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Effect of renal function on the pharmacokinetics and pharmacodynamics of trandolapril

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1 The pharmacokinetics and pharmacodynamics of a single dose of trandolapril, an angiotensin converting enzyme (ACE) inhibitor with an active metabolite, trandolaprilat, which is in part further metabolised prior to renal elimination, were evaluated in 31 subjects with a wide range of renal function (creatinine clearance 4–112 ml min^{-1} 1.73 m^{-2}).

2 The pharmacokinetics of trandolapril were unaffected by differences in renal function.

3 In contrast, there was a close correlation between the renal clearance (0–96 h) of trandolaprilat and creatinine clearance ($r = 0.95$, $P = 0.0001$). The maximum plasma concentration of trandolaprilat, and the area under the concentration curve (0–96 h) correlated inversely with creatinine clearance ($r = -0.59$, $P < 0.001$; and $r = -0.61$, $P < 0.001$ respectively).

4 Significant changes in plasma trandolaprilat concentrations were seen only in patients with creatinine clearances of 30 ml min^{-1} 1.73 m^{-2} or less, suggesting that a dose reduction in trandolapril might be advisable in severe renal impairment.

5 However, the majority of parameters of ACE inhibition were unrelated to creatinine clearance, although area under the curve for ACE inhibition (0–336 h) showed a weak negative correlation ($r = -0.49$, $P < 0.01$). Similarly, weighted mean changes in blood pressure were not influenced by renal function.

6 Therefore, while the pharmacokinetic parameters of trandolaprilat correlated with creatinine clearance, pharmacodynamic measurements (ACE inhibition and blood pressure changes) in general showed no such relationship, indicating that dose adjustment of ACE inhibitors in renal impairment should be based on pharmacokinetic results only in conjunction with pharmacodynamic data.

Keywords trandolapril renal failure pharmacokinetics pharmacodynamics

Introduction

Angiotensin converting enzyme (ACE) inhibitors are well-established in clinical practice for the management of hypertension (Breckenridge, 1988) and congestive cardiac failure (The Consensus Trial Study Group, 1987). Although such drugs have few contraindications, their safe use is dependent on renal status. In patients with bilateral renal artery stenosis or renal artery stenosis in a single kidney, ACE inhibition may cause reversible renal impairment (Farrow & Wilkinson, 1979; Hricik *et al.*, 1983). Furthermore, renal excretion is responsible, at least in part, for the elimination of the active forms of all drugs of this class (Williams, 1988). Thus, dose adjustment has been considered to be necessary in severe renal dysfunction (Begg *et al.*, 1989).

The non-sulphydryl ACE inhibitor, trandolapril, is an oral prodrug which is rapidly hydrolysed to its active diacid metabolite, trandolaprilat (Patat *et al.*, 1989). Trandolapril is six to ten times more potent than enalapril in animals and has a very rapid onset and prolonged duration of action (Chevillard *et al.*, 1989). In contrast to most other ACE inhibitors, the active moiety is metabolised further prior to excretion. After the administration of ^{14}C-labelled trandolapril, only 50% of radioactivity found in the urine is due to trandolaprilat

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(Roussel Uclaf, unpublished data). Thus trandolapril might have a particular role in the treatment of patients with renal impairment.

The aim of this study was to examine the influence of renal function on the pharmacokinetics and pharmacodynamics of a single oral dose of trandolapril.

Methods

Patients

Twenty-eight Caucasians aged 33–71 years with creatinine clearances 10–112 ml min^{-1} 1.73 m^{-2} were recruited from seven centres: three in France, three in Great Britain, and one in South Africa. In addition three patients had creatinine clearances < 10 ml min^{-1} 1.73 m^{-2}, these patients were outwith the planned entry criteria of the study and were included in analysis of correlations only. Subjects had body weight within 15% of the ideal for height and were free of serious ill health (other than renal impairment). Women of child-bearing potential and patients receiving concomitant medication such as enzyme-inducing or -inhibiting agents, or non-steroidal anti-inflammatory drugs which might interfere with the pharmacokinetics and pharmacodynamics of trandolapril were excluded.

Patients gave consent to the trial after full explanation of the procedures and risks involved. The protocol was approved by the ethics committee of each centre.

Procedure

Patients were admitted to hospital for the first 72 h of the study period. Following an overnight fast, each subject was given a single dose of trandolapril 4 mg with 150 ml water at 08.00 h on day 1. Patients remained standing for 2 min after drug administration. Blood samples were taken from an indwelling venous cannula. Plasma trandolapril and trandolaprilat concentrations were measured pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 h after drug administration. Plasma ACE activity was assayed pre-dose and at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 168, 336, and 672 h post-dose. Serum creatinine and potassium, plasma aldosterone and renin were measured pre-dose and at 24 h post-dose; in addition the endocrine measurements were performed 4 h post-dose.

Divided urine collections were made during the 24 h prior to trandolapril and for 4 days thereafter. After measurement of volume, aliquots were taken for electrolyte, creatinine and trandolaprilat assay. From days 1 to 3, subjects received a diet standardised to include 4 g sodium chloride and 1500–2000 ml water daily.

On all occasions, prior to blood sampling, supine blood pressure (Hawksley random-zero sphygmomanometer) and heart rate were measured in triplicate after 15 min rest. In addition triplicate measurements of blood pressure and heart rate were made after 1 min erect pre-dose and at 1, 1.5, 4, 8, 12 and 24 h post-dose. Mean values at each time were used for analysis.

All adverse events occurring during the study were documented. Serum biochemistry and haematology were performed at the start, on day 2, and at the end of the study.

Laboratory techniques

Plasma and urine creatinine were measured using an enzymatic colorimetric technique. Specific radioimmune assays were used to quantify plasma renin activity, aldosterone, trandolapril and trandolaprilat concentrations at the Roussel Uclaf Institute and at the Hoechst Pharmaceutical Research Laboratories. The detection threshold of trandolapril and trandolaprilat in plasma was 0.2 ng ml^{-1}, and of trandolaprilat in urine was 10 ng ml^{-1}. A spectrophotometric method was used to assay ACE activity (Harjanne, 1984). Biochemical and haematological tests were conducted according to the routine techniques used in the hospital laboratories of each centre.

Data analysis

Creatinine clearance was calculated from plasma and urinary creatinine concentrations, and adjusted for surface area estimated from the Du Bois formula (Du Bois & Du Bois, 1916). For analysis patients were divided into four groups:

Group 1—creatinine clearance 10–30 ml min^{-1} 1.73 m^{-2}
Group 2—creatinine clearance 31–50 ml min^{-1} 1.73 m^{-2}
Group 3—creatinine clearance 51–80 ml min^{-1} 1.73 m^{-2}
Group 4—creatinine clearance > 80 ml min^{-1} 1.73 m^{-2}

The following pharmacokinetic parameters were calculated for both trandolapril and trandolaprilat: maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve (AUC) using the trapezoidal rule, and mean residence time in the body (MRT). Renal clearance of trandolaprilat was calculated by dividing the total amount eliminated in the urine by the corresponding area under the concentration-time curve. Trandolapril elimination half-life was calculated using a monoexponential expression in patients where this was appropriate.

For plasma angiotensin converting enzyme activity the following parameters were used: maximum percent inhibition (I_{max}), time to I_{max} (t_{max}), inhibition 24 h after dosing (I_{24h}), and area under the curve for inhibition (AUCI). Comparisons between the groups were made using one-way analysis of variance. Weighted mean changes in blood pressure were calculated by dividing area under the curve for changes in blood pressure by time. Relationships between pharmacokinetic and pharmacodynamic parameters, and creatinine clearance in all subjects (including those with creatinine clearance < 10 ml min^{-1} 1.73 m^{-2}) were explored using Pearson correlation coefficients.

Results

Thirty-one patients completed the study: 16 men and 15 women. Twenty-seven had chronic renal failure with creatinine clearances 4–77 ml min^{-1} 1.73 m^{-2} (mean ±

Table 1 Demographic characteristics for all subjects receiving a single oral dose of trandolapril 4 mg

Creatinine clearance (ml min^{-1} 1.73 m^{-2})	*Age (years)*	*Sex (M = male, F = female)*	*Height (cm)*	*Weight (kg)*	*Initial supine blood pressure (mm Hg)*
4	33	F	142	42	121/68
5	58	F	165	68	150/89
5	45	M	178	81	160/110
Group 1					
10	61	F	152	46	130/60
10	47	F	157	49	167/92
11	48	F	154	55	136/82
12	71	F	143	48	172/103
15	33	F	154	69	157/100
17	49	M	181	78	140/92
18	55	F	173	58	150/88
18	42	F	160	47	160/109
18	61	M	165	61	160/100
20	64	F	159	59	122/62
20	40	M	177	78	152/99
29	56	M	168	68	209/115
Group 2					
31	65	M	178	88	195/111
43	61	F	166	69	145/82
45	59	M	188	78	158/97
47	47	M	169	70	147/88
Group 3					
52	65	M	185	86	162/91
54	43	M	177	86	102/80
57	60	M	171	57	132/82
57	65	M	180	65	152/71
69	64	M	173	72	142/92
72	37	F	154	57	100/60
74	44	F	164	61	132/82
77	70	F	158	46	121/67
Group 4					
84	50	M	175	80	119/76
91	64	M	175	79	167/88
94	34	M	179	66	112/70
112	48	F	153	59	144/96

s.d. 33 ± 3 ml min^{-1} 1.73 m^{-2}). These patients were distributed as follows:

Group 1—creatinine clearance 10–30 ml min^{-1} 1.73 m^{-2}, 12 patients
Group 2—creatinine clearance 31–50 ml min^{-1} 1.73 m^{-2}, 4 patients
Group 3—creatinine clearance 51–80 ml min^{-1} 1.73 m^{-2}, 8 patients

In addition three patients had a creatinine clearance < 10 ml min^{-1} 1.73 m^{-2}. The mean age of patients with chronic renal failure was 53.4 ± 2.2 years. Hypertension was present in 18 out of 27.

The remaining four patients (group 4) had creatinine clearances in the range 84–112 ml min^{-1} 1.73 m^{-2} (mean ± s.d. 95 ± 6 ml min^{-1} 1.73 m^{-2}) with an average age of 48.9 ± 6.1 years. One-way analysis of variance showed no significant differences in age, sex ratio, height, weight or baseline blood pressure between the groups of patients (Table 1).

Trandolapril pharmacokinetics

Plasma trandolapril concentration-time curves for groups 1–4 are shown in Figure 1. Trandolapril was detectable in the plasma of all but one individual half of an hour after drug administration (and in the remaining individual 1 h post-dose). Concentrations then decreased rapidly, in group 4 no patient had detectable levels at 16 h post-dose. In patients with chronic renal failure trandolapril remained detectable in two patients at 24 h and one patient at 48 h. Table 2 shows pharmacokinetic parameters for trandolapril. Data from only 18 patients could be utilised to calculate elimination half-life ($t_{½}$). Mean $t_{½}$ for trandolapril was 0.6 h (range 0.5 to 0.8 h)

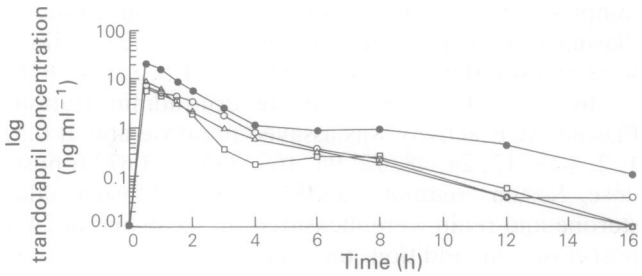

Figure 1 Log mean plasma trandolapril concentrations with time after administration of a single oral dose of 4 mg according to creatinine clearance (△ 10–30, ● 31–50, ○ 51–80 and □ > 80 ml min^{-1} 1.73 m^{-2}).

Table 2 Pharmacokinetic parameters for trandolapril after administration of a single oral dose of 4 mg according to creatinine clearance (CL_{CR}) ml min^{-1} 1.73 m^{-2}: mean (s.d.)

	CL_{CR} < 10 (n = 3)	*CL_{CR} 10–30 Group 1* (n = 12)	*CL_{CR} 31–50 Group 2* (n = 4)	*CL_{CR} 51–80 Group 3* (n = 8)	*CL_{CR} > 80 Group 4* (n = 4)	P *value** *(ANOVA)*
CL_{CR} (ml min^{-1} 1.73 m^{-2})	4.7 (0.3)	16 (4)	41 (4)	62 (3)	95 (6)	—
C_{max} (ng ml^{-1})	18.6 (7.4)	10.5 (1.2)	22.7 (11.3)	9.6 (2.1)	6.6 (1.6)	NS
t_{max} (h)	0.8 (0.3)	0.7 (0.1)	1.0 (0.4)	1.1 (0.3)	0.5 (0.0)	NS
AUC (ng ml^{-1} h)	29.8 (12.1)	14.0 (1.8)	38.9 (13.4)	15.5 (2.4)	11.1 (5.2)	< 0.05
MRT (h)	2.4 (0.8)	1.9 (0.2)	3.3 (0.9)	2.1 (0.2)	1.5 (0.4)	< 0.05

t_{max} = time to C_{max}.
MRT = mean residence time.
* ANOVA performed on groups 1–4 only.
NS = not significant.

Table 3 Pharmacokinetic parameters for trandolaprilat after administration of a single oral dose of trandolapril 4 mg according to creatinine clearance (CL_{CR}) ml min^{-1} 1.73 m^{-2}: mean (s.d.)

	CL_{CR} < 10 (n = 3)	*CL_{CR} 10–30 Group 1* (n = 12)	*CL_{CR} 31–50 Group 2* (n = 4)	*CL_{CR} 51–80 Group 3* (n = 8)	*CL_{CR} > 80 Group 4* (n = 4)	P *value** *(ANOVA)*
CL_{CR} (ml min^{-1} 1.73 m^{-2})	4.7 (0.3)	16 (2)	41 (4)	62 (3)	95 (6)	—
C_{max} (ng ml^{-1})	24.4 (8.0)	16.6 (1.3)	10.0 (2.0)	8.7 (0.9)	9.6 (2.3)	< 0.0001
t_{max} (h)	6.7 (0.7)	4.4 (0.4)	5.0 (0.6)	4.9 (0.4)	3.1 (0.6)	NS
AUC 0–24 h (ng ml^{-1} h)	349.8 (121.5)	211.4 (15.3)	128.3 (23.1)	108.9 (8.3)	98.7 (16.9)	0.0001
AUC 0–96 h (ng ml^{-1} h)	570.0 (197.8)	326.6 (18.0)	229.2 (35.3)	195.7 (14.0)	178.3 (15.5)	0.0001

* ANOVA performed on groups 1–4 only.

in subjects with normal renal function (n = 3), 0.8, 1.1 and 1.0 h in groups 1, 2 and 3 respectively (range 0.3 to 1.4 h) and 0.9 h in those with creatinine clearances < 10 ml min^{-1} 1.73 m^{-2} (n = 2). Pharmacokinetic indices for trandolapril did not correlate with creatinine clearance although C_{max} and AUC tended to be high in severe renal impairment.

Trandolaprilat pharmacokinetics

In all groups of patients time profiles for plasma trandolaprilat concentrations showed three phases: an appearance phase, a rapid elimination phase, and a prolonged terminal elimination phase (Figure 2).

Trandolaprilat was detectable in the plasma of 29 patients after 0.5 h, in all patients after 1 h, and remained detectable in 30 patients at 96 h. Pharmacokinetic data for trandolaprilat are displayed in Table 3. Maximum concentration (C_{max}) and areas under the concentration-time curves (AUC), both for 0–24 h and 0–96 h, were significantly greater in those with creatinine clearances < 30 ml min^{-1} 1.73 m^{-2} than in the three groups of patients with better renal function. There were no differences between groups 2–4. Renal trandolaprilat clearance (0–96 h) correlated positively with creatinine clearance (r = 0.95, P = 0.0001) (Figure 3); C_{max} and

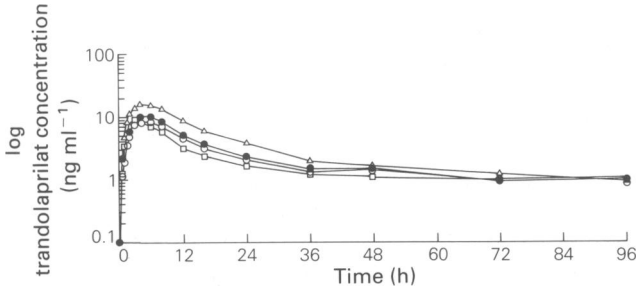

Figure 2 Log mean plasma trandolaprilat concentrations with time after administration of a single oral dose of trandolapril 4 mg according to creatinine clearance (△ 10–30, • 31–50, ○ 51–80 and □ > 80 ml min^{-1} 1.73 m^{-2}).

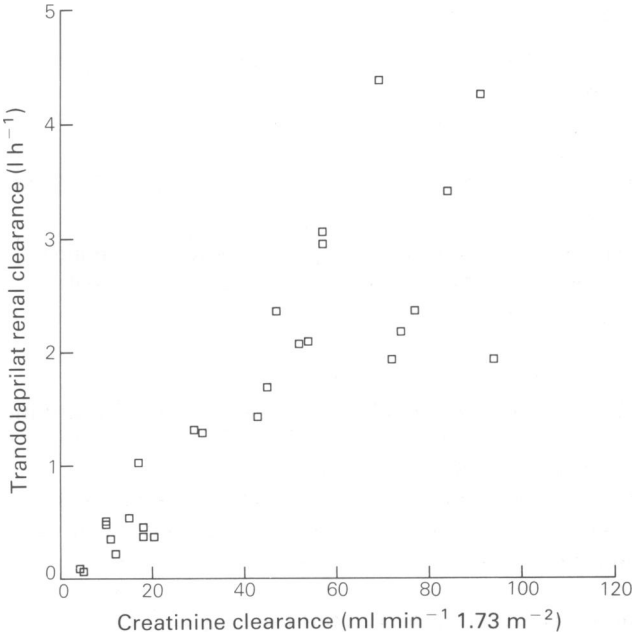

Figure 3 Relationship between the renal clearance of trandolaprilat (l h^{-1}) and creatinine clearance in 31 subjects given a single oral dose of trandolapril 4 mg.

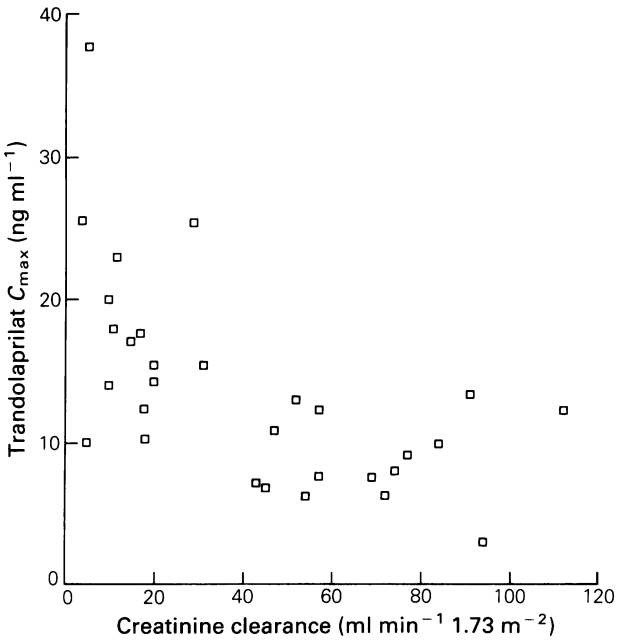

Figure 4 Relationship between maximum plasma trandolaprilat concentration (ng ml^{-1}) and creatinine clearance in 31 subjects given a single oral dose of trandolapril 4 mg.

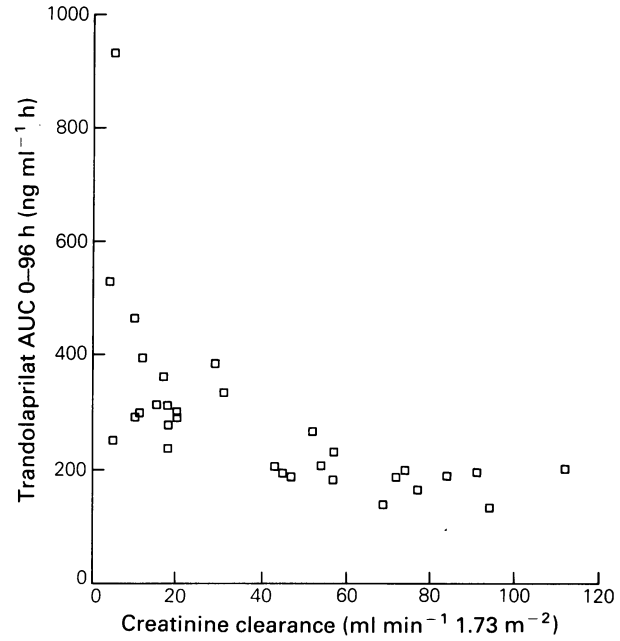

Figure 5 Relationship between area under the concentration-time curve for plasma trandolaprilat 0–96 h (ng ml^{-1} h) in 31 subjects given a single dose of trandolapril 4 mg.

AUC (0–96 h) correlated inversely with creatinine clearance ($r = -0.59$, $P < 0.001$; and $r = -0.61$, $P < 0.001$ respectively) (Figures 4 and 5).

Cumulative urinary excretion of trandolaprilat is shown in Figure 6. In all patients 80–90% of urinary excretion occurred within the first 24 h. Total urinary drug excretion was related to renal function. In group 4 the total excretion accounted for 15.2% of the administered dose compared with 13.3%, 9.9%, 5.1% and 0.8% for groups 3, 2, 1 and those with creatinine clearances < 10 ml min^{-1} 1.73 m^{-2} respectively.

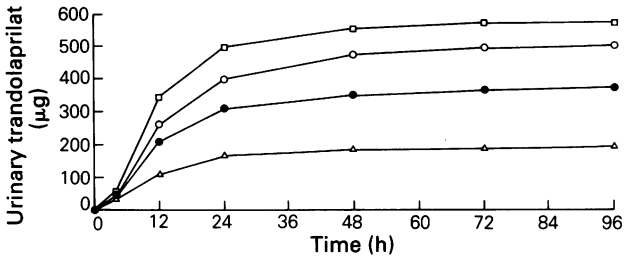

Figure 6 Mean cumulative urinary trandolaprilat excretion with time after administration of a single oral dose of trandolapril 4 mg according to creatinine clearance (△ 10–30, • 31–50, ○ 51–80 and □ > 80 ml min^{-1} 1.73 m^{-2}).

Pharmacodynamics

Inhibition of plasma ACE was present in all subjects 30 min after trandolapril administration. At 24 h inhibition was 45.9–73.6% in group 4 and 31.8–100% in patients with renal failure. Fourteen days (336 h) after drug administration, ACE was still inhibited in 28 out of 31 individuals; percent inhibition 11.7–59.9%.

Inhibition parameters for ACE (Table 4) showed no significant differences between the four groups of patients. There was no correlation between percent inhibition at 24 h (I_{24h}) and creatinine clearance. However, area under the curve for inhibition (AUCI 0–336 h) showed a weak negative correlation with creatinine clearance ($r = -0.49$, $P < 0.01$).

There were no significant differences between the four groups of patients in weighted mean blood pressure changes over 4, 24 or 672 h (28 days). Similarly there were no significant correlations between weighted mean changes in blood pressure and creatinine clearance; results for 0–24 h are shown in Figure 7. Similar values were found for 0–4 h, and 0–672 h: supine systolic blood

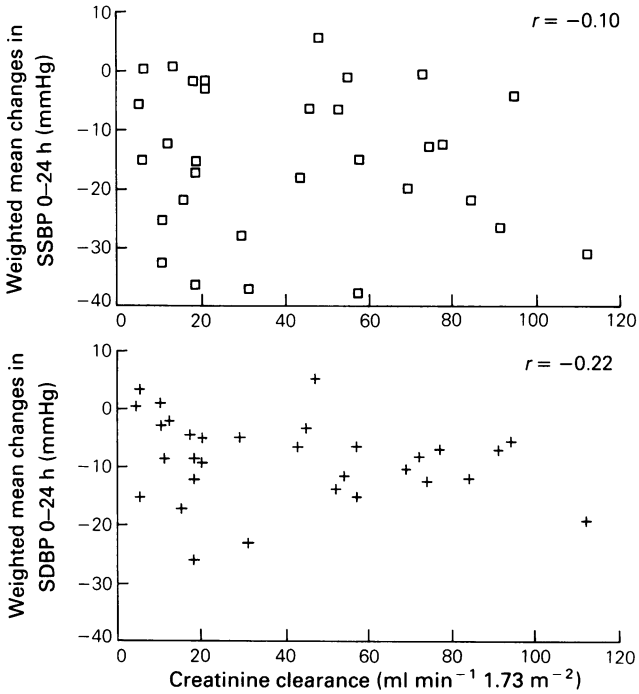

Figure 7 Relationship between weighted mean changes in supine systolic and diastolic blood pressure (day 1) and creatinine clearance in 31 subjects given a single oral dose of trandolapril 4 mg.

Table 4 Parameters for ACE inhibition after administration of a single oral dose of trandolapril 4 mg according to creatinine clearance (CL_{CR}) ml min^{-1} 1.73 m^{-2}: mean (s.d.)

	CL_{CR} 10–30 Group 1 (n = 12)	*CL_{CR} 31–50 Group 2 (n = 4)*	*CL_{CR} 51–80 Group 3 (n = 8)*	*CL_{CR} > 80 Group 4 (n = 4)*	P *value (ANOVA)*
I_{max}	93.8 (2.8)	91.1 (5.3)	92.1 (3.0)	88.9 (4.8)	NS
t_{max} (h)	5.4 (2.1)	9.5 (5.0)	4.5 (0.8)	6.0 (2.0)	NS
I_{24h} (%)	75.2 (5.6)	82.0 (6.6)	77.3 (4.1)	59.6 (5.8)	NS
AUCI 0–336 h (% h)	18,294 (1571)	19,026 (1428)	14,614 (2389)	13,548 (1433)	NS

I_{max} = maximum inhibition.
t_{max} = time to I_{max}.
I_{24h} = inhibition 24 h post-dose.

Table 5 Plasma renin activity and plasma aldosterone concentrations after administration of a single dose of trandolapril 4 mg according to creatinine clearance (CL_{CR}) ml min^{-1} 1.73 m^{-2}: mean (s.d.)

Time post-dose (h)	*CL_{CR} 10–30 Group 1 (n = 12)*	*CL_{CR} 31–50 Group 2 (n = 4)*	*CL_{CR} 51–80 Group 3 (n = 8)*	*CL_{CR} > 80 Group 4 (n = 4)*
Plasma renin activity (ng ml^{-1} h^{-1} angiotensin I) Normal range 0.2–2.8				
0	0.7 (0.1)	2.3 (1.2)	1.4 (0.3)	2.4 (1.0)
4	1.7 (0.5)	3.3 (1.5)	3.4 (1.1)	3.0 (0.6)
24	1.5 (0.3)	10.7 (6.7)	3.4 (1.3)	3.0 (0.6)
Plasma aldosterone (pg ml^{-1}) Normal range 15–150				
0	331 (58)	322 (95)	105 (25)	89 (10)
4	237 (24)	229 (71)	90 (42)	69 (9)
24	187 (25)	164 (26)	96 (18)	89 (30)

pressure $r = 0.05$, and $r = 0.23$ respectively; supine diastolic blood pressure $r = -0.13$, and $r = -0.11$ respectively.

Before trandolapril administration plasma renin activity was elevated in three subjects. Trandolapril caused an increase in plasma renin activity in all groups of patients (Table 5) this increase being least in those with normal renal function.

With the exception of one subject, those with creatinine clearances < 50 ml min^{-1} 1.73 m^{-2} entered the study with elevated plasma aldosterone concentrations; 191–921 pg ml^{-1}. Trandolapril decreased plasma aldosterone concentrations (Table 5); percentage reduction was greatest in those with the severest renal impairment.

Adverse effects

Two patients had symptomatic postural hypotension 1.5 h after drug administration, continuing until 8 h in one and 12 h in the other; a further two patients suffered postural lightheadedness at 4 h post-dose but without a fall in blood pressure. In addition marked, but asymptomatic, falls in supine blood pressure were noted in four patients. Although maximum plasma trandolaprilat concentrations tended to be slightly higher than the average in these eight subjects, events did not appear to be related to age or creatinine clearance (Table 6).

A facial and forearm erythematous rash developed in one patient on the first day of the study and spontaneously disappeared after 3 days. Gout developed in one subject on day 26; two patients complained of headache. No clinically significant changes in serum biochemistry or or haematology were seen during the study; in particular no clinically significant hyperkalaemia was noted. The highest serum potassium measurements were 5.2 mmol l^{-1} at 24 h after trandolapril administration in a patient whose baseline serum potassium was 4.1 mmol l^{-1}; and 5.6 mmol l^{-1} at 28 days after trandolapril administration in a patient whose serum potassium was 4.1 mmol l^{-1} 24 h post-dosing.

Discussion

The ACE inhibitors are a rapidly expanding group of drugs which differ from one another according to the presence or absence of a sulphydryl group, administration in active form or as a prodrug, speed of onset and duration of action, metabolism, elimination and potency (Kostis, 1988). In common with enalapril, cilazapril, quinapril and ramipril, trandolapril is a prodrug which is rapidly converted to its active metabolite. We have shown little evidence of change in the metabolism of trandolapril dependent on renal function. This is consistent with findings for ramipril (Debusmann *et al.*, 1987), and is to be expected for a molecule that is almost totally metabolised, although the ester hydrolyses of enalapril, cilazapril and quinapril are prolonged in renal failure (Begg *et al.*, 1990; Fillastre *et al.*, 1989; Till *et al.*, 1984). The pharmacokinetic parameters calculated for subjects with normal renal function in this study are in agreement with those noted previously (Roussel Uclaf, unpublished data).

Table 6 Characteristics of patients who suffered postural lightheadedness or hypotension, or marked falls in supine blood pressure after administration of a single oral dose of trandolapril 4 mg

Creatinine clearance ($ml\ min^{-1}\ 1.73\ m^{-2}$)	C_{max} *trandolaprilat* ($ng\ ml^{-1}$)	*Age (years)*	*Adverse effect*
4	25.5	33	Postural lightheadedness
5	37.6	58	Postural hypotension
10	14.0	61	Marked fall in supine blood pressure
31	15.3	65	Marked fall in supine blood pressure
57	7.6	60	Marked fall in supine blood pressure
77	9.1	70	Postural hypotension
84	9.9	50	Marked fall in supine blood pressure
91	13.3	64	Postural lightheadedness and marked fall in supine blood pressure

In our subjects the elimination half-life of trandolapril varied from 0.6–1.1 h. However, thirteen individuals demonstrated a biphasic elimination curve for trandolapril with a a slow terminal elimination phase. This precluded the inclusion of these individuals in our calculations of mean elimination half-life. Similar biphasic elimination has been shown for cilazapril (Fillastre *et al.*, 1989). In one patient from group 2 (creatinine clearance 43 ml min^{-1} 1.73 m^{-2}) plasma trandolapril concentrations, C_{max} and AUC were markedly higher than in all other patients. Such marked interindividual variability has been demonstrated previously in healthy volunteers (Roussel Uclaf, unpublished data). No corresponding alterations in plasma trandolaprilat concentrations were seen. However, as group 2 was small ($n = 4$) this patient artificially elevated the mean C_{max} and AUC for trandolapril in this group. Analysing patients in groups according to creatinine clearance is complicated since day to day variability within individuals can be considerable. Thus correlations of individual patient data for trandolapril pharmacokinetics with creatinine clearance are probably more reliable than comparisons between the four groups of patients.

This study indicates that the renal clearance of trandolaprilat is highly dependent on creatinine clearance; and that both the C_{max} and AUC are inversely correlated with creatinine clearance. In contrast with most other ACE inhibitors, trandolaprilat is in part further metabolised prior to excretion. This does not appear to alter the strong correlation between trandolaprilat elimination and renal function. For patients with a creatinine clearance between 10–30 ml min^{-1} 1.73 m^{-2}, C_{max} and AUC were approximately doubled in comparison with the results for subjects with normal renal function. Furthermore, altered protein binding in severe renal impairment might be expected to increase free concentrations of the parent drug and its metabolite.

A correlation between clearance of the active component of ACE inhibitors and renal function has been found consistently in all studies (Begg *et al.*, 1989). Similarly peak and trough concentrations of the active component are inversely proportional to creatinine clearance. Some work has suggested that the time to peak concentration is also usually slightly increased in renal impairment (Begg *et al.*, 1989). Although t_{max} was not related significantly to renal function in this study, it was markedly prolonged in those with creatinine clearances <10 ml min^{-1} 1.73 m^{-2}. No formal calculation of elimination half-life was possible due to the non-linear curve, but the elimination of trandolaprilat had a prolonged terminal phase, a characteristic which is probably common to all ACE inhibitors (Debusmann *et al.*, 1987; Fillastre *et al.*, 1989; Kelly *et al.*, 1986). Failure to detect a prolonged terminal elimination phase for captopril, lisinopril and quinaprilat may be due to insensitive assays and/or study periods of inadequate length (Begg *et al.*, 1989).

After administration of ACE inhibitors, duration of ACE inhibition is usually inversely proportional to renal function (Begg *et al.*, 1989). Following trandolapril 4 mg the intensity of ACE inhibition showed little modification with severity of renal failure but return to basal values tended to be slower in patients with the most severe renal impairment. Likewise changes in blood pressure did not vary in patients with differing levels of renal function. A previous trial of trandolapril, at doses between 0.125–32 mg in healthy volunteers demonstrated that ACE inhibition is dose-related from 0–2 mg, and is maximal after higher doses (Patat *et al.*, 1989). Thus a high degree of ACE inhibition would be expected in all patients given trandolapril 4 mg whatever their renal function.

It is well-recognised that ACE inhibition increases plasma renin activity and decreases plasma aldosterone concentration (Rotmensch *et al.*, 1988). These changes were seen with trandolapril in subjects with all degrees of renal impairment, and were most marked in patients with creatinine clearances < 50 ml min^{-1} 1.73 m^{-2}. Patients who suffered from marked falls in supine blood pressure or postural hypotension tended to have high plasma renin activity before treatment or large falls in plasma aldosterone concentrations after treatment.

However, these events and other side effects attributed to trandolapril were not related to renal function or trandolaprilat pharmacokinetics.

The hydrolysis of trandolapril to its active diacid metabolite, trandolaprilat, appeared to be unaffected by renal impairment but the elimination of trandolaprilat was related closely to creatinine clearance. Maximum plasma concentration and area under the curve for trandolaprilat correlated inversely with renal function and plasma ACE inhibition tended to be more prolonged in patients with severe renal failure. Thus a reduction in trandolapril dose in patients with severe renal impairment might be indicated. However, other indices of ACE inhibition, changes in blood pressure and adverse events did not vary with the degree of renal impairment suggesting that dosage adjustment may be unnecessary. These findings require cautious interpretation since some unwanted effects of ACE inhibitors may be mediated by mechanisms other than ACE inhibition and result from accumulation of the active metabolite. Nevertheless, our results support the importance of considering pharmacodynamic data as well as pharmacokinetic data when making dose recommendations for ACE inhibitors in renal impairment.

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