Preliminary studies of Ro 3-3528, a β-adrenoceptor blocking agent, in man

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Ro 3-3528 is a non-selective competitive β-adrenoceptor blocking drug (Haefely, Hürlimann & Thoenen, 1967; Hill & Turner, 1968). This communication compares its effect with that of propranolol and of placebo on inhibition of exercise tachycardia in man, using maximal and submaximal blocking doses orally, and single submaximal blocking doses intravenously. After oral administration, plasma concentrations of propranolol over 40 ng/ml (Coltart & Shand, 1970) and of Ro 3-3528 over 240 ng/ml, in our preliminary studies, were associated with maximal β-adrenoceptor blockade. Absorption was variable and oral doses were adjusted in each subject to produce comparable peak plasma concentrations of both drugs.

In the definitive studies, heart-rate after 4 min maximal exercise on a bicycle ergometer was measured electrocardiographically and blood was obtained for spectrophotofluorimetric estimation of propranolol (Shand, Nuckolls & Oates, 1970) and of Ro 3-3528 (Hicks, unpublished) at intervals after drug administration. Drugs were given weekly in random, balanced designs under double-blind conditions, by oral and intravenous routes.

In this and other kinetic studies the half-life of propranolol was 3·07 h (S.D. ±0·64) orally and 2·76 h (S.D. ±0·54) intravenously, of Ro 3-3528 2·31 h (S.D. ±0·35) orally and 2·42 h (S.D. ±0·33) intravenously. Both drugs produced significant dose dependent inhibition of exercise tachycardia (Fig. 1). Using a multivariate analysis (Cherrington & Smart, 1971) significant regression of change in heart rate (CHR) compared with

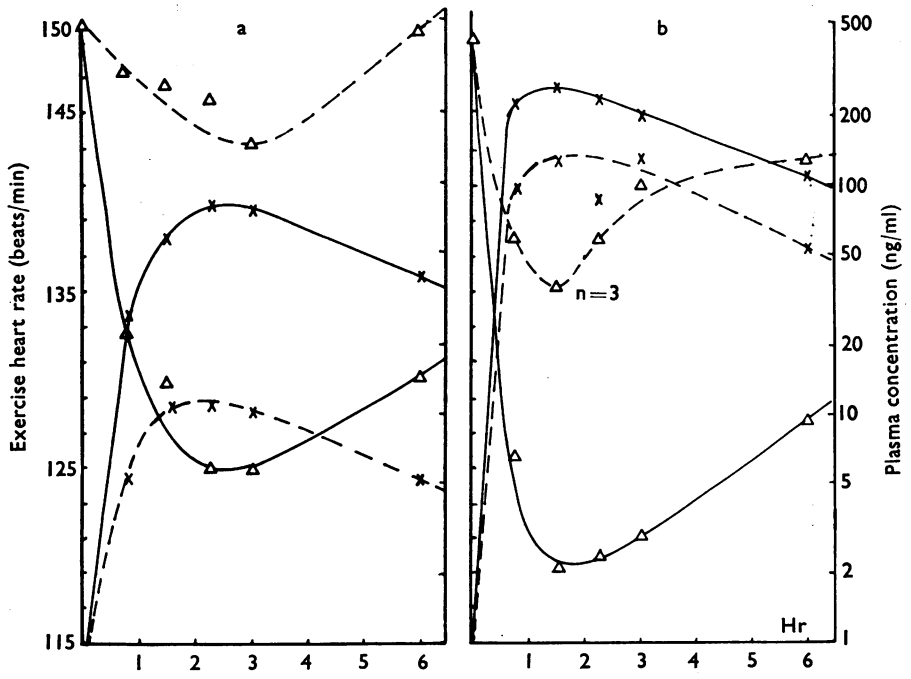

FIG. 1. Mean log plasma concentrations (×) and exercise heart rate (△) in normal volunteers after high (——) and low (- - -) doses of (a) propranolol (n=5) and (b) Ro 3-3528 (n=5) orally.

placebo both on the log plasma concentration of each drug and on time was shown. Adjustment for regression on time showed a residual significant regression of CHR on the log plasma concentration of both drugs in the oral but not in the intravenous study. Forty-five minutes after low oral doses, the slope of regression of CHR on the log plasma concentration (b) for propranolol was not significantly different from that for Ro 3-3528, with a dose ratio of 1 : 3·5 to 6, and common slope b=26·6, indicating that a 10-fold rise in plasma concentration after oral administration produced a mean fall in heart-rate after exercise of 26·6 beats/minute.

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α-Adrenoceptor inhibition from indoramin in man

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Indoramin, Wy 21901, 3-[2-(4-benzamidopiperid-1-yl)ethyl] indole hydrochloride was found to have a potent hypotensive action with α-adrenoceptor blocking properties in animals. It also had cardioinhibitory local anaesthetic and antihistaminic actions (Alps, Hill, Johnson & Wilson, 1970). The present study concerns our initial observations in man.

Blood pressure was recorded with the London School of Hygiene sphygmomanometer (Rose, Holland & Crowley, 1964) and heart rate by an electrocardiogram. In the first group of studies indoramin was given intravenously (0·12 mg/kg over 5 min) to normal volunteers, and its effect on supine blood pressure and pulse rate after head up to 80° tilt, and after graded exercise were studied. The tachycardia in response to Valsalva's manoeuvre, maintaining a pressure of 40 mmHg for 20 s, was recorded. α-Adrenoceptor blockade was investigated by studying the effect on the rise of blood pressure induced by phenylephrine infusions.

There was little effect on the supine blood pressure from indoramin. The average mean blood pressure (diastolic plus 1/3 pulse pressure) in the 80° tilt position was 76 mmHg before, 63 mmHg after indoramin, there was a considerable postural drop in blood pressure in two of the three subjects, those who showed sustained serum indoramin concentrations (see below). In all three subjects there was an increase in the tachycardia associated with tilting to 80° (average 94 beats/min before, 118 beats/min after indoramin) and also in the tachycardia induced by Valsalva's manoeuvre (average 122 beats/min before, 141 beats/min after indoramin). Phenylephrine infusions (50 μg/min) were commenced 15 min after indoramin and logarithmic