PRELIMINARY EVALUATION OF PINACIDIL IN HYPERTENSION

L.E. RAMSAY & S. FREESTONE

University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF

In a balanced single-blind placebo controlled study in six hypertensive patients treated with diuretic and β -adrenoceptor blocker, a single oral dose of 10 mg pinacidil lowered blood pressure significantly, by a maximum of 26/13 mm Hg lying and 15/12 mm Hg standing at 3 h. The duration of action was less than 6 h. Chronic treatment of four patients (mean dose 20 mg twice daily for 3–7 weeks) lowered blood pressure by only 15/7 mm Hg. All four patients experienced side-effects of the type often observed during treatment with potent vasodilators. In the formulation studied pinacidil is unlikely to offer any advantage over the antihypertensive drugs currently available.

Keywords pinacidil hypertension vasodilator

Introduction

In animal studies pinacidil (*N''*-cyano-*N*-4-pyridyl-*N'*-1,2,2-trimethyl-propylguanidine, monohydrate) has a hypotensive action due primarily to direct relaxation of vascular smooth muscle, with a potency greater than that of hydralazine (Arrigoni-Martelli *et al.*, 1980). In an uncontrolled study in untreated hypertensive patients a single oral dose of 25 mg pinacidil caused a substantial fall in blood pressure, accompanied by reduced total peripheral resistance, tachycardia and increased cardiac output (Carlsen *et al.*, 1981). The aims of the present study were to confirm the acute hypotensive action of pinacidil in a placebo controlled study, and to obtain preliminary information on chronic treatment with pinacidil.

Methods

Patients

We studied six patients with essential hypertension who had diastolic blood pressures consistently above 90 mm Hg (phase 5) while taking a β -adrenoceptor blocker (atenolol 100 mg) and diuretic (bendroflumazide 5 mg). These drugs were continued through the study. There were four women and two men with a mean age of 54 years (range 46–61); mean weight 63.6 kg (range 51–76); mean ($\pm$ s.e. mean) blood pressure, on β -adrenoceptor blocker and diuretic, of $174 \pm 11/101 \pm 5$ mm Hg lying and $155 \pm 12/97 \pm 6$ mm Hg standing; and all had normal renal function. The patients gave written informed consent to the study which was approved by the hospital ethics committee.

Single dose study

Patients were treated with pinacidil 10 mg orally, and with a matching placebo tablet, on consecutive days while recumbent at 09.00 h. The order of treatments was balanced between patients, and patients were unaware of which treatment was given. Blood pressure and pulse rate were measured by a Dinamap semi-automated recorder (Silas *et al.*, 1980) before treatment and at frequent intervals over the next 12 h. From 0–3 h after treatment patients remained recumbent and only lying blood pressure and pulse measurements were made. Between 3–12 h patients were ambulant, and measurements were made after lying down for 5 min, then immediately after standing. The results were analysed by the Friedman two-way analysis of variance (Siegel, 1956).

Chronic treatment

In four patients placebo pinacidil, one tablet twice daily, was added to the diuretic and β -adrenoceptor blocker, and blood pressure was then measured at three clinic visits over a 4 week period. Active pinacidil was then substituted for placebo at an initial dose of 10 mg twice daily and titrated up to a maximum dose of 30 mg twice daily, aiming to lower the recumbent diastolic blood pressure below 90 mm Hg. The duration of pinacidil treatment was limited to 7 weeks. Clinic blood pressures were the mean of three readings, measured by a trained nurse using a Hawkesley random-zero sphygmomanometer (phase 5 diastolic). The interval between the morning dose

of tablets and clinic measurements was relatively constant for each patient, but varied from 2–6 h between patients. Compliance with treatment was monitored by tablet counts and all returns were within $\pm 5\%$ of the correct values. The following tests were performed at 2 weeks and 1 day before treatment with pinacidil, and after 3 days, 2 weeks, 5 weeks and 7 weeks of pinacidil treatment; serum urea, creatinine, electrolytes, glucose, urate and liver function tests; full blood count; urine chemistry, microscopy and culture; and electrocardiogram. Chest X-ray and antinuclear factor were performed at entry to the study and on completion.

Results

Single dose study

Blood pressures were similar immediately before placebo treatment (155/91 mm Hg lying, 147/92 mm Hg standing) and pinacidil treatment (154/90 mm Hg lying, 149/96 mm Hg standing). Oral pinacidil, 10 mg, reduced blood pressure within 30 min, with a return to placebo values after 6 h (Figure 1). The differences from placebo over the 6 h period were significant for lying systolic ($P < 0.05$), lying diastolic ($P < 0.02$) and standing diastolic ($P < 0.05$) blood pressures, but not for the standing systolic pressure. The maximum hypotensive effect of pinacidil, observed at 3 h, was (mean $\pm$ s.e. mean) $25.8 \pm 10.9/13.0 \pm 5.6$ mm Hg lying, and $14.8 \pm 9.1/12.3 \pm 3.6$ mm Hg standing. A trend for the pulse rate to increase after pinacidil (Figure 1) was not significantly different from placebo in the overall analysis of variance, but it was significant at a few individual time points (lying pulse at 3 h, $+5.2 \pm 1.9$ beats/min, $P < 0.05$; at 4 h $+5.2 \pm 1.4$ beats/min, $P < 0.02$; standing pulse at 4 h, $+4.5 \pm 1.5$ beats/min, $P < 0.05$).

Chronic treatment

Three of four patients had side-effects while taking pinacidil 20 mg twice daily, leading to discontinuation of the drug in one patient and dose reduction in the other two. The fourth patient had side-effects with pinacidil 30 mg twice daily. The side-effects reported were headache (3), depression (2), postural dizziness (2), oedema (1), palpitations (1), facial flushing (1), tiredness (1) and nasal congestion (1). At the final dose (mean 20 mg twice daily, range 10 mg–30 mg twice daily) the reduction in lying blood pressure from placebo run-in values averaged $15.3/7.3$ mm Hg, from $156 \pm 13/100 \pm 4$ mm Hg to $141 \pm 11/93 \pm 4$ mm Hg. The individual falls in blood pressure were; 26/10 on 30 mg twice daily, 8/1 on 10 mg twice daily, 8/8 on 20 mg twice daily, and 19/10 on 20 mg twice daily.

Figure 1 Changes in blood pressure and pulse from placebo values after pinacidil 10 mg orally at time 0. Mean, vertical bars s.e. mean, results for six patients. ● = lying values, ○ = standing values. Significance of differences from placebo by Friedman two-way analysis of variance: lying: systolic, $\chi^2_8 = 16.2$, $P < 0.05$; diastolic, $\chi^2_8 = 18.9$, $P < 0.02$; pulse $\chi^2_8 = 10.3$, $P < 0.1$; standing: systolic, $\chi^2_3 = 5.0$, $P < 0.1$; diastolic, $\chi^2_3 = 8.9$, $P < 0.05$; pulse, $\chi^2_3 = 5.6$, $P < 0.1$.

Body weight increased by a mean of 0.5 kg. Measurements of biochemistry, haematology and urinalysis showed no abnormality. Serial electrocardiograms showed deep T wave inversion in one patient, similar to that observed frequently during minoxidil treatment (Hall *et al.*, 1980).

Discussion

This placebo controlled study confirms the acute hypotensive effect of pinacidil reported by Carlsen *et al.* (1981), with a single oral dose of 10 mg lowering blood pressure by 26/13 mm Hg lying and 15/12 mm Hg standing 3 h after treatment. The effect was short-

lived and was no longer evident 6 h after treatment. There was a small but significant increase in pulse rate, as would be expected with a vasodilator acting predominantly on precapillary resistance vessels. This was observed despite background treatment with a β -adrenoceptor blocker. Our experience of chronic treatment is limited, but it does not support the suggestion that pinacidil is remarkably free from side-effects (Carlsen *et al.*, 1981). All four patients experienced side-effects of the type expected with a potent vasodilator, and in three they were troublesome enough to limit treatment. Again this was despite background treatment with a β -adrenoceptor blocker. The chronic hypotensive effect of pinacidil (15/7 mm Hg, with an average dose of 20 mg twice daily) was smaller than might have been predicted from the single dose results. Twice daily dosing may have been

inappropriate in view of the short duration of action (Figure 1), or the hypotensive effect may have been blunted by false tolerance, i.e. by expansion of the plasma and extracellular fluid volumes during pinacidil treatment (Ramsay *et al.*, 1980). The development of overt oedema in one patient despite treatment with a thiazide diuretic supports the latter suggestion.

The study was terminated because of the short duration of action and the side-effects encountered with pinacidil. In its present formulation pinacidil is unlikely to prove a satisfactory antihypertensive drug, but a sustained release formulation might warrant further evaluation.

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