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

increments were given at the end of 7 min infusion at each dose level. Indoramin produced approximately 2-fold decrease in sensitivity to phenylephrine. Plasma indoramin concentrations were similar in all three subjects 3 min after the end of drug injection. Samples at 30 min, during the phenylephrine infusions, showed one subject had concentrations (7 ng/ml) less than half that seen in the other two (15 and 17 ng/ml) in spite of similar inhibition of the pressor response to phenylephrine. However, at 70 min after drug administration the subject with lower serum concentrations (3 ng/ml at 60 min, 4 ng/ml at 100 min) showed no postural drop in blood pressure or exercise hypotension. The other two subjects at this time still showed marked postural hypotension and fall in diastolic pressure on exercise (serum indoramin, 18 and 11 ng/ml at 60 min, 11 and 8 ng/ml at 110 min).

In duration of action studies after oral indoramin (50 mg), the effect of the response to posture, exercise and infusions was studied. Control supine mean blood pressure was 76 mmHg; it fell to 71 mmHg and by 6 h had returned to 74 mmHg. Before indoramin there was a rise of mean blood pressure of 4 mm on tilting to 80°, post exercise mean blood pressure was 70 mmHg and noradrenaline (8 μg/min) produced rise in mean pressure to 98 mmHg. After drug administration on tilting the mean blood pressure fell by 16 mmHg, the post-exercise mean blood pressure fell to 34 mmHg and the rise after noradrenaline was reduced to 85 mmHg. Maximum effects, which coincided with each other, were seen 2–3 h after drug administration and responses returned to control values by about 6 hours.

It is concluded that indoramin is an effective α-adrenoceptor blocking drug in man and that it inhibits cardiovascular responses in a way that is characteristic of sympathetic inhibition to blood vessels (Prichard 1969). It might be expected that this will be reflected in hypertensives treated with indoramin; this is being investigated.

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Initial clinical experience with indoramin, a new antihypertensive agent

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Indoramin, 3-(2-(4-benzamidopiperid-1-yl)ethyl)indole hydrochloride, is a new antihypertensive agent which in animals combines both competitive α-adrenoceptor blocking and cardioinhibitory properties (Alps, Johnson & Wilson, 1970). Studies in human volunteers confirmed its competitive α-adrenoceptor blocking action, together with a potent antihistamine effect (Coltart, Lockhart, Royds & Turner, 1971).

Preliminary investigations in patients were undertaken. It was established in volunteers that 25 mg of indoramin was a suitable starting dose, and that, at this dose, there was no evidence of drug accumulation.