Lisinopril: Dose-peak effect relationship in essential hypertension

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1 The dose-peak effect relationship of lisinopril was evaluated in a double-blind, parallel study in 83 patients with mild to moderate essential hypertension (supine diastolic blood pressure = 95–115 mm Hg).

2 After a 4 week placebo washout, patients were randomly assigned to one of four treatments: lisinopril 2.5, 10, 20 or 80 mg day⁻¹ for 1 week.

3 Lisinopril 10 and 20 mg day⁻¹ produced similar peak antihypertensive effects which were greater than that produced by 2.5 mg day⁻¹, but less than that of 80 mg day⁻¹. If the incidence of first-dose symptomatic hypotension is related to the peak effect, then an initial lisinopril dose of 20 mg should not pose any greater risk than a 10 mg dose.

4 The magnitude of antihypertensive response at 24 h postdrug appeared to be dose related across the 2.5 to 80 mg day⁻¹ range.

Keywords lisinopril angiotensin converting enzyme dose-response hypertension

Introduction

Lisinopril is an orally-active, long-acting, angiotensin-converting-enzyme (ACE) inhibitor that is not metabolized or bound to plasma proteins (Gomez *et al.*, 1987), and is eliminated primarily, if not exclusively, by the kidneys (Ulm *et al.*, 1982). Lisinopril effectively reduces blood pressure in patients with essential (Pool *et al.*, 1987; Bolzano *et al.*, 1987; Morlin *et al.*, 1987; Zachariah *et al.*, 1987) and renovascular (Fyhrquist *et al.*, 1987; Donohoe *et al.*, 1987) hypertension, and improves signs, symptoms and exercise capacity in congestive heart failure (Powers *et al.*, 1987; Chalmers *et al.*, 1987). Experience to date indicates that lisinopril is well tolerated, and has a good safety profile (Rush & Merrill, 1987).

It is commonly believed that an increase in dose of an ACE inhibitor, such as captopril and enalapril, serves only to extend its duration of

action, and not the magnitude of the blood pressure reduction. However, this has not been demonstrated in properly designed clinical trials. The existence of a relationship between single daily doses of lisinopril and duration of action (assessed at 24 h postdose) has been reported (Gomez *et al.*, 1985; Nelson *et al.*, 1985), but a relationship between dose and maximum blood pressure reduction (peak) has not. The purpose of the present study was to determine the relationship between the dose of lisinopril and its peak antihypertensive effect.

Methods

Eighty-three patients (82 Caucasian, 1 Negro) with mild to moderate essential hypertension (supine diastolic blood pressure [SDBP] = 95–

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115 mm Hg) participated in the study. Their mean age was 51 years (range 24–65 years); 67 were men and 16 were women. Nine of the women were menopausal, one was hysterectomized and six had IUDs *in situ*. Informed consent was obtained from every patient, and the study was conducted in accordance with the Declaration of Helsinki and local laws. Entry criteria included an untreated SDBP of 95–115 mm Hg with no history of renal, hepatic or haematological disorders.

This was a double-blind, parallel study with a 1-week treatment period preceded by a 4 week placebo washout period. If their SDBP remained in the 95–115 mm Hg range after the washout, the patients were then randomly assigned to one of four treatments: lisinopril 2.5, 10, 20 or 80 mg day⁻¹. All tablets were in identical image. There were no diet restrictions.

Since the efficacy of lisinopril had already been established in a placebo-controlled study (Gomez *et al.*, 1987), a placebo group was not included here. Also, the doses of lisinopril did not increase in a strictly four-fold progression, because a comparison of 10 and 20 mg (possible recommended starting doses) was of paramount interest.

Patients reported to the clinic to have their supine blood pressure measured hourly from –2 to 8 h after taking the last placebo tablet (Day –1), the first active-treatment tablet (Day 1) and the last active-treatment tablet (Day 7). Blood pressure was also recorded hourly from 22 to 24 h after receiving the last placebo tablet, the first active-treatment tablet and the last active-treatment tablet. Baseline was the mean of hours –2, –1 and 0 on Day 1, and 24 h values on Days 1 and 7 were means of hours 22, 23 and 24 postdose.

Blood pressure measurements were made with a mercury sphygmomanometer by the same experienced observers who were blinded to the treatments. Systolic blood pressure was noted when the first Korotkoff sound was heard, and the point of disappearance of the fifth Korotkoff sound was taken as diastolic blood pressure. Supine blood pressure was measured after the patients had been recumbent for at least five minutes.

Patients were thoroughly examined at the first visit during the placebo washout period, and at the last visit of the treatment period. A 12-lead ECG was taken, and a routine laboratory analysis was done which included haematology, blood chemistry and urinalysis.

Statistical analysis

Analysis of covariance (ANCOVA) was used to compare the treatment groups with respect to

blood pressure at each timepoint and for peak and 24 h effects. A repeated measures analysis (including the time factor) was not used, because of uncertainty about the behaviour of variance relative to necessary assumptions. In addition, pairwise comparisons at each timepoint were anticipated due to the expected occurrence of a treatment-by-time interaction. Baseline day 1 value was used as the covariate. The final ANCOVA model included the factors treatment group (four levels) and baseline (continuous covariate). Assumptions for the ANCOVA model were verified by testing the following factors which were added to the model for evaluation, then removed from the final model: (baseline $\times$ baseline) and baseline-by-treatment interaction. These two effects were nearly always nonsignificant and, therefore, not included in the final model. Pairwise comparisons among the treatment groups were *t*-tests among the treatment means adjusted for the baseline covariate. Results were obtained by using SAS Type III sums of squares and LSMEANS (SAS, 1985).

Baseline comparisons were made using one-way analysis of variance with treatment group (four levels) as the factor.

The sample size of $n = 20$ completed patients per treatment group has 80% power to detect (at $\alpha = 0.05$, two-tailed) a 7 mm Hg difference in mean peak supine diastolic blood pressure response between any pair of treatments. This is based on a s.d. of 8 mm Hg from previous data of hourly blood pressure recordings with lisinopril.

The assumption of normality of residuals from ANOVA and ANCOVA was tested using the KOLMOGOROV D statistic for goodness of fit. The homogeneity of variance assumption was tested using Hartley's $F_{\max}$ statistic. These assumptions were found to be satisfied in nearly every case. In the few cases when a departure from assumptions was encountered, the departure was small and ANOVA/ANCOVA on overall relative ranks of the data corroborated the parametric results. Thus, only the parametric results are reported herein.

Results

Peak effect

Mean maximum decreases in supine systolic blood pressure (SSBP), diastolic blood pressure (SDBP) and mean arterial pressure (SMAP) were significantly greater after 10, 20 and 80 mg than after 2.5 mg of lisinopril on days 1 and 7 (Table 1). Ten and 20 mg had similar peak

Table 1 Mean (range) supine blood pressure

<i>Lisinopril</i> (mg day ⁻¹)	n	Baseline (mm Hg)	Decrease from baseline (mm Hg)*			
			Peak		24 h	
			Day 1	Day 7	Day 1	Day 7
<i>Systolic</i>						
2.5	21	151 (123, 205)	16 (6, 42)	17 (-4, 34)	4 (-7, 19)	4 (-9, 23)
10	21	149 (135, 175)	27 (12, 41)	26 (-4, 67)	12 (3, 23)	10 (-9, 27)
20	20	148 (131, 168)	27 (9, 52)	25 (0, 44)	15 (3, 31)	15 (-6, 29)
80	21	153 (136, 197)	33 (12, 57)	33 (15, 67)	16 (-3, 47)	18 (1, 41)
Pooled s.d.		14.4	9	11	7	8
<i>Diastolic</i>						
2.5	21	100 (93, 115)	13 (5, 28)	13 (3, 24)	4 (-1, 10)	4 (-3, 11)
10	21	101 (95, 117)	21 (11, 43)	21 (-4, 47)	8 (-5, 24)	6 (-5, 17)
20	20	102 (94, 114)	21 (5, 36)	22 (2, 34)	10 (-1, 25)	10 (-3, 22)
80	21	102 (95, 114)	22 (11, 39)	24 (12, 36)	10 (1, 23)	10 (-3, 21)
Pooled s.d.		5.4	7	8	5	6
<i>Mean arterial pressure</i>						
2.5	21	117 (104, 139)	13 (7, 33)	14 (4, 27)	4 (-2, 12)	4 (-2, 12)
10	21	117 (109, 136)	22 (12, 39)	22 (2, 54)	9 (-2, 24)	7 (-4, 19)
20	20	117 (108, 132)	22 (4, 39)	22 (1, 36)	12 (1, 26)	12 (-2, 24)
80	21	119 (109, 135)	25 (13, 40)	27 (13, 40)	12 (1, 24)	13 (3, 25)
Pooled s.d.		7.5	8	8	5	6

* Adjusted for baseline covariate

effects on days 1 and 7 (Figures 1 and 2). The 80 mg dose produced greater mean peak decreases than the 10 and 20 mg doses for SSBP ($P < 0.05$), SMAP ($P = 0.06$) and SDBP ($P > 0.10$) on days 1 and 7.

Time to peak effect

The mean time to peak effect for SSBP on day 1 was 4.5–5 h after all four treatments; it was about 4 h for SDBP. The 10 to 80 mg doses had similar mean times to peak effect, approximately 4 h on day 7. The mean for 2.5 mg on day 7 was 5 h. Scattered significant differences were observed among doses in mean time at which peak effects occurred; however, they were not consistent with a dose-response relationship. On day 7 the 2.5 mg group exhibited a longer mean time to peak effect for SSBP, SDBP and SMAP than the other three dosage groups, reaching significance for SSBP vs 10 ($P = 0.01$) and 20 mg ($P = 0.03$) and for SMAP vs 10 mg ($P = 0.01$), and approaching significance for SMAP vs 80 mg ($P = 0.06$).

24 h effect

Increasing mean reductions in SSBP were observed with increasing dose of lisinopril (Figure 1). Adjusted mean 24 h reductions on

day 7 were 4, 10, 15 and 18 mm Hg for the 2.5, 10, 20 and 80 mg groups, respectively (Table 1). All pairwise differences were significant ($P < 0.05$), except that between 20 and 80 mg ($P > 0.20$). Mean SDBP reduction increased from 4 mm Hg after 2.5 mg to 6 after 10 mg to 10 after 20 mg (Figure 2). However, no further increase in response was observed after 80 mg (adjusted mean 10 mm Hg). The 80 and 20 mg doses were significantly different from the 2.5 and 10 mg doses, but differences between the lower two and higher two were not. Results for SMAP were midway between those for SSBP and SDBP in that the 20 to 80 mg difference was less pronounced than for SSBP (Table 1). Results on day 1 were similar to those on day 7 except that the 2.5 vs 10 mg difference was significant.

Undesirable effects

There were no instances of first-dose symptomatic hypotension or asymptomatic abrupt drops in blood pressure in this study. None of the patients in the lisinopril 2.5, 10 and 20 mg groups had a clinical adverse experience. Two patients taking lisinopril 80 mg day experienced mild to moderate headaches. No clinically important changes were observed in any laboratory tests.

Figure 1 Supine systolic blood pressure changes on Days 1 and 7 in response to lisinopril 2.5 mg (□, $n = 21$), 10 mg (Δ, $n = 21$), 20 mg (○, $n = 20$) and 80 mg (●, $n = 21$).

Figure 2 Supine diastolic blood pressure changes on Days 1 and 7 in response to lisinopril 2.5 mg (□, $n = 21$), 10 mg (Δ, $n = 21$), 20 mg (○, $n = 20$) and 80 mg (●, $n = 21$).

Discussion

Increasing the dose of lisinopril from 10 to 20 mg did not affect the extent of the peak blood pressure reduction, but the magnitude of response at 24 h appeared to be dose related. If the incidence of first-dose symptomatic hypotension is related to the peak effect, then an initial lisinopril dose of 20 mg should not pose any greater risk than a 10 mg dose.

Similar results have been reported for enalapril, a congener of lisinopril, in diuretic-treated patients: 10 and 20 mg doses were indistinguishable in terms of peak reductions in supine and erect systolic and diastolic blood pressure, but the hypotensive effect of the 20 mg dose persisted longer (Webster *et al.*, 1987).

The profile of antihypertensive effects on days 1 and 7 were comparable; therefore, the response to the first dose may be predictive of the steady-state response, assuming that the day 7 response is characteristic of the chronic response.

It is becoming clear that ACE inhibitors are well tolerated, and that first-dose symptomatic hypotension is only observed in a small number of patients who are at high risk. This angiotensin-dependent, highly susceptible group is now well characterized, and includes hypovolaemic and hyponatraemic patients as well as patients on high doses of diuretics (Packer *et al.*, 1984). Particularly at risk are patients with severe con-

gestive heart failure (Cleland *et al.*, 1984, 1985; Mujais *et al.*, 1984) and hypertensive individuals with bilateral renal artery stenosis or stenosis of the artery to a single remaining kidney (Hrick *et al.*, 1983). These are the patients who should start therapy with a low dose of ACE inhibitor under close medical supervision. When symptomatic hypotension occurs, it usually responds rapidly to intravenous fluids. Clinical experience in this high-risk group indicates that the return of blood pressure to normal levels precedes the disappearance of ACE inhibition. Presumably, this is a result of compensatory increases in the activity of the other pressor mechanisms—*viz.*, the sympathetic nervous system and vasopressin—that take over after acute inhibition of the renin-angiotensin-system (Hatzinikolaou *et al.*, 1982).

There was little additional fall in blood pressure by increasing the lisinopril dose from 20 to 80 mg. However, it is clear from other work (Gomez *et al.*, 1987) that, with long-term (6 weeks) therapy, 80 mg produces a significantly greater reduction in blood pressure than 20 mg.

In conclusion, lisinopril 10 and 20 mg day⁻¹ produced similar peak antihypertensive effects which were greater than that produced by 2.5 mg day⁻¹, but less than that of 80 mg day⁻¹. The magnitude of the antihypertensive response at 24 h postdrug appeared to be dose related across the 2.5 to 80 mg day⁻¹ range.

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