The effects of long-acting pinacidil on intra-arterial blood pressure

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We have tested the efficacy of a new long-acting preparation of pinacidil, an arterial vasodilator, using continuous intra-arterial ambulatory blood pressure recording. An acute dose produced a measurable effect lasting for 12 h. The duration of this effect was less during chronic twice daily drug administration. Side effects were common, causing two out of nine patients to withdraw from the study. Tilt testing produced no postural hypotension and there was no evidence of rebound hypertension on the withdrawal day.

Keywords long-acting pinacidil hypertension intra-arterial blood pressure tilt test side effects

Introduction

Pinacidil (cyanoguanidine) is an anti-hypertensive arterial vasodilator. In single dose studies, it has been shown to reduce arterial blood pressure (BP) and total peripheral resistance, and to increase cardiac output and stroke volume (Carlsen *et al.*, 1981, 1983). A single-blind study of the effects of pinacidil in hypertension revealed typical vasodilator side effects whilst the BP reduction lasted less than 6 h (Ramsay & Freestone, 1983).

A slow-release formulation of pinacidil was developed in the hope of overcoming these side effects and increasing the duration of action. The present study was designed to examine the duration of action and the useful dose-range of the new formulation, which consists of acrylic-coated pellets, half of which release pinacidil freely, whilst the other half release pinacidil only at a pH greater than 7.

Methods

Patients

Patients were recruited from the hypertension clinic at Northwick Park Hospital. They had a

mean supine diastolic BP of 100–129 mm Hg (phase V), having received no drugs for 1 month.

Methodology

There were two 48 h periods of intra-arterial BP recording, separated by 4 to 6 weeks' dose titration of pinacidil. During the first 24 h the patients were untreated, then a single dose of either 37.5 mg or 25 mg (see **Results**) of pinacidil was administered orally and the BP was recorded for a further 24 h.

Oral pinacidil was then started at a dose of 25 mg twice daily increasing by 12.5 mg twice daily every 2 weeks until a maximum dose of 50 mg twice daily was reached, or BP control was achieved (cuff diastolic BP of less than 90 mm Hg, or a fall in diastolic BP of more than 15 mm Hg). After 2 weeks' maintenance treatment, intra-arterial BP recording was repeated.

During the first 24 h of this second recording, the patients continued to take the pinacidil; the drug was then stopped for the second 24 h, to examine the possibility of rebound hypertension.

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Figure 1 Plot of 24 h BP and heart rate responses to chronic pinacidil treatment. Results are mean $\pm$ s.e. mean for seven patients. $\bullet$ = untreated values, $\circ$ = treated values. *** = $P < 0.001$, ** = $P < 0.01$, * = $P < 0.05$.

Three patients ended the study taking the maximum dose of pinacidil of 50 mg twice daily, one taking 37.5 mg, twice daily, and three taking 25 mg twice daily.

There were no changes in the blood count, liver function tests or urinalysis during the study.

Discussion

This study confirms the antihypertensive efficacy of the long-acting formulation of

pinacidil. At the dose of 37.5 mg, side effects were common and severe enough to preclude this as a starting dose. At the dose of 25 mg, the drug was well tolerated acutely and produced a measurable effect on BP lasting for up to 12 h. The intermittent loss of BP control during twice-daily chronic drug treatment suggested that the acute effect was not fully maintained during chronic therapy, raising the possibility of tachyphylaxis.

During chronic drug administration side effects were frequent, causing withdrawal of two

patients from the study who were taking the lowest dose. This suggests that the side effects were not dose related. These observations on the frequency of side effects, and the shorter duration of action after chronic administration correspond very closely to those of Ramsay & Freestone (1983) and Ward (1984) in their studies with the original pinacidil formulation.

Pinacidil appears to produce a tachycardia, particularly at night. Tachycardia in response to arterial vasodilation is thought to be a consequence of baroreceptor stimulation by falling BP (Koch-Weser, 1976) but if this is true, the maximum heart rate response should be seen during the day when the BP reduction is maximal.

It may be that the heart rate response is obscured by the increased rate due to daytime physical activity. This suggestion seems to be inconsistent with the linear correlation described by Carlsen *et al.* (1981) between mean BP reduction and heart rate increase.

Long-acting pinacidil appears to be a safe and effective drug, but the duration of action is insufficient to allow twice daily administration and to maintain 24 h BP reduction.

The frequency and nature of side effects suggest that the drug may be tolerated better if used with a diuretic, a combination which might also produce a more uniform reduction of BP over the whole 24 h.

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