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.

Five patients were admitted to hospital for two consecutive days, after routine pretreatment investigation. The object of the study was fully explained to them. Fluid and food intake were controlled and the patients were rested for 1 h before blood pressure and pulse rate were recorded in the supine and in the erect position after standing for 2 minutes. Blood pressure was measured with a London School of Hygiene sphygmomanometer (Rose, Holland & Crowley, 1964). The readings were repeated at half hourly intervals for 7 hours. Placebo was administered on the first, and indoramin (25 mg) on the second day. When compared with placebo, indoramin produced small falls in supine and erect blood pressures over 6 h with no effect on pulse rate. In a further patient, of 104 kg body weight, indoramin (0·5 mg/kg) produced a marked fall in supine and erect systolic and diastolic blood pressure without a commensurate increase in pulse rate, the fall in the supine systolic blood pressure being of the order of 50 mmHg, and 70 mmHg in the erect systolic pressure.

Six patients have taken indoramin for 6–24 weeks as outpatients and adequate control of their blood pressure has been achieved with divided doses of 90–210 mg daily. In one patient the addition of bendrofluazide to his treatment regime, and later its discontinuance, appeared to make little difference to the blood pressure. However, in another patient bendrofluazide enhanced the antihypertensive effect of indoramin.

All patients complained of nasal stuffiness and a dry mouth. Two of six male patients have experienced failure of ejaculation. No evidence of adverse haematological or biochemical effects have been observed.

From initial clinical experience, indoramin would appear to be an effective antihypertensive agent in man, and further trials in larger numbers of hypertensive patients seem to be justified.

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Computer-assisted prescribing of kanamycin for patients with renal insufficiency (T)

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