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Hemodynamic Responses to Angiotensin I in Normal Volunteers and the Antagonism by the Angiotensin-Converting Enzyme Inhibitor Cilazapril

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Summary: According to classic pharmacologic theory, agonist/antagonist competition can be used to quantify an antagonist's potency by measurement of agonist dose–response curves in the presence of varying doses of the antagonist. We used this principle to characterize the interaction between angiotensin I (AI) and the angiotensin-converting enzyme (ACE) inhibitor cilazapril in humans. In addition, by comparing the effects of AI and angiotensin II before and after administration of a 30-mg dose of cilazapril, we could show the specific AI antagonism of the ACE inhibitor in humans. To obtain the antagonist's dose–response curves, six healthy male volunteers received five single oral doses of cilazapril, 0.5–8.0 mg. Enalapril, 10 mg, and captopril, 12.5 mg, served as positive controls and placebo as the negative control. Dose–response curves following intravenous infusions of AI were established 4 h after oral ingestion of the ACE inhibitors. Noninvasively measured systolic and diastolic blood pressures and total peripheral resistance assessed AI effects. Cilazapril dose dependently shifted the AI dose–response curve rightward, with 1.0 mg inducing a twofold shift. Enalapril and captopril appear less potent, on a milligram basis, in antagonizing AI effects 4 h after drug intake. The methodology could be a useful tool for a rational testing and comparison of ACE inhibitors in clinical pharmacology. **Key Words:** Angiotensin I—ACE inhibitors—Cilazapril—Enalapril—Captopril.

Orally active angiotensin-converting enzyme (ACE) inhibitors are gaining increasing importance in the treatment of hypertension and heart failure (1). These drugs apparently act by several mechanisms, including inhibition of bradykinin breakdown and interactions with prostaglandins and the sympathetic system (1,2). One main mechanism of action of these drugs is the competitive inhibition (3) of the conversion of the prohormone angiotensin I (AI) into the active angiotensin II (AII). AII is a powerful constrictor of smooth muscle, especially the vascular smooth muscle (4). In the intact cardiovascular system it predominantly induces a drastic increase in peripheral resistance, followed by an increase in blood pressure and a decrease in cardiac output.

Previous clinical pharmacologic investigations of ACE inhibitors in humans included determining the inhibition of plasma ACE by ACE inhibitors or measuring the reduction in blood pressure effects after bolus doses of AI (5–7). The competition between AI and ACE inhibitors derived from in vitro studies (8,9) should also allow application of the classic pharmacologic approaches to receive a more quantitative estimation of the inhibition (3,21,23).

The aim of the present study therefore was to establish dose–response curves of AI in humans in the presence of varying doses of an ACE inhibitor. The pharmacodynamic effects of AI were assessed by using noninvasive methods to detect changes in blood pressure and peripheral resistance. For the inhibition of ACE, the new enzyme inhibitor cilazapril (10,11) was used at different dose levels. En-

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alapril and captopril, in single doses within the therapeutic range, served as positive controls, and placebo was the negative control.

METHODS

Six ambulatory male volunteers, ages 18–27 years (mean, 23 ± 3.3 years) and weighing from 72 to 88 kg (mean, 80.3 ± 6.6 kg), participated in the study after giving full informed written consent. Each subject was healthy, as determined by history, physical examination, electrocardiogram, and blood biochemical analysis. No restrictions concerning food were made and no drug intake (but the test drugs) was permitted during the study. The study followed a randomized, double-blind, crossover, placebo-controlled design. Each volunteer received the following drug dosages: cilazapril, 0.5, 1.0, 2.0, 4.0, and 8.0 mg; captopril, 12.5 mg; and enalapril, 10 mg. Although the sequence of the drugs was randomized, cilazapril was given in ascending dosage sequence. On the first and the last experimental days placebos were given. A 7-day washout period was observed between the test days. On each day an AI dose–effect curve was derived. The human AI (Senn Chemicals, Dielsdorf, Switzerland) was in lyophilized form. A sterile stock solution of this substance containing 50 μg/ml in physiologic saline was prepared and passed through a Millex GV filter (Millipore, Molsheim, France). Further dilutions were prepared with saline to reach final concentrations of 1.2 and 4 μg AI/ml for the infusion solution. From pilot studies it was obvious that responses reach steady state within 3 min (G. G. Belz, unpublished results, 1985, 1986); therefore, for safety reasons and to approach steady state, we selected continuous infusions rather than bolus injections. We infused AI using an automatic pump (Perfusor/Braun Melsungen), in increasing doses (3 min each) of 0.1, 0.3, 0.9, 2.0, 3.9, 6.0, 9.0, 12.0, 15.0, and 18.0 μg/min.

From 6 p.m. of the preceding evening until the completion of the measurements on each study day no strenuous activities, caffeinated drinks, alcohol, or nicotine were allowed. On the mornings of the study days the fasting subjects swallowed the respective drug dose with 100 ml water. The subjects received an indwelling venous cannula and the electrodes were affixed.

All cardiovascular parameters were recorded with the subjects in supine position with the head elevated 15°. After a 15-min rest period, three baseline recordings were made 5 min apart. Four hours after the drug intake the AI infusion began. During the last 30 s of each dose level the cardiovascular parameters were recorded. There were two measurements of the blood pressure—one before and one following the cardiographic registrations—and their mean was used for further evaluations. For clinical safety, an additional blood pressure recording was made within the 1st min of each AI dose level. The AI infusion was stopped when the diastolic blood pressure (BP dias) reached 120 mm Hg.

The methods for the noninvasive cardiovascular assessments are described in detail elsewhere (12). In brief, ECG lead CM_5, phonocardiogram filter m_2, carotid pulse tracing, and an electrical thoracic impedance cardiogram (Minnesota impedance cardiograph, model 400) were recorded simultaneously using a four-channel Cardirex 3T jet recorder (Siemens-Elema). Twenty-five complexes at 10 mm/s were obtained, immediately followed by 10 complexes at 100 mm/s, during which the subject held his breath after a normal expiration. For ethical reasons intraarterial monitoring of blood pressure was avoided; an ordinary cuff mercury manometer was used and Korotkoff's phase I and V sounds determined the systolic blood pressure (BPsys) and BPdias. Heart rate was computed from the last 20 RR intervals of the 10-mm/s registration. The means of the first five complexes of 100-mm/s registration traces were used for the systolic time intervals, ECG, and impedance parameters. Electromechanical systole, left ventricular ejection time, and preejection period were corrected for heart rate as usual (12). From the impedance cardiogram, the dZ/dt signal was obtained and used for calculation of stroke volume, cardiac output, and total peripheral resistance (TPR) by the standard methods (12). Stroke volume and cardiac output derived from electrical impedance cardiography have been validated by simultaneous measurements using echocardiography (13), angiocardiography (14), and electrical flowmetry (15), as well as Fick's method (16,17). High correlations have been shown for the impedance method. The reproducibility of results derived using this methodology has been demonstrated in several works done by our group (12,18), as well as in the results of others (17,19). In addition, the reproducibility is obvious from the low variability of TPR following administration of the placebos in this study.

In an additional experiment the specificity of the effect of cilazapril on the effects induced by the AI infusion was tested. For this study, four of the volunteers were selected randomly. Following the procedure described above, an AI dose–effect curve was established. After the values had returned to baseline (within 10 min), the procedure using the same dose steps was repeated, using AII-analogous angiotensin amide (Hypertensin, CIBA-GEIGY, Basel, Switzerland). Thereafter, the volunteers swallowed 30 mg cilazapril, and 3 h later the infusions with AI and AII were repeated.

Evaluation of data

The analysis of data was based on the following assumptions. First, the maximal capacity of the AI effects (E_{max}) is not changed in the presence of an ACE inhibitor in vitro (9). Since E_{max} (i.e., response relative to baseline) cannot be measured under in vivo conditions in humans, it was set arbitrarily at 200 mm Hg for BPsys and BPdias and 2,000 dyn · s · cm^{-5} for TPR. These arbitrary values are more than 20-fold higher than ACE inhibitor–induced changes in baseline. Thus, the rightward shifts of the different AI dose–response curves due to ACE inhibition are not relevantly influenced by changes in baseline (3). Furthermore, the choice of a model assuming identical capacity of effects (E_{max}) does not yield different rightward shifts. The second assumption is that a given fractional response (relative to E_{max}) is only dependent on the relative portion of receptive sites occupied by the agonist. This problem was discussed extensively previously (20).

The families of AI dose–effect data were described by a simultaneous, nonlinear, least squares fitting procedure using the equation

$$E_A = E_{max} / (1 + K_A^h / (DR_n \cdot A^h) \cdot (1 + I_n/K_i)) + b_n \quad \text{Eq. 1}$$

Where E_A denotes effect, E_{max} the maximal capacity of effect, A the dose of AI, K_A the ED_{50}, h the slope of the

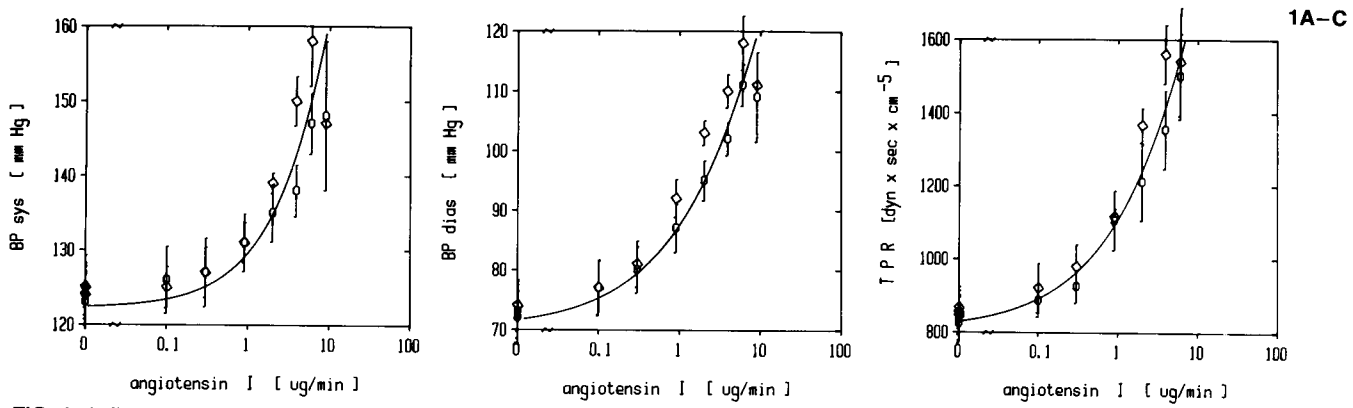

FIG. 1. Influence of angiotensin I on systolic (BPsys) **(A)** and diastolic (BPdias) **(B)** blood pressures, and total peripheral resistance (TPR) **(C).** Presented are mean values ± SEM (n = 6). The curve was fitted using the data from two experiments with placebo administration prior to the angiotensin I infusion. Symbols: diamond, placebo 1; circle, placebo 2.

curves (restricted to values 0.85–1.15), b their lower asymptote (basal values), I the dose of ACE inhibitor, and K_i the respective ED_{50} (3). n indicates the n^{th} dose of ACE inhibitor and DR_n the respective n^{th} dose ratio of A (relative to placebo) necessary to bring about equivalent effects (n = 1–9: with 1 and 2 = placebo; 3 = 0.5 mg, 4 = 1.0 mg, 5 = 2.0 mg, 6 = 4.0 mg, 7 = 8.0 mg cilazapril; 8 = 10 mg enalapril; 9 = 12.5 mg captopril).

For each of the three parameters shown (BPsys, BPdias, and TRP), such a simultaneous fitting procedure was carried out separately. The reciprocal of the mean variance of each data point was used as a weight. Depicted are mean values ± SEM. The upper and lower boundaries of the univariate 95% confidence intervals of each parameter were derived iteratively using the sum of squared deviations at 1‰ increasing or decreasing steps of the parameter in an *F* test. For further details of the mathematical procedure see Wellstein et al. (21).

RESULTS

Effects of AI

The effects of AI in the two placebo phases are shown in Fig. 1. Dose dependently, AI increased BPsys and BPdias and TPR. It is evident from the figures that there was only minor variability of these responses as established on the two occasions, one at the beginning (placebo 1), the other at the end (placebo 2), of the complete study (Fig. 1 and Table 1). There was no significant shift detectable in AI response between the two occasions ($p > 0.05$).

The other noninvasive parameters showed a typical spectrum of effects. Heart rate and cardiac output decreased, and the heart rate–corrected preejection period and the corrected electromechanical systole lengthened, whereas the corrected left ventricular ejection time was shortened (not depicted).

Specificity of the action of cilazapril

To test the site of antagonistic action of cilazapril, dose–effect curves of AI and AII were established in the absence and in the presence of a high dose of cilazapril. Figure 2 demonstrates the effects of AI and AII on the BPdias. The mean basal values (b in Eq. 1) were between 75 and 78 mm Hg before and between 61 and 63 mm Hg following administration of 30 mg cilazapril. As can be seen from the upper panel of Fig. 2, administration of cilazapril does not reduce the effects of AII. Rather, a small "sensitization" becomes obvious. In contrast to this observation, after cilazapril administration the effects of AI in the dose range up to 2.0 μg/min are abolished. BPsys and TPR behaved in the same manner (results not depicted). From this it becomes evident that our methodology using AI infusions specifically reflects the effects of ACE inhibition. The inhibitory effects of cilazapril

TABLE 1. *Basal values calculated from the dose–response relationship of angiotensin I (b in Eq. 1)*

Treatment (mg)	BPsys (mm Hg)	BPdias (mm Hg)	TPR (dyn · s · cm^{-5})
Placebo 1	122 (117–127)	70 (67–74)	806 (757–854)
Placebo 2	126 (123–128)	76 (72–80)	851 (791–911)
Cilazapril (0.5)	121 (117–124)	70 (65–75)	878 (808–948)
Cilazapril (1.0)	117 (115–119)	66 (63–70)	760 (684–836)
Cilazapril (2.0)	116 (114–119)	68 (65–72)	852 (776–929)
Cilazapril (4.0)	115[a] (114–116)	64[a] (62–67)	804 (764–845)
Cilazapril (8.0)	115[a] (114–116)	61[a] (58–63)	759 (714–805)
Enalapril (10)	117 (115–119)	61[a] (60–62)	734 (697–771)
Captopril (12.5)	121 (116–126)	70 (68–72)	871 (827–914)

Values are means, with 95% confidence intervals in parentheses. BPsys systolic blood pressure; BPdias, diastolic blood pressure; TPR, total peripheral resistance.

[a] $p < 0.05$ versus placebo.

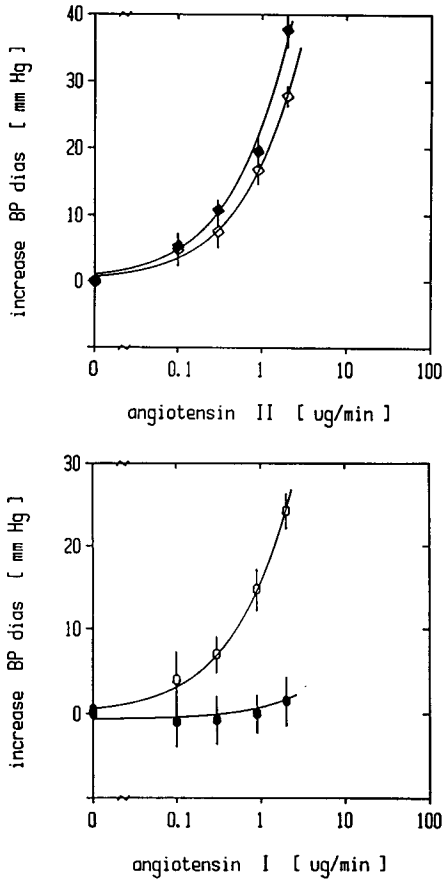

FIG. 2. Comparison of the effects of cilazapril (30 mg orally) on angiotensin I **(bottom)** and angiotensin II **(top)** effects. Presented are mean changes (±SEM; n = 4) as compared with baseline. Symbols: open circles before cilazapril; closed circles after cilazapril.

can be overcome by the administration of higher doses of AI, pointing in the direction of a competitive mechanism. The rightward shift of the AI dose–effect curve derived in this experiment using AI doses of up to 18 μg/min amounted to a dose ratio (DR)-1 of 28.2 for the BPdias.

Influence of ACE inhibitors on the effects of AI

Captopril (12.5 mg) and enalapril (10 mg), substances with well-known ACE-inhibiting properties (1,5) which served as positive controls in our study, produced a rightward shift of the AI dose–effect curves (Fig. 3) (captopril < enalapril). The baseline values for blood pressures showed a reduction under enalapril influence (Table 1), in agreement with observations of Millar et al. (22).

Cilazapril dose dependently induced a rightward and downward shift of the AI dose–effect curve (Fig. 4; depicted are the results of 1.0 and 8.0 mg). With cilazapril the basal plateau of blood pressures was lowered significantly for the 4.0- and 8.0-mg doses.

Table 2 shows the rightward shifts (DR-1) for the different treatments. For cilazapril, a dose dependency of the shift is obvious. A DR-1 of ~1, i.e., a twofold rightward shift of the dose–effect curve (23), was observed after 1.0 mg cilazapril for each of the parameters. Four to eight milligrams yielded a DR-1 value similar to 10 mg enalapril. Thus, cilazapril appears to be about twofold more potent on a milligram basis.

DISCUSSION

Cilazapril is a new, orally active, potent, and long-acting ACE inhibitor (11). This substance had been sought with the aid of molecular graphics and is the prodrug form of a potent ACE inhibitor (10). In the present study in humans, a classic pharmacologic approach (23) characterized the antagonistic action of cilazapril by means of shifts in AI dose–effect curves. For each of the three hemodynamic parameters, BPsys and BPdias and TPR, we obtained rightward shifts of the AI dose–effect curves which were proportional to the cilazapril doses given (Table 2).

AI in the dosage used produces no effects by itself, but after biologic conversion to AII brings

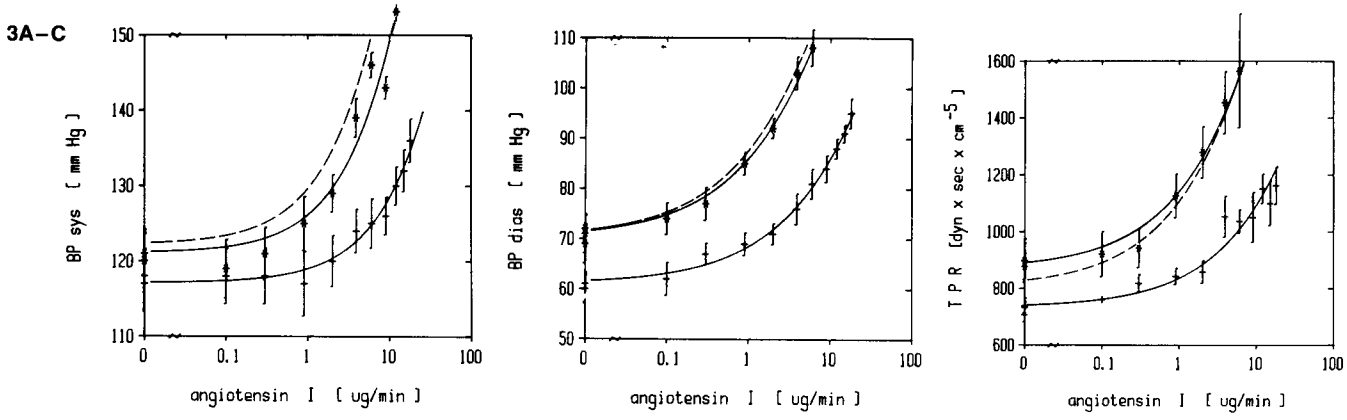

FIG. 3. Influence of captopril 12.5 mg (asterisk) and enalapril 10 mg (cross) on angiotensin I response on systolic (BPsys) **(A)** and diastolic (BPdias) **(B)** blood pressures, and total peripheral resistance (TPR) **(C)** 4 h after oral drug administration. The dotted line indicates the function following placebo (Fig. 1).

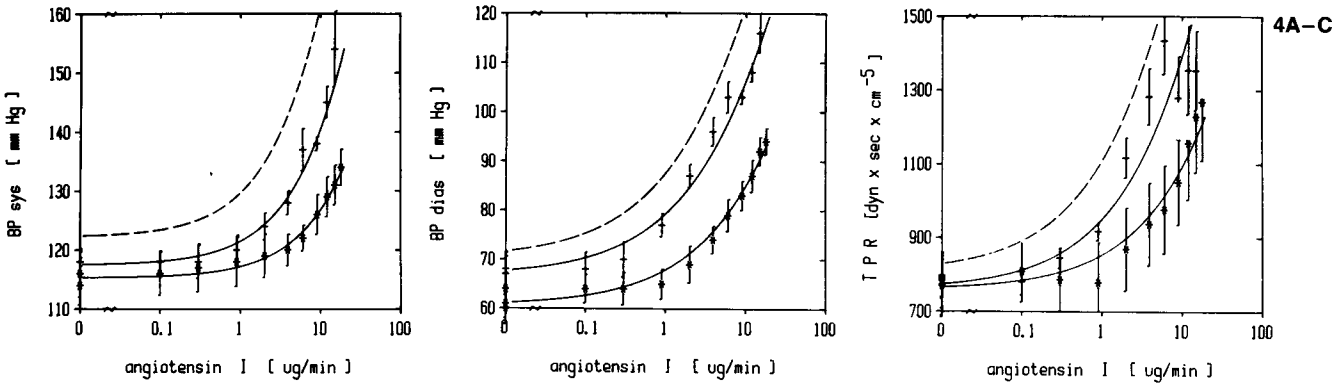

FIG. 4. Influence of cilazapril, 1.0 (cross) and 8.0 (asterisk) mg, on angiotensin I response 4 h after oral drug administration on systolic (BPsys) **(A)** and diastolic (BPdias) **(B)** blood pressures, and total peripheral resistance (TPR) **(C).** The dotted line indicates the function following placebo (Fig. 1).

about the effects observed. ACE inhibitors do not influence the effects of AII. Results presented in Fig. 2 help delineate this phenomenon. Our method used, therefore, is highly specific for detection of ACE-inhibiting drugs. The observed rightward shifts of AI dose–effect curves are due to ACE inhibition which might in principle be competitive or noncompetitive.

In vitro studies with ACE inhibitors indicate a competitive mechanism (8,9). For the in vivo situation in humans no information was available on the type of antagonistic mechanism. Available from our study are AI dose–effect curves in the presence of a series of different doses of cilazapril; therefore, we could attempt to achieve further insight into the mechanism of its antagonism by subjecting our data to an analysis according to Schild (23). It should be recalled that this methodology was developed to evaluate antagonists in in vitro studies in intact tissues (23,24). The parameters that can be measured in vivo in humans represent complex physiologic entities. Therefore, application of this tool of basic pharmacology should only be applied with caution. The theory assumes that an identical fractional response is obtained at an identical receptor occupancy by an agonist (23–25). In the presence of an antagonist, a higher agonist dose (resp. concentration) is required to yield a predefined receptor occupancy and thus response. It is thus sufficient (as also done in vitro) to titrate a given effect in the absence and in the presence of an antagonist.

In Fig. 5 the Schild plot for the BPdias (data from Table 2) is shown. The slope of the correlation line is not significantly different from 1 ($p > 0.05$), which suggests a competitive mechanism. A more reliable analysis, however, would require a wider dose range. From the present results, an apparent K_i dose (20) (i.e., that dose which induces a twofold shift of the AI dose–effect curve) of ~1 mg cilazapril can be derived. This value would represent a 50% inhibition of ACE activity with respect to the pharmacologic effects of AI. Enalapril and, more so, captopril appear less potent (cf. Table 2). It

TABLE 2. *Rightward shifts (given are dose ratios minus one, of the angiotensin I dose–effect curves) 4 h after single oral doses of angiotensin-converting enzyme inhibitors*

Treatment (mg)	BPsys (mm Hg)	BPdias (mm Hg)	TPR (dyn · s · cm^{-5})
Cilazapril (0.5)	0.05 (−0.19–0.41)	0.25 (−0.1–0.82)	0.01 (−0.36–0.77)
Cilazapril (1.0)	1.19 (0.87–1.61)	0.85 (0.48–1.33)	1.36 (0.32–4.18)
Cilazapril (2.0)	4.31 (2.93–6.94)	3.12 (1.97–5.02)	4.39 (2.07–10.37)
Cilazapril (4.0)	3.05 (2.49–3.74)	2.97 (2.21–4.00)	5.29 (3.59–8.06)
Cilazapril (8.0)	4.56 (3.73–5.63)	4.07 (3.06–5.49)	7.31 (4.48–12.71)
Enalapril (10)	4.73 (3.87–5.94)	3.88 (3.24–4.61)	6.17 (3.80–10.69)
Captopril (12.5)	0.64 (0.28–1.18)	0.21 (0.03–0.43)	0.22 (−0.16–0.88)

The shifts are calculated on the base of the effects of angiotensin I following placebo 1 and placebo 2 administration. Abbreviations as in Table 1.

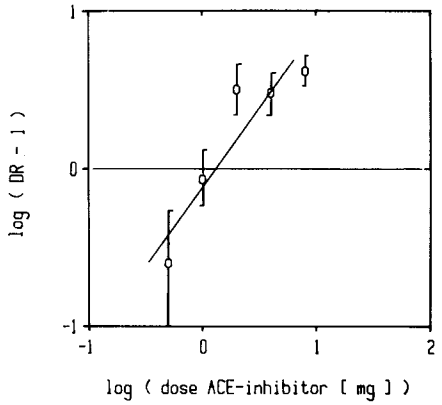

FIG. 5. Relations between the log dose of cilazapril and the log dose ratio (DR-1) of angiotensin I response for diastolic blood pressure 4 h after administration of cilazapril, 0.5–8.0 mg. Presented are means with 95% confidence intervals. ACE, angiotensin-converting enzyme.

should be noted that different elimination half-lives of the drugs investigated could bias these results, since measurements began 4 h after drug administration. The sequence of potency of the three ACE inhibitors, however, remains unaffected with respect to the time of measurement (Belz et al., unpublished observations).

From studies testing cilazapril in mildly to moderately hypertensive patients, a daily dose of 1.25 mg is effective in lowering blood pressure (26). It is noteworthy that in our present study in healthy normotensive volunteers a 1.0-mg dose induces a twofold rightward shift of the AI dose–effect curve. Establishing AI dose–effect curves and evaluating the effects of various doses of ACE inhibitors on them appears to be a suitable tool for the clinical pharmacologic evaluation of ACE inhibitors.

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