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Captopril: pharmacokinetics, antihypertensive and biological effects in hypertensive patients

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1 The kinetics of captopril plasma levels and of the drug-induced plasma converting enzyme activity (PCEA), plasma renin activity (PRA) and diastolic blood pressure (DBP) modifications were studied over 24 h after oral administration of captopril, 1 mg/kg, to ten hypertensive patients.

2 Free unchanged captopril pharmacokinetic parameters were: $t_{½,\alpha}$: 0.45 ± 0.06 h; t_{max}: 0.98 ± 0.13 h; C_{max}: 1.31 ± 0.20 mg l^{-1}; $t_{½,z}$: 0.66 ± 0.13 h; V: 0.614 ± 0.104 1 kg^{-1} and CL_{tot}: 0.690 ± 0.082 l h^{-1} kg^{-1}. At 6 h captopril was no longer detectable in plasma.

3 The onset of PCEA inhibition and of DBP decrease closely followed the rise of captopril's plasma levels, while that of PRA increase was delayed. In contrast, while captopril rapidly disappeared from plasma, its biological and antihypertensive effects were long-lasting.

4 The lack of correlation between the relative bioavailability of captopril and the induced reduction in DBP (evaluated by the corresponding AUCs) suggests that free unchanged captopril plasma monitoring is not an adequate indicator of hypertensive patients' potential responsiveness to captopril's blood pressure lowering effects.

Keywords captopril pharmacokinetics hypertension

Introduction

Angiotensin I-converting enzyme inhibitors have been shown to be effective antihypertensive drugs, lowering blood pressure in animals and in patients with hypertension, especially when renovascular in origin (Horovitz, 1981). Captopril, the first orally active drug available in this group, induces a strong converting enzyme inhibition, reduces plasma angiotensin II and aldosterone levels, increases plasma renin activity and produces a significant decrease in blood pressure in hypertensive patients (Horovitz, 1981). However, the correlation between blood pressure reduction and converting enzyme inhibition remains controversial (Waeber *et al.*, 1980; Campbell *et al.*, 1982). Furthermore, because reliable plasma assay of captopril has for long not been available, the possible relationships between the drug's pharmacokinetics, its effects on the renin-angiotensin-aldosterone system and its antihypertensive properties have not yet been studied simultaneously. Therefore, the recent advent of appropriate methods for plasma captopril determination (Kawahara *et al.*, 1981; Jarrott *et al.*, 1981; Duchin *et al.*, 1982) led us to investigate these relationships after administration of a single oral dose of captopril to moderate hypertensive patients and to determine whether the relative bioavailability of the

drug could be predictive of hypertensive patients' potential responsiveness to captopril's blood pressure lowering effects.

Methods

Patients

The study was conducted in 10 patients (eight males), aged 31–73 years (mean 48.5 years). All had a diagnosis of permanent hypertension on the basis of three ambulatory blood pressure readings above 160/95 mm Hg (Table 1). All underwent a standardized aetiological work-up as previously described (Ménard *et al.*, 1982) and none had evidence of secondary forms of hypertension. Briefly, iatrogenic hypertension was excluded by a carefully taken history (Degoulet *et al.*, 1980), a renal parenchymal disease was ruled out by measurement of blood and urinary creatinine and proteins, hyperaldosteronism was excluded by determination of blood and urinary electrolytes and measurement of plasma renin activity (PRA) (Plouin *et al.*, 1980) and finally phaeochromocytoma was excluded by measurement of the 24 h excretion of total metanephrines (Plouin *et al.*, 1981). Moreover, intravenous pyelography was performed in case of a lateralized abdominal murmur, of a severe hypertension (diastolic at rest above 120 mm Hg and/or fundus grade III or IV) (Ménard *et al.*, 1979) and when a history of proteinuria, nephritis or repeated urinary infections was present. All patients gave informed consent to take part in the study. They were studied as in-patients, usually on the third day of an hospitalization intended to make a standard aetiological work up and to determine appropriate antihypertensive treatment. Six patients had never been given any antihypertensive drug and had a 100 mmol/day sodium diet. Two patients were currently treated with a β-adrenoceptor blocking drug which was continued throughout the study and had a 100 mmol/day sodium diet. Finally, two patients were receiving a thiazide diuretic at admission; this treatment was discontinued but the patients had a 10 mmol/day sodium diet. Since sodium diet was not likely to interfere with the individual results as expressed as the changes from basal individual values, we felt that a standardized diet was not necessary provided that each patient was in a steady state: thus the experimental protocol was started when natriuresis had been constant on two consecutive days (Table 1).

Table 1 Clinical and biochemical characteristics of the ten hypertensive patients.

Subject/Sex	*Age* (*years*)	*Height/Weight* (*cm/kg*)	*Kalaemia* (*mmol/l*)	*Natriuresis* (*mmol/24 h*)	*Creatinine clearance* (*ml/min*)	*SBP/DBP*[a] *supine* (*mm Hg*)	*SBP/DBP*[a] *erect* (*mm Hg*)	*HR*[a] *supine/erect* (*beats/min*)
1 M	33	167 / 67.8	3.8	154	65	162 / 118	160 / 124	82 / 102
2 M	54	174 / 68.8	4.2	86	81	182 / 90	162 / 104	60 / 88
3 M[b]	36	164 / 72	3.8	24	58	154 / 102	140 / 96	58 / 66
4 M	31	176 / 95	4.1	108	90	158 / 118	142 / 112	75 / 75
5 F[b]	73	149 / 52.5	4.3	25	78	172 / 84	182 / 94	84 / 75
6 M	47	155 / 63.5	4.1	99	97	182 / 108	178 / 112	81 / 81
7 M	45	168 / 75	3.9	58	120	194 / 118	188 / 130	105 / 120
8 M	53	167 / 73	3.8	107	96.5	164 / 108	168 / 118	75 / 87
9 M	59	165 / 76	3.5	84	102	214 / 120	206 / 116	84 / 78
10 F	53	152 / 76.5	3.8	120	105	197 / 114	182 / 118	69 / 72
Mean	48.4	163.7 / 72.0	3.9	86.5	89.2	177.9 / 108.0	170.8 / 112.4	77.3 / 84.4
± s.e. mean	± 4.1	± 2.8 / ± 3.4	± 0.1	± 13.0	± 6.0	± 6.1 / ± 4.0	± 6.5 / ± 3.6	± 4.3 / ± 5.1

[a]: BP and HR recorded at admission.
[b]: low sodium diet.

Study design

On the first experimental day (day 1), an automatic heart rate (HR) and blood pressure (BP)

monitor (Sentron, Roche) was set at 07.00 h on the right arm to recumbent, fasting patients and programmed to record HR, systolic (SBP) and diastolic (DBP) blood pressure every 3 min until 11.00 h. At 08.00 h, blood samples for captopril plasma levels, plasma renin activity (PRA) and, in six patients, for plasma converting enzyme activity (PCEA) were drawn into tubes containing *p*-BPB (captopril, see below) or heparin (PRA and PCEA). The plasma was separated and stored at −20°C (PRA and captopril) or at −80°C (PCEA). The fasting patients were then immediately given captopril, 1 mg/kg, orally, and blood sampling was performed 20, 30, 40, 1, 1.5, 2 and 3 h after captopril. At 11.00 h, the patients were allowed up to walk about and have lunch at 12.00 h. At 13.30 h, they were asked to stay supine for 30 min before the sixth hour BP and HR measurements and plasma sampling. Dinner was served at 19.00 h. Finally, on day 2 the BP and HR monitor was set again in the supine patients from 07.00–08.00 h, time at which the last plasma sampling and HR and BP recordings (24th hour) were made. The two automated HR and BP readings obtained immediately before and after a given blood sample were averaged and their mean value considered to be contemporary of plasma captopril, PRA and PCEA values in this sample.

Analytical methods

Captopril pharmacokinetics The method used for captopril determination was derived from that described by Kawahara *et al.* (1981). In brief, whole blood free form of unchanged captopril was trapped with *p*-bromo phenacylbromide (*p*-BPB), which was used as a coupling reagent for the thiol function, thus ensuring its stability, and the addition product was evaluated by h.p.l.c. Venous blood (10 ml) was collected in a Sarsted plastic tube containing 30 mg of *p*-BPB. After 5 min stirring, the tube was left for 15 min at laboratory temperature allowing the reaction between captopril and *p*-BPB to occur and then centrifuged for 5 min at 2500 rev/min. The serum was separated and frozen at −18°C. An internal standard solution (thiosalicylic acid, 250 mg, derived with *p*-BPB, 500 mg, in 100 ml acetone) was prepared according to Kawahara *et al.* (1981). For captopril determination, 150 μl of this internal standard solution was added to 3 ml of serum, which was then extracted as described by Kawahara *et al.* (1981). The final residue was dissolved in 100 μl of the following mobile phase: acetonitrile-water-acetic acid (55:44.5:0.5) and 20 μl were injected into the h.p.l.c. [Waters μ-Bondapak C18 column, Lirec A 801 pump (mobile phase flow: 1 ml/min), Waters 480 detector (254 nm) and Linear chart recorder]. Detection threshold was 20 ng/ml and a good linearity was obtained in the range of 20 ng/ml to 2.5 μg/ml.

Captopril kinetics (absorption half life $t_{1/2\alpha}$, time to peak blood levels t_{max}, elimination half-life $t_{1/2,z}$, area under the concentration-time curve up to 6 h $AUC_{6\,h}$, distribution volume V and total plasma clearance CL_{tot}) were calculated for each patient (Graphakin program) on a Tektronix 4052 computer according, because of the sensitivity of the captopril determination technique, to a one-compartment model and averaged.

Plasma renin activity (PRA) was measured using a radioimmunoassay for angiotensin I generated during a standard incubation procedure (Ménard *et al.*, 1972).

Plasma converting enzyme activity (PCEA) was quantified using the technique described by Cushman & Cheung (1971).

Treatment of data

The results are reported as means ± s.e. mean.

Paired data were compared by Student's *t*-test.

The kinetics of the captopril-induced increase in PRA (ΔPRA) and percent inhibition of PCEA were calculated for each patient using the same program (Graphakin) as for captopril plasma levels. The following parameters: (a) half-life of the appearance phase for the increase in PRA and PCEA% inhibition, (b) time to obtain a maximal effect on these parameters and (c) half-life of the disappearance phase for the increase in PRA and PCEA% inhibition, were determined individually and averaged.

Finally the areas under the response-time (0→6 h) curves ($AUC_{0\to 6\,h}$) for ΔPRA, PCEA% inhibition and decrease in DBP (ΔDBP) were calculated for each patient. The existence of a possible correlation between captopril plasma levels, ΔPRA, PCEA% inhibition and ΔDBP was tested by fitting the $AUC_{0\to 6\,h}$ of captopril plasma levels against the $AUCs_{0\to 6\,h}$ of the induced effects with a least square linear regression.

Results

Free unchanged captopril pharmacokinetics

Table 2 indicates the evolution with time of captopril mean plasma levels for the ten patients. At 6 h, captopril could be detected in only two patients and at 24 h in none. Table 3 summarizes

Table 2 Mean values (± s.e. mean) for plasma captopril levels, diastolic blood pressure (DBP), heart rate (HR) and plasma renin activity (PRA) before and after captopril (1 mg/kg, orally) administration in the ten hypertensive patients.

	Time (h)									
	0	*0.33*	*0.5*	*0.66*	*1*	*1.5*	*2*	*3*	*6*	*24*
Plasma captopril levels (mg/l)	0	0.37 ± 0.19	0.64 ± 0.27	0.79 ± 0.22	0.94 ± 0.14	0.81 ± 0.12	0.28 ± 0.05	0.10 ± 0.03	0	0
DBP (mm Hg)	92.0 ± 3.1	89.4 ± 3.5	85.9[b] ± 3.1	83.7[b] ± 3.5	84.4[a] ± 4.2	79.3[c] ± 3.9	78.3[c] ± 3.5	77.6[c] ± 3.7	77.5[c] ± 3.6	80.8[c] ± 4.7
HR (beats/min)	70.1 ± 2.9	70.0 ± 3.2	67.3 ± 3.0	69.2 ± 3.2	70.0 ± 3.4	70.2 ± 3.8	67.4 ± 2.8	69.3 ± 3.5	71.3 ± 3.3	65.4 ± 2.0
PRA (ng ml^{-1} h^{-1})	1.07 ± 0.35	1.65 ± 0.38	2.08 ± 0.81	2.31 ± 0.90	2.36 ± 0.90	2.67 ± 0.96	3.55 ± 1.31	3.21[a] ± 0.98	3.03[a] ± 0.81	1.58 ± 0.61

Value significantly different from time zero measurement: [a]: $P < 0.05$; [b]: $P < 0.01$; [c]: $P < 0.001$ (paired Student's *t*-test).

Table 3 Mean (± s.e. mean) pharmacokinetic parameters of captopril after oral administration (1 mg/kg) in the ten hypertensive patients

t_{max} (h)	0.98 ± 0.13
C_{max} (μg/ml)	1.31 ± 0.20
Elimination half-life (h)	0.66 ± 0.13
Volume of distribution (l kg^{-1})	0.614 ± 0.104
Total clearance (l h^{-1} kg^{-1})	0.690 ± 0.082

the mean pharmacokinetic parameters of captopril. The time to peak plasma levels was approximately 60 min and the elimination half-life of captopril was around 40 min.

Diastolic blood pressure, heart rate and plasma renin activity

Table 2 depicts the effects of captopril on DBP and HR during the 24 h following oral administration. DBP started to decrease as soon as 30 min, the maximum reduction being observed after 6 h. DBP remained significantly lowered at 24 h. HR was not drug-affected. PRA mean values in the eight patients receiving no β-adrenoceptor blocking drugs are also indicated in Table 2. This parameter was significantly increased by captopril 3 and 6 h after administration.

Plasma converting enzyme activity

Figure 1 illustrates the evolution with time of mean % inhibition of PCEA in the six patients in whom this parameter was investigated. It also depicts for the same six patients the concomitant evolutions of mean captopril plasma levels, ΔPRA and ΔDBP. PCEA% inhibition was maximal (93.0 ± 1.3%) 1.5 h after captopril administration and then declined slowly.

Correlations

Table 4 indicates for captopril plasma levels, PCEA% inhibition and ΔPRA the values of the half-lives of their appearance phase, reflecting the rate of the effects' onset, of the time to the maximal effects and of the half-lives of their disappearance phase, reflecting the rate of the effects' decline. The rises of captopril plasma levels and of PCEA% inhibition appeared to occur concomitantly whereas that of ΔPRA was delayed. Furthermore, the times to peak captopril plasma levels and to maximal PCEA% inhibition were similar while that to maximal ΔPRA increase was also delayed. In contrast, while captopril plasma levels' decline was very rapid, those of PCEA% inhibition and ΔPRA were slower and of approximately similar value.

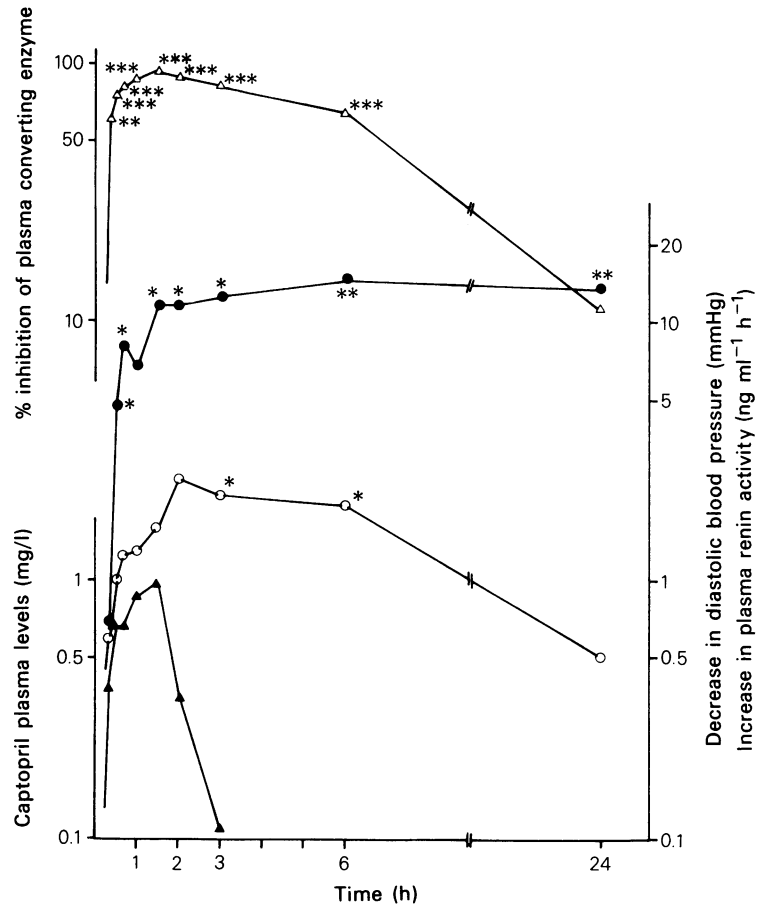

Figure 1 Kinetics of captopril plasma levels (▲) and captopril-induced plasma converting enzyme activity percent inhibition (△), plasma renin activity increase (○) and diastolic blood pressure decrease (●).
Significant variations: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Up to 6 h after captopril administration, there was no correlation between captopril relative bioavailability and (a) the decrease in DBP (r = 0.110, NS) (b) PCEA% inhibition (r = 0.207, NS) and (c) the increase in PRA (r = 0.257, NS) and there was no correlation between PCEA% inhibition and (a) the decrease in DBP (r = 0.226, NS) and (b) the increase in PRA (r = 0.491, NS), all these parameters being quantified by their $AUCs_{0\rightarrow 6\ h}$. Finally, there was no correlation (r = 0.165, NS) between the pre-captopril PRA values and the fall in DBP.

Discussion

Since appropriate methods for plasma captopril monitoring have only recently become available,

Table 4 Mean (± s.e. mean) values for half-life of appearance phase, time to peak variation t_{max} and half-life of disappearance phase of captopril plasma levels. PCEA% inhibition and ΔPRA in six hypertensive patients.

	Captopril plasma levels	*PCEA % inhibition*	*ΔPRA*
$t_{1/2}$ of appearance phase (h)	0.45 ± 0.06	0.43 ± 0.10	1.48 ± 0.29
t_{max} (h)	1.17 ± 0.17	1.50 ± 0.13	3.79 ± 0.65
$t_{1/2}$ of disappearance phase (h)	0.66 ± 0.09	8.85 ± 3.16	12.65 ± 4.62

pharmacokinetic data on this drug are relatively scarce. Moreover, studies involving simultaneous evaluation of captopril plasma levels and captopril-induced renin-angiotensin system blockade and blood pressure reduction in hypertensive patients are lacking. The present investigation clearly shows that there are no correlations between measurable captopril blood levels, which declined rapidly and were almost undetectable beyond 3 h and either the renin-angiotensin system blockade, which persisted up to at least 6 h as evidenced by significant PCEA blockade and PRA increase, or the long-lasting antihypertensive effect of captopril which was maximum at 6 h. A statistically significant reduction in DBP was still present at 24 h. Although the use of an automatic BP recorder should have reduced non specific bias, the persistent drop in DBP at 24 h was probably not due to the sole captopril ingestion. Hence, this led us to consider only the first 6 h following drug administration in the evaluation of the present data.

Our pharmacokinetic data (t_{max} = 0.98 ± 0.13 h and $t_{½,z}$ = 0.66 ± 0.13 h) for free unchanged captopril are well within the ranges of those previously reported in normal subjects (t_{max} = 0.7–0.9 h; $t_{½,z}$ = 0.35–1.7 h) (Kripalani *et al.*, 1980; Onoyama *et al.*, 1981; Duchin *et al.*, 1982) or in hypertensive patients (t_{max} = 0.6–0.9 h; $t_{½,z}$ = 0.6–1.6 h) (Jarrott *et al.*, 1981, 1982) whatever the one- (Onoyama *et al.*, 1981) or two-compartment (Duchin *et al.*, 1982) pharmacokinetic model used. Captopril absorption is rapid since its half-life was 0.45 h and since after 20 min mean plasma levels were already 40% of their maximal values which were reached within 60 min. However, although administered to fasting subjects as suggested by Duchin *et al.* (1982) to improve absorption, captopril showed great interindividual variability in this parameter.

Induction of PCEA inhibition was almost concomitant with the increase in captopril plasma levels since for these two parameters the half-life of the first phase (0.43 ± 0.10 h and 0.45 ± 0.06 h respectively) and the times to peak effect (1.5 ± 0.13 h and 1.17 ± 0.17 h respectively) were similar. Simultaneously, DBP also showed an early decrease in relation with PCEA inhibition-induced suppression of angiotensin II synthesis, the reduction in DBP reaching 88% of its maximum value after 1.5 h. As previously observed by Campbell *et al.* (1982), the maximum reduction in DBP occurred later than the maximum PCEA inhibition, which might indicate that converting enzyme inhibition elsewhere than in plasma, e.g. in the vessels' wall could also be responsible for the hypotensive effect. In contrast, PRA decrease developed more slowly, the observed delay being probably accounted for by the secretory and excretory mechanisms involved in the feed-back stimulation of renin release by the juxtaglomerular apparatus.

There were also differences in the kinetics of the declines of the various measured parameters. Thus while captopril plasma levels were no longer detectable beyond 3 h, PCEA inhibition, PRA increase and DBP decrease persisted much longer. Thus, the decline in PRA and PCEA% inhibition exhibited almost the same kinetics while that of DBP decrease, although relatively imprecise because of the lack of BP measurements between the sixth and 24th hours, appeared to be slower.

In this study, two patients were female, two were on a low sodium diet and two were on a β-adrenoceptor blocking drug treatment and this raises the question of the influence of these factors on our results. Despite the small number of individuals in these three subgroups, which forbids stratification of the data for statistical analysis, these patients did not appear at first sight to behave differently from the whole group regarding the effects of captopril on the $AUCs_{0\rightarrow 6\ h}$ for DBP decrease and PCEA% inhibition. As expected, captopril-induced increase in PRA was blunted in the two patients receiving a β-adrenoceptor blocking drug. Finally, there was a slight trend to an increase in the $AUCs_{0\rightarrow 6\ h}$ for captopril plasma levels and to a decrease in both volume of distribution and total clearance of the drug in the two female and in the two low sodium diet patients, but as mentioned earlier, the small number of subjects forbids any conclusion in this respect.

Finally, our data indicate that in hypertensive patients there is no correlation between captopril's relative bioavailability and its effects on PCEA, PRA and DBP, all these parameters being quantified by their $AUC_{0\rightarrow 6\ h}$. The longer duration of the biological and clinical effects relative to captopril's kinetics may be due to *in vivo* formation of captopril disulphide of disulphide linkages between captopril and endogenous sulphhydryl-containing compounds and thiol groups of proteins. These compounds which are not measured by the determination technique used since their sulphhydryl function is not free (Kawahara *et al.*, 1981), may act as a reservoir from which captopril could be released slowly, as suggested by Duchin *et al.* (1982) and hence prolong the duration of captopril's effects. It may also be argued that the captopril assay is not sensitive enough to look for a possible correlation between captopril's kinetics and biological and clinical effects. However, even when free unchanged ^{35}S- or ^{14}C-captopril plasma levels are measured (Kripalani *et al.*, 1980; Duchin *et al.*, 1982), the drug's plasma elimina-

tion half-life (1.7 h), although longer than in our study, is still very short as compared to those of the disappearance phase of the biological parameters modifications (Table 4). On the other hand, one may question the value of the methods used to measure the biological parameters. PCEA was determined with all the precautions required, e.g. the plasma samples were stored at −80°C in order to sustain captopril-induced PCEA inhibition (Roulston *et al.*, 1980; Imbs *et al.*, 1981) and the enzymatic assays were performed at two different dilutions. Angiotensinogen plasma levels decrease during captopril chronic treatment (Rasmussen *et al.*, 1981) and hence it could be argued that our PRA values underestimate the ultimate renin concentration in the plasma. However, this phenomenon is unlikely to be a serious problem in our experiments where captopril was administered only once, although a slight and transient decrease in angiotensinogen has been reported after a single dose of enalapril (Millar *et al.*, 1982). Finally, measurement of angiotensin II plasma levels which was not performed here might have been more relevant than PRA to investigate potential correlations between captopril's pharmacokinetics and biological effects but, besides the possible risk of cross-reactions between angiotensin I and the angiotensin II antibody in the radioimmunoassay, Brunner *et al.* (1981) have shown with enalapril a good correlation between PRA increase and plasma angiotensin II decrease.

Regarding the lack of correlation between PCEA inhibition and DBP reduction, Waeber *et al.* (1980) also found a discrepancy between captopril-induced PCEA inhibition and PRA increase on the one hand and the drug's antihypertensive effect on the other and concluded that BP response to captopril was not completely accounted for by the renin-angiotensin system inhibition. In contrast, Campbell *et al.* (1982) found a strong correlation between BP reduction and PCEA inhibition, but it must be pointed out that in their experiments a low dose (25 mg) of captopril was used which did not induce a complete PCEA blockade while in our experiments and those by Waeber *et al.* (1980) an almost complete PCEA inhibition was obtained. Finally, the lack of correlation between the fall in DBP and the pre-captopril PRA values in our experiments is probably due to the fact that such a correlation can only be found when large numbers of subjects from all three renin subgroups are analyzed as shown by Gavras *et al.* (1981).

In conclusion, our results demonstrate that immediately after captopril oral administration, the onset of PCEA inhibition and of DBP decrease closely follows the rise of the drug's plasma levels while PRA increase is slightly delayed. However, captopril's biological and antihypertensive effects last at least 6 h while captopril disappears very rapidly from plasma. Hence, the lack of correlation between the relative bioavailability of captopril and the decrease in DBP (evaluated by the corresponding $AUCs_{0\to 6\ h}$ suggests that free unchanged captopril plasma levels monitoring is not an adequate indicator of hypertensive patients' potential responsiveness to captopril's blood pressure lowering effects. Finally, it appears that such monitoring cannot be reliably used in the purpose of (a) adapting captopril dosage in the individual hypertensive patient and (b) evaluating patients' compliance to captopril treatment.

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