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Lisinopril dose-response relationship in essential hypertension

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1 This was a multicentre, double-blind, parallel study in 216 patients with mild to moderate (supine diastolic blood pressure = 95–115 mm Hg) essential hypertension.

2 After a 4-week placebo washout, patients were randomized to placebo or lisinopril 1.25, 5, 20 or 80 mg once daily for 6 consecutive weeks. Supine and erect blood pressure was measured 24 h postdose at the end of weeks –2, 0, 2, 4, and 6.

3 There was a linear dose-response relationship for both supine and erect blood pressure. Diastolic blood pressure reductions in the lisinopril 20 and 80 mg day^{-1} groups were significantly greater than in the placebo or lisinopril 1.25 and 5 mg day^{-1} groups.

4 Lisinopril, at doses up to 80 mg day^{-1}, was well tolerated.

Keywords lisinopril angiotensin converting enzyme inhibitor hypertension dose-response relationship

Introduction

Lisinopril, an orally-active, long-acting, angiotensin-converting-enzyme (ACE) inhibitor, 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 lowers blood pressure in patients with essential (Bolzano *et al.*, 1987; Morlin *et al.*, 1987; Pool *et al.*, 1987; Zachariah *et al.*, 1987) and renovascular (Donohoe *et al.*, 1987; Fyhrquist *et al.*, 1987) hypertension, and improves signs and symptoms in congestive heart failure (Chalmers *et al.*, 1987; Powers *et al.*, 1987). Clinical experience to date indicates that lisinopril is safe and well tolerated (Rush & Merrill, 1987).

Dosage recommendations for antihypertensive drugs are often based on postmarketing clinical experience, suggesting that the therapeutic dose range was not truly established during the drug development process. Recognizing this flaw, several authors have proposed systematic approaches for defining dose (Gomez & Cirillo, 1985; Turri & Stein, 1986; Schmid, 1988; Gomez *et al.*, 1989) which have as a common feature characterization of the dose-response relationship.

This paper reports the results of the first multicentre study to investigate the dose-response relationship of lisinopril, over a 64-fold range of doses, in patients with essential hypertension. Abstracts of preliminary data, based upon smaller numbers of patients, have been published (Gomez *et al.*, 1985; Nelson *et al.*, 1985).

Methods

Subjects

Two hundred sixteen patients with mild–moderate, uncomplicated essential hypertension were studied at seven centres (Table 1). Fifty-two percent of the patients were from the USA and 48% from Sweden. Informed consent was

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Table 1 Demographics

	Placebo	*Lisinopril (mg day^{-1})* 1.25	5	20	80
n	47	41	41	44	43
Sex					
Male	40	38	37	42	37
Female	7	3	4	2	6
Age (years)					
Mean	56	58	56	54	57
Range	33–71	32–70	31–70	24–70	30–70
Race					
Caucasian	38	34	32	35	32
Negro	8	6	9	8	10
Other	1	1	0	1	1
Duration of hypertension (years)					
Mean	6.7	13.3	7.9	8.1	10.1
Range	0.1–22	0.8–44	0.1–22	0.8–41	0.4–28

obtained from every patient, and the study was conducted in accordance with the Declaration of Helsinki (Sweden) and FDA regulations (USA). Entry criteria included an untreated supine diastolic blood pressure (SDBP) of 95–115 mm Hg with no history of renal, hepatic or hematological disorders.

Study design

In this multicentre, double-blind, parallel study all antihypertensive medication was discontinued, and the patients were given placebo for 4 weeks. If at the end of that time their SDBP was 95–115 mm Hg, they were randomly allocated to one of five treatments: placebo or lisinopril (L) 1.25, 5, 20 or 80 mg day^{-1}.

Medication was given once daily at 09.00 h for 6 consecutive weeks. There were no diet restrictions. As a safety precaution, the patients in the L-80 group received 40 mg day^{-1} for the first 2 weeks and then 80 mg day^{-1} for the last 4 weeks.

Blood pressure was measured with mercury sphygmomanometers by the same experienced observers at the end of weeks –2, 0, 2, 4 and 6. Systolic pressure was noted when the first Korotkoff sound was heard, and diastolic at the point of disappearance of the fifth Korotkoff sound. Supine measurements were made after the patient had been recumbent for at least 5 min. Erect pressure was measured after the patient had been standing for at least 1 min. All values were an average of at least two readings taken immediately before the daily dose of medication; i.e., 24 h after the preceding dose. Baseline was defined as blood pressure values at the last placebo visit.

Statistical analysis

Blood pressure changes were analyzed using an analysis of variance on the overall relative ranks (Iman, 1974) with study and baseline categories as blocks. Within-treatment-group changes were evaluated using a multiclinic extension of the Wilcoxon Signed-Rank test.

All pairwise differences were assessed at the 0.05 significance level (two-tailed).

Since treatment results between the USA and Swedish centres revealed no significant differences the data were pooled for analysis.

Results

Efficacy

Two hundred sixteen patients entered the double-blind treatment period, and 205 completed the study. Eleven patients were discontinued (see safety section), and a further 12 with incomplete data were excluded from the efficacy analysis. Therefore, 193 patients provided dose-response data.

All blood pressure measurements were taken at the end of a 24 h dosing interval. Therefore, these data represent trough effects; i.e., the minimum antihypertensive effect observed over a 24 h period.

Supine diastolic blood pressure (SDBP) Decreases from baseline ($P < 0.01$) in SDBP were noted at each week in the placebo and all of the lisinopril groups, and ranged from approximately 4 mm Hg for the placebo and L-1.25

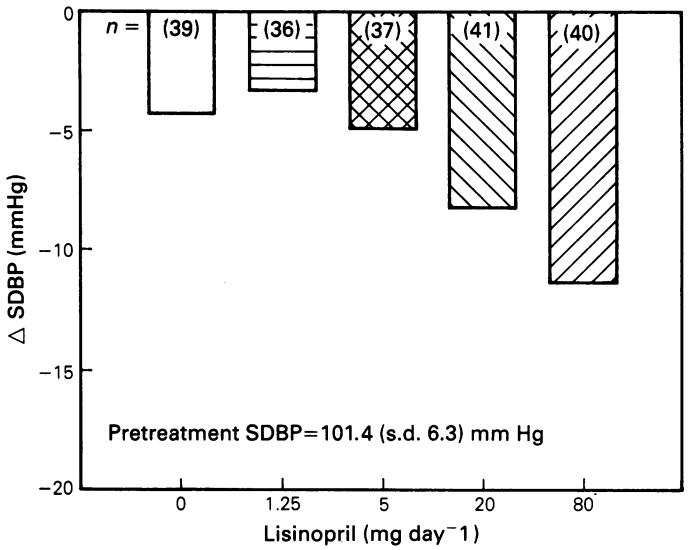

Figure 1 Mean change in supine diastolic blood pressure (24 h postdrug) after 6 weeks of therapy.

Table 2 Mean supine systolic/diastolic blood pressure (mm Hg) 24 h postdose at week 6

Lisinopril (mg day^{-1})	n	*Baseline*	*Week 6*	*Decrease from baseline (mm Hg)*	*95% C.I.*
Placebo	39	160.5/100.4	158.2/96.0	2.3/4.4	−0.8,7.9/1.5,5.2
1.25	36	157.6/100.3	157.3/97.0	0.4/3.3	−2.9,3.0/0.7,5.6
5	37	159.0/99.6	150.7/94.7	8.2*,†/4.9	2.7,13.9/2.7,7.8
20	41	158.4/102.4	145.7/94.1	12.8**,††/8.2*,†	9.8,17.3/4.6,10.2
80	40	160.6/101.1	142.8/89.8	17.8**,††,‡/11.3**,††,‡‡	12.2,21.4/8.0,13.8

*,**Different from placebo, $P < 0.05$, $P < 0.01$
†,††Different from L-1.25 mg, $P < 0.05$, $P < 0.01$
‡,‡‡Different from L-5 mg, $P < 0.05$, $P < 0.01$

groups to approximately 11 mm Hg for the L-80 group. At each timepoint, the L-80 group had significantly greater decreases than placebo, L-1.25 and L-5. The L-20 group showed significant differences from the latter three groups at isolated timepoints. The L-1.25 and L-5 groups were not significantly different from placebo (Figure 1). The data for week 6 are summarized in Table 2. A significant ($P < 0.001$) linear dose response for SDBP was detected at each week.

Supine systolic blood pressure (SSBP) Decreases from baseline ($P < 0.01$) in SSBP were noted at each week in the L-5, L-20 and the L-80 groups. The L-80 group had a significantly larger decrease than each of the other groups (except the L-20 group at week 6 where $P = 0.11$). The L-20 group was significantly different from the L-1.25 and placebo groups. At week 6 the L-5 group was significantly different from both of these groups. No significant difference was found between the L-1.25 and placebo groups. The week 6 data are summarized in Table 2. A significant ($P < 0.001$) linear dose response for SSBP was detected at each week.

Erect diastolic blood pressure (EDBP) The data for week 6 are summarized in Table 3. Decreases from baseline in EDBP ($P < 0.01$) were noted at each week in the placebo and all of the lisinopril groups ($P < 0.05$ for L-1.25 at week 6). The minimum decrease was seen in the L-1.25 group at week 6 (2 mm Hg) while the maximum decrease occurred in L-80 group at week 4 (11 mm Hg). The L-80 group showed significantly larger decreases than the placebo, L-1.25 and L-5 groups. No differences were found between the placebo, L-1.25 and L-5 groups. A significant ($P = 0.001$) linear dose response for EDBP was detected at each week.

Table 3 Mean erect systolic/diastolic blood pressure (mm Hg) 24 h postdose at week 6

Lisinopril (mg day^{-1})	n	*Baseline*	*Week 6*	*Decrease from baseline (mm Hg)*	*95% C.I.*
Placebo	39	159.6/105.6	153.9/100.6	5.7/5.0	1.5,11.0/2.9,7.4
1.25	36	154.3/102.7	151.9/100.0	2.5/2.2	−2.1,6.0/−0.4,4.7
5	37	157.4/105.0	149.7/100.0	7.7/5.0	0.4,12.8/1.8,7.6
20	41	157.7/108.2	144.2/98.7	13.5**,††,‡/9.6††	8.8,17.9/6.4,13.1
80	40	156.1/104.6	136.6/93.6	19.5**,††,‡‡/11.0**,††,‡‡	14.2,24.4/7.4,13.8

*,**Different from placebo, $P < 0.05$, $P < 0.01$
†,††Different from L-1.25 mg, $P < 0.05$, $P < 0.01$
‡,‡‡Different from L-5 mg, $P < 0.05$, $P < 0.01$

Table 4 Incidence of adverse experiences

		Placebo	*Lisinopril (mg day^{-1}) 1.25*	*5*	*20*	*80*
Number of patients evaluated	Clinical	47	41	41	44	43
	Laboratory	44	38	37	41	42
Patients with adverse experience	Clinical	10	12	9	6	9
	Laboratory	10	11	7	7	9
Patients with serious adverse experience	Clinical	0	0	0	0	1
	Laboratory	0	0	0	0	0
Patients discontinued because of adverse experience	Clinical	0	0	1	0	1
	Laboratory	0	0	0	0	0

Erect systolic blood pressure (ESBP) The data for week 6 are summarized in Table 3. Decreases from baseline in ESBP ($P < 0.01$) were noted at each week in the L-5, L-20 and L-80 groups. The mean decreases were in the order of 3 to 6 mm Hg for the placebo and L-1.25 groups and 13 to 19 mm Hg for the two higher dose groups. The L-80 group had significantly larger decreases than the placebo, L-1.25 and L-5 groups. The L-20 group was significantly different from placebo and L-1.25 (except week 2). There were no significant differences among the placebo, L-1.25 and L-5 groups. A significant ($P < 0.001$) linear dose response for ESBP was detected at each week.

Heart rate No significant between-treatment differences were observed for supine and erect heart rates at weeks 2, 4 and 6.

Safety There were no significant differences among treatment groups regarding the incidence of clinical and laboratory adverse experiences (Table 4). Eleven patients were discontinued: two (1 L-5; 1 L-80) for adverse clinical experiences; six (2 placebo; 1 L-1.25, 1 L-20; 2 L-80) for inadequate control of blood pressure and three (1 placebo; 2 L-1.25) for extraneous reasons. Only one of these patients had a serious adverse experience: a 40-year-old black woman developed acute epigastric pain, nausea and vomiting after 18 days of treatment in the L-80 group. Therapy was discontinued, and she recovered without residual effects.

Serum potassium increased slightly with L-5 (0.14 mmol l^{-1}), L-20 (0.13 mmol l^{-1}) and L-80 (0.18 mmol l^{-1}); however, these changes were not clinically significant.

Discussion

This study employed a wide range of doses (64-fold). Lisinopril dosages were quadrupled because experience with its congener, enalapril (Bergstrand, *et al.*, 1988), indicated that the dose-response curve for this class of compounds is relatively flat. Thus, no difference between adjacent doses was expected.

After 6 weeks of treatment there was a significant linear relationship between the dose of lisinopril and the extent of reduction of systolic and diastolic blood pressure. In most instances, the blood pressure reductions with L-20 and

L-80 were significantly greater than those seen with placebo or L-1.25 and L-5. No significant differences were noted between L-1.25 or L-5 and placebo.

Lisinopril was well tolerated. There was no indication that the frequency of adverse experiences was any greater with higher doses of lisinopril than with lower doses. These results corroborate those from previous lisinopril multicenter studies where clinical and laboratory adverse experiences were clearly not dose related (Gomez *et al.*, 1988). It appears that lisinopril can be titrated up to the maximum recommended dose of 80 mg day^{-1} without compromising tolerability.

In conclusion, there was a linear dose-response relationship for both supine and erect systolic and diastolic blood pressure. While the antihypertensive effect of the 1.25 and 5 mg doses of lisinopril differed little from placebo, the 20 and 80 mg doses were effective in controlling blood pressure for 24 h in patients with mild to moderate essential hypertension.

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