Pharmacokinetics and effects on renal function following cilazapril and hydrochlorothiazide alone and in combination in healthy subjects and hypertensive patients

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- 1 Possible interactions between cilazapril and hydrochlorothiazide with respect to pharmacokinetics and renal effects were investigated in healthy subjects (single dose) and in hypertensive patients (multiple dosing).
- 2 No significant pharmacokinetic interaction was found between cilazapril and hydrochlorothiazide.
- 3 Cilazapril showed weak saluretic properties as compared with hydrochlorothiazide, but increased the saluretic effects of hydrochlorothiazide.
- 4 Cilazapril attenuated the hypokalaemia observed with hydrochlorothiazide in hypertensive patients.
- 5 The effect on blood pressure reduction obtained from the combination of cilazapril and hydrochlorothiazide lasted longer than that of cilazapril alone.

Keywords cilazapril hydrochlorothiazide pharmacokinetics ACE-inhibition renal function

Introduction

Cilazapril is an esterified pro-drug without a sulphhydryl moiety. It is rapidly converted by hydrolysis to yield the free acid cilazaprilat, an active form with angiotensin converting enzyme (ACE) inhibiting properties (Francis *et al.*, 1987). The combination of ACE inhibitors with thiazide diuretics has been shown to be effective in the treatment of hypertension, often in patients who have not responded adequately to the individual drugs (Todd & Heel, 1986). A potentiation of the antihypertensive effects have been demonstrated (Andrén *et al.*, 1983). Furthermore, there are several reports on the renal actions of ACE inhibitors, indicating that they may improve renal function and alter the diuresis and electrolyte excretion of thiazide diuretics (Bauer, 1984; Leary *et al.*, 1985).

The objectives of these two consecutive studies were to investigate possible interactions between cilazapril and hydrochlorothiazide mainly with reference to pharmacokinetics and renal function. Both studies were performed in accordance with the Declarations of Helsinki/Tokyo/Venice and were approved by the Norwegian Drug Control Authorities and the local Ethics Committee.

Methods

Nine healthy male subjects aged 24 to 35 years, received 5 mg cilazapril, 25 mg hydrochlorothiazide (HCT) or the combination as single oral doses in a randomized double-blind three way

cross over study. The wash out period between each treatment was 1 week. Blood and urine were collected at intervals up to 96 and 24 h, respectively, for measurement of drug concentrations, ACE-inhibition and electrolytes. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were determined by inulin and *p*-amino hippuric acid (PAH) constant infusion techniques, respectively.

Sixteen patients of both sexes with essential hypertension (WHO grade I and II) and aged 40 to 62 years, received 2.5 mg cilazapril, 25 mg HCT or the combination 2.5 + 25 mg of the respective drugs once daily for 2 weeks in a randomized double-blind two way cross over study. After an initial wash out period of 3 weeks, eight patients received cilazapril and eight patients HCT for 2 weeks, thereafter changing directly to the combination for 2 weeks. After a wash out period of 2 weeks a full cross over was performed. On the last days of administration of each regimen at steady state, blood and urine were collected at intervals up to 24 h for detection of drugs and electrolytes. Cilazaprilat (Francis *et al.*, 1987) and ACE (Fasanella d'Amore *et al.*, 1987) activities were determined by radioenzymatic assays and HCT (Shiu *et al.*, 1986) by a modified h.p.l.c. methodology with hydrofluoromethiazide as internal standard for plasma analysis. ACE inhibition was calculated by reference to the pre-dose level of ACE activity.

For comparison of treatments, Student's *t*-test for paired differences was used. $P < 0.05$ was considered statistically significant.

Results

The plasma concentration-time profiles of cilazaprilat and ACE inhibition in healthy subjects are shown in Figure 1. The plasma levels increased rapidly to yield peak levels at 2 h after both treatments. The decline of cilazaprilat plasma levels with time, a fast decline up to 8 h and a slower one from 22 h, was not affected by the concomitant administration of HCT.

From a mean (s.e. mean) baseline ACE activity of $17.2 (1.7) \text{ u l}^{-1}$, ACE inhibition increased rapidly after administration of cilazapril and showed a 90% inhibition after 1 h and a maximum inhibition of 98.9% after 2 h. The inhibition was $\geq 90\%$ up to 8 h. No significant changes in the ACE inhibition pattern of cilazapril was observed up to 24 h by concomitant administration of HCT. The small deviation in % inhibition observed from 24 to 96 h was not statistically significant. ACE activity was inhibited $< 5\%$ by HCT alone.

A plot of the mean diastolic blood pressure (standing) vs the mean ACE inhibition is shown in Figure 2 for cilazapril alone and for the combination. The points were connected in order of time. It appeared that up to 90% of ACE inhibition there was only a small effect on blood pressure, whereas there was a marked effect from 90–100% of ACE inhibition after cilazapril alone. In the presence of HCT the threshold value was about 50% ACE inhibition and the curve was much less steep in the range from 50–100% of ACE inhibition. In both cases no indication of a hysteresis effect was found.

Figure 1 Plasma concentration-time profiles of cilazaprilat (closed symbols) and ACE inhibition (open symbols) in healthy subjects after single oral doses of 5 mg cilazapril ($\triangle$) and 5 mg cilazapril + 25 mg hydrochlorothiazide ($\blacksquare$).

Figure 2 Diastolic blood pressure (standing) versus ACE inhibition in healthy subjects after single oral doses of 5 mg cilazapril (—▲—) and 5 mg cilazapril + 25 mg hydrochlorothiazide (—■—).

The urinary excretion rate profiles of cilazaprilat and the total amount excreted were not significantly affected by HCT, showing a maximum cilazaprilat excretion rate in the 1–2 h interval of 0.50 and 0.46 mg h⁻¹ and a 0–24 h excretion of 39.5 and 35.2% of dose, respectively, for cilazapril alone and in combination with HCT.

The plasma concentration-time profile of HCT was not significantly influenced by cilazapril in healthy subjects. Neither were the urinary excretion rate profiles of HCT and the total amount excreted, showing identical maximum HCT excretion rates in the 1–2 h interval of 3.1 mg h⁻¹ and a 0–24 h excretion of 66.1 and 67.5%

of dose, respectively, for HCT alone and in combination with cilazapril.

The multiple dose kinetics of cilazaprilat and HCT alone or in combination in hypertensive patients confirmed the results presented for healthy subjects on the lack of pharmacokinetic interactions between cilazapril and HCT. Some important pharmacokinetic parameters for cilazaprilat alone and in combination both in healthy subjects and in hypertensive patients are given in Table 1.

Figure 3 shows the effects of cilazapril and HCT alone or in combination on the glomerular filtration rate (inulin clearance) and renal plasma flow (PAH clearance) in healthy subjects. Neither cilazapril nor HCT alone affected GFR. However, although not statistically significant, the combination increased the GFR by 8%. Cilazapril increased RPF by about 6%, and the combination by about 12%, ($P < 0.05$) while HCT tended to decrease RPF.

In healthy volunteers the urinary excretion of sodium and chloride was increased by all treatments ($P < 0.05$). The effect of HCT was more pronounced than that of cilazapril ($P < 0.05$) while the combination was more effective than HCT ($P < 0.05$). The 0–24 h urinary excretion rate profiles of sodium are shown in Figure 4.

Figure 5 shows the urinary excretion rates of sodium vs HCT after administration of HCT alone and in combination with cilazapril. The curves indicate that HCT alone is capable of increasing the urinary excretion rate of sodium only over a very limited range of HCT concentrations, while the addition of cilazapril increases the range over which HCT is able to increase sodium excretion.

In hypertensive patients the effects of

Table 1 Mean (s.e. mean) pharmacokinetic parameters for cilazaprilat in healthy subjects* and in hypertensive patients**

Parameters/ Treatments	C _{max} (ng ml ⁻¹)	t _{1/2} (2–8 h) (h)	t _{1/2} (24–94 h) (h)	AUC ⁺ (μg l ⁻¹ h)	Cl _r (l h ⁻¹)	Urine ⁺⁺ (% dose)
Cilazapril (healthy)	83.8 (7.4)	1.4 (0.08)	41.9 (3.5)	396 (20)	6.4 (0.5)	39.5 (2.9)
Cilazapril + HCT (healthy)	81.5 (5.6)	1.6 (0.05)	45.8 (3.6)	415 (21)	5.5 (0.6)	35.2 (3.2)
Cilazapril (hypertension)	48.4 (7.5)	2.1 (0.07)		181 (10)		
Cilazapril + HCT (hypertension)	47.6 (4.5)	2.1 (0.07)		196 (7.4)		

* HCT: 25 mg, Cilazapril: 5 mg, single dose

** HCT: 25 mg, Cilazapril: 2.5 mg, multiple dosing

+ Healthy: 0–∞ h, Hypertensive: 0–24 h

++ 0–24 h collection interval

Figure 3 Glomerular filtration rate (GFR) and renal plasma flow (RPF) in healthy subject controls (A), after single oral doses of 5 mg cilazapril (B), 25 mg hydrochlorothiazide (C) and 5 mg cilazapril + 25 mg hydrochlorothiazide (D).

Figure 4 Mean urinary excretion rates of sodium in healthy subjects after single doses of 5 mg cilazapril (—▲—), 25 mg hydrochlorothiazide (—○—) and 5 mg cilazapril + 25 mg hydrochlorothiazide (—■—).

Figure 5 Urinary excretion of sodium vs urinary excretion of HCT in healthy subjects after single oral doses of 25 mg hydrochlorothiazide (—○—) and 25 mg hydrochlorothiazide + 5 mg cilazapril (—■—).

cilazapril, HCT and the combination on urinary excretion rates of sodium and chloride at steady state were similar to that observed in healthy subjects after single doses. No changes were found in the plasma concentration of sodium and chloride.

HCT reduced the plasma concentration of potassium in hypertensive patients during the first 2 weeks of treatment from 4.3 to 3.85 ($P < 0.05$) while no effects were seen with cilazapril. However, the addition of cilazapril to HCT tended to increase plasma potassium and the addition of HCT to cilazapril tended to reduce plasma potassium. The reduction in plasma potassium was statistically greater ($P < 0.05$) when HCT was given alone as compared with the combination of HCT and cilazapril.

Discussion

The present study suggests that there is no pharmacokinetic interaction between cilazapril and HCT in healthy subjects or in hypertensive patients during single or multiple dosing.

The fact that none of the two phases of elimination for cilazaprilat was affected by HCT indicates that neither the elimination of free cilazaprilat nor the binding of cilazaprilat to plasma ACE was influenced by the diuretic. This is further validated by the profiles of ACE inhibition with and without HCT which were not statistically different. However, it can not be ruled out that the discrepancy in the % inhibition of ACE after 22 h in Figure 1 could indicate some sort of an interaction between the two drugs on ACE. This might explain the longer lasting blood pressure reduction with the combination than from cilazaprilat alone. HCT did not alter the peak concentration or time to peak concentration of cilazaprilat which indicates that HCT does not affect the absorption or the hydrolysis of cilazapril.

The pharmacokinetics of HCT was only slightly influenced by cilazapril. A 9% decrease in the AUC in the presence of cilazaprilat in healthy subjects ($P < 0.05$), and a corresponding decrease in AUC of 4% (NS) in hypertensive

patients at steady state would be unlikely to be of clinical significance.

The fall in blood pressure after cilazapril alone correlated with plasma ACE inhibition in a non-linear way. The curve was very flat up to 90% of ACE inhibition and very steep in the range from 90–100% of ACE inhibition. No hysteresis effect was found with time, suggesting that the change in angiotensin II concentration with ACE inhibition occurs rapidly. Although plasma ACE probably do not reflect ACE at the site of action (i.e. in the blood vessel wall, kidney) at steady state, there should be some relationship between the activities of plasma and tissue ACE. For these reasons correlations after single dose studies probably have limited predictive value for long term treatment. On the other hand, it was shown by this correlation that after combination with HCT less ACE inhibition was needed to produce a fall in blood pressure.

An additive saluretic effect (sodium and chloride urinary excretion rates) was found after the combination in healthy subjects and in hypertensive patients, the most pronounced effect occurring 1–2 h after medication. However, during multiple dosing in hypertensive patients, the 0–24 h excretion at steady state was not significantly different for cilazapril and HCT during single dose therapy, and the plasma concentrations remained constant during the whole trial.

An interesting observation was the potassium saving effect of cilazapril in hypertensive patients when combined with HCT, which could counteract the potassium loss usually found during thiazide therapy. The site for this effect on potassium has not been clearly identified as the urinary excretion rate of potassium did not decrease during the combined therapy.

From the present investigations it can be concluded that there is no significant pharmacokinetic interaction between cilazaprilat and HCT. Cilazapril has weak saluretic properties in comparison with HCT, but increases the diuretic effects of HCT in combined therapy. Cilazapril attenuates the potassium depleting effect of HCT, and potentiates renal plasma flow (RPF) in combination with HCT. Cilazapril produces a longer lasting effect on blood pressure when combined with HCT.

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