Influence of chronic renal failure on captopril pharmacokinetics and clinical and biological effects in hypertensive patients

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1 The pharmacokinetic parameters of unchanged plasma captopril and the kinetics of the drug effects on plasma converting enzyme activity (PCEA), plasma renin activity (PRA), plasma aldosterone (PA) and mean blood pressure (MBP) were studied over 24 h after oral administration in three groups of hypertensive patients: with normal renal function (group 1, plasma creatinine < 110 $\mu\text{mol/l}$, $n = 10$), with moderate chronic renal failure (group 2, $135 < \text{plasma creatinine} < 450 \mu\text{mol/l}$, $n = 10$) and with severe chronic renal failure (group 3, plasma creatinine > 500 $\mu\text{mol/l}$, $n = 10$).

2 Renal impairment had no effect on plasma captopril C_{max} , CL_{tot} and relative bioavailability (AUC). In contrast, captopril k_{el} decreased while $T_{1/2}$ increased progressively from group 1 to group 3.

3 PCEA blockade ($T_{1/2}$ and AUC) was increased significantly and proportionally to the degree of renal impairment. However, there were no differences between the three groups regarding captopril-induced modifications of PRA and PA.

4 Although the maximal reduction in MBP was identical in the three groups, the overall antihypertensive effect (AUC) of captopril increased significantly and progressively from group 1 to group 3, especially in duration.

5 There was no correlation between basal plasma creatinine values and unchanged captopril relative bioavailability (AUC) and between unchanged captopril relative bioavailability (AUC) and the drug effects (AUC) on PCEA, PRA, PA and MBP. However there was a correlation between basal plasma creatinine values and plasma captopril $T_{1/2}$, PCEA blockade (AUC) and overall antihypertensive effect (AUC).

6 The apparent discrepancy between the lack of effects of chronic renal failure on plasma unchanged captopril bioavailability and its potentiating effects on PCEA blockade and MBP reduction may be accounted for by the renal impairment-induced accumulation of captopril metabolites.

Keywords captopril chronic renal failure pharmacokinetics converting enzyme blockade antihypertensive effect

Introduction

Captopril, the first orally active inhibitor of the angiotensin I converting enzyme available, has been found to be effective in the treatment of renovascular and essential hypertension and of congestive heart failure (Heel *et al.*, 1980; Horovitz, 1981; Awan *et al.*, 1981). Since captopril is mainly eliminated by urinary excretion (Kripalani *et al.*, 1980; Duchin *et al.*, 1982) and since impairment of renal function is often associated with severe hypertension, this study was designed to investigate in three groups of hypertensive patients with various degrees of renal dysfunction the influence of renal impairment on (a) the pharmacokinetics of plasma unchanged captopril after administration of a single oral dose, (b) the kinetics of the induced plasma converting enzyme blockade and related biological modifications and (c) the kinetics of the acute antihypertensive effect of the drug. In addition, we investigated the possible relationships between plasma unchanged captopril bioavailability and its biological and clinical effects in the three groups of patients.

Methods

Patients

The study was performed in 30 hypertensive patients divided in three groups: with normal renal function (group 1, plasma creatinine < 110 $\mu\text{mol/l}$, $n = 10$), with moderate chronic renal failure (group 2, $135 < \text{plasma creatinine} < 450 \mu\text{mol/l}$, $n = 10$) with severe chronic renal failure (group 3, plasma creatinine > 500 $\mu\text{mol/l}$, $n = 10$). Chronic renal insufficiency was stable as judged by plasma creatinine levels at 15 day intervals. Plasma creatinine (mean $\pm$ s.e. mean) was $85 \pm 4 \mu\text{mol/l}$ in group 1, $246 \pm 32 \mu\text{mol/l}$ in group 2 and $653 \pm 42 \mu\text{mol/l}$ in group 3.

The other characteristics of the patients are summarized in Table 1. Excluded were the patients with labile or malignant hypertension, and with hypertension secondary to phaeochromocytoma, hyperaldosteronism or renal artery stenosis. In addition, only patients without signs of cardiac failure were enrolled in the protocol.

Antihypertensive medications had been discontinued for 15 days and patients were given a controlled sodium diet (100 mmol/day) during the 3 days preceding the study and on the following days. Before the study, the casual blood pressure averaged $184 \pm 3/113 \pm 2 \text{ mm}$

Hg in group 1, $188 \pm 7/118 \pm 2 \text{ mm Hg}$ in group 2 and $183 \pm 6/115 \pm 3 \text{ mm Hg}$ in group 3. Informed consent was obtained from all the patients.

Experimental protocol

Patients remained in supine position from 07.00 to 19.00 h. Blood pressure (mercury sphygmomanometer) was measured four consecutive times and the mean value was calculated; blood pressure and heart rate were recorded before (control) and after captopril administration, immediately before each blood sampling. At 09.00 h, patients were given captopril, 1 mg/kg, orally together with 150 ml of water. In this study, this usual antihypertensive dosage was administered as a single dose in order to allow measurable drug plasma levels for pharmacokinetic calculations. This dose was adjusted to the nearest 6.25 mg multiple (63.7 ± 3.6 , 69.4 ± 3.8 and $68.7 \pm 4.3 \text{ mg}$ in groups 1, 2 and 3, respectively). Water intake was repeated every other hour for 10 h. A low lipid meal was allowed at the third and the eighth hour after captopril intake. Blood samples for plasma unchanged captopril determination were collected before and 20 min, 40 min, 60 min, 90 min, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h and 24 h after drug intake. Blood samples for converting enzyme activity (PCEA), plasma renin activity (PRA) and plasma aldosterone (PA) determinations were obtained before and 1 h, 3 h, 6 h, 10 h and 24 h. The blood samples were drawn into tubes containing *p*-bromophenacylbromide (*p*-BPB) (captopril, see below) or heparin (PRA, PA and PCEA). The plasma was separated and stored at -20°C (captopril, PRA, PA) or at -80°C (PCEA) (Roulston *et al.*, 1980; Imbs *et al.*, 1981).

Analytical methods

Captopril pharmacokinetics. The method used derived from that initially developed by Kawahara *et al.* (1981) has previously been described (Richer *et al.*, 1984). In brief, whole free form of unchanged captopril was trapped with *p*-BPB, which was used as a coupling reagent for the thiol function, thus ensuring its stability, and the addition product was evaluated by high pressure liquid chromatography (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 r/min. The serum was separated and frozen at -20°C . An internal

Table 1 Aetiological diagnosis and basal clinical and biological parameters of the 29 hypertensive patients.

Patients/sex	Age (years)	Weight (kg)	Plasma creatinine ($\mu\text{mol/l}$)	Casual blood pressure (mm Hg)	Basal PRA ($\text{ng ml}^{-1} \text{h}^{-1}$)	Basal PA (ng/100 ml)	Basal PCEA ($\text{nmol ml}^{-1} \text{min}^{-1}$)	Aetiological diagnosis
Group 1								
1/M	32	69	92	170/110	2.5	7.0	23.5	EH
2/F	47	65	90	180/120	0.4	5.8	17.0	EH
3/M	47	72	84	180/110	1.0	7.5	20.1	EH
4/F	62	62	65	190/120	1.3	4.5	22.5	EH
5/F	39	50	62	180/110	1.5	5.8	21.5	EH
6/M	65	56	104	180/115	0.3	8.8	12.5	EH
7/M	53	49	85	200/120	0.2	5.2	22.1	EH
8/M	65	85	105	180/110	0.5	4.8	17.8	EH
9/M	55	64	84	200/110	0.6	9.5	15.7	EH
10/M	59	63	97	180/110	0.8	ND	29.4	EH
Mean	48.4	63.5	86.8	184/113	0.9	6.5	20.2	
$\pm$ s.e. mean	± 5.8	± 3.4	± 4.6	$\pm 3/\pm 2$	± 0.2	± 0.6	± 1.5	
Group 2								
1/F	63	69	438	210/110	1.2	5.3	25.3	PN
2/M	47	79	215	170/110	2.2	11.5	25.8	PK
3/F	54	81	135	180/120	0.9	5.2	18.5	NAS
4/M	52	55	187	230/130	0.8	9.0	22.5	Und.
5/F	61	71	178	210/130	0.1	5.2	19.4	NAS
6/M	54	86	293	170/110	1.3	20.0	26.7	GN
7/M	44	58	405	180/120	3.9	6.6	17.8	GN
8/F	41	52	241	180/120	4.8	20.0	15.7	GN
9/M	51	73	157	170/110	1.8	6.8	19.7	GN
10/M	49	67	213	180/120	0.3	20.0	8.6	PN
Mean	42.7	69.1	246.2 ^c	188/118	1.8	11.0	20.0	
$\pm$ s.e. mean	± 6.5	± 3.6	± 32.5	$\pm 7/\pm 2$	± 0.5	± 2.1	± 1.7	
Group 3								
1/F	52	51	580	180/110	4.7	25.0	29.0	PN
2/M	53	81	546	170/120	1.8	11.5	9.9	PK
3/M	52	75	781	170/110	1.6	3.4	19.3	PN
4/M	40	63	501	180/120	3.0	10.9	22.8	RH
5/M	62	69	547	170/100	0.2	6.9	17.5	PN
6/M	29	65	796	180/120	1.1	11.7	22.2	GN
7/M	57	61	538	170/110	0.2	15.5	22.6	PK
8/M	51	59	632	220/130	4.0	17.0	29.4	NAS
9/F	61	93	727	210/120	1.0	10.0	12.0	GS
Mean	50.8	68.5	627.6 ^{c,f}	183/115	1.9	12.4 ^a	20.5	
$\pm$ s.e. mean	± 3.5	± 4.2	± 37.5	$\pm 6/\pm 3$	± 0.5	± 2.1	± 2.2	

EH: essential hypertension; PN: chronic pyelonephritis; PK: polykystic kidney disease; NAS: nephroangiosclerosis; GN: chronic glomerulonephritis; RH: renal hypoplasia; GS: glomerulosclerosis; Und: undetermined.

Value significantly different from corresponding value in group 1: a: $P < 0.05$; c: $P < 0.001$.

Value significantly different from corresponding value in group 2: d: $P < 0.05$; f: $P < 0.001$.

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, Lirc A 801 pump (mobile phase flow: 1 ml/min), Waters 480 detector (254 nm) and Linear chart recorder). Captopril detection threshold was 20 ng/ml and a good linearity was obtained in the range of 20 ng/ml–2.5 $\mu\text{g/ml}$.

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

Plasma aldosterone (PA). This was measured using the radioimmunoassay described by Pham Huu *et al.* (1974).

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

Treatment of data

The results are reported as means $\pm$ s.e. mean. Captopril kinetics (time to peak blood levels $T_{\max}$, maximum concentration $C_{\max}$, elimination constant k_{el} , elimination half-life $T_{1/2}$, area under the concentration-time curve AUC, distribution volume V and total plasma clearance CL_{tot}) were calculated for each patient (Graphokin program) on a Tektronix 4052 computer according, because of the sensitivity of the captopril determination technique, to a one-compartment model and averaged.

The kinetics of the captopril-induced percent inhibition of PCEA, increase in PRA (Δ PRA), decrease in PA (Δ PA) and decrease in mean blood pressure (Δ MBP) were calculated for each patient and averaged in each group. In addition, the time to peak effect $t_{\max}$, the intensity of this maximum effect $C_{\max}$, the area under the effect-time curve AUC and the $T_{1/2}$ of the disappearance phase of the effect of captopril on percentage inhibition of PCEA and on Δ PRA, Δ PA and Δ MBP were calculated for each patient and averaged in each group.

Comparisons of the basal values and of the captopril-induced modifications of each parameter in the three groups of patients were performed by analysis of variance.

Finally, and taking into account the patients from all three groups the existence of possible correlations between (a) basal creatinine values

and free unchanged plasma captopril pharmacokinetic parameters ($T_{\max}$, k_{el} , $T_{1/2}$, AUC, CL_{tot} , V), PCEA blockade kinetics ($T_{1/2}$, AUC_{CE}) and Δ PRA ($\text{AUC}_{\Delta \text{PRA}}$), Δ PA ($\text{AUC}_{\Delta \text{PA}}$) and Δ MBP ($\text{AUC}_{\Delta \text{MBP}}$) kinetics, (b) free unchanged plasma captopril bioavailability (AUC) and PCEA blockade kinetics ($T_{1/2}$, AUC_{CE}), Δ PRA ($\text{AUC}_{\Delta \text{PRA}}$), Δ PA ($\text{AUC}_{\Delta \text{PA}}$) and Δ MBP ($\text{AUC}_{\Delta \text{MBP}}$) kinetics, (c) PCEA blockade (AUC_{CE}), and Δ PRA ($\text{AUC}_{\Delta \text{PRA}}$), Δ PA ($\text{AUC}_{\Delta \text{PA}}$) and Δ MBP ($\text{AUC}_{\Delta \text{MBP}}$) kinetics and (d) basal PRA values and Δ MBP ($\text{AUC}_{\Delta \text{MBP}}$) was tested with a least square linear regression.

Results

Basal values

Table 1 indicates the individual as well as the mean values of the biological, clinical and biochemical parameters of the patients of the three groups. Analysis of variance indicated that the groups were comparable regarding age, weight, casual blood pressure, basal PCEA and basal PRA although there was a tendency to a progressive increase of this last parameter from group 1 to group 3. Basal PA was significantly higher in group 3 than in group 1 ($P < 0.05$).

Figure 1 Kinetics of unchanged captopril plasma levels in hypertensive patients with normal renal function (group 1, $\circ$), with moderate chronic renal failure (group 2, $\bullet$) and with severe chronic renal failure (group 3, $\blacktriangle$).

Unchanged captopril pharmacokinetics

In one patient from group 3, no captopril plasma levels could be detected at any time after administration, although the drug elicited its usual biological and antihypertensive effects. Hence, all the data from this patient (plasma levels, effects on PCEA, PRA, PA, MBP) have been excluded from the results reported below, where $n = 9$ in group 3.

Figure 1 shows the evolution with time of captopril mean plasma levels. Five hours after its administration, captopril was no longer detectable in the plasma of any patient. Table 2 indicates the calculated pharmacokinetic parameters of captopril in the three groups of patients. It clearly appears that renal impairment had no effect on unchanged captopril $C_{\max}$, CL_{tot} and bioavailability (AUC). In contrast, k_{el} was progressively decreased while $T_{1/2}$ progressively and significantly increased from group 1 to group 3. V also showed a tendency to progressively increase from group 1 to group 3. Finally, $t_{\max}$ was increased, probably accidentally, in group 2 as compared to the two other groups.

PCEA blockade

Figure 2 shows the evolution with time of PCEA blockade and Table 3 indicates its calculated kinetic parameters in the three groups of patients. $t_{\max_{\text{CE}}}$ was significantly increased in groups 2 and 3 as compared to group 1. $T_{1/2}$ and AUC_{CE} were also significantly increased and proportionally to the degree of renal impairment.

Δ PRA and Δ PA

Figure 3 shows the evolution with time of Δ PRA and Δ PA and Table 3 indicates the

kinetic parameters of these two parameters in the three groups of patients. With the exception of $t_{\max_{\Delta \text{PRA}}}$ which was significantly lengthened in group 2 as compared to group 1 ($P < 0.05$), there were no significant differences between the three groups regarding those two parameters.

Δ MBP

Figure 4 shows the evolution with time of Δ MBP and Table 3 indicates the kinetic parameters of this parameter in the three groups of patients. Although the maximal decrease in MBP was identical in the three groups, $t_{\max_{\Delta \text{MBP}}}$ were progressively and significantly lengthened as the degree of renal impairment increased. Finally, the overall antihypertensive effect, as reflected by $AUC_{\Delta \text{MBP}}$, increased progressively from group 1 to group 3.

Correlations

There was no correlation between the basal creatinine values and (a) any of the following plasma unchanged captopril pharmacokinetic parameters: $t_{\max}$, k_{el} , CL_{tot} , V and AUC or (b) the Δ PRA and Δ PA kinetic parameters ($t_{\max}$, AUC). In contrast, there was a correlation between the basal creatinine values and (a) unchanged plasma captopril $T_{1/2}$ ($r = 0.439$, $P < 0.02$), (b) the kinetic parameters of PCEA blockade ($T_{1/2_{\text{CE}}}$: $r = 0.681$, $P < 0.01$; AUC_{CE} : $r = 0.812$, $P < 0.01$) and (c) the overall antihypertensive effect ($AUC_{\Delta \text{MBP}}$: $r = 0.476$, $P < 0.02$). As a result, there was no correlation between plasma unchanged captopril bioavailability (AUC) and the drug's effects on PCEA (AUC_{CE}), PRA ($AUC_{\Delta \text{PRA}}$), PA ($AUC_{\Delta \text{PA}}$) and MBP ($AUC_{\Delta \text{MBP}}$).

PCEA blockade (AUC_{CE}) was correlated

Table 2 Pharmacokinetic parameters of plasma unchanged captopril in the three groups of patients.

	Group 1	Group 2	Group 3
$t_{\max}$ (h)	0.98 ± 0.07	1.30 ± 0.13^a	0.85 ± 0.08
$C_{\max}$ (mg l ⁻¹)	1.21 ± 0.18	1.05 ± 0.15	1.00 ± 0.14
k_{el} (h ⁻¹)	1.25 ± 0.18	0.86 ± 0.10	0.80 ± 0.14^a
$T_{1/2}$ (h)	0.56 ± 0.06	0.92 ± 0.11^a	1.07 ± 0.18^b
CL_{tot} (l h ⁻¹ kg ⁻¹)	0.71 ± 0.10	0.65 ± 0.10	0.77 ± 0.19
V (l kg)	0.58 ± 0.11	0.73 ± 0.13	0.93 ± 0.12
AUC (mg l ⁻¹ h)	1.673 ± 0.213	2.043 ± 0.338	1.934 ± 0.390

Value significantly different from the corresponding value in group 1: a: $P < 0.05$; b: $P < 0.01$.

Figure 2 Kinetics of captopril-induced plasma converting enzyme activity percent blockade in hypertensive patients with normal renal function (group 1, ○), with moderate chronic renal failure (group 2, ●) and with severe chronic renal failure (group 3, ▲).

Value significantly different from the corresponding value in group 1: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Value significantly different from the corresponding value in group 2: † $P < 0.05$; †† $P < 0.001$.

with the overall antihypertensive effect ($AUC_{\Delta MBP}$: $r = 0.407$, $P < 0.05$) but not with Δ PRA and Δ PA kinetic parameters (t_{max} , AUC).

Finally, there was a correlation between PRA basal values and the overall antihypertensive effect ($AUC_{\Delta MBP}$: $r = 0.467$, $P < 0.02$).

Table 3 Kinetic parameters of PCEA blockade, Δ PRA, Δ PA and Δ MBP in the three groups of patients.

	Group 1	Group 2	Group 3
PCEA blockade			
t_{max} (h)	1.0 ± 0.1	2.9 ± 0.4^c	2.3 ± 0.3^a
$T_{1/2CE}$ (h)	8.1 ± 0.8	17.7 ± 4.3^a	$74.9 \pm 17.4^{c,f}$
AUC_{CE}	916 ± 65	1332 ± 129^b	$1775 \pm 66^{c,e}$
Δ PRA			
t_{max} (h)	5.1 ± 1.1	13.2 ± 3.7^a	9.2 ± 2.9
Maximal value ($ng\ ml^{-1}\ h^{-1}$)	3.9 ± 1.7	1.7 ± 0.8	3.6 ± 1.6
$AUC_{\Delta PRA}$	37.0 ± 13.3	27.9 ± 14.8	52.8 ± 27.6
Δ PA			
t_{max} (h)	3.8 ± 0.6	8.0 ± 1.9	9.7 ± 2.9
Maximal value ($ng/100\ ml$)	3.8 ± 0.5	6.2 ± 1.3	6.7 ± 1.7
$AUC_{\Delta PA}$	39.0 ± 10.0	93.7 ± 20.9	96.8 ± 24.2
Δ MBP			
t_{max} (h)	3.8 ± 0.5	5.2 ± 0.5	8.3 ± 2.2^a
Maximal value (mm Hg)	20.6 ± 2.1	22.3 ± 2.2	24.7 ± 4.4
$AUC_{\Delta MBP}$	156 ± 20	248 ± 60	322 ± 67^a

Value significantly different from corresponding value in group 1: a: $P < 0.05$; b: $P < 0.01$; c: $P < 0.001$.

Value significantly different from corresponding value in group 2: d: $P < 0.05$; e: $P < 0.01$; f: $P < 0.001$.

Figure 3 Kinetics of captopril-induced increases in plasma renin activity (PRA) and decreases in plasma aldosterone in hypertensive patients with normal renal function (group 1, $\circ$), with moderate chronic renal failure (group 2, $\bullet$) and with severe chronic renal failure (group 3, $\blacktriangle$). Value significantly different from the corresponding value in group 1: * $P < 0.05$.

Figure 4 Kinetics of captopril-induced decreases in mean arterial blood pressure in hypertensive patients with normal renal function (group 1, $\circ$), with moderate chronic renal failure (group 2, $\bullet$) and with severe chronic renal failure (group 3, $\blacktriangle$). Value significantly different from the corresponding value in group 1: * $P < 0.05$; ** $P < 0.01$.

Discussion

Since appropriate methods for plasma unchanged captopril monitoring have only recently become available, pharmacokinetic data on this drug are relatively scarce, especially in hypertensive patients with renal impairment. Moreover, studies involving evaluation of captopril plasma levels and captopril-induced renin-angiotensin system blockade and blood pressure reduction in hypertensive patients with renal dysfunction are lacking. The present investigation clearly shows that although there is no correlation between the degree of renal failure and plasma captopril bioavailability, there is a correlation between the former and the captopril-induced plasma converting enzyme blockade and reduction in blood pressure.

Our pharmacokinetic data for plasma unchanged captopril in group 1 (hypertensive patients with normal renal function) ($t_{\max}$: 0.98 ± 0.07 h; $T_{1/2}$: 0.56 ± 0.06 h) are in good agreement with those previously reported in normal subjects ($t_{\max}$: $0.7-0.9$ h; $T_{1/2}$: $0.35-1.7$ h) (Kripalani *et al.*, 1980; Onoyama *et al.*, 1981; Duchin *et al.*, 1982) or in hypertensive subjects ($t_{\max}$: $0.6-0.9$ h; $T_{1/2}$: $0.6-1.6$ h) (Jarrott *et al.*, 1981, 1982; Richer *et al.*, 1984) whatever the one- (Onoyama *et al.*, 1981; Richer *et al.*, 1984) or two-compartment (Duchin *et al.*, 1982) model used. Moreover, our data from groups 2 (hypertensive patients with mild renal impairment) and 3 (hypertensive patients with severe renal impairment) demonstrate that unchanged captopril k_{el} decreases and $T_{1/2}$ increases significantly and proportionally to the degree of renal impairment. However, there are no differences between the three groups of patients regarding the other unchanged captopril pharmacokinetic parameters ($C_{\max}$, CL_{tot} , V) and especially its relative bioavailability (AUC) which suggests that captopril does not accumulate in case of renal dysfunction.

In contrast, our data indicate that captopril-induced PCEA blockade is considerably lengthened by renal impairment. Thus PCEA blockade $T_{1/2}$ ($T_{1/2 \text{ CE}}$) increased two- and nine-fold respectively in groups 2 and 3 as compared to group 1, confirming the previous results by Campbell *et al.* (1982a). Furthermore, there was a strong correlation between the degree of renal impairment on the one hand and $T_{1/2 \text{ CE}}$ and the overall PCEA blockade (AUC_{CE}) on the other. Although intergroup differences did not reach statistical significance, the captopril-induced variations in PRA and PA were also always more pronounced and long-lasting in groups 2 and 3 than in group 1, which is in good agreement with the renal impairment-induced

prolongation of PCEA blockade. Finally, almost similar findings were made regarding the captopril-induced reduction in blood pressure. Although the absolute maximal reduction in MBP was identical in the three groups of patients, the time to peak antihypertensive effect was retarded. Furthermore, the duration of this effect increased as the degree of renal impairment augmented, there being a correlation between $AUC_{\Delta \text{ MBP}}$ on the one hand and basal creatinine values on the other.

There is thus an apparent discrepancy between the lack of effects of renal impairment on plasma unchanged captopril bioavailability and its potentiating effects, especially in duration, on PCEA blockade and MBP reduction. This could be due to the fact that protein binding is reduced during renal failure (Reidenberg *et al.*, 1971) resulting in higher unbound captopril plasma levels. However, since captopril protein binding is relatively small (McKinstry *et al.*, 1978), this mechanism is probably of limited importance. More likely, the discrepancy between captopril unchanged plasma bioavailability and enhanced biological and clinical effects in renal impairment might be due to the fact that, in contrast to the parent drug, captopril metabolites, which are not measured by our captopril determination technique, do accumulate in case of renal dysfunction. These metabolites, i.e. captopril disulphide and disulphide linkages between captopril and endogenous sulphhydryl-containing compounds and thiol groups of proteins (cysteine, glutathione, etc.) could act as a reservoir from which captopril could be released slowly (Duchin *et al.*, 1982) but at concentrations below its plasma detection threshold. Hence, these metabolites could in case of accumulation prolong the duration of captopril biological and clinical effects. It must be pointed out that during chronic renal impairment (a) in the plasma there are higher levels of sulphhydryl-containing compounds (Kopple, 1983) and (b) in the liver there is an increased hepatic blood flow (Bianchetti *et al.*, 1976), two arguments that could support the hypothesis of an increased formation of captopril metabolites. Furthermore, it is not unconceivable that captopril itself does accumulate because of renal impairment, but that the increase in the drug's plasma bioavailability which should then logically be observed is blunted by the concomitant increase in metabolites formation. Finally, one cannot exclude that the lack of correlation between the pharmacokinetics of free unchanged captopril and its pharmacological effects may partly be due to the fact that in our study captopril plasma bioavailability

was possibly slightly underestimated. It is indeed possible that, a currently undetectable decay phase of plasma captopril concentrations operates over the 6–24 h period following drug intake.

A correlation was found in this study between PCEA blockade and MBP reduction. Although not a systematic observation in hypertensive patients (Waeber *et al.*, 1980; Richer *et al.*, 1984), a similar correlation has previously been reported by others (Campbell *et al.*, 1982b) and the reasons for these discrepancies remain unclear. Finally, when considering all patients from the three groups, there was in our study a correlation between the captopril-induced fall in MBP and the pre-drug PRA values, a finding already previously reported by Gavras *et al.* (1981) in a large series of patients.

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