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Haemodynamic and humoral effects of oral perindopril, an angiotensin converting enzyme inhibitor, in man

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1 The tolerance to and dynamic effects of 1 week's oral treatment with the angiotensin converting enzyme inhibitor, perindopril, were assessed in a placebo controlled, parallel group study in 36 normotensive males. The daily dose of perindopril was 1, 2, 4, 8 or 16 mg.
2 The drug was well tolerated and produced no change in routine haematology or serum biochemistry tests.
3 Dose related inhibition of plasma angiotensin converting enzyme was observed. Perindopril 16 mg produced 90% inhibition 4 h after dosing and 60% after 24 h.
4 A dose related rise in plasma renin activity followed doses of 4 mg and over. The renin remained above the normal range for 24 h.
5 Perindopril caused a modest lowering of plasma aldosterone levels but had no effect on plasma adrenaline or noradrenaline levels.
6 Standing diastolic blood pressure was lowered, particularly with 16 mg daily of perindopril but only a slight rise in heart rate occurred.
7 Perindopril appears to be a well tolerated inhibitor of plasma angiotensin converting enzyme, with predictable effects on the renin angiotensin system and blood pressure. An appropriate dose range for further study would appear to be 4 to 16 mg daily.

Keywords perindopril blood pressure heart rate angiotensin converting enzyme inhibitor renin-aldosterone

Introduction

Perindopril is a new orally active inhibitor of angiotensin converting enzyme. It has a nonthiol structure (Figure 1) and although it is itself relatively inactive, it is rapidly hydrolysed *in vivo* to the active diacid metabolite S-9780. This compound is a potent and long-lasting inhibitor of angiotensin converting enzyme in animals (Laubie *et al.*, 1984) and in preliminary single dose studies in man (Institut de Recherches Internationales Servier: personal communication). This paper describes a study of the tolerance and dynamic effects of oral perindopril for 7 days in healthy normotensive volunteers. Part of the work included in the paper was presented to the British Pharmacological Society in Dundee in September 1984 (Lees & Reid, 1985b); part has also been presented to the Medical Research Society (Lees & Reid, 1985a).

Methods

Subjects

Thirty-six male volunteers were recruited from the staff of Stobhill General Hospital. They were screened prior to entry by history, general examination, urinalysis, electrocardiograph and

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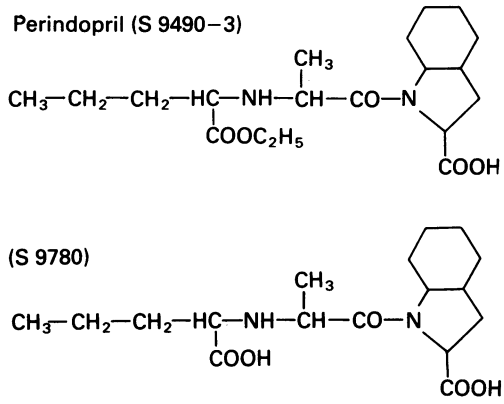

Figure 1 Chemical structure of perindopril and of its active diacid metabolite, S-9780.

routine laboratory tests of haematology and serum biochemistry to ensure good health. Two further volunteers were rejected, one because of mild iron deficiency and the other because he was found to have Gilbert's disease. Written, informed consent was obtained from all subjects and the study design was approved by the local Ethics Review Committee. The mean age of the volunteers was 25 years (range 18–35), their mean weight was 72 kg (range 59–92) and their mean height was 176 cm (range 162–188). There was no statistical difference between the subgroups. No salt restriction was imposed and although salt status was not measured on this occasion subsequent experience with a group of these subjects showed 24 h urinary sodium excretion to be 226 mmol (range 124–406, $n = 8$) and 24 h urinary potassium excretion to be 82 mmol (range 10–141, $n = 8$).

Study design

This was an open dose ranging study in six parallel groups; blocked randomisation of 12 subjects to either placebo or 8 mg or perindopril was carried out, however, and these subjects were studied in double-blind fashion. The other doses studied were 1, 2, 4 and 16 mg. Each dose was administered for 7 consecutive days to six subjects.

The subjects arrived at the Clinical Pharmacology Research Unit at 08.30 h on the first study day. They had fasted since 22.00 h on the previous night and had avoided all drugs for the previous 2 weeks. No smoking, caffeine or alcohol ingestion was permitted during the study. An indwelling venous cannula was inserted into an antecubital vein and the subjects rested supine until the start of the study. Blood pressure and heart rate were measured in duplicate by Sentron semiautomatic sphygmomanometer (Bard Biomedical) after 10 min supine rest and 5 min standing before dosing and at the following intervals after dosing: 1, 2, 4, 6, 8, 10, 12 and 24 h. Blood samples were drawn for plasma angiotensin converting enzyme activity at the same times that blood pressure was measured. Samples were also collected for plasma renin activity, aldosterone, adrenaline and noradrenaline levels, predosing and after 4, 8 and 24 h. Capsules containing the appropriate dose of drug or placebo were administered orally with 200 ml of water at 09.00 h and the subjects remained fasting for a further 2 h. A light standard meal was provided after 4 h and 8 h. Free fluids were permitted after 4 h and after this time the volunteers were no longer restricted to bed between recordings. On the 2nd to 6th days of dosing the volunteers were reviewed and the drug was administered at 09.00 h. On the 7th day of treatment the protocol for the first day was repeated exactly.

The subjects were questioned about any symptoms at each recording time, and the prestudy screening investigations were repeated both during the week of the study and after completion.

Laboratory methods

(1) *Plasma angiotensin converting enzyme activity* Plasma angiotensin converting activity was assayed by measuring the rate of generation of hippuric acid in an incubation mixture containing plasma and hippuryl-histidyl-leucine (Cushman & Cheung, 1971). Hippuric acid was measured by high pressure liquid chromatography as described by Chiknas (1979). Inter and intra assay coefficients of variation were 6.1% and 2.3% respectively and the limit of detection was 0.5 eu l^{-1}. Samples were assayed within four weeks of collection. The normal range for the laboratory was 15.3 to 26.9 eu l^{-1} (95% confidence interval).

(2) *Plasma renin activity* Plasma renin activity was determined by a specific radioimmunoassay of angiotensin I formed upon cleavage by renin of its substrate angiotensinogen (Derkx *et al.*, 1979). The limit of detection of the assay was 1 ngAI ml^{-1} h^{-1} and the inter and intra assay variations were 7% and 5.5% respectively.

(3) *Plasma aldosterone* Plasma aldosterone concentrations were measured by a direct radio-

immunoassay using the method of McKenzie *et al.* (1974). The limit of the assay was 10 pg ml^{-1} and the inter and intra assay coefficients of variation were 11% and 7.3% respectively.

(4) *Plasma catecholamines* Adrenaline and noradrenaline concentrations in plasma were determined by a radioenzymatic assay based on the method of da Prada & Zurcher (1976). The method is dependent upon the determination of the methylation of the catecholamines with tritiated S-adenosyl methionine by the action of purified catechol-*o*-methyltransferase. The limit of detection for noradrenaline was 0.1 nmol l^{-1} and for adrenaline was 0.03 nmol l^{-1}. The inter and intra assay variations were respectively 15% and 13% for noradrenaline and 20% and 15% for adrenaline.

Statistical analysis

Repeated measures analysis of variance or co-variance was undertaken to compare with placebo the effects of the different doses on the haemodynamic and humoral parameters. The pretreatment blood pressure and pretreatment aldosterone levels were taken as co-variates in order to limit the variation caused by examining parallel groups. Where appropriate, confidence intervals were constructed using Dunnet's *t*-statistic (1955) for the difference between treated groups and placebo, making allowance for the multiple comparisons. The plasma hormone data were transformed to logarithms before analysis to normalise the distribution.

Results

Tolerance

The drug was well tolerated by all subjects. Headache was frequently observed during both active treatment and placebo. Lightheadedness was noted with some intermediate doses but was not related to any postural fall in blood pressure. These symptoms were nearly all confined to the 1st and 7th days of treatment: the days of intensive recordings. One subject complained of impotence during treatment with 4 mg daily. This resolved on completion of the study. There was no change in the screening tests either during or after treatment in any subject.

Angiotensin converting enzyme activity

Perindopril inhibited plasma angiotensin converting enzyme in a dose related manner ($P < 0.001$; Figure 2). A daily dose of 16 mg produced over 90% inhibition 4 h after dosing, with more than 80% inhibition from 1 to 12 h after dosing on chronic once daily treatment. Even 24 h after dosing, approximately 60% inhibition persisted with 8 mg and 16 mg daily. An increase in inhibition on the 7th day compared with the first was only noted with 1 mg, 2 mg and 4 mg daily ($P < 0.001$).

Plasma renin activity

Perindopril (4 mg or more) raised plasma renin activity after the first dose ($P < 0.001$). A rise was also noted with 1 mg and 2 mg but the baseline renin was different in these two groups. All doses, 1 to 16 mg, caused a further rise in renin after 7 days of treatment (Figure 2). The area under the curve for plasma renin activity (after logarithmic transformation) clearly shows a dose related increase (Figure 3). After 7 days of treatment 4 mg and over maintained the renin above the normal range (4–12 ngAI ml^{-1} h^{-1}) even 24 h after dosing.

Plasma aldosterone

The pretreatment aldosterone levels in several treatment groups differed from those in the placebo group. Correction for this difference was made initially by expressing the results as a percentage of the pretreatment level before analysis. The variation in the results obtained concealed any significant difference which may have been present (Lees & Reid, 1985a). Subsequent examination of the raw data by analysis of co-variance revealed a treatment effect ($P = 0.034$) and treatment-time interaction ($P = 0.01$). The aldosterone levels are displayed in Figure 2.

Plasma catecholamines

Perindopril had no effect on the plasma adrenaline or noradrenaline levels at the times of sampling ($P = 0.59$, $P = 0.99$ respectively).

Blood pressure

Standing diastolic blood pressure fell with active treatment ($P = 0.023$), particularly with 16 mg of perindopril. No significant change in supine diastolic pressure or in systolic blood pressure was detected. Supine heart rate was not altered by active treatment ($P = 0.13$), but a treatment-time interaction was present for standing heart rate ($P = 0.017$). Comparison of the heart rates at individual times after dosing reveals that perindopril 16 mg daily caused a significant rise

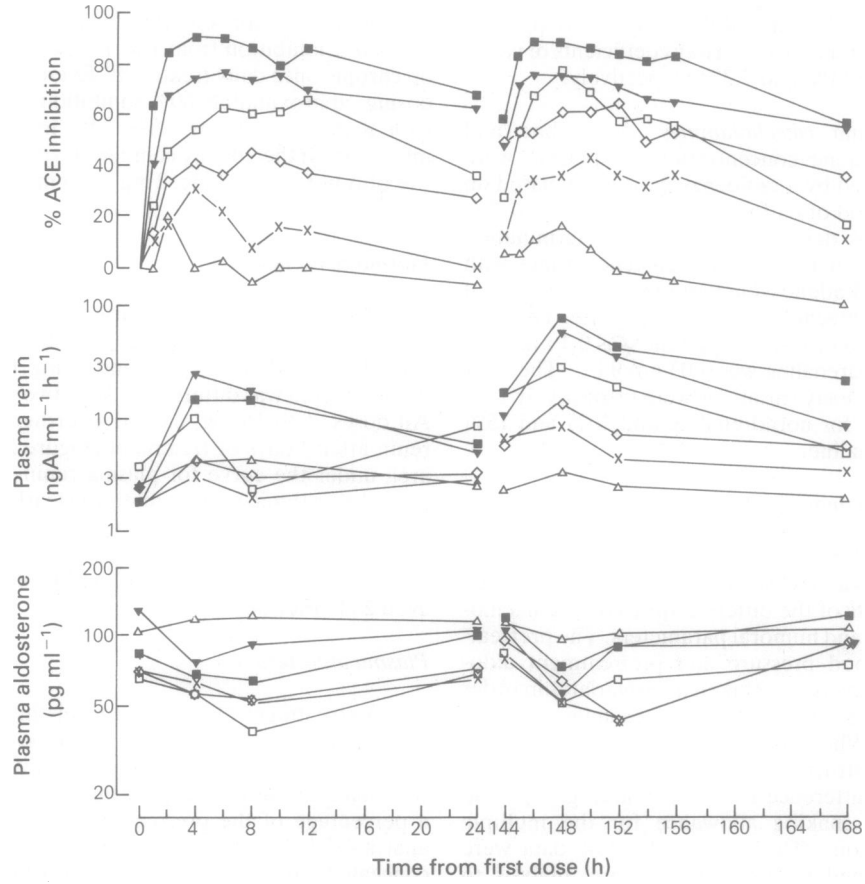

Figure 2 Plasma angiotensin converting enzyme inhibition, renin activity and aldosterone concentrations following the 1st and 7th daily administrations of placebo (△) and of 1 mg (x), 2 mg (◇), 4 mg (□), 8 mg (▼) and 16 mg (■) of perindopril orally. The effects were significant by analysis of variance: ACE inhibition ($P < 0.001$); renin activity ($P < 0.001$); and aldosterone ($P < 0.05$). Each point represents the mean for six subjects.

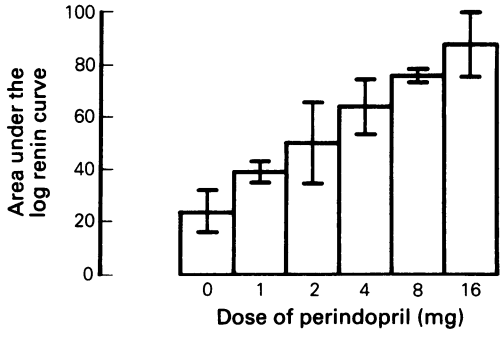

Figure 3 Areas under the curve for logarithm of plasma renin activity on the 7th day of treatment (mean ± s.d., $n = 6$). Units are given by h × log (ngAI ml^{-1} h^{-1}).

in heart rate only in one recording after 1 week's treatment. The standing blood pressure and heart rate data are displayed in Figure 4.

Discussion

The study design may seem a little unusual. Since only single dose studies in man had been performed it seemed appropriate to monitor closely the biochemical effects of repeated doses of perindopril in an open study design. Following these initial stages it was considered justifiable to embark on a placebo controlled stage and to extend the dose range studied.

Perindopril was well tolerated in doses of up to 16 mg daily for 7 days. The incidence of minor symptoms was similar in all groups including placebo. Although impotence occurred in one

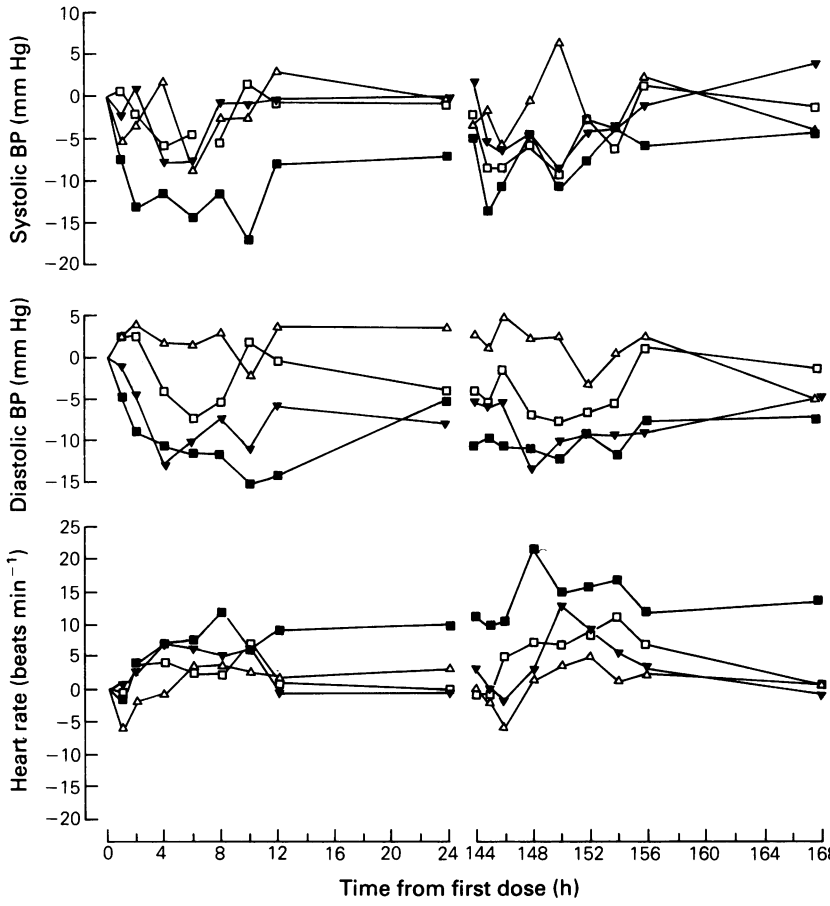

Figure 4 Standing blood pressure and heart rate following the 1st and 7th daily administrations of placebo (△) and 4 mg (□), 8 mg (▼) and 16 mg (■) of perindopril orally; the data for 1 mg and 2 mg are omitted for clarity. The effects on diastolic blood pressure were significant by analysis of variance ($P < 0.05$) but systolic pressure did not change ($P = 0.13$). A time-treatment interaction for heart rate was present ($P < 0.05$).

subject taking 4 mg this cannot with certainty be attributed to the drug. No untoward effect was found on routine physical examination or laboratory screening.

The effects of perindopril on plasma angiotensin converting enzyme were dose-dependent in the range studied. With 16 mg, peak exhibition of 90% was achieved and significant inhibition persisted, around 60%, 24 h after dosing with 8 mg or 16 mg. As would be expected plasma renin activity was elevated by active treatment. Doses of 4 mg and over caused the plasma renin activity to be maintained above the normal range.

Despite the profound elevation of plasma renin activity the reduction in the plasma aldosterone levels was modest and variable. The normal range for aldosterone is wide, however, and the parallel group design of the study made detection of changes in aldosterone relatively difficult.

Perindopril clearly lowered erect diastolic blood pressure. It may be difficult to demonstrate hypotensive activity in normal subjects, particularly when no salt restriction is imposed. Thus, the lack of change in supine pressure is not unexpected. Some increase in heart rate occurred after 7 days treatment at the highest dose. This is in contrast to the reported effects of other angiotensin converting enzyme inhibitors (Hatton *et al.*, 1981; Millar *et al.*, 1982; Niarchos *et al.*, 1982) and perindopril acutely (Ajayi *et al.*, 1986). We have no explanation at present for this increase which although statistically significant was small and not likely to be clinically relevant.

The absence of any effect of perindopril on circulating catecholamine levels is consistent with results after enalapril (Millar *et al.*, 1981).

The profile of angiotensin converting enzyme inhibition after perindopril is different to that seen after captopril (Richer *et al.*, 1984) and enalapril (Millar *et al.*, 1982): perindopril causes longer lasting inhibition for a given peak effect. Nevertheless, since enalapril is recognised to possess antihypertensive activity lasting for 24 h or more after a 10 mg oral dose, when about 40% angiotensin converting enzyme inhibition persists (Millar *et al.*, 1982), it appears reasonable to infer from our data with perindopril that a useful clinical dose will fall in the range 4–16 mg and that it is reasonable to evaluate this agent on the basis of once a day dosing.

In conclusion, perindopril appears to be a safe and well tolerated inhibitor of plasma angiotensin converting enzyme in man. The effects on the renin angiotensin system and blood pressure are predictable. Further studies in volunteers and hypertensive patients are justified.

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