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Dose finding studies with imidapril—a new ACE inhibitor

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1 We describe an approach involving a smaller, shorter study, leading onto a longer, larger study in which the antihypertensive effects of ascending doses of imidapril, a new ACE inhibitor, were investigated. Both studies were planned prospectively, assuming a clinically useful fall in BP to be 8 mm Hg (s.d. = 9). The studies included patients with mild to moderate essential hypertension (baseline sitting diastolic blood pressure (SDBP) 95–115 mm Hg). After a placebo run-in of 2–3 weeks patients received either placebo or imidapril 2.5, 5, 10 or 20 mg in the 2 week study (n = 91) or imidapril 5, 10, 20 or 40 mg in the 4 week study (n = 162).

2 The overall mean baseline SDBP was 103.4 mm Hg (s.d. 0.62) in the initial study and 101.5 mm Hg (s.d. 0.41) in the 4 week study.

3 Compared with placebo, imidapril 10, 20 and 40 mg significantly reduced SDBP. There was no significant difference between these doses, suggesting that 10 mg achieved maximal ACE inhibition in most patients. The 2.5 mg dose showed no significant effect. The 5 mg dose gave an intermediate effect. In both studies the overall incidence of adverse events was similar in the imidapril and placebo groups, and was not worrying.

Keywords essential hypertension ACE-inhibition dose-finding
24 h blood pressure control

Introduction

Angiotensin-converting enzyme (ACE) inhibitors are increasingly being viewed as potential first-line antihypertensive agents alongside more established drugs such as diuretics and β-adrenoceptor blockers [1].

Longstanding essential hypertension is characterised by a rise in total peripheral resistance associated with a normal or slightly reduced cardiac output [2, 3]. ACE inhibitors are known to produce vasodilatation predominantly by withdrawal of the vasoconstricting action of endogenous angiotensin II, although the possible involvement of the accumulation of vasodilator bradykinins cannot be excluded [4]. A number of clinical studies have shown that acute, and to a greater extent, chronic administration of ACE inhibitors result in an antihypertensive effect which is mediated almost exclusively through a reduction of total peripheral resistance [5]. Compared with other vasodilators, the antihypertensive effect of ACE inhibitors is characterized by several specific properties [6] and their effect is evident in mild to severe essential hypertension [7–12].

Imidapril is a new potent oral ACE inhibitor. It contains no sulphydryl group (thought to be responsible for some of the side-effects associated with the first ACE inhibitor captopril) and is a pro-drug that is converted by the liver to its pharmacologically active diacid metabolite, imidaprilat (Tanabe Pharma. Imidapril (TA-6366). Investigator's brochure). The ACE inhibiting activity and the effect on blood pressure of imidapril have been shown by pharmacological studies. Imidapril is as potent as, or slightly more potent than enalapril, but much more potent than captopril with a duration of action similar to that of enalapril.

Dose-finding of antihypertensive therapies has been difficult. We describe an approach involving a small, short study leading onto a larger, longer study in which the antihypertensive effects of different doses of imidapril were investigated. Specifically the objective of the two studies was to evaluate the antihypertensive action and safety of imidapril at various once-daily oral doses compared with placebo and to identify the minimum effective doses in patients with mild to moderate essential hypertension under controlled, double-blind study conditions.

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Acute and steady state 24 h blood pressure profiles, plasma ACE activity and drug concentrations were also evaluated.

Methods

Patient population

The two trials were designed as multicentre, randomized, placebo-controlled, double-blind studies.

Outpatients with mild to moderate uncomplicated essential hypertension (sitting diastolic blood pressure (DBP) ranging from 95–115 mm Hg), of any race and either sex were eligible for inclusion in the studies. In the initial, smaller study the age range was 30–70 years and in the second larger study 18–70 years. All patients were previously untreated or could be safely withdrawn from their current antihypertensive therapy. Patients with secondary, malignant or accelerated hypertension were therefore not eligible for study entry. Pre-existing cardiac disorders including heart failure, acute myocardial infarction within 6 months, ischaemic heart disease requiring medication and obstructive valvular heart disease were also grounds for exclusion. Other exclusion criteria were Grade III or IV hypertensive retinopathy, cerebrovascular disease, significant renal or hepatic disease, history of symptomatic orthostatic hypotension, insulin-dependent or poorly controlled diabetes mellitus and a history of autoimmune, collagen disease or major allergies. Drugs likely to affect blood pressure were prohibited. The study protocols were reviewed and approved by independent review boards prior to the start of treatment and the studies were undertaken in accordance with the principles of the Declaration of Helsinki.

Study design

Study 1 All previous antihypertensive therapy was discontinued at least 1 week before the entry visit to the placebo run-in period, which lasted 2–3 weeks. Patients with stable blood pressure readings (i.e. a variation of ± 10 mm Hg or less in sitting DBP at two consecutive weekly visits) within the range of 95 to 115 mm Hg were entered into the double-blind phase of the study on an out-patient basis. Patients were randomized to 2 weeks of treatment with placebo or with one of four doses of imidapril: 2.5, 5, 10 or 20 mg. Study medication was taken as one tablet once a day in the morning.

Patients were seen weekly during both the placebo period and the comparative treatment period. During these visits, blood pressure was measured in both the sitting and standing positions 24 h ± 2 after the last dose using a mercury in glass sphygmomanometer. Three blood pressure readings were taken in the sitting position over a period of 5 min after the patient had been resting for 10 min. A further measurement was taken in the standing position after 1 min. Supine and standing heart rates were also recorded.

Laboratory tests, chest X-ray, and a complete physical examination were performed prior to entry into the placebo period. An ECG was recorded at the second placebo visit and at the final study visit. Laboratory safety profiles were performed weekly through the double-blind period. At each visit during the study, vital signs, concomitant illnesses and medications and adverse events were recorded.

Study 1—Blood pressure profiles and ACE activity At the first and last visits of the comparison treatment period a 24 h blood pressure profile was performed. Patients were requested to take their dose of study medication in the clinic and to remain in-house on the study site for 10 h. During this time sitting and standing blood pressures were recorded at hourly intervals. Patients returned on the following day for a 24 h post-dose blood pressure reading. For the measurement of ACE inhibition and drug assay, blood samples were taken pre-dose and at 4, 8 and 24 h post-dose for ACE inhibition and at 4, 8 and 24 h post-dose for the drug assay.

Study 2 The protocol for Study 2 was essentially similar to that for Study 1. A standard mercury in glass sphygmomanometer was used for all BP determinations. Each BP measurement was taken from the same arm and at the same time of day as far as possible. Patients were not allowed to smoke, drink coffee or alcohol, take physical exercise or be exposed to cold for a minimum of 30 min prior to the readings being taken, and BP measurements were always performed before any blood sampling or ingestion of food.

Three measurements of BP were recorded after 10 min rest in the sitting position. The diastolic BP was taken at the disappearance of the audible pulse beat (Korotkoff Phase V). The arithmetical mean of these three measurements was used as the reference value. Standing BP was recorded once after 1 min in the standing position. In this study BP was measured 24 ± 3 h after the most recent drug intake as experience in study 1 had shown that patients had difficulty keeping to a regimen of 24 ± 2 h. Therefore patients were instructed not to take their medication before breakfast on visit days, but to wait until after the BP measurement.

The placebo baseline period lasted 2 weeks and the comparison treatment period, 4 weeks. Patients were randomized to treatment with placebo or imidapril 5, 10, 20 or 40 mg. Patients were seen weekly. During each visit, vital signs, concomitant illnesses and medication and adverse events were recorded. During the visit before randomisation a full physical examination, ECG laboratory profile and fundoscopy were performed. Laboratory profiles were again performed after 2, 4 and 6 weeks of treatment. In addition after 3 weeks of therapy creatinine and potassium determinations were obtained. An ECG was performed at the end of weeks 2 and 6 of the study as well as a physical examination.

Statistical analysis

The primary comparisons for efficacy between imidapril and placebo groups were performed using the 'intent to treat' data sets, i.e. including all patients who received at least one dose of active medication.

Quantitative characteristics at baseline were analyzed for comparability using a standard two-way (treatment × centre) analysis of variance technique. For qualitative parameters recorded at baseline, comparisons were made using the Chi-squared test.

For efficacy variables, the mean changes of blood pressure were compared between groups using a two-way analysis of variance. A Student-Newman-Keuls multiple comparison test was performed to identify groups of treatments that did not differ significantly from each other. For within group comparisons each group was analysed separately using the mean blood pressure values at each visit. The mean values at the first and last visits were compared using Dunnett's test.

The safety variables were compared between groups using a three-way analysis of variance (treatment × centre × time). The proportion of patients in each treatment group experiencing one or more adverse event in the comparative treatment period were compared using Fisher's Exact test.

Statistical significance was set at the 5% level. All analyses were made with the SAS statistical procedures within SAS 6.04 using a P.C. Network.

Results

Study 1—Patients

A total of 112 patients were recruited in seven centres. Ninety-one patients entered the randomized, comparative treatment phase. Of the 91 patients who were randomized, 17 patients were randomized to placebo, 18 to imidapril 2.5 mg, 19 to imidapril 5 mg, 19 to imidapril 10 mg and 18 to imidapril 20 mg. These patients formed the intent to treat population.

Analysis of the demographic characteristics demonstrated that height, weight, age and sex were comparable between all treatment groups (Table 1). All patients were Caucasian.

Treatment groups had a similar length of history of hypertension with an overall mean duration of 76 months. Fifty-four percent of randomized patients had received previous antihypertensive therapy. No significant between group differences for blood pressures and heart rate were seen at baseline ($P > 0.05$ in all cases).

Study 1—Efficacy

The primary measure of efficacy was the change in sitting diastolic blood pressure on an endpoint basis. The mean changes in mm Hg (s.e. mean) in sitting DBP after 1 week of treatment was −6.5 (1.9) for placebo, −5.5 (1.8) for imidapril 2.5 mg, −7.3 (1.8) for imidapril 5 mg, −11.1 (1.8) for imidapril 10 mg and −15.2 (1.9) for imidapril 20 mg (Table 2). There was a significant difference between treatment groups ($P = 0.05$), and a significant linear dose response ($P = 0.003$), confirming a significant dose relationship. All treatment groups showed a significant reduction in sitting DBP at the 5% level. The Student-Newman-Keuls test showed a significant difference at the 5% level between imidapril 20 mg and each of placebo, 2.5 mg and 5 mg, but not with imidapril 10 mg.

Control of hypertension was defined as 'normalization' if sitting diastolic BP fell to ≤ 90 mm Hg and 'favourable' if sitting diastolic BP fell by at least 10 mm Hg. Higher doses of imidapril were associated with progressively better therapeutic responses. The best results were seen with imidapril 20 mg which resulted in 50% normalization and 83% favourable responses compared with placebo with 29% normalization and 35% favourable responses. Imidapril 2.5 mg showed a very similar result to that of placebo. Imidapril 5 mg gave a 32% normalization and a 42% favourable response while imidapril 10 mg showed a 47% normalization with a 58% favourable response.

Significant reductions in standing DBP and standing systolic BP (SBP) were seen between placebo and imidapril 20 mg (Table 2). For standing SBP there was also a significant difference between placebo and imidapril 10 and 20 mg. Although a trend was observed for a dose response, sitting SBP failed to show a significant difference on linear or multiple comparison tests (Table 2).

Study 1—Tolerability

No serious adverse event leading to premature withdrawal occurred during the comparative treatment period. The proportions of patients who did not experience any event during the comparative treatment period were 65% in the placebo group, 74% in the imidapril groups. A total of 25 patients recorded a total of 31 adverse events. The most commonly recorded adverse event was headache.

There were no clinically relevant changes in vital signs and body weight observed at the end of the study compared with baseline for any of the treatment groups. There were trivial changes in the ECGs of five patients treated with imidapril (sinus bradycardia, mild left ventricular hypertrophy, ectopic beats). However no patient required dose adjustment or discontinuation during the treatment period.

Although intra-group analysis showed a statistically

Table 1 Study 1: Baseline demographics (mean ± s.e. mean)

		Imidapril (mg)			
	Placebo (n = *17*)	*2.5* (n = *18*)	*5* (n = *19*)	*10* (n = *19*)	*20* (n = *18*)
Sex (male/female)	11/6	9/9	14/5	11/8	10/8
Age (years)	59.3 ± 1.7	57.7 ± 1.5	59.6 ± 2.2	56.9 ± 2.8	60.5 ± 1.3
Baseline sitting DBP (mm Hg)	102.0 ± 1.4	103.7 ± 1.5	101.9 ± 1.2	103.4 ± 1.3	105.7 ± 1.6
Duration of hypertension (months)	86.3 ± 18.4	78.8 ± 16.4	56.2 ± 11.5	86.3 ± 13.5	72.8 ± 21.2

Table 2 Study 1: Effects of 2 weeks imidapril therapy on sitting and standing blood pressure (mm Hg, mean ± s.e. mean)

	Placebo (n = *17*)	*Imidapril (mg)* *2.5* (n = *18*)	*5* (n = *19*)	*10* (n = *19*)	*20* (n = *18*)
Sitting position SBP					
Baseline	168.4 ± 7.2	167.2 ± 4.8	171.0 ± 4.2	172.3 ± 3.6	165.9 ± 4.4
Week 2	160.1 ± 5.1	157.4 ± 4.7	159.9 ± 3.5	157.5 ± 3.7	144.7 ± 4.6
Change from baseline	−8.3 ± 3.6	−9.7 ± 4.6	−11.1 ± 2.7	−14.8 ± 3.0	−21.2 ± 5.1
95% confidence interval†	—	−12.9, 9.1	−10.6, 11.2	−16.3, 5.6	−19.0, 2.6
Sitting position DBP					
Baseline	102.0 ± 1.4	103.7 ± 1.5	101.9 ± 1.2	103.4 ± 1.3	105.7 ± 1.6
Week 2	95.5 ± 1.9	98.2 ± 2.4	94.6 ± 1.9	92.3 ± 2.2	90.5 ± 2.1
Change from baseline	−6.5 ± 1.9	−5.5 ± 1.8	−7.3 ± 1.8	−11.1 ± 1.8	−15.2 ± 1.9*
95% confidence interval†	—	−5.0, 6.5	−7.0, 4.4	−8.9, 2.6	−12.8, −1.5
Standing position SBP					
Baseline	168.0 ± 7.5	165.2 ± 4.3	168.5 ± 4.8	170.3 ± 4.0	168.7 ± 4.7
Week 2	165.9 ± 5.2	155.0 ± 4.8	159.3 ± 4.0	151.4 ± 3.7	146.6 ± 3.8
Change from baseline	−2.1 ± 4.0	−10.2 ± 4.0	−9.2 ± 3.2	−18.9 ± 3.2*	−22.1 ± 4.4*
95% confidence interval†	—	−20.0, 3.4	−14.9, 8.4	−27.0, −3.7	−27.1, −4.1
Standing position DBP					
Baseline	105.3 ± 1.8	105.7 ± 2.2	107.9 ± 1.7	105.1 ± 1.3	108.3 ± 1.6
Week 2	103.4 ± 2.6	101.9 ± 2.4	98.6 ± 2.1	96.4 ± 2.4	97.1 ± 2.4
Change from baseline	−1.9 ± 2.4	−3.9 ± 1.9	−9.3 ± 1.8	−8.7 ± 1.8	−11.3 ± 2.4*
95% confidence interval†	—	−8.9, 4.8	−13.3, 0.2	−12.8, 0.7	−15.6, −2.3

*Significant difference with placebo (Student-Newman-Keuls test, $P = 0.05$).
†Negative values indicate a larger reduction of blood pressure on imidapril compared with placebo.

significant increase in serum potassium in the imidapril 20 mg group (4.0 to 4.3 mmol l^{-1}; $P < 0.01$), (reference range 3.6 to 5.0 mmol l^{-1}) there were no clinically meaningful changes in any of the laboratory tests performed. The only statistically significant within group change for creatinine was seen in the imidapril 10 mg group where a mean rise of 5 μmol l^{-1} occurred ($P = 0.04$). No significant between group differences were detected for serum creatinine.

Study 1—Blood pressure profiles and ACE activity

After the first dose, imidapril 5, 10 and 20 mg significantly lowered sitting DBP over a 10 h period compared with placebo (Figure 1). The timing of peak drug effect in the placebo group at the randomization and final visit showed a marked fall in sitting DBP to a nadir between 5 and 6 h followed by a rise to 10 h. Similar profiles were seen for each of the active treatment groups (Figure 1).

After 2 weeks treatment the BP reduction profile was maintained and was of clinical significance (Figure 1). The effects of imidapril on sitting SBP and on standing blood pressures closely mirrored those of sitting DBP. Imidapril had a consistent and constant effect in lowering both systolic and diastolic BP at 8 h and 24 compared with placebo, implying a true 24 h control of BP.

Angiotensin-converting enzyme (ACE) activity was also measured at baseline and after 2 weeks therapy (Figure 2). No significant between-group differences in ACE activity were observed at baseline. The first dose of imidapril in each of the active treatment groups was followed by a rapid fall in plasma ACE activity which reached a minimum level between 4 and 8 h. ACE activity remained low for the remainder of the 24 h, in spite of a fall in plasma imidaprilat levels during this period (Figure 3). Although analysis of variance revealed a significant effect of both treatment and plasma imidaprilat levels upon ACE activity, Figure 2 shows that at least 50% ACE inhibition was observed with the 2.5 mg dose, while each of the three higher doses was associated with closely similar degrees of ACE inhibition during the 24 h following dosing, with peaks in the range of 65–80% reduction. After 2 weeks treatment, due to steady state conditions, all four active doses were associated with a steady 60–80% inhibition of ACE activity throughout the 24 h (except for an inexplicable value for 20 mg at 4 h). Once again analysis of variance showed significant effects of treatment and plasma imidaprilat levels.

Increasing first doses of imidapril were associated with increasing peak plasma imidaprilat levels. Plasma levels following 2.5 and 5.0 mg doses were low and no clear peak could be determined in keeping with the four sampling points. Both the 10 and 20 mg doses showed a peak at 8 h post-dosing. After repeated administration, imidaprilat peaked at the 4th and 8th hour for the 20 mg and 10 mg dose respectively (Figure 3).

Study 2—Patients

A total of 179 patients were recruited in 14 centres. One hundred and sixty-two patients entered the randomized, comparative treatment period. Of the 162 patients who were randomized, 35 patients were randomized to placebo, 33 to imidapril 5 mg, 31 to imidapril 10 mg, 31 to imidapril 20 mg and 32 to imidapril 40 mg. These patients formed the intent to treat population.

The demographic characteristics demonstrated that height, weight, age and sex were comparable between

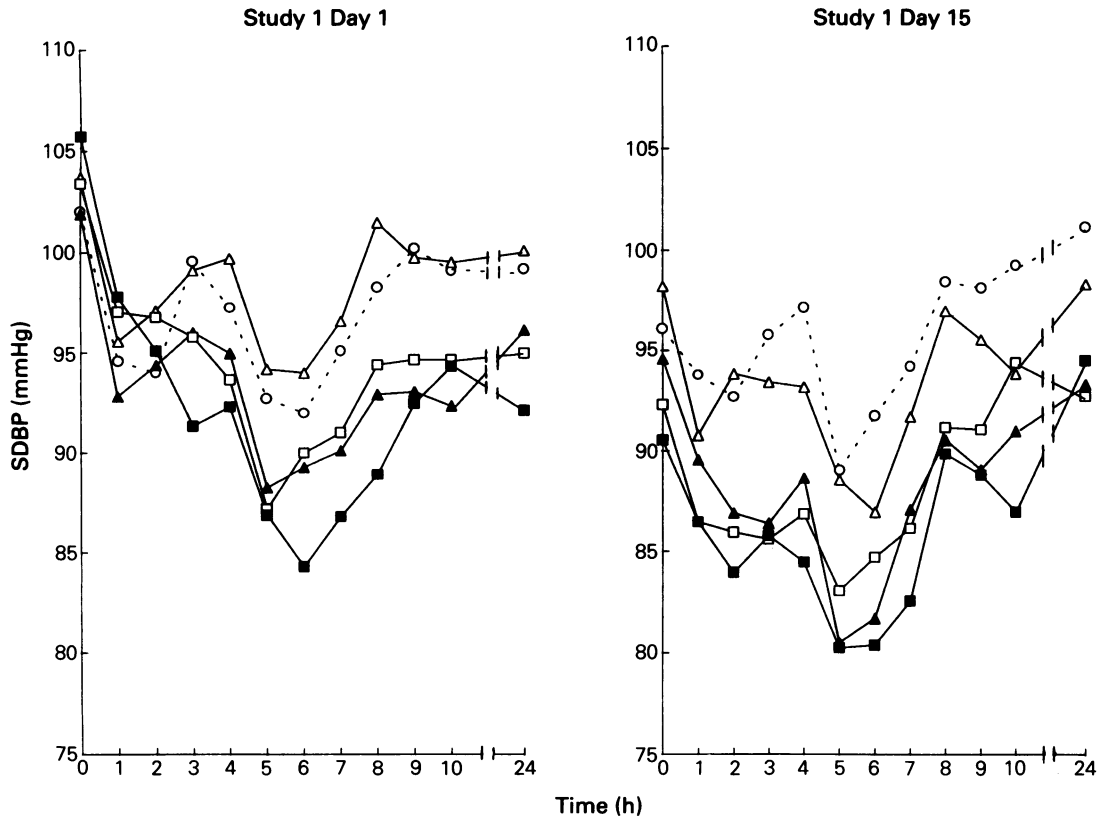

Figure 1 Effect of imidapril (△ 2·5 mg, ▲ 5 mg, □ 10 mg, ■ 20 mg) or placebo (○) on mean sitting diastolic blood pressure (SDBP) after single dose administration (day 1) and after 2 weeks therapy (day 15).

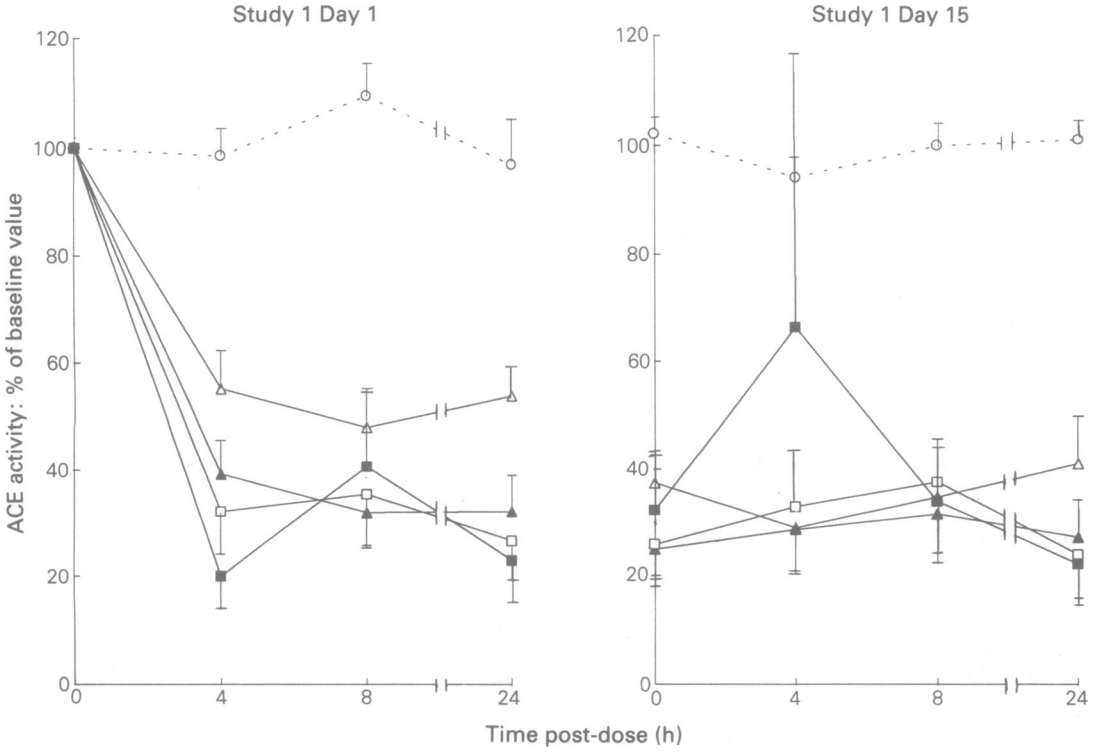

Figure 2 ACE activity (mean of percentages of baseline value ± s.e. mean) after initial administration and 2 weeks of chronic therapy with imidapril (△ 2·5 mg, ▲ 5 mg, □ 10 mg, ■ 20 mg) or placebo (○).

all treatment groups (Table 3). All but three patients were Caucasian. Treatment groups had a similar length of history of hypertension with an overall mean duration of 74 months. Fifty-nine percent of patients entering the trial had received previous antihypertensive therapy. No significant between group differences for blood pressure and heart rate were seen at baseline ($P > 0.05$ in all cases).

Study 2—Efficacy

The mean changes in mm Hg (s.e. mean) in sitting DBP from baseline to the final visit after 4 weeks of therapy were −4.7 (1.7) for placebo, −7.9 (1.3) for imidapril 5 mg, −12.1 (1.7) for imidapril 10 mg, −11.0 (1.6) for imidapril 20 mg and −11.2 (1.7) for imidapril 40 mg (Table 4). There was a significant difference between treatment groups ($P = 0.04$). All treatment groups showed a significant reduction in sitting DBP at the 5% level. The Student-Newman-Keuls test showed a significant difference at the 5% level between placebo and each of imidapril 10, 20 and 40 mg.

The best therapeutic response during study 2 was seen with imidapril 20 mg, which resulted in 65% normalization and a 65% favourable response compared with 29% normalization and 40% favourable response in the placebo group. Imidapril 5 mg gave a 39% normalization and a 42% favourable response, while imidapril 10 mg and 40 mg showed a 58% and 44% normalization respectively and a favourable response of 65% and 56% respectively.

Significant reductions in standing DBP, sitting SBP and standing SBP were seen between placebo and each of imidapril 10 mg, 20 mg and 40 mg (Table 4).

Study 2—Tolerability

No serious adverse events occurred during the study. Four randomized patients withdrew because of adverse events. Two patients receiving placebo withdrew, one due to dizzy spells and the other due to 'stabbing heart pains'. One patient receiving imidapril 40 mg withdrew due to 'discomfort, nervousness and palpitations'. A further two patients had their treatment suspended—one in the imidapril 20 mg group due to 'raging hunger'

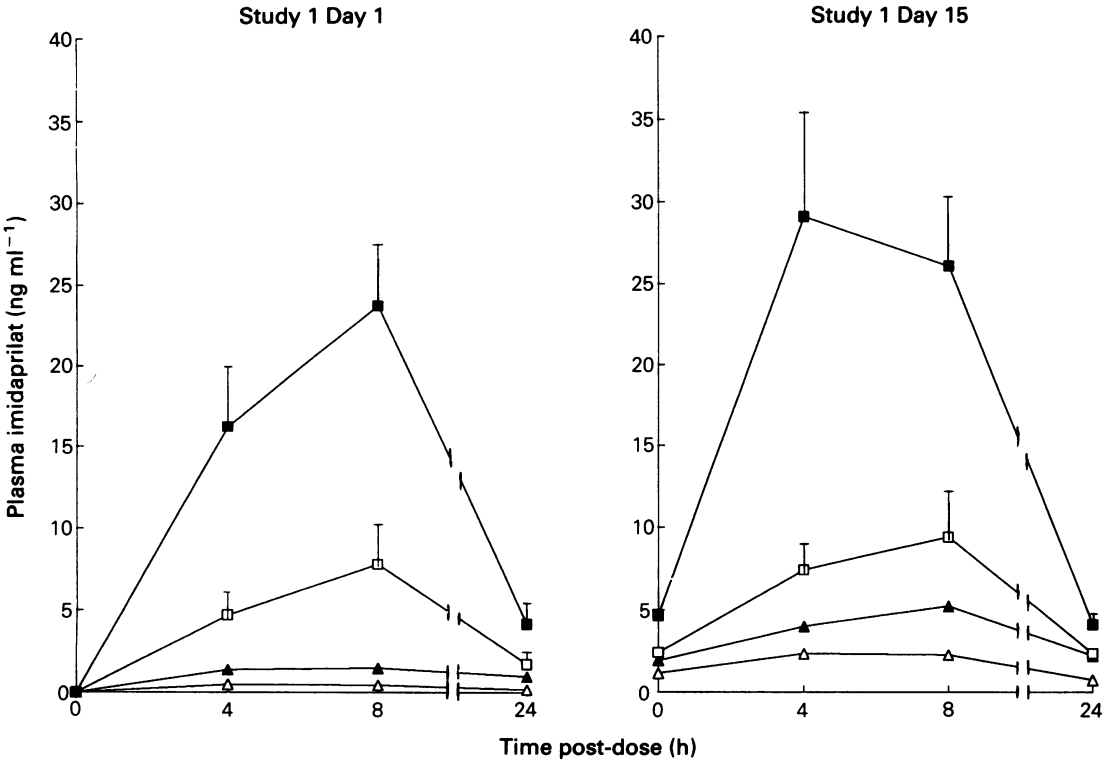

Figure 3 Plasma imidaprilat concentrations (mean value ± s.e. mean) after initial administration and 2 weeks of chronic therapy with imidapril (△ 2·5 mg, ▲ 5 mg, □ 10 mg, ■ 20 mg).

Table 3 Study 2: Baseline demographics (mean ± s.e. mean)

		Imidapril (mg)			
	Placebo (n = *35*)	*5* (n = *33*)	*10* (n = *31*)	*20* (n = *31*)	*40* (n = *32*)
Sex (male/female)	20/15	21/12	18/13	16/15	21/11
Age (years)	51.9 ± 2.0	53.2 ± 2.1	52.3 ± 2.1	52.5 ± 1.8	49.8 ± 2.4
Baseline sitting DBP (mm Hg)	101.3 ± 0.9	102.3 ± 1.0	100.8 ± 0.8	101.0 ± 1.0	102.2 ± 0.9
Duration of hypertension (months)	87.2 ± 15.0	83.4 ± 12.6	54.3 ± 7.5	68.5 ± 15.1	74.1 ± 14.6

and the other in the imidapril 40 mg group due to vomiting.

The proportions of patients without any adverse event during the comparative treatment period was 63% in the placebo group, 60% in the imidapril groups. Sixty-four patients recorded a total of 106 adverse events, the most common being headache and dizziness.

There were no clinically relevant changes in vital signs and body weight observed at the end of the study compared with baseline for any of the treatment groups. There were trivial changes in the ECGs of four patients treated with imidapril (ventricular extra-systole, PQ of 0.2 s with a heart rate of 61, resolution of ST changes in lateral leads, improvement of the ECG). None of these changes required treatment or withdrawal.

By intra-group analysis there was a statistically significant, though not clinically important, increase in potassium in the imidapril 20 mg group from 4.19 mmol l^{-1} at baseline to 4.38 mmol l^{-1} at endpoint (reference range 3.6 to 5.0 mmol l^{-1}). There were no clinically meaningful changes in any of the other laboratory tests performed. The analysis of the changes in serum creatinine did not show any significant treatment effect, visit effect, or within group changes.

Discussion

The results of these two multicentre, randomised, placebo-controlled, double-blind studies show that imidapril is an effective antihypertensive drug in patients with mild to moderate essential hypertension.

The first study reported here showed that imidapril lowers systolic and diastolic blood pressure 24 h after administration in a dose-dependent manner. These changes in blood pressure were reflected in the proportions of patients whose blood pressure normalized or showed a favourable response, with the 5 mg, 10 mg and 20 mg doses being associated with progressively better results. The 2.5 mg dose gave results similar to placebo.

The time profiles of imidaprilat levels, ACE inhibition and blood pressure at first dose and steady state allow interesting comparisons. Inhibition of plasma ACE activity had a non-linear relationship to imidaprilat level and continued long after imidaprilat levels had fallen. The implication is that inhibition is caused by a small fraction of the total plasma imidaprilat which binds to ACE and remains bound even in the face of falling free imidaprilat levels. The time profile of BP thus more closely follows ACE inhibition than imidaprilat levels [13].

The results of this study confirm the long-lasting action of imidapril since ACE activity was still suppressed to under 40% of the baseline value 24 h after the 5, 10 and 20 mg doses. ACE activity remained suppressed throughout the 2 week treatment period. These results compare favourably with what is observed with other compounds of the same therapeutic group [14].

The results of the larger second study, confirmed those of the first, with imidapril again being shown to lower both systolic and diastolic blood pressure in a dose-dependent manner. The results indicate that imidapril has a significant antihypertensive effect 24 h after administration, but there was no significant evidence of a greater reduction being obtained in the imidapril 20 or 40 mg groups than in the 10 mg group.

The drug appeared to be well tolerated, although it

Table 4 Study 2: Effect of 4 weeks imidapril therapy on sitting and standing blood pressure (mm Hg, mean ± s.e. mean)

		Imidapril (mg)			
	Placebo (n = 35)	*5* (n = 33)	*10* (n = 31)	*20* (n = 31)	*40* (n = 32)
Sitting position SBP					
Baseline	156.8 ± 2.3	163.6 ± 2.7	164.6 ± 3.8	160.1 ± 2.6	158.7 ± 3.4
Week 4	151.0 ± 2.5	152.9 ± 2.8	149.9 ± 4.2	141.4 ± 3.3	142.3 ± 3.7
Change from baseline	−5.8 ± 2.5	−10.7 ± 2.1	−14.7 ± 2.8*	−18.7 ± 3.0*	−16.4 ± 2.4*
95% confidence interval†	—	−10.6, 4.1	−16.2, −1.2	−18.7, −3.7	−15.3, −0.5
Sitting position DBP					
Baseline	101.3 ± 0.9	102.3 ± 1.0	100.8 ± 0.8	101.0 ± 1.0	102.2 ± 0.9
Week 4	96.6 ± 2.0	94.4 ± 1.7	88.7 ± 2.1	90.0 ± 1.6	91.0 ± 1.9
Change from baseline	−4.7 ± 1.7	−7.9 ± 1.3	−12.1 ± 1.7*	−11.0 ± 1.6*	−11.2 ± 1.7*
95% confidence interval†	—	−6.2, 2.7	−11.1, −2.0	−9.9, −0.8	−8.1, 0.9
Standing position SBP					
Baseline	156.9 ± 2.6	165.2 ± 2.9	166.5 ± 4.0	160.4 ± 2.6	160.9 ± 3.2
Week 4	153.3 ± 2.3	156.3 ± 3.0	150.4 ± 4.3	143.0 ± 3.6	143.1 ± 4.1
Change from baseline	−3.6 ± 3.0	−8.9 ± 2.8	−16.2 ± 2.9*	−17.4 ± 2.9*	−17.8 ± 3.1*
95% confidence interval†	—	−14.2, 2.5	−17.7, −0.7	−19.8, −2.8	−18.2, −1.4
Standing position DBP					
Baseline	103.6 ± 1.1	104.6 ± 1.2	104.6 ± 1.2	104.1 ± 1.0	105.2 ± 1.1
Week 4	100.6 ± 2.0	99.5 ± 1.9	94.0 ± 2.4	94.4 ± 2.1	95.6 ± 2.1
Change from baseline	−3.0 ± 1.8	−5.2 ± 1.5	−10.6 ± 1.9*	−9.7 ± 2.0*	−9.6 ± 1.8*
95% confidence interval†	—	−7.2, 3.2	−12.7, −2.2	−10.8, −0.3	−9.5, 1

*Significant difference with placebo (Student-Newman-Keuls test, $P = 0.05$).
†Negative values indicate a larger reduction of blood pressure on imidapril compared with placebo.

must be remembered that there are limits to the safety data available from studies of this size and length. In particular no evidence was seen for an excessive first dose hypotensive effect, nor for reflex tachycardia in response to vasodilatation. Imidapril resembles other ACE inhibitors in this respect [15–16].

ECG and laboratory data were unremarkable and showed no worrying trends. In conclusion the results of these studies indicate that imidapril 10 mg is probably the main therapeutic dose, but that some individuals will benefit from 5 mg or 20 mg. At these doses, imidapril appears to be effective and well tolerated, and the side effect profile of imidapril in these studies did not deteriorate at higher doses.

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