Interactions between cilazapril and propranolol in man; plasma drug concentrations, hormone and enzyme responses, haemodynamics, agonist dose-effect curves and baroreceptor reflex

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1 The pharmacokinetics, hormonal and haemodynamic responses at rest and during challenges with angiotensin I (blood pressure), isoprenaline (heart rate), and noradrenaline (blood pressure) were investigated in six healthy male volunteers following a 1 week treatment with placebo, propranolol (120 mg day⁻¹), cilazapril (2, 5 mg day⁻¹), and a combination of both in a double-blind cross-over design.

2 Both drugs reduced systolic and diastolic blood pressure by about 7 mm Hg as compared with placebo. After coadministration, this drop in blood pressure was doubled and lasted longer than after the administration of the individual components.

3 Following cilazapril, a pronounced increase in plasma renin activity (PRA) was found (factor ~10 at drug peak concentrations). Coadministration of both drugs resulted only in a moderate increase in the PRA (factor ~3). Significant changes in plasma catecholamines were not observed.

4 Propranolol shifted the isoprenaline dose-effect curve to the right, and cilazapril that of angiotensin I, irrespective of the presence of the other drug. Cilazapril tended to shift the noradrenaline dose-effect curve somewhat to the right.

5 The gain of the baroreceptor reflex (angiotensin-stimulation) was not influenced by cilazapril but was lowered by propranolol, irrespective of the presence of the ACE inhibitor.

6 Except for a statistically not significant decrease in the peak concentrations of each drug during the combined therapy, a pharmacokinetic interaction between the two drugs was not found.

Keywords ACE inhibitors β -adrenoceptor antagonists interactions angiotensin I blood pressure isoprenaline noradrenaline baroreceptor reflex activity

Introduction

ACE inhibitors and β -adrenoceptor antagonists are drugs frequently used in the treatment of various cardiovascular diseases. However, their combination is generally not recommended for treating hypertension (Zanchetti, 1987) since both drugs presumably act at least in part via the same mechanism, namely, by suppressing the renin-angiotensin-system and by interfering with the sympathetic system (Douglas, 1985; MacGregor *et al.*, 1985; Kondowe *et al.*, 1987). However, in the treatment of various diseases, a combined use of the two drug groups is sometimes unavoidable. Therefore, an evaluation of the possible pharmacokinetic and dynamic interactions of compounds belonging to these groups seemed justified. For this investigation, we selected cilazapril, a potent new ACE inhibitor (Belz *et al.*, 1987; Wellstein *et al.*, 1987a), and propranolol, the prototype of a β -adrenoceptor antagonist. The half-life of their effects is about 5 h, and nearly identical, as determined from agonist responses (Wellstein *et al.*, 1988, 1987b). The purpose of this study was to evaluate:

- 1) the influences of each individual drug and combinations thereof on the haemodynamics and circulating hormones and enzymes of the renin-angiotensin-system, 2) the respective effect on the responses to isoprenaline, noradrenaline, and angiotensin I challenges and 3) possible pharmacokinetic interactions.

Methods

Six ambulatory healthy male volunteers, between 24 and 30 (mean 26.0 ± 3.2) years of age, weighing between 65 and 86 (mean 73.9 ± 8.4) kg participated in this study; they were permitted their normal diet. A pre-study physical examination and laboratory tests were performed and repeated at the end of the study. The protocol was in accordance with the Declaration of Helsinki and informed consent was obtained in writing. The study protocol was approved by the institutional ethics committee.

The study followed a cross over design with a 7 day wash-out period between the four phases. The protocol called for four 7 day treatment periods. Using double-blind double dummy techniques, each volunteer was allocated in randomized fashion to the following four treatment regimens:

- 1) placebo plus placebo, 2) cilazapril 2.5 mg plus placebo, 3) placebo plus propranolol 120

mg and 4) cilazapril 2.5 mg plus propranolol 120 mg. The drugs were dispensed once a day in the morning with 100 ml of water approximately 1 h before breakfast and under supervision.

The heart rate (HR) and blood pressure were measured daily immediately before drug intake. Blood for determining the drug trough concentrations was withdrawn on days 0, 1, 3, and 5 of each treatment period.

On day 7 of each study period, the subjects reported to the institute at 08.00 h, exactly 24 h after the last drug dose and overnight fasting. The subjects refrained from alcohol, caffeine containing beverages and nicotine for 24 h prior to and during the study. Four hours after drug intake, a light standardized meal was served. Upon arrival, the volunteers remained in a reclining position for the entire day. Electrodes for monitoring ECG (lead CM₅) were affixed and an indwelling venous cannula was inserted for blood sampling. All basal measurements were started after 15 min (i.e. blood sampling and agonists dose-effect curves). The drugs were then ingested. The identical procedure was repeated 2 h after drug intake. Drug concentrations, heart rate and blood pressure were measured 1, 2, 4, 6, 8 and 24 h after drug intake.

Agonists dose-effect curves

These challenges were performed on day 7 before and 2 h after drug intake in the sequence described below. Before starting the infusions, basal measurements of blood pressure and heart rate were made in triplicate. Between the three challenge tests, the blood pressure and heart rate returned to baseline. All dose-effect curves were derived by increasing the agonist's infusion dosage in 3 min intervals. With all agonists, the heart rate and blood pressure were measured during the last 30 s of each dose step.

Angiotensin I

A stock solution of angiotensin I (Senn Chemicals, Dielsdorf, Switzerland) containing 50 mg ml^{-1} in 0.9 % NaCl was prepared. Angiotensin I dose-effect curves were constructed after a continuous infusion of angiotensin-I via an infusion pump (VP-1000, Fresenius, Bad Homburg, FRG) at dosages ranging between 0.1 and $18 \mu\text{g min}^{-1}$, as discussed in the previous detailed descriptions (Belz *et al.*, 1987; Wellstein *et al.*, 1987b). The angiotensin I dosage was not further increased when the diastolic blood pressure exceeded the baseline values by 25 mm Hg.

Noradrenaline (NA)

The content of Arterenol® ampoules (1 mg ml⁻¹) was diluted with a 0.9 % NaCl and 1 mg ml⁻¹ vitamin C solution. NA dose-effect curves were constructed after continuous infusion of NA (Perfusor ED2, Braun, Melsungen, FRG) at dosages of 1, 2, 3, 4 and 6 µg min⁻¹. The dosage was not further increased when either systolic or diastolic blood pressure had increased by about 25 mm Hg or the HR had dropped below 35 beats min⁻¹.

Isoprenaline (ISO)

Aludrin® ampoules containing 0.2 mg ml⁻¹ isoprenaline were diluted as described for NA. ISO dose-effect curves were constructed after continuous infusion of ISO (Perfusor ED2) at dosages ranging from 0.5, 1, 2, 4, 8, 16, 32, 48 to 64 µg min⁻¹. The dosage was not further increased when the heart rate had reached about 25 beats min⁻¹ above baseline.

Measurement of blood pressure and heart rate

An ordinary cuff mercury manometer was used for measurements on days 0 to 6. Phase I and V sounds defined systolic and diastolic blood pressures. The heart rate was determined over a period of 30 s.

In addition to auscultation on all day 7 determinations, blood pressure was measured and documented using an Infraton-Tensiomat (Bertam *et al.*, 1982, Boucke, Tübingen FRG). The recordings were made with an ECG recorder and the heart rate was derived from 20 heart cycles.

Blood sampling

Blood was sampled in ice cooled vials. Heparinized vials for propranolol, cilazapril and ACE activity were used; EDTA-K vials for plasma renin activity, angiotensin I and II and EGTA-gluthation for catecholamine concentrations.

Drug assays

Propranolol concentrations in plasma were assayed by h.p.l.c. using fluorescence detection (excitation/emission wave-length: 286/336 nm) following a liquid/liquid extraction. The limits of quantification in 0.5 ml plasma were 5 ng ml⁻¹ with an inter-assay coefficient of variation between 7 and 3% at concentrations of 20 and 900 ng ml⁻¹, respectively.

Cilazaprilat plasma concentrations and ACE

activity in plasma were determined by a radioenzymatic assay (Francis *et al.*, 1987) with a coefficient of variation of less than 7% for cilazaprilat and less than 4% for ACE activity. Radio-labelled Hip-His-Leu was used as a substrate.

Determination of biochemical parameters

Plasma renin activity (PRA) was assessed by radioimmunological detection of angiotensin I formation (Sealy & Laragh, 1973). The inter-assay coefficient of variation was < 10% ranging between 3.8 and 7.3 ng ml⁻¹ h⁻¹. The plasma noradrenaline and adrenaline concentrations were measured by a combined h.p.l.c./THI method (Bioscientia, personal communication 1987). The interassay coefficient of variation was below 10% for adrenaline concentrations between 130 and 970 ng l⁻¹, and for noradrenaline between 420 and 1100 ng l⁻¹. The detection limit was 50 ng l⁻¹. Plasma angiotensin I and II were analyzed by radioimmunoassay after solid liquid extraction (C 18 bondapack, Millipore, Molsheim) according to the methods described by Ganten *et al.* (1983), Morton & Webb, (1985), Oster *et al.* (1973), and Hackenthal *et al.* (1977).

The crossreactions of the antibody of Ileu⁵-angiotensin II were: 41% for Val⁵-angiotensin II, 0.2% for Ileu³-angiotensin I, 28% for Arg¹-heptapeptide, and 35% for Val¹-hexapeptide (Bauknecht *et al.*, 1975).

Pharmacokinetic evaluations

Peak concentrations ($C_{\max}$) and the time to reach the peak concentration ($t_{\max}$) of propranolol and cilazaprilat were the observed values. The area under the plasma concentration time curve (AUC) was determined using the linear trapezoidal rule. For cilazaprilat, the AUC 0–24 h was calculated, whereas for propranolol, the AUC 0–8 h was determined.

Evaluation of the agonist's dose-effect curve data and statistics

The underlying pharmacological principles and mathematical transformation of the data have been described previously (Wellstein *et al.*, 1985, 1987b; Belz *et al.*, 1987). The dose-ratios minus one (DR–1) were calculated in relation to the first agonist dose-response curve established at 08.00 h baseline on day 7 of the placebo treatment period. They are presented with the 95% confidence intervals.

For statistical comparisons a three-way analysis of variance (ANOVA) was used for global testing, followed by F-Tukey test. *P*-values of <

0.05 were considered to be statistically significant. For the comparison of the pharmacokinetic results a *t*-test for dependent values was used.

The baroreceptor function was deduced from the response to the angiotensin I infusions by plotting the heart rate vs systolic blood pressure.

Results

Heart rate and blood pressure (Figure 1)

The measurements at drug trough conditions over a period of 7 days did not show any differences between the various treatments (only the results from day 7 are depicted). The different effects of the various treatments were only visible during the time course of day 7. The systolic and diastolic blood pressures following the two drug treatments were similarly lowered by an average of about 7 mm Hg and returned to baseline within 4 to 6 h. The coadministration of both drugs reduced the blood pressure by about 12 mm Hg for at least 8 h. Only cilazapril tended to accelerate the heart rate (+ 5 beats min^{-1}).

Isoprenaline dose-response curves (Figure 2)

The heart rate was selected as the main parameter for detecting isoprenaline effects. In the control experiment, the increased heart rate was

dose dependent, averaging about 25 beats min^{-1} . Identical effects were observed before and 2 h after placebo (symbols 0 and 1 in Figure 2). As expected, propranolol shifted the isoprenaline dose-effect curve to the right. The effect at drug trough concentrations (DR - 1 = 1.52, C.I. 0.81 to 2.98) is distinctly less pronounced than at drug peak concentrations (DR - 1 = 28.9, C.I. 23.1 to 37.5). Cilazapril alone somewhat increased the basic heart rate but did not influence the response to isoprenaline. The effect of propranolol was not influenced by the coadministration of cilazapril. The combination resulted in DR - 1 values of 1.37 (C.I. 0.54 to 3.72) at trough and 32.7 (26.3 to 42.5) at peak respectively.

Noradrenaline dose-response curves

Diastolic blood pressure was selected as the main parameter for assessing NA effects. Some changes in baseline values before noradrenaline infusion similar to those in Figures 2 and 3 were detectable. Cilazapril alone at drug peak concentration shifted the NA curve slightly to the right, resulting in a DR-1 of 0.69 (C.I. 0.13 to 2.18). This effect was similar after the combination (DR-1 = 0.39, C.I. 0.07 to 0.94). At drug trough concentration and after propranolol, NA effects resembled those observed under placebo.

Figure 1 Blood pressure on the last day of a 1 week treatment period with: $\square$ = placebo, $\triangle$ = propranolol (120 mg day^{-1}), $\circ$ = cilazapril (2.5 mg day^{-1}), $\bullet$ = propranolol (120 mg day^{-1}) plus cilazapril (2.5 mg day^{-1}). The mean values ($n = 6$) are shown. Statistical significances * vs placebo, * vs cilazapril, * vs propranolol, single symbol $P < 0.05$, double symbols $P < 0.01$, triple symbols $P < 0.001$.

Figure 2 Isoprenaline dose-response curves for heart rate after 1 week pretreatment at drug trough and peak concentrations. The following medications were administered daily: placebo (0/1), propranolol 120 mg (2/3), cilazapril 2.5 mg (4/5), and propranolol 120 mg plus cilazapril 2.5 mg (6/7). The mean values calculated from $n = 6$ are represented by the numbers in the figure.

Figure 3 Angiotensin I dose-response curves for diastolic blood pressure (BPdiast) after 1 week pre-treatment with medications according to Figure 2.

Angiotensin I dose response-curves (Figure 3)

Diastolic blood pressure was selected as the main parameter for detecting angiotensin I effects. Under all treatments, a more or less equivalent range of blood pressure increase was achieved. In addition to some baseline changes, the angiotensin I dose-effect curves were almost identical under placebo or propranolol. At drug peak concentration, cilazapril shifted the angiotensin I dose-effect curve to the right (DR - 1 = 13.1, C.I. 10.8 to 20.0). However, at the drug trough concentration 24 h post dose, this effect was almost absent (DR - 1 = 0.77, C.I. 0.34 to 2.1).

The shifts were not significantly influenced by the coadministration of propranolol (at trough: (DR - 1 = 0.3, C.I. -0.3 to 1.3; and at peak: 11.5, C.I. 10.2 to 16.3).

Plasma renin activity (PRA) (Table 1)

PRA increased under cilazapril. There was only a weak effect at 24 h post dose but a very intense one at 2 h post dose (factor ~10 compared with placebo). Under propranolol, there was no significant effect on PRA. Following coadministration of both drugs (most pronounced at 2 h post dose), the cilazapril induced increase in PRA was markedly reduced (factor ~3).

Plasma angiotensin-I concentrations (Table 1)

The behaviour of angiotensin I concentrations paralleled that of plasma renin activity. As with PRA the highest concentrations were seen 2 h after cilazapril administration. This increase was distinctly lowered by the coadministration of propranolol.

Plasma angiotensin-II concentrations (Table 1)

The only changes were indicated 2 h after drug intake, though none of the observed changes were statistically significant at the 5% level. Cilazapril induced only a small (~10%) reduction of plasma angiotensin II concentrations, whereas they were not influenced by propranolol alone. Following the coadministration of both drugs, angiotensin II concentrations decreased by about 30%.

Table 1 Influence of a 1 week treatment with placebo, cilazapril, propranolol, and the combination of cilazapril plus propranolol on plasma enzyme and hormone concentrations (means with s.d.)

		Placebo	Cilazapril (2.5 mg day ⁻¹)	Propranolol (120 mg day ⁻¹)	Cilazapril 2.5 mg day ⁻¹ plus propranolol 120 mg day ⁻¹
Plasma renin activity (ng ml h ⁻¹)	trough 24 h post-dose 6	1.6 (1.7)	3.1 (0.9) ^{×⊕}	1.7 (1.0) ⁺	3.0 (1.5)
	peak 2 h post-dose 7	1.6 (1.1)	17.9 (6.1) ^{×××⊕⊕⊕}	1.0 (0.4) ⁺⁺⁺	5.2 (7.0) ⁺
Plasma angiotensin I (pg ml ⁻¹)	trough 24 h post-dose 6	129 (72)	194 (98)	113 (32)	183 (72)
	peak 2 h post-dose 7	112 (41)	699 (302) ^{××⊕⊕}	89 (23) ^{×++}	296 (326) ⁺
Plasma angiotensin II (pg ml ⁻¹)	trough 24 h post-dose 6	29 (9.0)	34 (17)	40 (16)	40 (17)
	peak 2 h post-dose 7	34 (11)	30 (9)	32 (8)	25 (9)

Statistically significant differences: [×] vs placebo, ⁺ vs cilazapril, [⊕] vs propranolol, one symbol = $P < 0.05$, two symbols = $P < 0.01$, three symbols = $P < 0.001$

Plasma noradrenaline and adrenaline concentrations

There were no significant changes under the various treatment regimens (results not depicted).

Pharmacokinetics (Table 2)

The concomitant treatment with propranolol did not significantly affect the plasma concentration time course of cilazaprilat. $C_{\max}$ values showed a tendency towards lower concentrations without reaching statistical significance, $t_{\max}$ and AUC 0–24 h values remained unaltered.

Similar changes (not reaching statistical significance) were observed for the pharmacokinetic parameters of propranolol in the presence of cilazapril. $C_{\max}$ was somewhat lower after the administration of cilazapril. The mean $t_{\max}$ value was slightly larger in the combination treatment,

which was mainly caused by one subject. AUC 0–8 h remained essentially unchanged.

Plasma ACE-activity (Table 2)

ACE was almost completely inhibited 2 h after drug intake. A gradual decline to approximately 60% of ACE inhibition was observed 24 h after dosing. The coadministration of propranolol had no effect on the ACE inhibition time course.

Effects of propranolol, cilazapril and a combination of two on the baroreceptor reflex (Figure 4)

The left panel of Figure 4 shows a similar increase in systolic blood pressure after angiotensin I infusion for all treatment regimens. The correlation between systolic blood pressure and heart rate under the influence of angiotensin I allows insight into the function of the baroreceptor reflex. It is obvious from the right panel of

Table 2 a, b, c Pharmacokinetic parameters of cilazaprilat (CLAT) and propranolol after single and combined administrations of both drugs and the corresponding ACE activities

a) Pharmacokinetic parameters of cilazaprilat following oral doses of cilazapril alone and in combination with propranolol						
	CLAT AUC 0–24 h (ng ml ⁻¹ h) alone	CLAT AUC 0–24 h (ng ml ⁻¹ h) combination	CLAT $C_{\max}$ (ng ml ⁻¹) alone	CLAT $C_{\max}$ (ng ml ⁻¹) combination	CLAT $t_{\max}$ (h) alone	CLAT $t_{\max}$ (h) combination
Mean (n = 6)	147.7	149.3	31.4	26.3	1.8	2.2
s.d.	26.6	25.0	6.5	5.4	0.4	1.0
b) Pharmacokinetic parameters of propranolol following oral doses of propranolol alone and in combination with cilazapril						
	AUC 0–8 h (ng ml ⁻¹ h) alone	AUC 0–8 h (ng ml ⁻¹ h) combination	$C_{\max}$ (ng ml ⁻¹) alone	$C_{\max}$ (ng ml ⁻¹) combination	$t_{\max}$ (h) alone	$t_{\max}$ (h) combination
Mean (n = 6)	482.7	418.8	119.8	105.8	1.7	2.7
s.d.	378.5	265.7	108.7	68.0	1.2	1.0
c) Inhibition of plasma ACE after oral doses of cilazapril alone and in combination with propranolol						
Time (h)	ACE inhibition (%) cilazapril alone		ACE inhibition (%) combination			
	mean	s.d.	mean	s.d.		
0	60.9	5.6	58.3	5.3		
1	92.4	12.0	87.4	9.4		
2	97.8	0.6	96.6	2.0		
4	95.0	1.1	95.8	2.0		
6	89.5	1.9	91.5	2.8		
8	83.4	2.9	85.6	3.8		
24	58.5	4.4	57.8	4.2

Figure 4 a) Angiotensin I dose-response curves for the systolic blood pressure (BP syst) after 1 week pretreatment with medications according to Figure 2. b) Correlation between the systolic blood pressure and heart rate during the experiments presented in the left panel. Placebo (○), cilazapril 2.5 mg day^{-1} (▲), propranolol 120 mg day^{-1} (□), and combined treatment with both drugs (◆). The mean values for the various angiotensin I dose steps are shown.

Figure 4 that this increase in systolic BP under placebo was followed by a linear decrease in the heart rate. Pretreatment with cilazapril was responsible for the increased linear extension to the left, i.e. the ACE inhibitor lowered the initial blood pressure but did not interfere with the linear dependency of the drop in heart rate on the increase of the systolic blood pressure.

Propranolol lowered the heart rate irrespective of whether or not cilazapril was coadministered. Parallel to the increasing systolic blood pressure under the influence of angiotensin I, the heart rate was further decreased. However, the gain of the reflex activity was distinctly lower than in the experiments without propranolol. Both correlation curves intercepted at a systolic blood pressure of $\sim 130 \text{ mm Hg}$ and a HR of $\sim 40 \text{ beats min}^{-1}$.

Discussion

This study clearly showed that even in normotensive volunteers, the hypotensive effect of the cilazapril and propranolol combination was more pronounced and longer lasting than the individual components. These effects can not be explained by pharmacokinetic changes in the two drugs. Even though the peak concentrations of cilazapril were lower in the presence of propranolol and consequently giving a higher t_{max} , the ACE inhibition time course remained essentially unaltered. Since AUC values and therefore also the apparent oral clearance did not change, the slightly varying concentration time course may be related to small differences in the absorption rate during the coadministration of pro-

pranolol. The same phenomenon was found for the kinetic parameters of propranolol in the presence of cilazapril. Although these changes may theoretically cause some delay in the onset of action, this effect is probably not of any importance. The effect on blood pressure can most readily be explained by pharmacodynamic factors.

It has been widely suggested that both drugs, although at a different level, lower blood pressure by reducing the activity of the renin-angiotensin-system (MacGregor *et al.*, 1985) though this effect is only one of several mechanisms. If the dominating mechanism of both drugs would be identical, no major effect increases should be noticeable when both drugs were coadministered. On the other hand, some studies suggested an additive hypotensive action and a prolongation of the effects following at the administration of captopril and propranolol (MacGregor *et al.*, 1985; Staessen *et al.*, 1981).

The well known increase of PRA following ACE inhibition (Douglas, 1985) was distinctly attenuated by the coadministration of propranolol, a result similar to that obtained with captopril and propranolol (MacGregor *et al.*, 1985). From the propranolol dose administered in the present study (120 mg orally), more than 90 % β_1 - and β_2 -receptor occupancy can be assumed after 2 h (Wellstein *et al.*, 1988). This caused the isoprenaline dose-effect curves to shift to a DR-1 of ~ 30 . The propranolol concentration can therefore completely suppress even a strong endogenous sympathetic stimulus. For these reasons, the detected PRA increase following coadministration can only be explained by a mechanism independent of the sympathetic

system (probably the decrease in blood pressure) (Douglas, 1985). The results also indicate that the increase in PRA following ACE inhibitors is more or less equally mediated via the adrenergic and via other mechanisms. Plasma angiotensin II concentrations were only moderately decreased by the ACE inhibitor alone and hardly affected by propranolol alone. After the two drugs were combined, the drop in the angiotensin II concentrations seemed more pronounced. This may be related to the suppression of renin release (Table 2) following the administration of propranolol. Compared with cilazapril alone, the amount of angiotensin I available as a substrate for conversion and as a competitor at the enzyme site (Belz *et al.*, 1987; Wellstein *et al.*, 1987a) is thereby reduced. These biochemical changes may contribute to the more intense blood pressure effect observed after the coadministration of both drugs. Considering the drug effects on angiotensin II concentrations, the limitation of these results have to be clearly seen: None of the observed changes reached statistical significance. This may at least in part be due to the complexity of the determination of angiotensin II in plasma. Nussberger *et al.* (1986) have shown that cross reacting metabolites and *in vitro* generation of true angiotensin II can result in falsely high angiotensin II concentrations. Although the applied method was rather specific, we can not definitely exclude such bias. The conclusions drawn from this present results with angiotensin II should be seen as hints which need confirmation in further experiments.

There was no evidence of interaction at the level of competitive antagonism for the β -receptor and ACE. The β -adrenoceptor maintained its antagonistic activity as shown in the isoprenaline dose-effect curve. The ACE inhibitor also maintained its effect on the angiotensin I dose-response in spite of the presence of the other drug.

The baroreceptor reflex system was examined by correlating the systolic blood pressure with the heart rate under the influence of angiotensin I. An increase in blood pressure is followed by a decrease in the heart rate (*c.f.* Figure 4) due to a reduction in sympathetic and an increase in parasympathetic tone. The slope of the correlation line represents the gain of the reflex (Kirchheim, 1976). The reflex responsiveness was not at all influenced by the ACE inhibitor cilazapril, as shown in Figure 4 (right panel). The baseline values, however, were shifted. This is congruent with the results obtained by Guidicelli *et al.* (1985) with enalapril. Following β -adrenoceptor blockade, the reflex intensity is distinctly lowered i.e. an identical increase in blood pressure resulted

in a distinctly less pronounced decrease of the heart rate. This indicates that a reduction of the sympathetic tone via the baroreceptor reflex can no longer influence the heart rate. The persisting heart rate reduction following the increased blood pressure reflects that part of the reflex activity which is mediated via an increasing parasympathetic tone. Our results on the influence of propranolol on the baroreceptor reflex activity contrast with other findings: Pickering *et al.*, (1972) using phenylephrine as a pressor agent demonstrated an increase in the reflex responsiveness in healthy humans; Deering *et al.* (1987) did not find a change in the responsiveness of the baroreceptor using methoxamine and α -methylnoradrenaline as pressor agents. One possible explanation for these discrepancies may be the fact that we challenged the blood pressure using angiotensin. It seems conceivable that this compound at least in the doses used in our experiment, should provide a more pure vasoconstriction than sympathomimetic drugs. Direct effects of angiotensin on the heart rate should appear rather improbable. The adrenergic drugs may also have directly affected the heart and masked the true bradycardic effects of the increase in blood pressure (Deering *et al.*, 1987).

Animal data suggest the possibility of an interaction between the ACE inhibitors and the sympathetic system (*c.f.* Kondowe *et al.*, 1987). From the human data presented by Kondowe *et al.*, 1987, and substantiated by our study, we were not able to detect changes in the response to noradrenaline at trough concentrations of the ACE inhibitor. However, at cilazaprilat peak concentrations, a small shift to the right of the noradrenaline response curve was detected in our volunteers, exerting a DR-1 of 0.69 (95% confidence intervals 0.13–2.18). This result may indicate some sympatholytic activity of cilazapril in man, though the effect is much lower than that observed with specific antagonists such as prazosin.

The present study suggests that the combination cilazapril/propranolol in the tested dosages resulted at least in an additive and a long-lasting effect on blood pressure, which can not be explained by changes in the pharmacokinetics of the drugs. Propranolol inhibited the drastic increase in plasma renin activity following ACE inhibition, resulting in lower angiotensin II concentrations after administration of the combination. This may contribute to the additive effect on blood pressure. Challenge tests using specific agonists demonstrated that each substance exerts its specific competitive antagonistic effects without interfering with the other substance. Whether or not such a combination of ACE inhibitor and

β -adrenoceptor antagonist is useful in the treatment of hypertensive patients should be further investigated with controlled studies.

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