Pharmacokinetic and pharmacodynamic interactions between the ACE inhibitor cilazapril and β -adrenoceptor antagonist propranolol in healthy subjects and in hypertensive patients

G. G. BELZ¹, J. ESSIG¹, K. ERB¹, K. BREITHAUPT¹, J. F. W. HOOBKAMER², J. KNEER² & C. H. KLEINBLOESEM²

¹Zentrum für Kardiovaskuläre Pharmakologie, Ze Ka Pha GmbH, Wiesbaden, Federal Republic of Germany and ²Department of Clinical Research, Hoffmann-La Roche & Co. Ltd, Basle, Switzerland

- 1 Six healthy subjects received cilazapril (2.5 mg once daily), propranolol (120 mg once daily), the combination of both and placebo for a period of 1 week each (wash-out phase 1 week).
- 2 Propranolol and cilazapril reduced systolic and diastolic blood pressure (BP) by 7 mm Hg at peak when compared with placebo. However after the combination, this reduction was more than doubled (18 mm Hg) and lasted longer.
- 3 There was a trend to lower and later peak concentrations for both drugs after administration of the combination. No clinically relevant pharmacokinetic interactions between cilazapril and propranolol were found.
- 4 The effects on blood pressure were confirmed in hypertensive patients (BP diastolic > 95 mm Hg). Thirteen patients were randomly allocated cilazapril (2.5 mg day⁻¹) or propranolol (120 mg day⁻¹) as part of a cross-over design. This was then followed by the combination. All treatment periods were of 3 weeks duration and all measurements were done 2 h after drug administration.
- 5 Cilazapril lowered the median sitting diastolic BP by 8 mm Hg, and propranolol by 9 mm Hg, whereas the combination reduced the diastolic BP by 19 mm Hg.
- 6 The results of these studies, attempting to elucidate drug–drug interactions, showed that combined use of propranolol and cilazapril resulted in a more pronounced and longer lasting blood pressure reduction, in healthy subjects and in patients with hypertension.

Keywords cilazapril propranolol interaction hypertension

Introduction

About 50% of the patients suffering from hypertension can be adequately treated with angiotensin-converting-enzyme (ACE)-inhibitors alone and approximately 80% by the addition of a diuretic (Prichard, 1987; Belz *et al.*, 1986). Recently published guidelines for combining ACE-inhibitors with other drug groups for the

treatment of hypertension do not recommend combining ACE-inhibitors with β -adrenoceptor blocking agents (Zanchetti, 1987), since both drug groups are considered to act mainly via the same mechanism, namely by suppressing the renin-angiotensin-system (MacGregor *et al.*, 1985). Therefore, it has been assumed that the

combination is relatively ineffective, although some results have suggested a further decrease in blood pressure after the administration of propranolol with captopril (Staessen *et al.*, 1981).

However, in the treatment of various cardiovascular diseases, the combined use of ACE-inhibitors and β -adrenoceptor blocking agents may frequently occur in general practice. Therefore, an evaluation of the possible pharmacokinetic and -dynamic interactions of compounds belonging to these groups was justified. For these investigations, we selected cilazapril, a potent new ACE-inhibitor (Belz *et al.*, 1987; Fasanella d'Amore *et al.*, 1987; Nussberger *et al.*, 1987; Wellstein *et al.*, 1987a, b), and propranolol, the prototype of β -adrenoceptor antagonists. The half-life or their effects is about 5 h, and nearly identical, as determined from agonist responses (Wellstein *et al.*, 1987b, 1988). The purpose of these studies in healthy volunteers and hypertensive patients was to evaluate: 1) possible pharmacokinetic interactions and, 2) the influences of each individual drug and their combinations on haemodynamic effects and on various components of the renin-angiotensin-system.

Methods

1) Study in healthy volunteers

Six ambulatory healthy male volunteers, between 24 and 30 years of age, weighing between 65 and 86 kg participated in this study; they were permitted their normal diet.

The randomized study followed a cross-over design with a 7 day wash-out period between the four phases and 7 day treatment periods. Each volunteer was allocated to one of 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.

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 were affixed and an indwelling venous cannula was inserted for blood sampling.

The drugs were then ingested. Drug concentrations and ACE activity were measured before, 1, 2, 4, 6, 8 and 24 h after drug intake.

2) Study in patients

Ten male and three female patients suffering from essential hypertension participated in this study. These patients were between 43 and 62 years of age and weighed between 64 and 106 kg. The patients were not taking other drugs which might have influenced the cardiovascular system, and they were all on their normal diet. Except for three patients, none had received antihypertensive medication for at least 2 weeks prior to the start of a 2 week placebo phase. After this period, sitting diastolic blood pressure was ≥ 95 and < 125 mm Hg. Thereafter, the patients were randomly allocated to cilazapril (2.5 mg day⁻¹) or propranolol (120 mg day⁻¹) as part of a cross-over design. This was then followed by the combination. All treatment periods were of 3 weeks duration.

Measurement of blood pressure and heart rate

In addition to auscultation (Korotkov Phase I and V) blood pressure was measured using an Infraton-Tensiomat (Bertram *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. We used heparinized vials for propranolol, cilazapril and ACE activity; EDTA-K vials for plasma renin activity.

Drug assays

Propranolol concentrations in plasma were assayed by h.p.l.c. using fluorescence detection (excitation/emission wavelength: 286/336 nm) following a liquid/liquid extraction. Cilazaprilat plasma concentrations and ACE activity in plasma were determined by a radioenzymatic assay.

Plasma renin activity (PRA) was assessed by radioimmunological detection of angiotensin I formation.

Pharmacokinetic evaluations

The area under the plasma concentration-time curve (AUC) was determined using the linear trapezoidal rule. For cilazaprilat, the AUC(0-24)

Figure 1 Mean inhibition of ACE activity (%) and mean plasma cilazaprilat concentrations on the last day of 1 week treatment periods with cilazapril 2.5 mg day⁻¹, and propranolol (120 mg day⁻¹) plus cilazapril (2.5 mg day⁻¹). The mean values ($\pm$ s.e. mean) are shown for $n = 6$ healthy volunteers. ■ ACE inhibition after cilazapril, ● ACE inhibition after the combination, ▲ cilazaprilat concentration after cilazapril and ▼ cilazaprilat concentration after the combination.

was calculated, whereas for propranolol, the AUC(0–8) was determined.

Statistics

For statistical comparisons of the results in healthy volunteers 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 results of the patient study were analysed using Friedman's rank sum test. These results are presented as box and whisker plots.

Results

Pharmacokinetics and ACE activity

The concomitant treatment with propranolol did not significantly affect the plasma concentration-

Figure 2 Plasma concentration-time curves of propranolol (parent compound) following the last dose of 1 week treatment periods with: ● propranolol (120 mg day⁻¹), and ○ propranolol (120 mg day⁻¹) plus cilazapril (2.5 mg day⁻¹). The mean values ($\pm$ s.e. mean) are shown for $n = 6$ healthy volunteers.

time course of cilazaprilat (Figure 1). $C_{\max}$ values showed a tendency towards lower concentrations without reaching statistical significance, $t_{\max}$ and AUC(0–24) values remained unaltered. ACE was almost completely inhibited 2 h after drug intake. A gradual decline to 50–60% of ACE-inhibition was observed between 9 and 24 h after dosing. The coadministration of propranolol had no effect on the ACE-inhibition time course (Figure 1).

Similar changes were observed for the pharmacokinetic parameters of propranolol in the presence of cilazapril (Figure 2). $C_{\max}$ 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) remained essentially unchanged. None of these changes was statistically significant.

Blood pressure in healthy volunteers (Figure 3)

On day 7 the systolic and diastolic blood pressures following the two drug treatments were decreased by a similar amount of 7 mm Hg and returned to baseline within 4 to 6 h. The coadministration of both drugs reduced the diastolic blood pressure by about 18 mm Hg for at least 8 h. Cilazapril produced a small increase in heart rate ($+ 5$ beats min⁻¹). The other treatments did not differ from placebo.

Figure 3 Blood pressure on the last day of a 1 week treatment period with: □ = placebo, △ = propranolol (120 mg day⁻¹), ○ = cilazapril (2.5 mg day⁻¹), ● = 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 $P < 0.001$. (Reprinted from Belz et al., 1988a).

Blood pressure in hypertensive patients (Figure 4)

Cilazapril lowered the median sitting diastolic BP by 8 mm Hg, and propranolol by 9 mm Hg, whereas the combination reduced the diastolic BP by 19 mm Hg. The χ^2 value was 24.53 (3 degrees of freedom). The null hypothesis was therefore rejected ($P < 0.0005$). The results clearly show that the combined treatment lowered the diastolic blood pressure of the vast majority of the patients to less than 95 mm Hg. If a response is defined as a diastolic BP of ≤ 90 mm Hg, then 4/13 patients responded to cilazapril, 2/13 to propranolol and 10/13 to the combination. The individual drugs, as well as the combination, were well tolerated. One patient showed little response to either the individual components or to the combination. The blood pressure of another patient was markedly lowered by the combination. This patient also complained of dizziness.

Plasma renin activity (PRA) (Figure 5)

The plasma renin activities with placebo were the same in normals and hypertensives. As expected, PRA was increased by cilazapril. This effect was more pronounced in the healthy volunteers compared with the hypertensive patients. Propranolol had no significant effect on PRA. Following the coadministration of both drugs the cilazapril induced increase in PRA was distinctly reduced.

Figure 4 Influence of placebo (> 2 weeks), cilazapril 2.5 mg day⁻¹, propranolol 120 mg day⁻¹ and the combination of both active drugs on the diastolic blood pressure in 13 hypertensive patients. Box and whisker plots of the sitting diastolic blood pressure. Ranges, upper and lower quartiles, means (intersection in box) and medians (+) are shown.

Figure 5 Influence of placebo, cilazapril 2.5 mg day⁻¹, propranolol 120 mg day⁻¹ and the combination thereof on the plasma renin activity. Results (mean $\pm$ s.e. mean, 2 h after drug intake) compiled from a study in supine healthy volunteers (□, $n = 6$, treatment periods 1 week each) and sitting hypertensive patients (▨, $n = 13$, treatment periods with active drug 3 weeks each).

Discussion

These studies clearly showed that in normotensive volunteers and in hypertensive patients the blood pressure lowering effects of the cilazapril and propranolol combination were more

pronounced than those of the individual components. These effects cannot 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 in healthy volunteers. 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 propranolol. 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 in different ways, lower blood pressure by reducing the activity of the renin-angiotensin-system (MacGregor, 1985). However, this effect is only one of several mechanisms involved in the lowering of blood pressure. If the dominating mechanisms of action of both drugs were identical, no major decreases in blood pressure would be noticeable when both drugs were coadministered. On the other hand, some studies have 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 (Belz *et al.*, 1988b) was distinctly attenuated by the coadministration of propranolol, a result similar to that obtained with captopril and propranolol (MacGregor *et al.*, 1985). The effect was more pronounced in the healthy volunteers compared with hypertensives. The present study suggests that the combination cilazapril/propranolol in the dosages given resulted in an additive effect on blood pressure, which cannot be explained by changes in the pharmacokinetics of the drugs. Propranolol reduced the increase in plasma renin activity following ACE-inhibition. This may contribute to the additive effect on blood pressure. At present, a combination of ACE-inhibitors and β -adrenoceptor blocking agents should be thoroughly investigated for the treatment of hypertension, since the optimal dosages and the pros and cons of such a treatment have not yet been fully established. The results of the present study should encourage physicians not to *a priori* exclude the combination of an ACE-inhibitor and a β -adrenoceptor blocker from their considerations in treating hypertension.

The results were excerpted in part from medical theses submitted by K.E.

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