SHORT COMMUNICATION

THE EFFECT IN MAN OF (+)-PROPRANOLOL AND RACEMIC PROPRANOLOL ON RENIN SECRETION STIMULATED BY ORTHOSTATIC STRESS

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SUMMARY

1. The time-course of the rise in plasma renin activity (PRA) in response to an acute postural stimulus was demonstrated in four normal subjects over 90 min.
2. The ability of racemic propranolol to inhibit this rise was confirmed.
3. This inhibition is shown to be due to antagonism of beta-adrenergic receptors rather than to the membrane-stabilizing properties of racemic propranolol.

Key words: plasma renin activity, renin secretion, propranolol, (+)-propranolol, orthostatic stress, posture, beta-adrenergic blockade.

Renin secretion is enhanced by stimulation of the sympathetic nervous system, as seen in haemorrhage, the upright posture and renal nerve stimulation; it is also enhanced by infusion of catecholamines (Vander, 1967). Propranolol has been shown to reduce renin secretion following sympathetic stimuli in man (Winer, Chokshi, Yoon & Freedman, 1969) and dogs (Assaykeen, Clayton, Goldfien & Ganong, 1970). This effect of the drug is attributed to its beta-adrenergic antagonist action. However, propranolol which is available for ordinary therapeutic purposes, is a racemic mixture of (+)- and (-)-propranolol, and has membrane stabilizing (local anaesthetic) properties in addition to its beta-blocking effect. The individual isomers have approximately equal membrane-stabilizing potency, but the (+) form (R absolute configuration, Dukes & Smith, 1971) has only 1–2% of the beta-adrenergic antagonist potency of the (−) form (Barrett & Cullum, 1968). Further, Winer, Chokshi & Walkenhorst (1971) reported that the (+) and (−) isomers are equally effective in blocking isoprenaline-induced renin secretion in dogs.

To find out if the action of propranolol on renin secretion is due to its beta-adrenergic blocking properties, plasma renin activities (PRA) were measured in subjects submitted to orthostatic stress, preceded on separate occasions by racemic propranolol or (+)-propranolol.

A summary of the material of this paper has already appeared (Tobert, Slater, Fogelman, Lightman, Kurtz & Payne, 1972).

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MATERIALS AND METHODS

Subjects
The subjects were five healthy male paid volunteers, aged 17–22. Their informed consent and the approval of the hospital clinical investigation panel were obtained. All volunteers were subjected to a trial experiment with orthostatic stress preceded by an intravenous injection of 0.13 mg of racemic propranolol/kg given over 10 min, with electrocardiogram (ECG) and respiratory peak-flow monitoring. Several potential subjects experienced pre-syncopal symptoms and had to be rejected. No ECG abnormalities or significant bronchoconstriction were produced.

Experimental procedure
Experiments were started between 15.00 and 17.00 hours. Subjects were asked to avoid caffeine-containing beverages for at least 4 h before the experiment. The subjects were recumbent for 60–90 min and then stood leaning against a wall for 90 min, with the exception of one subject, P.B., who developed pre-syncopal symptoms on the first (dummy) experiment and was permitted to stand free from the wall. At 15 min before standing up, subjects were given an intravenous infusion, lasting 10 min, of 10 ml of 0.15 M-NaCl or 0.13 mg of (+)-propranolol/kg or racemic propranolol ('Inderal', ICI). Blood samples for renin estimation were drawn by venepuncture 20 min and 2 min before standing and at 15-min intervals after standing for 90 min. Approximately 100 ml were drawn off in each experiment. Arterial blood pressure was measured by sphygmomanometer and expressed as mean blood pressure (diastolic+one-third pulse pressure), and heart rate was counted by the radial pulse at 30 and 15 min before standing, and at 10, 20, 35, 50, 65, 80 and 91 min after standing.

Three experiments were performed on each subject, preceded by a dummy experiment to familiarize the subjects with the procedure and reduce their anxiety. In the dummy experiment saline was given and the procedure was the same as in the actual experiment except that the samples were not assayed for renin. The subjects then received, on separate occasions, (+)-propranolol or racemic propranolol in random order and finally a control experiment with 0.15 M-NaCl; they were unaware of the nature of individual infusions. There was an interval of at least 3 days between successive experiments on a given subject.

Assay methods
The blood samples were placed immediately in EDTA-containing tubes in melting ice, the cells separated off by centrifugation, and 50 µl aliquots of plasma assayed for renin activity using a labelled antibody to angiotensin I (Kurtz, 1971). Racemic propranolol, added to samples of plasma to give a concentration several times higher than could possibly be attained in our subjects' plasma, did not affect the assay results.

RESULTS
In one subject (T.C.), plasma renin activity failed to rise in the control experiment and therefore he could not be used to ascertain the effect of the drugs.

Heart rates for the remaining four subjects were: supine 70±2 (mean±SEM of the average in each subject of the values at 30 and 15 min before standing, n = 12); erect—control, 87±3; after (+)-propranolol, 89±3; after racemic propranolol, 72±3 (mean±SEM of the average
of the seven values from 10 to 91 min after standing, \( n = 4 \). Racemic propranolol thus significantly reduced the pulse increment on standing \( t (\text{paired}) = 6.1, P < 0.01 \). Mean blood pressures, calculated in the same way were: supine 88 ± 3 mmHg; erect—control, 89 ± 3; after

\( (+)-\text{propranolol}, 90 ± 4; \) after racemic propranolol, 84 ± 4. These differences are not significant.

Fig. 1 shows the plasma renin activities of the four subjects plotted against time (min). Drug or saline infused −15 to −5 min, erect posture assumed at time zero. Saline, ○; \( (+)-\text{propranolol}, \triangle; \) racemic propranolol, □.
highest values by 45 min, thereafter declining. Racemic propranolol decreased PRA in all four subjects, whereas (+)-propranolol had no consistent effect. The effects of the drugs were expressed for each subject as

\[ \int_{0}^{90} PRA \, dt \text{(drug)} / \int_{0}^{90} PRA \, dt \text{(saline)} \]

For (+)-propranolol the mean value for the ratio was 1.04±0.12 (SEM) and for racemic propranolol it was 0.47±0.09. The latter value was significantly less than unity \((t = 6.1, 3 \text{ degrees of freedom}, P<0.01)\) and also significantly less than the value for (+)-propranolol \((t = 3.9, 6 \text{ degrees of freedom}, P<0.01)\).

**DISCUSSION**

*Renin response without drug*

It is well known that assumption of the upright posture increases the plasma renin concentration (Vander, 1967). The increased PRA has been assumed to be due to a greater rate of renin secretion, but decreased renin clearance may be a contributory factor. Also, the haemoconcentration that occurs when erect probably increases PRA by a few %. Renin is metabolized mainly, if not completely, by the liver and the hepatic extraction ratio is not altered by severe haemorrhage in dogs (Schneider, Johnson, Davis & Baumber, 1971) or 80° tilt in hypertensive man (Kokot, Kuska & Czekala, 1968). Thus the decrease in renin clearance should be proportional to the decrease in hepatic blood flow. Data on the effect of orthostatic stress on this parameter is sparse, but it appears that hepatic blood flow decreases appreciably only if circulatory embarrassment is severe (Culbertson, Wilkins, Ingelfinger & Bradley, 1951; Parr, 1957). These reports and the magnitude of the observed increases in PRA lead us to conclude that these increases are predominantly due to increased renin secretion.

*Renin response with drug*

Increased clearance is an unlikely cause of the lower PRA following racemic propranolol administration, since this drug diminishes cardiac output in man in both supine and 45° head-up tilt position (Sannerstedt, Julius & Conway, 1970); and, following moderate haemorrhage in the dog a (sympathetic stimulus comparable to orthostatic stress), propranolol caused no significant change in hepatic blood flow (Zeig, Buckley & Macy, 1968). Thus propranolol probably acts by inhibiting renin secretion, and this inhibition should correspond closely with the decrease in PRA shown in Fig. 1. It is possible that complete inhibition could be achieved with higher doses of the drug, since the dose used (the maximum clinically recommended intravenous dose), though sufficient to cause considerable decrease in the pulse increment on standing, was probably insufficient for complete beta-adrenergic blockade (Coltart & Shand, 1970; Michelakis & McAllister, 1972).

(+)-Propranolol, which has negligible beta-blocking properties but membrane-stabilizing potency equal to that of the (−)-propranolol isomer, was ineffective in blocking the rise in plasma renin activity. We conclude, therefore, that the action of racemic propranolol is dependent on the beta-adrenergic antagonist action of the (−) isomer. This suggests that
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a major component of the rise in PRA during orthostasis is mediated by beta-adrenergic receptors.

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REFERENCES


