when the dose was increased fourfold to 20 mg 8-hourly (60 mg daily), only small additional falls in these variables were observed, suggesting that large, and possibly near maximal, blockade of resting heart rate and plasma renin activity can be obtained at very low doses of propranolol. This possibility is strengthened by the observation that 75 per cent or more of the isoprenaline-induced changes of heart rate and plasma renin activity are blocked by this dose. Consonant with this finding is the study of Leonetti *et al.* (1975) who treated patients with hypertension with propranolol in increasing doses from 40 to 160 mg daily. They found that near maximal falls of resting heart rate and of plasma renin activity were achieved

at the 40 mg/day dose, which was the lowest dose they studied, there being relatively small additional falls when the dose of propranolol was increased stepwise to 160 mg daily. A further point of interest is the effect of propranolol on arterial pressure, a change that followed closely those of heart rate and plasma renin activity. Thus, systolic pressure fell by 6 mmHg on the lower dose and 11 mmHg on the higher, and similarly diastolic pressure fell on both doses. Our results, therefore, show that propranolol given in low doses can lower arterial pressure in normal subjects, and that this effect occurs within 36 hours.

A potential criticism of our study is that the small falls of arterial pressure that we have observed might be the result of a placebo effect or of observer bias. However, the order in which the studies were conducted was randomised to minimise these effects and the nurse-observer was unaware of the dosing sequence. Furthermore, the basal values of heart rate and arterial pressure were checked in the fourth study when no drugs were administered and no blood drawn. Indeed the extent of the falls of these variables with these doses was quite unexpected, and the effects on resting plasma renin activity and on the isoprenaline responses are unlikely to be susceptible to placebo effects or to observer bias. Furthermore, other workers have reported falls of arterial pressure in normal subjects. Thus, Le Winter *et al.* (1975) found a small but significant fall in arterial pressure after the administration of propranolol (160 mg daily for 2 weeks) to normal young subjects, and Miller *et al.* (1975) found that blood pressure fell significantly in normotensive patients who were receiving propranolol for angina

pectoris. In the context of these earlier studies, our results extend this observation to a lower dose level.

To what extent does this study clarify our understanding of the mechanisms by which propranolol lowers arterial pressure? By using very small doses of propranolol administered short term, it can be assumed that the site of action is limited to peripheral beta-receptors, since it is generally agreed that such blood pressure lowering effect as propranolol may have, due to a central action, is seen with relatively large doses (Hollifield *et al.*, 1975). In common with Leonetti *et al.* (1975) we have observed striking reductions of heart rate and plasma renin activity after doses of propranolol far below those required to exert an effect on the central nervous system (Offerhaus and Van Zweiten, 1974; Hollifield *et al.*, 1975). Moreover, in the present study these effects were accompanied by a small but significant fall of arterial pressure, and it seems probable that this is also a consequence of peripheral beta-blockade. Two possible mechanisms have been proposed to explain this blood pressure lowering effect: first, by blockade of cardiac receptors, reducing heart rate and cardiac output, and secondly, by blockade of renal receptors reducing plasma renin activity. The blood pressure lowering effect of propranolol has been attributed to a reduction of cardiac output by a number of groups (Ulrych *et al.*, 1968; Johnsson *et al.*, 1969; Pritchard *et al.*, 1970; Sannerstedt *et al.*, 1970), though more recently the Cleveland group, who were the main proponents of this view, have found that the antihypertensive response was predictable neither by control measurements of cardiac function nor by changes in cardiac function induced by propranolol therapy (Tarazi and Dustan, 1972). The alternative view, that propranolol's antihypertensive effect is mediated by its renin-lowering action, was first suggested by Bühler *et al.* (1972). While this view has been supported by several studies (Casterfors *et al.*, 1973; Hansson and Zweifler, 1974), it has been contested by others (Birkenhäger *et al.*, 1971; Stokes *et al.*, 1974; Bravo *et al.*, 1975). An argument that has figured prominently in opposing the view that propranolol can lower blood pressure by its renin-lowering action is the apparent temporal dissociation between the fall of plasma renin activity, which occurs early, and the fall of arterial pressure, which some workers have suggested is delayed (Frohlich *et al.*, 1968; Pritchard, 1970). Manifestly this is not necessarily the case, as has been shown in this and other studies (Ulrych *et al.*, 1972; Leonetti *et al.*, 1975; Fitzgerald, 1976; Stumpe *et al.*, 1976; Taylor *et al.*, 1976). Similarly, the view held by some workers (Pritchard and Gillam, 1969; Zacharias, 1969; Michelakis and McAllister, 1972)

that a higher dose of propranolol is required for the antihypertensive effect compared with the renin-lowering effect, which has also been used as evidence against these effects being related, is not supported by our study or by that of Leonetti *et al.* (1975). While this present study in no way excludes a second influence at high doses, it does define a close association between the blood pressure lowering effect of propranolol and peripheral beta-blockade. The relative contributions of the effects on cardiac and renal receptors require further dissection.

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