Eur J Clin Pharmacol (1983) 24: 661–665

European Journal of Clinical Pharmacology

Pharmacokinetics of Hydrochlorothiazide in Relation to Renal Function

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Summary. The pharmacokinetics of hydrochlorothiazide (HCT) was investigated in 23 subjects with normal renal function or widely varying degrees of renal failure. The half-life of elimination increased from 6.4 h in subjects with normal renal function to 11.5 h in patients with mild renal impairment (endogenous creatinine clearance between 30 and 90 ml/min), and to 20.7 h in patients with an endogenous creatinine clearance below 30 ml/min. The cumulative urinary excretion and the renal HCT clearance were correspondingly reduced in patients with impaired kidney function. In normal subjects HCT was mainly excreted by tubular secretion, but as renal HCT clearance in patients with renal impairment did not differ significantly from endogenous creatinine clearance, it was concluded that the secretory mechanism is most markedly impaired. In patients with an endogenous creatinine clearance of 30 to 90 ml/min, the dosage of HCT should be reduced to ½ and in patients with a endogenous creatinine clearance below 30 ml/min to ¼ of the normal daily dose to avoid dose dependant side-effects.

Key words: hydrochlorothiazide, pharmacokinetics; renal failure, dosage adjustment, excretory mechanism

Hydrochlorothiazide (HCT), one of the thiazide-type diuretics, has been known for more than 20 years. It is frequently used in the treatment of arterial hypertension and oedema. As hypertensive patients often have compromised renal function, drugs mainly eliminated by renal excretion should be used with caution in them. Anderson et al. [1] and Beermann and Groschinsky-Grind [7] showed that at least 95% of an intravenous dose of HCT was excreted unchanged by the kidneys, so it must be expected that on long term treatment HCT would accumulate if it were administered to patients suffering from renal failure and the dosage regimen was not adjusted. This would lead to an increase in the dose-dependant side effects, as hypokaliaemia, hyperuricaemia and impairment of blood sugar control.

Although the pharmacokinetics of HCT in normal subjects has been thoroughly investigated there is only inadequate information about the influence of reduced kidney function on the pharmacokinetics of HCT. Anderson et al. [1] showed in 2 patients with the Kimmelstiel-Wilson syndrome that only 25% of an intravenous dose and 9% of an oral dose were excreted unchanged within 24 h [1]. Another patient with elevated serum creatinine who eliminated HCT more slowly was reported by Beermann and Groschinsky-Grind [7]. In a more recent study, Beermann and Groschinsky-Grind also showed in 7 patients suffering from cardiac failure, that the elimination rate and renal clearance of HCT were reduced in those who showed renal impairment [5]. Three children suffering from renal failure and chronically treated with HCT had plasma levels of the drug up to 40 µg/ml [12]. The aim of the present study was to investigate the influence of renal impairment on the elimination of HCT in patients with widely varying renal function.

Materials and Methods

Patients

23 subjects, aged 23 to 82 years, with widely differing degrees of renal function were investigated. Three subjects were in good health and the others suffered

Table 1. Details of the patients

Subject	Cl_{cr} [ml/min]	Age [years]	Weight [kg]	Sex	Diagnosis
A	120	42	68.5	m	healthy subject
B	110	50	62.0	m	healthy subject
C	106	71	96.3	m	arter. hypertens.
D	105	66	60.0	m	arter. hypertens.
E	103	48	66.0	m	healthy subject
F	100	23	55.2	f	cholelithiasis
G	80	68	63.0	m	chronic glomerulonephritis, liver cirrhosis
H	78	49	67.0	m	cystic kidneys
I	73	88	62.0	m	arter. hypertens. apoplect. insult.
K	70	76	68.0	m	parkinsonism
L	67	54	61.0	f	cystic kidneys
M	67	54	45.5	f	arrhythmia
N	50	80	63.0	m	prostata adenoma
O	45	72	54.5	f	pneumonia
P	34	50	75.3	m	chronic glomerulonephritis
Q	31	81	77.4	m	arter. hypertens., toxic hepatitis
R	30	82	54.7	m	chronic glomerulonephritis
S	30	74	57.6	f	chronic glomerulonephritis
T	30	81	63.5	m	chronic glomerulonephritis
U	18	80	70.0	m	chronic glomerulonephritis
V	11	59	72.2	m	chronic glomerulonephritis
W	10	76	55.0	f	chronic glomerulonephritis
X	7	50	62.3	f	chronic glomerulonephritis

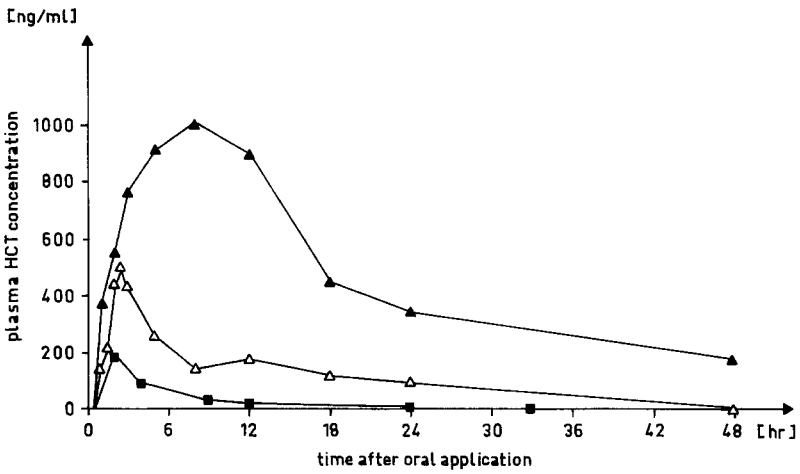

Fig. 1. Plasma concentration-time curve of oral hydrochlorothiazide 50 mg in 3 patients with different endogenous creatinine clearances, Cl_{cr}. ■—■ $Cl_{cr} = 106$ ml/min, Patient C; ▲—▲ $Cl_{cr} = 30$ ml/min, Patient S; ▲—▲ $Cl_{cr} = 10$ ml/min, Patient W.

from various internal diseases. The subjects were divided into 3 groups according to their renal function as determined by the endogenous creatinine clearance (Cl_{cr}); 6 subjects had normal renal function ($Cl_{cr} \geq 100$ ml/min; Group 1); 10 patients had mild renal impairment ($30 \text{ ml/min} < Cl_{cr} < 100 \text{ ml/min}$; Group 2); and in 7 patients renal failure was moderate to severe ($Cl_{cr} \leq 30$ ml/min; Group 3). Details of all the subjects are given in Table 1.

The patients were maintained on their usual therapeutic regimens, except that diuretic agents were discontinued for at least 3 days prior to the administration of HCT if they had received these drugs. Hydrochlorothiazide 50 mg (2 Esidrix® tablets, Ciba-Geigy) were administered to the subjects in the morning, in the fasting state. Thereafter fluid intake and diet were not restricted.

Serial blood samples were collected before and up to 48 h after dosing (at 0.5, 1, 1.5, 2, 2.5, 3, 5, 8, 12, 24 and 48 h). Complete 72 h urine specimens were obtained from the subjects, in fractions at 1, 2, 3, 4, 5, 6, 12, 24, 30, 36, 42, 48, 54, 60, 66 and 72 h. After col-

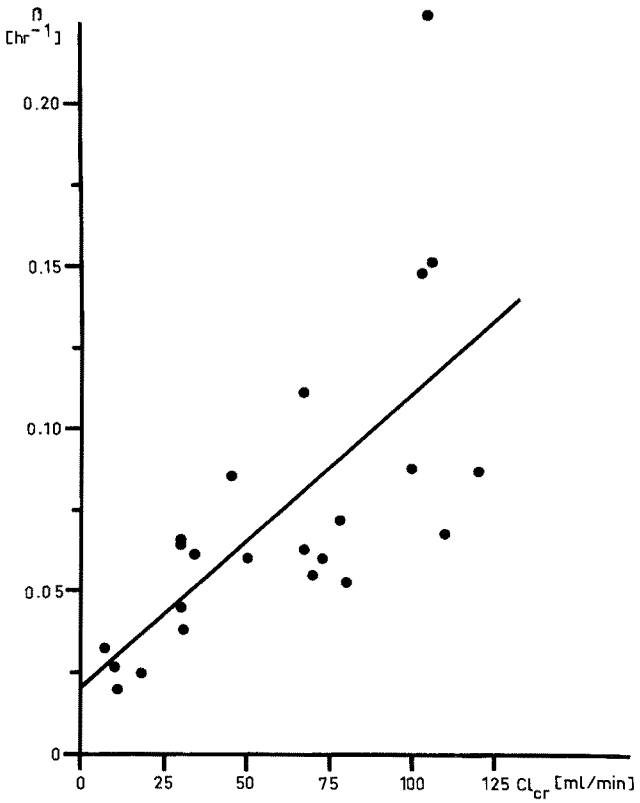

Fig. 2. Relationship between elimination rate constant (β) and endogenous creatinine clearance (Cl_{cr})

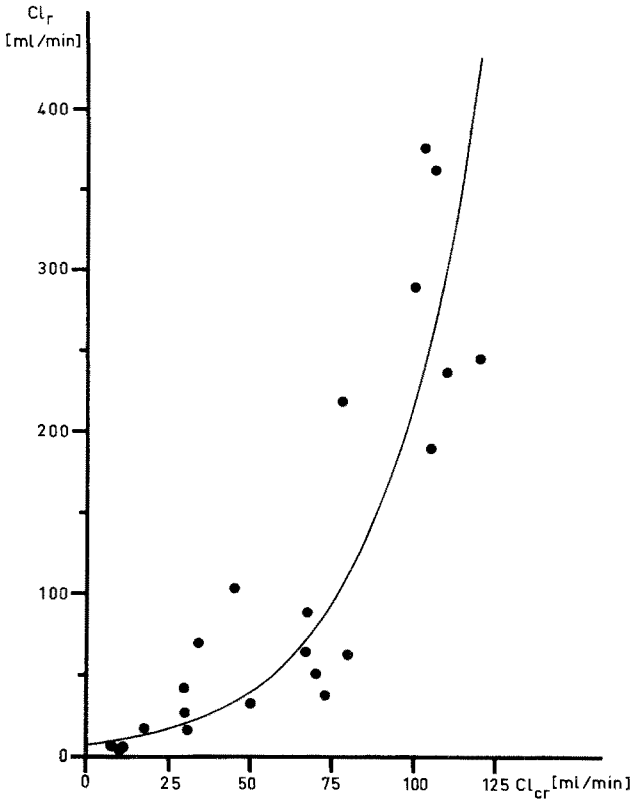

Fig. 3. Relationship between renal clearance (Cl_r) of hydrochlorothiazide and endogenous creatinine clearance (Cl_{cr}) in patients with different degrees of renal failure

Table 2. Definitions and equations

Term	Definitions and equations
Cl_{cr}	Endogenous creatinine clearance $= A_u^{24}/AUC_{0-24}$
β	Elimination rate constant calculated by least squares non-linear regression analysis
$t_{½}$	Half-life of elimination $= \ln 2/\beta$
AUC	Area under the plasma level time curve calculated by the trapezoidal rule up to 24 (12) hours and extrapolated to infinity
A_u	Cumulative urinary excretion
Cl_r	Renal clearance $= A_u/AUC$
C_{max}	Maximum plasma concentration
t_{max}	Time of peak plasma level

lection, blood was centrifuged and plasma and urine specimens were stored frozen (−20 °C) until analysed.

HCT in plasma and urine was determined by fluorescence measurement on thin-layer chromatograms, as described earlier [14]. Pharmacokinetic parameters of each patient were calculated as defined in Table 2. Statistical evaluation of pharmacokinetic data was performed with Student's *t*-test.

Results

Oral administration of HCT yielded plasma levels as depicted in Fig. 1. Maximal plasma levels (C_{max}) were found 2 to 5 h after administration of the drug; they ranged from 108 ng/ml to 846 ng/ml (see Table 3). The mean peak plasma level increased from 183 ng/ml in subjects with normal renal function to 334 ng/ml in patients with mild renal impairment, and to 415 ng/ml in those with moderate to severe renal insufficiency. The areas under the plasma level – time curves (AUC) were related to kidney function, the AUC's being greater in patients with impaired kidney function than in the controls. The correlation between 1/AUC and Cl_{cr} was highly significant ($r = 0.88$). The increasing HCT plasma levels led to an increase in the area under the plasma level – time curve from 1418 ng $ml^{-1}h$ (Group 1) to 4700 $ml^{-1}h$ (Group 2) and to 12001 ng $ml^{-1}h$ (Group 3).

As renal impairment became more severe the excretion rate of HCT was reduced. The half-life of elimination ($t_{½}$) increased from an average of 6.4 h in subjects with normal renal function to 11.5 h in the patients in Group 2 and to 20.7 h in Group 3. The rise is statistically significant ($p < 0.01$) for both groups of patients suffering from renal impairment. The rela-

Table 3. Pharmacokinetic data calculated from plasma levels and urinary excretion following a single oral dose of HCT 50 mg

Subject	Cl_{cr} [ml/min]	Cl_r [ml/min]	β [h^{-1}]	$t_{½}$ [h]	t_{max} [h]	C_{max} [ng/ml]	AUC [ng·ml^{-1}h]	A_u [mg]
A	120	246	0.0866	8.0	2	127	1319	19.5
B	110	239	0.0680	10.2	2.5	186	1147	16.4
C	106	363	0.1520	4.6	5	173	1929	42.0
D	105	191	0.2271	3.1	3	300	1508	20.5
E	103	377	0.1486	4.7	2	206	1201	27.5
F	100	291	0.0881	7.9	3	108	1401	27.1
$\bar{x}$	107	285	0.1284	6.4	3	183	1418	25.5
±SEM	3	30	0.0243	1.2	0.5	28	115	3.8
G	80	63	0.0522	13.3	5	218	2455	13.3
H	78	219	0.0716	9.6	2.5	179	2155	28.5
I	73	38	0.0596	11.6	1.5	153	3773	9.6
K	70	52	0.0547	12.6	3	323	7615	23.5
L	67	65	0.0628	11.0	5	266	4639	19.6
M	67	89	0.1113	6.2	2.5	640	4383	25.7
N	50	31	0.0593	11.7	3	442	7462	19.6
O	45	104	0.0856	8.1	3	246	3092	19.4
P	34	69	0.0612	11.4	2	505	4418	22.1
Q	31	17	0.0382	19.8	3	366	7005	8.9
$\bar{x}$	60	75	0.0657	11.5	3	334	4700	19.0
±SEM	6	18	0.0064	1.2	0.4	49	638	2.2
R	30	27	0.0648	10.7	3	284	3684	6.6
S	30	18	0.0453	15.4	2	484	6522	6.8
T	30	42	0.0649	10.7	2	399	4654	14.5
U	18	17	0.0255	26.6	12	284	10425	13.1
V	11	5	0.0201	34.7	4	300	18724	2.6
W	10	3	0.0268	25.7	2.5	846	28272	7.6
X	7	8	0.0330	21.0	4	305	11726	4.2
$\bar{x}$	19	17	0.0401	20.7	4	415	12001	7.9
±SEM	4	5	0.0071	3.4	1	77	3330	1.8

tion between the elimination rate constant (β) and the creatinine clearance for each patient is shown in Fig. 2; the correlation coefficient is $r=0.69$ ($p<0.001$). The mean nonrenal elimination rate constant, derived from the intercept of the straight line on the ordinate, was 0.0203 h^{-1}, and the corresponding half-life of elimination was calculated to be 34.2 h. From the amount of HCT recovered from urine, the mean cumulative renal excretion (A_u) of HCT was calculated to be 51.0% of the oral dose in patients with normal renal function. In patients with mild renal impairment, mean cumulative renal excretion was reduced to 38.0% and in patients with moderate to severe renal insufficiency it fell to 15.8%. The decrease in cumulative urinary excretion was significant for the patients of Group 3 ($p<0.01$). Prolongation of the collection period over more than 72 h did not significantly increase urinary recovery of the drug.

In patients with normal renal function, the renal clearance (Cl_r) of HCT was calculated to be 285 ml/min, and therefore significantly ($p<0.01$) to exceed the creatinine clearance. In patients with compromised kidney function, the renal clearance of HCT was reduced to a mean of 75 ml/min in Group 2 and to 17 ml/min in Group 3, and did not differ significantly from the endogenous creatinine clearance ($p>0.05$). The renal clearance in both groups of patients with renal impairment was significantly different from the renal clearance of HCT in subjects with normal kidney function ($p<0.001$). The relationship of the renal clearance of HCT to the endogenous creatinine clearance for each subject is shown in Fig. 3. The data are best fitted by a nonlinear regression line $Cl_r = 7.050\, e^{0.034\, Cl_{cr}}$ ($r=0.90$, $p<0.001$).

Discussion

The experiments have shown that orally administered HCT is mainly excreted via the kidneys in undegraded form, urinary recovery amounting to about 50 to 60% of the dose in healthy volunteers. This finding is in agreement with previous reports [1, 2, 3, 4, 6, 7, 9, 11]. In patients with impaired kidney function, cumulative urinary excretion of HCT was significantly reduced, and only about 10% of an oral dose was recovered in the urine from preuremic patients. This finding is believed not to be due to re-

duced intestinal absorption of HCT in kidney disease, since the AUC's were always greater at low creatinine clearance than in healthy people. Only comparison of intravenous and oral administration will definitely elucidate the influence of kidney function on HCT absorption.

The mean half-life of elimination of HCT in subjects with normal kidney function was 6.4 h, which is in accordance with the value of 5.2 h reported by Cooper et al. [9], but is lower than the half-life of elimination of the β-phase of 5.6–14.8 h reported by Beermann and Groschinsky-Grind [6, 7]. The correlation between the elimination rate constant and the creatinine clearance was relatively poor ($r=0.69$). The renal clearance of HCT showed a much closer correlation with the endogenous creatinine clearance ($r=0.90$). It is remarkable that the correlation was best described by a nonlinear regression line (correlation coefficient for the straight line $r=0.84$). As the renal clearance of HCT considerably exceeds the glomerular filtration rate in healthy subjects, HCT must be mainly eliminated by tubular secretion via the non-specific proximal tubular carrier mechanism. However, glomerular filtration of HCT also contributes to drug elimination, as albumin binding of HCT has been reported to be 22% [8] to 55% [13]. In the Group 3 patients, HCT clearance averaged 17 ml/min and so was identical to the mean endogenous creatinine clearance. Therefore, in patients with reduced kidney function tubular secretion of HCT must be more impaired than glomerular filtration and probably than tubular reabsorption.

A striking finding was the drastic reduction in urinary HCT recovery in patients suffering from renal failure. Doubling the collection period did not significantly increase the extent of urinary recovery, which can easily be explained by the assumption of non-renal excretion in those patients.

Dose Adjustment of HCT in Patients with Kidney Disease

The mean half-life of elimination of 34.2 h in anephric patients exceeds about fivefold the half-life of elimination in subjects with normal kidney function. Therefore, dose adjustment in patients with renal impairment is necessary to avoid dose dependant side-effects. Dosage rules for those patients are given by Dettli [10]. We advise a reduction to one half of HCT dosage in patients with an endogenous creatinine clearance between 30 and 90 ml/min. Administration of a loop diuretic is prefered in patients whose endogenous creatinine clearance is < 30 ml/min, as thiazide diuretics normally are uneffective in them. However, if HCT is indicated, the quantity should be reduced to ¼ of the normal therapeutic dose.

Acknowledgements. Financial support from the Doktor Robert Pfleger-Stiftung, Bamberg, and Röhm-Pharma, Darmstadt, FRG, is gratefully acknowledged. The authors thank Mrs. S. Podkowik for excellent technical assistance.

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Received: July 17, 1982
in revised form: November 13, 1982
accepted: December 20, 1982

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