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Effective dose range of enalapril in mild to moderate essential hypertension

R. BERGSTRAND[1], H. HERLITZ[2], SAGA JOHANSSON[1], G. BERGLUND[2], A. VEDIN[1], C. WILHELMSSON[1], H. J. GOMEZ[3], V. J. CIRILLO[3] & J. A. BOLOGNESE[4]
[1]Department of Medicine, Östra Hospital and [2]Department of Medicine I, Sahlgrenska Hospital, Göteborg, Sweden and Department of [3]Cardiovascular Clinical Research and [4]Clinical Biostatistics, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey, USA

1 The dose-response relationship of enalapril was evaluated in a double-blind, balanced, two-period, incomplete-block study in 91 patients with mild to moderate essential hypertension.

2 Patients were randomly assigned to two of six treatments: placebo, 2.5, 5, 10, 20 and 40 mg/day of enalapril maleate. There were two 3-week treatment periods, each preceded by a 4-week, single-blind placebo washout.

3 Each dose of enalapril produced significant decreases in standing and supine systolic and diastolic blood pressure after 2 and 3 weeks of treatment. There were no significant changes on placebo.

4 There was a significant linear dose response relationship for both mean blood pressure and mean change from baseline in blood pressure ($P < 0.01$ for systolic and mean arterial pressure, and $P < 0.05$ for diastolic pressure).

5 Enalapril was associated with an increasing dose-response relationship across the 2.5–40 mg/day range. The 2.5 mg/dose is effective in some patients; however, doses $\geq$ 10 mg/day may be necessary to achieve satisfactory blood pressure control.

Keywords enalapril angiotensin converting enzyme inhibitor dose-response relationship

Introduction

In recent years much interest has been focused on angiotensin converting enzyme (ACE) inhibitors for treatment of hypertension and congestive heart failure. Captopril, the first orally active ACE inhibitor, has been shown to be effective in renovascular and essential hypertension, either as monotherapy or in combination with diuretics (Vidt *et al.*, 1982). Along with the documented efficacy of captopril some side effects have been observed, *viz.*, skin rashes, taste impairment, proteinuria and membranous glomerulonephritis (Vlasses *et al.*, 1982). Neutropenia has also been reported in patients with renal impairment treated with high doses of captopril. The side effects of captopril may be related to its chemical structure and not its ACE inhibiting activity, since they are similar to those observed with penicillamine, which also has a sulphydryl group.

A new group of nonsulphydryl containing ACE inhibitors (Patchett *et al.*, 1980) is being evaluated clinically for the treatment of hypertension and congestive heart failure. One of these drugs, enalapril maleate (MK-421), seems to suppress the formation of angiotensin II for longer periods (Gomez *et al.*, 1983a, Biollaz *et*

Correspondence: Dr R. Bergstrand, Department of Medicine, Östra Hospital, S–416 85 Göteborg, Sweden

al., 1981) and to be more potent than captopril (Gomez & Cirillo, 1983).

Patients with renovascular (Hodsman *et al.*, 1983) and essential hypertension (Gavras *et al.*, 1981) have been treated successfully with enalapril used either as monotherapy in doses ranging from 2.5 to 40 mg/day (Gomez *et al.*, 1983a; Simon *et al.*, 1983; Wilkins *et al.*, 1983; Chrysant *et al.*, 1983) or in combination with thiazides (Gomez *et al.*, 1984).

The purpose of the present study was to establish the minimally effective dose and investigate the dose-response relationship of enalapril in patients with mild to moderate essential hypertension.

Methods

Ninety-one caucasians with mild to moderate essential hypertension from two outpatient clinics in Göteborg participated in the study. Thirty-seven were women (mean age 56 years, range 45–64 years) and 54 men (mean age 55 years, range 33–65 years). All gave their informed consent and the study was done in accordance with the Declaration of Helsinki and local laws.

Entry criteria included an untreated supine diastolic blood pressure (SDBP) of 90–115 mm Hg without a history of renal, hepatic or haematological disorders.

This was a double-blind, balanced, two-period, incomplete-block design. There were two 3-week, double-blind treatment periods, each preceded by a 4-week, single-blind placebo washout period. If their SDBP remained in the 90–115 mm Hg range after the first washout-placebo period, the patients were randomly assigned to two of the following six treatments, one during each treatment period: placebo, 2.5, 5, 10, 20 and 40 mg/day of enalapril maleate (hereafter referred to as enalapril). One half of each daily dose was taken at 09.00 h and the other at 21.00 h. If the SDBP increased 10 mm Hg or more during the first treatment period or the second washout placebo period, the patients could start the second treatment period directly. There were no diet restrictions.

The patients visited the outpatient clinics at the end of the second and fourth week during the placebo-washout periods and at the end of the second and the third weeks during the treatment periods. At each visit (07.00 h–09.00 h) the patient stayed in the clinic for at least 1 h during which supine and standing blood pressures and pulse rates were determined three times before the daily dose of medication. Standing pulse was not measured at the Hypertension Clinic at Sahlgrenska Hospital. At the end of each visit the patients met with a physician who inquired about side effects, collected leftover capsules and gave the patient enough medication to last until the following visit.

Measurements of blood pressure and pulse were made by the same observers throughout the study. Blood pressure was always measured to the nearest 2 mm Hg with a mercury sphygmomanometer. 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 pressure. Supine blood pressure and pulse were measured after the patients had been recumbent for at least 5 min, and standing measurements were carried out after at least 2 min in the erect position. Heart rates were determined by doubling the radial pulse counted over a 30 s period.

A patient was considered to be controlled if the SDBP was below 90 mm Hg, having at the same time a decrease of at least 10 mm Hg in SDBP, and to have responded to the treatment if the decrease of the SDBP was 10 mm Hg or more whether or not a diastolic pressure of 90 mm Hg was achieved.

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

Statistical analysis

Analysis of variance was used to analyze vital signs. Carryover effect (model 1), investigator-by-treatment interaction (model 2) and treatment effect in each period (model 3) were tested by models containing effects as indicated below. Investigator-by-treatment interaction was not tested for standing heart rate and urine excretion data since these were only gathered at one clinic.

Model 1	*Model 2*	*Model 3*
Subject	Subject	Subject
Period	Period	Period
Treatment	Treatment	Treatment
Carryover	Investigator-by-treatment	

Comparison between the combined enalapril doses and placebo, between placebo and other treatments, and between 40 mg and other treatments were made using contrasts of treatment means adjusted for subject and period effects. The linear and quadratic dose-response effects were tested by orthogonal contrasts of adjusted treatment means. Within-treatment tests and

the pre- post weight comparison were *t*-tests. All tests were two-tailed and carried out at alpha = 0.05. The design did not permit analysis of any treatment-by-period interaction, but examination of the data in each period revealed consistent relationships among the treatments.

The proportions of patients controlled/responded were analyzed using the method of Grizzle *et al.* (1969) for categorical data. The model contained the terms investigator and treatment. Pairwise comparisons to placebo and to 40 mg, tests of the combined enalapril *vs* placebo effect, and the orthogonal linear and quadratic dose-response effects were made using contrasts on the model parameters.

Before any description of results of treatment comparisons can be made, the presence of carryover and/or period effects needs to be addressed. Carryover effects are those due to the Period I treatment affecting the results in Period II, however, these effects are different depending on the Period I treatment. In designs balanced for carryover effects, they can be estimated and treatment comparisons can be made without influence of carryover effects.

Period effects are those resulting from an overall difference between results in Period I *vs* those in Period II. These are observed similarly for each treatment sequence. They may have been caused by an effect of Period I treatment on results in Period II, but they are similar following each Period I treatment. These effects have no influence on the comparisons among treatments.

Results

Statistical tests revealed no significant carryover effects on any blood pressure variable at any week ($P > 0.20$). Significant period effects were observed at weeks −2 and 0 (Period II baselines were significantly lower than Period I baselines) but not at weeks 2 and 3. This means that if the period effect resulted from the effect of Period I treatment on that of Period II, then it was similar for all Period I treatments (because no carryover effects were observed and the effect subsided by weeks 2 and 3 of Period II (because no period effects were observed at weeks 2 and 3). Hence the comparisons among treatments based on the combined Period I and II data are valid. No significant investigator-by-treatment interactions were observed; hence, all subsequent results derive from Model 3. Blood pressures and heart rates reported in the results have consequently been adjusted for subject and period effects.

SDBP increased 10 mm Hg or more in eight patients during the first treatment period or the second washout period, and they entered the second treatment period directly.

Supine blood pressure

Each dose of enalapril, except 5 mg at Week 3, produced significant decreases in systolic, diastolic and mean arterial (MAP) blood pressure after 2 and 3 weeks, while there were no significant changes on placebo (Table 1). Systolic blood pressure decreases after 3 weeks of treatment were significantly smaller on 2.5 ($P < 0.05$) and 5 ($P < 0.01$) than on 40 mg/day of enalapril. The MAP decreases following each enalapril dose were all greater than those following placebo treatment, significantly so for all except the 5 mg/day dose at Week 3. Diastolic blood pressure and MAP decreases after 3 weeks treatment were significantly smaller on 2.5 mg ($P < 0.05$), 5 mg ($P < 0.01$) and 20 mg ($P < 0.05$) than on 40 mg/day enalapril (Table 1).

After 3 weeks of treatment, the linear dose response relationship was significant for change from baseline in blood pressure [$P < 0.01$ for systolic and MAP (Figure 1) and $P < 0.05$ for diastolic pressure]. None of the quadratic dose-response effects in pressure change from baseline was significant ($P > 0.19$ in each case).

Standing blood pressure

The standing blood pressures after 2 and 3 weeks of treatment were similar to the supine pressures. The blood pressures during the placebo period and after 2 and 3 weeks of treatment were generally greater in the standing than in the supine position, but the magnitude of changes and differences among and between treatments were similar (Table 2). Significant differences in standing blood pressures were observed in nearly the same instances as in the supine blood pressures.

Heart rates

Mean changes in supine and standing heart rates during enalapril treatment were all near zero and nonsignificant. Overall treatment effects, linear and quadratic effects, and differences between combined enalapril doses and placebo were all nonsignificant ($P > 0.20$).

Controlled and/or responding patients

There was a significant difference between the blood pressure at the end of the first and the second washout period. However, the blood pressures during the two treatment periods did

Table 1 Adjusted** mean change from baseline in supine systolic (S) and diastolic (D) blood pressure (mm Hg) after 2 and 3 weeks of treatment with enalapril

Treatment	*Daily dose (mg)*	*Baseline* n	*S/D*	*2 weeks S*	*D*	*Baseline* n	*S/D*	*3 weeks S*	*D*
Placebo	0	28	156/96	4†	0†	27	157/96	1†	−1†
Enalapril	2.5	32	157/96	−8‡*	−5†*	32	157/96	−10‡*†	−5‡*†
Enalapril	5	31	158/97	−9‡*	−6‡*	27	155/97	−4†	−4‡†
Enalapril	10	28	161/98	−10‡*	−5‡*	27	161/98	−15‡*	−8‡*
Enalapril	20	28	159/95	−14‡*	−5‡	28	159/95	−13‡*	−4‡†
Enalapril	40	31	159/96	−15‡*	−8‡*	29	159/96	−20‡*	−10‡*
Pooled within Patient s.d.			10/5	13	7		9/5	12	7

**Adjusted for period and patient effects
‡Significant decrease from baseline, $P < 0.05$
*Significant difference from placebo, $P < 0.05$
†Significant difference from enalapril 40 mg, $P < 0.05$

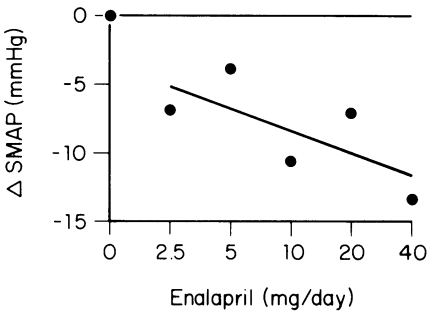

Figure 1 Mean change from baseline in supine mean arterial pressure (SMAP) after 3 weeks of enalapril therapy.

not differ between the corresponding treatment groups. Therefore, only data from the first period were analyzed (Table 3). Patients receiving enalapril 10 mg/day or more responded to a significantly greater extent than did the placebo-treated patients. There was a significantly greater portion of controlled patients in the group on enalapril 40 mg/day than in any other treatment group.

Adverse effects

Eight placebo-treated patients reported adverse effects during the randomized treatment period. One patient on enalapril 5 mg/day had mild

Table 2 Adjusted** mean change from baseline in standing systolic (S) and diastolic (D) blood pressures (mm Hg) after 2 and 3 weeks of treatment with enalapril

Treatment	*Daily dose (mg)*	*Baseline* n	*S/D*	*2 weeks S*	*D*	*Baseline* n	*S/D*	*3 weeks S*	*D*
Placebo	0	28	156/103	2†	0†	27	157/104	0†	−1†
Enalapril	2.5	32	154/104	−7‡	−7‡*	32	154/103	−8‡†	−6‡
Enalapril	5	31	156/104	−8‡*	−7‡*	27	153/103	−3†	−1†
Enalapril	10	28	160/104	−11‡*	−6‡	27	160/104	−16‡*	−8‡*
Enalapril	20	28	158/103	−14‡*	−6‡	28	156/102	−13‡*	−4†
Enalapril	40	31	155/103	−12‡*	−7‡*	29	156/103	−18‡*	−10‡*
Pooled within Patient s.d.			10/5	14	8		9/5	13	7

**Adjusted for period and patient effects
‡Significant decrease from baseline, $P < 0.05$
*Significant difference from placebo, $P < 0.05$
†Significant difference from enalapril 40 mg, $P < 0.05$

Table 3 Number and percentages of patients controlled (SDBP below 90 mm Hg with a decrease ≥ 10 mm Hg and/or responding (SDBP decrease of 10 mm Hg or more) whether or not reaching ≤ 90 mm Hg after 3 weeks of enalapril treatment (Period I). Analysis by the method of Grizzle *et al.* (1969) for categorical data.

Treatment	*Daily dose (mg)*	n	*Baseline SDBP (mm Hg)*	*Responding*		*Controlled*	
				No.	*(%)*	*No.*	*(%)*
Placebo		16	99	0	(0)	0	(0)
Enalapril	2.5	14	97	1	(7)	1	(7)
Enalapril	5	16	97	4	(25)	3	(19)
Enalapril	10	14	97	5*	(36)	4*	(29)
Enalapril	20	15	98	7**	(47)	4**	(27)
Enalapril	40	15	96	8**	(53)	8**	(53)
Pooled s.d.			6				

*$P < 0.05$, **$P < 0.01$ (difference from placebo group)

orthostatic symptoms during the first few days of treatment. One patient on enalapril 20 mg/day felt dizzy for 6 days and another on the same dosage had indigestion for 8 days. One patient had mild vertigo for 14 days on enalapril 20 mg/day; the same patient reported 2 days of mild vertigo during the second treatment period while taking enalapril 10 mg/day. Five patients (one on placebo and four on various doses of enalapril) experienced mild elevations in their serum creatinine, none of which was thought to be drug related.

Discussion

Enalapril reduced systolic and diastolic blood pressures significantly in all treatment groups. However, 10 mg/day or more were needed to produce a satisfactory hypotensive effect; *viz.*, a SDBP reduction ≥ 10 mm Hg and achievement of blood pressure control (SDBP ≤ 90 mm Hg). After 3 weeks of treatment there was a significant linear dose-response relationship, and the blood pressure response in the groups on 2.5 and 5 mg/day were significantly smaller than in the group on the highest dosage. In an earlier study, 2.5 mg did not produce a significant blood pressure reduction and 20 mg/day lowered the blood pressure to the same extent as 10 mg/day with the difference that the effect was more prolonged in the high dosage group (Gavras *et al.*, 1981). However, it has been shown that 2.5 mg of enalapril in a single dose blunts the effect of the blood pressure responses to exogenous angiotensin I (Biollaz *et al.*, 1981). The present study showed that although 2.5 mg gave a statistically significant blood pressure decrease, 10 mg/day or more are needed to achieve satisfactory blood pressure reduction. It also showed that there is an increased response up to 40 mg/day and that a further response to even higher dosages may be anticipated.

The quadratic dose-response effect is a measure of curvature (departure from linearity) in the dose-response relationship. It could also indicate a levelling off of effect. The lack of any significant quadratic effect supports the linearity of the dose-response relationship across the 2.5–40 mg/day range.

A twice-a-day dosage regimen was used in this study. However, it has been observed subsequently that once-daily dosing is as effective as half the dose administered twice daily (Gomez *et al.*, 1983a,b). Although the relationship of dose to the 24 h blood pressure effect may be important, it could not be assessed in this study.

The number of patients with a controlled blood pressure (SDBP ≥ 90 mm Hg) as well as the number of patients responding with at least a 10 mm Hg decrease in SDBP could only be studied during the first treatment period due to the period effect discussed above. However, about 40% of the patients were controlled and about 50% showed a significant blood pressure response on the two highest dosage levels. This agrees with the results of captopril where 47% were controlled on dosages up to 450 mg/day (Fernandez-Cruz *et al.*, 1982).

The combination of captopril and hydrochlorothiazide has been reported to give a synergistic blood pressure lowering response. This has also been shown for enalapril (Ferguson *et al.*, 1982; Vidt, 1984); therefore, coadministered diuretics may alter considerably the dose-response to enalapril.

Several studies of ACE inhibitors in essential hypertension have shown transient heart rate increases (Santucci *et al.*, 1982), heart rate decreases (Rabinad-Estrada *et al.*, 1982) or no change in heart rates (Stumpe *et al.*, 1982). In the present study no change in heart rate was

observed, although theoretically an increase in heart rate would be anticipated due to the vasodilating effect of enalapril. However, it has been shown that enalapril does not influence the sympathetic nervous system (Millar *et al.*, 1982; Ibsen *et al.*, 1983). The lack of heart rate increase is unclear, but it has been suggested that it might be due to an increased parasympathetic activity during treatment with ACE inhibitors (Ibsen *et al.*, 1983; Reid *et al.*, 1983).

In conclusion, enalapril was associated with an increasing dose-response relationship across the 2.5–40 mg/day range. The 2.5 mg/dose is effective in some patients; however, doses $\geq$ 10 mg/day may be necessary to achieve satisfactory blood pressure control.

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