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Paracetamol Disposition and Metabolite Kinetics in Patients with Chronic Renal Failure

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Summary. The disposition of paracetamol following an oral dose of 1.0 g was compared in 10 healthy volunteers, 7 patients with moderate chronic renal failure and 6 patients with end stage renal failure on maintenance haemodialysis.

Paracetamol absorption was normal in the patients with renal failure. The mean plasma half-life of paracetamol from 2 to 8 h was similar in the 3 groups (2.1 to 2.3 h) but from 8 to 24 h it disappeared much more slowly in the renal failure patients (half-life 11.7 compared with 4.9 h in the healthy volunteers). Plasma concentrations of paracetamol glucuronide and sulphate conjugates were greatly increased in the patients with moderate renal failure and the mean plasma half-lives were 30.5 and 21.8 h respectively compared with about 3 h in the healthy volunteers. Plasma concentrations of these metabolites were even higher in the dialysis patients and there was no significant fall over 24 h. The cysteine and mercapturic acid conjugates of paracetamol could only be measured in plasma in the patients with renal failure and concentrations were very low.

The fractional urinary recovery of paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates was similar in healthy volunteers and patients with moderate renal failure. The mean renal clearances of paracetamol and its glucuronide and sulphate conjugates in the healthy volunteers and patients with moderate renal failure were 15.7, 137 and 172, and 5.9, 14.5 and 14.8 ml/min respectively. In the latter patients the mean renal clearances of the cysteine and mercapturic acid conjugates were much greater at 35.4 and 80.2 ml/min. In the patients with moderate renal failure the AUC's of the glucuronide and sulphate conjugates were related to the plasma creatinine and there were significant negative correlations with the renal clearances of these metabolites and total urinary recovery. Marked cumulation of the polar glucuronide and sulphate conjugates of paracetamol would seem inevitable in patients with renal failure and the parent drug is apparently regenerated to a limited extent from retained metabolites.

Key words: paracetamol, renal failure; drug disposition, polar metabolites, cumulation, pharmacokinetics

The disposition of drugs is often abnormal in patients with chronic renal failure [1-3], and those which are excreted largely unchanged by the kidney or converted to active metabolites are usually given to patients with renal failure in reduced dosage to avoid cumulation and toxicity [4, 5]. However, drugs which are primarily inactivated by metabolism in the liver are often continued in full dosage and in such circumstances marked cumulation of their polar metabolites is inevitable unless there are alternative routes of elimination. Under normal conditions these metabolites may be inactive but at the remarkably high concentrations which must be achieved during chronic therapy in patients with renal failure their biological effects are unknown. Such patients are particularly susceptible to adverse drug reactions and in some cases unsuspected toxicity may be caused by cumulation of drug metabolites [6, 7].

Paracetamol (acetaminophen) is one of the most commonly used drugs and about 90% of a therapeutic dose is normally excreted in the urine in 24 h as glucuronide, sulphate and glutathione-derived conjugates [8]. The excretion rate of the glucuronide and sulphate conjugates is markedly reduced in patients with renal failure following paracetamol overdosage [9] while in patients with end-stage renal

Table 1. Clinical details of patients with renal failure

Patient	Weight (kg)	Age (years)/ Sex	Diagnosis	Hb ($g \cdot dl^{-1}$)	Albumin ($g \cdot l^{-1}$)	ALT ($u \cdot l^{-1}$)	Bili-rubin ($\mu mol \cdot l^{-1}$)	Alk Phosph ($u \cdot l^{-1}$)	Creatinine ($\mu mol \cdot l^{-1}$)	Creatinine clearance ($ml \cdot min^{-1}$)	Drugs
1	76.4	46/M	CF	16.3	44	17	14	40	334	17	AT
2	77.4	57/M	AG, RA	11.9	39	13	4	114	440	23	NF
3	85.3	43/M	PK	12.1	47	20	8	67	484	22	MT, BD, PZ
4	83.6	49/M	DB, HT	10.3	41	12	5	96	442	19	MT, NF, PZ, IN
5	68.4	46/M	CG	7.6	44	18	5	89	946	HD	AT, NF
6	79.5	33/M	CG, AN	7.2	45	24	4	128	1127	HD	
7	74.5	70/M	CG, NE	10.3	23	16	3	119	727	9	NF, MZ, BU
8	64.9	65/M	GP	5.5	40	13	4	74	752	HD	
9	61	48/F	PK	10.7	46	15	3	56	879	5	NF, QD, SB
10	83.1	65/M	PK, HT	11.3	43	14	11	59	378	17	NF, MT
11	76.9	39/M	CF	6.9	45	22	5	51	760	HD	
12	64.7	62/M	RA, AM	7.4	37	11	6	46	641	HD	MT, BP
13	65.7	60/F	CF	4.8	39	12	4	60	1175	HD	

HD = Haemodialysis, CF = Chronic renal failure of unknown aetiology, AG = Analgesic nephropathy, AN = Anephric, AM = Amyloidosis, NE = Nephrotic syndrome, CG = Chronic glomerulonephritis, DB = Diabetes, GP = Goodpasture's syndrome, HT = Hypertension, PK = Polycystic kidneys, RA = Rheumatoid arthritis. AT = Atenolol, BD = Bendrofluazide, BP = Buprenorphine, BU = Bumetanide, IN = Insulin, MT = Metoprolol, MZ = Metolazone, NF = Nifedipine, PZ = Prazosin, QD = Quinidine, SB = Salbutamol

failure the elimination of these metabolites is greatly impaired and haemodialysis appears to be the major route for their removal from the body [10, 11]. We report detailed studies of the disposition and kinetics of paracetamol and its polar metabolites in patients with moderate to severe impairment of renal function.

Methods, Patients and Subjects

Eleven men and 2 women with chronic renal impairment were studied. Their mean age was 53 (11) years and their body weight was 74 (8) kg. Seven had moderate to severe renal failure but were not being treated with dialysis, and 6 with more advanced disease were receiving long-term haemodialysis 2 or 3 times a week. Their clinical details are summarized in Table 1. Ten healthy male volunteers with a mean age of 29 (7) years and body weight 72 (11) kg served as controls. They did not take drugs regularly or smoke and they denied excessive regular consumption of ethanol. Physical examination was normal as were liver function tests, haemoglobin and plasma urea and creatinine concentrations estimated by standard automated methods. The study was approved by the local Ethics Committee and all patients and volunteers gave informed consent.

Drug Administration and Sampling

After an overnight fast, the patients and volunteers took 1.0 g of soluble paracetamol in 200 ml of water at approximately 08.30 h. They remained recumbent for the next 3 h and received 200 ml of water every 2 h up to 12 h. The usual diet was resumed 4 h after dosing. Blood was sampled at frequent intervals for 24 h and except in the haemodialysis patients (who produced little or no urine), divided urine collections were made over the same period. In the latter patients the study was carried out on a day preceding dialysis.

Drug Analysis

Paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates in plasma and urine were assayed by high performance liquid chromatography using UV detection. Electrochemical detection was also used for low concentrations of paracetamol and cysteine and mercapturic acid conjugates in the presence of potentially interfering peaks [12]. Variable blank values were obtained in some patients with renal failure and these were subtracted to give corrected concentrations. In Patient 7 paracetamol sulphate could not be measured in urine because of interference. The amount excreted was therefore estimated from the relative areas under the plasma concentration time curves of the glucuronide and sulphate conjugates and the urinary recovery of glucuronide assuming that both metabolites had the same renal clearance and volume of distribution.

Data Analysis

The plasma half-life ($t_{1/2}$) of paracetamol and its metabolites was determined from the log-linear phases of the concentration-time curves by weighted linear re-

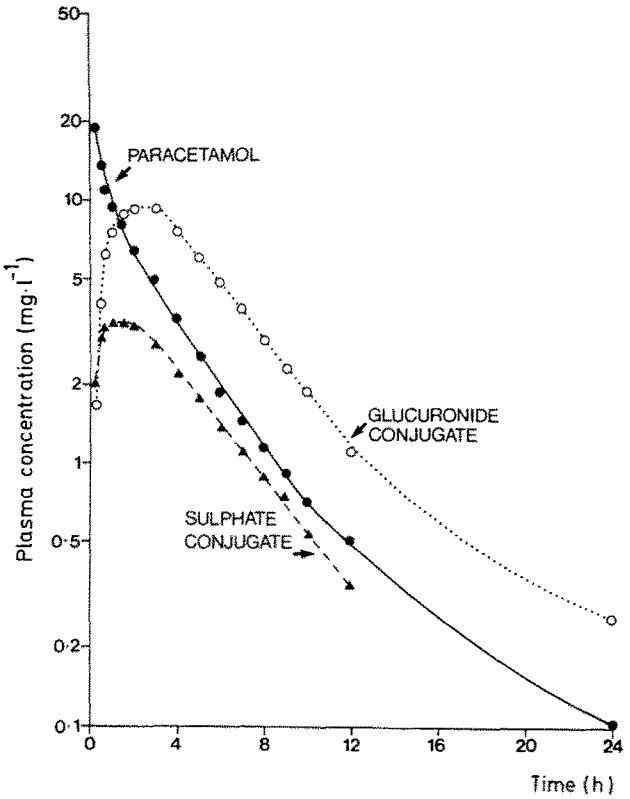

Fig. 1. Mean plasma concentrations of paracetamol and its glucuronide and sulphate conjugates in 10 healthy volunteers following an oral dose of 1.0 g

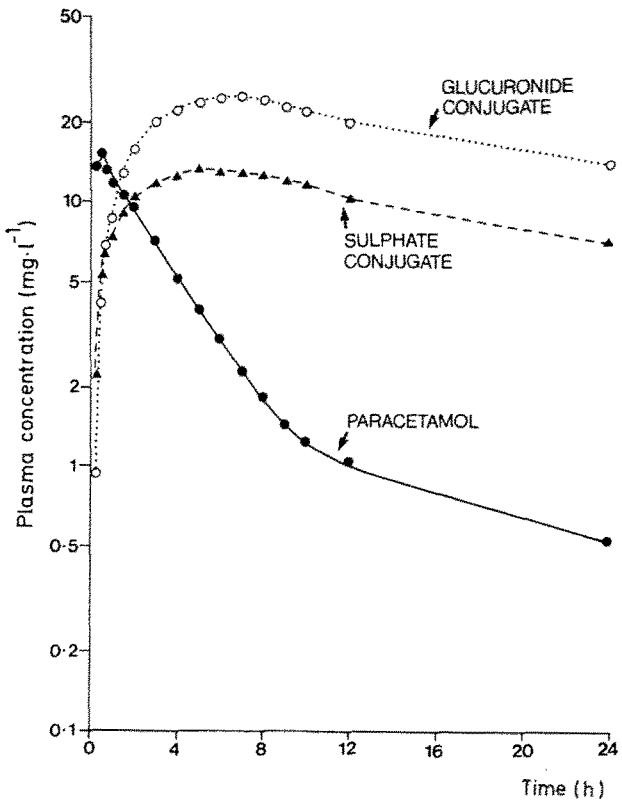

Fig. 2. Mean plasma concentrations of paracetamol and its glucuronide and sulphate conjugates in 7 patients with moderate renal failure following an oral dose of 1.0 g

gression and the area under the curve (AUC) was estimated by the trapezoidal method. Renal clearance in the healthy volunteers and patients with moderate renal failure was calculated by dividing the amount recovered in the urine by the corresponding AUC. The "SIPHAR"[1] modeling and parameter estimation programme was used for compartmental and model-independent analysis of the plasma paracetamol and metabolite concentration data. To obtain the volumes of distribution (V) of the glucuronide and sulphate conjugates in the patients with moderate renal failure, the "dose" of conjugate was taken as the amount formed from the administered dose of paracetamol (1.0 g × the fractional 24-h urinary recovery of the metabolite). V_z was calculated as total clearance/β and V_{ss} as the product of the clearance and mean residence time. It was assumed that the absorption of paracetamol was complete and that there was no extra-renal loss of the conjugates.

Results are given as means (SD) and metabolite concentrations are expressed as paracetamol equivalents. Differences between means were compared by the Mann-Whitney test or non-parametric analysis of variance with $p = < 0.05$ as the level of significance.

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Results

Plasma Paracetamol

Paracetamol was rapidly absorbed in the healthy volunteers and renal failure patients with mean peak plasma concentrations of 20.0 and 17.9 $mg \cdot l^{-1}$ occuring on average at 0.35 and 0.5 h respectively after administration. The mean plasma half-life from 2 to 8 h was similar in the volunteers, patients with moderate renal failure and dialysis patients (2.2 (0.3), 2.3 (0.5) and 2.1 (0.4) h). However, after 8 h there were significant differences between the groups (Figs. 1-3). Paracetamol continued to disappear rapidly from 8 to 24 h in the healthy volunteers with a mean half-life of 4.9 (2.1) h while low levels persisted in the renal patients and the corresponding half-life in both renal groups combined was 11.7 (5.2) h ($p = < 0.001$). As a result, the total AUC for paracetamol was greater in the renal patients than in the healthy volunteers (Table 2) and there was a highly significant difference in the area from 8 to 24 h (12.4 compared with 6.7 $mg \cdot l^{-1} \cdot h$, $p = < 0.005$).

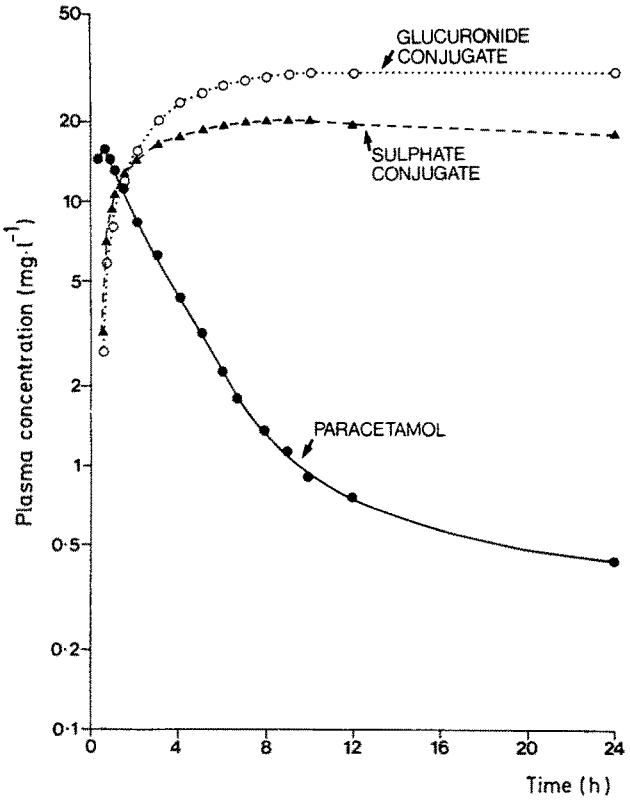

Fig. 3. Mean plasma concentrations of paracetamol and its glucuronide and sulphate conjugates in 6 patients with end-stage renal failure on maintenance haemodialysis following an oral dose of 1.0 g

Table 2. Mean plasma half-life (h) from 8 to 24 h and area under the plasma concentration-time curve (AUC, $mg \cdot l^{-1} \cdot h$) from 0 to 24 h for paracetamol and its glucuronide and sulphate conjugates in healthy volunteers and patients with renal failure

	Paracetamol		Glucuronide conjugate		Sulphate conjugate	
	$t_{1/2}$	AUC	$t_{1/2}$	AUC	$t_{1/2}$	AUC
Healthy volunteers	4.9 (2.1)	45 (11)	2.9 (0.3)[a]	66 (16)	3.5 (1)[a]	21.4 (4.5)
Moderate renal failure patients	11.0 (5.3)	63 (12)	30.5 (40.7)	431 (157)	21.8 (15.2)	232 (108)
Dialysis patients	12.7 (5.5)	57 (15)	-	671 (204)	-	438 (101)

[a] 4 to 12 h

Table 3. Mean maximum plasma concentration (C_{max}, $mg \cdot l^{-1}$) of paracetamol and its glucuronide and sulphate conjugates, and the time to peak concentrations (t_{max}, h) in healthy volunteers and patients with chronic renal failure following an oral dose of 1.0 g of paracetamol

	Paracetamol		Glucuronide		Sulphate	
	C_{max}	t_{max}	C_{max}	t_{max}	C_{max}	t_{max}
Healthy volunteers	20.0 (8.4)	0.35 (0.17)	9.4 (2.6)	2.0 (4.4)	3.7 (0.9)	1.1 (0.5)
Moderate renal failure patients	17.3 (8.2)	0.54 (0.44)	25.2 (8.9)	6.0 (1.6)	13.7 (5.9)	5.6 (1.5)
Dialysis patients	18.6 (4.7)	0.46 (0.29)	31.4 (7.4)	13.8 (8.5)	20.8 (6.5)	8.3 (1.2)

Plasma Concentrations of Paracetamol Conjugates

The plasma concentrations of the glucuronide and sulphate conjugates of paracetamol were greatly elevated in the patients with moderate renal failure, and were even greater in the dialysis patients (Figs. 1-3). There were corresponding highly significant increases in the mean AUC with more than 10- and 20-fold increases for glucuronide and sulphate respectively in the dialysis patients (Table 2). The mean peak plasma concentrations of glucuronide and sulphate (C_{max}) and the time to reach peak concentrations (t_{max}) were significantly increased in the renal patients with the greatest increase in those on dialysis (Table 3).

The elimination of the glucuronide and sulphate conjugates was very slow in the patients with moderate renal failure and the mean plasma half-lives were 30.5 and 21.8 h compared with 2.9 and 3.5 h respectively in the healthy volunteers ($p = < 0.001$, Table 2). There was gross retention of these metabolites in the dialysis patients with no significant fall in concentrations up to 24 h (Fig. 3). In the patients with moderate renal failure there were significant correlations between the plasma creatinine concentration and the AUCs of the glucuronide and sulphate conjugates ($r = 0.91$ and 0.84, $p = < 0.02$).

The cysteine and mercapturic acid conjugates could not be measured in plasma in the healthy volunteers and concentrations were low in the patients with renal failure. Cysteine conjugate concentrations were consistently higher than those of the mercapturic acid conjugate and it disappeared slowly in both groups of renal patients. In the dialysis patients there was no significant fall in plasma mercapturic acid conjugate concentrations up to 24 h (Fig. 4).

Renal Excretion of Paracetamol and Metabolites

In the healthy volunteers a mean of 82.5% of the administered dose of paracetamol was recovered in the urine in 24 h. The mean recovery in the patients with moderate renal failure was 56.9% (range 30-86%) and there was a significant negative correlation with the plasma creatinine concentration ($r = -0.77$, $p = < 0.05$). There were no important differences between the groups in respect of the fractional urinary recovery of paracetamol and its metabolites (Table 4).

In the patients with moderate renal failure the renal clearances of the glucuronide and sulphate conjugates were greatly reduced (mean 14.5 and 14.8 ml · min^{-1} versus 137 and 172 ml · min^{-1} respectively in the healthy volunteers), and were inversely related to the plasma creatinine concentration ($r = -0.87$ and -0.84, $p = < 0.02$). In contrast, the decrease in renal clearance of unchanged paracetamol in these patients ws proportionately much smaller (Table 5) and there was no significant correlation with plasma creatinine or creatinine clearance. As expected, the renal clearance of paracetamol was correlated with the urine flow rate ($r = 0.96$, $p = < 0.01$) and there was no such relationship with the glucuronide and sulphate conjugates.

The renal clearances of the cysteine and mercapturic acid conjugates in the patients with moderate renal failure were surprisingly high (Table 5) and greatly exceeded the creatinine clearance in every case.

Distribution Volumes of the Glucuronide and Sulphate Conjugates

The volumes of distribution of the glucuronide and sulphate conjugates were similar. The respective mean values for V_z and V_{ss} were 0.24 (0.05), 0.28 (0.04), 0.27 (0.06) and 0.29 (0.06) l · kg^{-1}.

Discussion

The absorption of paracetamol appeared to be normal in the patients with renal failure but there were major abnormalities in other aspects of its disposition. Not only were the glucuronide and sulphate conjugates retained as expected, but the elimination of paracetamol itself was also impaired. The rate at which it disappeared from the plasma during the first 8 h was virtually identical in the healthy volunteers and patients with renal failure but in the latter low concentrations persisted after this time and the half-life from 8 to 24 h was greatly prolonged. The healthy volunteers were younger than the renal patients and thus not ideal controls, but it is most unlikely that these differences could be related to factors other than renal disease.

After rapid oral absorption or bolus intravenous administration, paracetamol normally disappears from the plasma in 3 distinct phases. Distribution is largely complete in 1 to 1.5 h, and the log-linear decline from 2 to about 8 h is normally used to calculate the elimination half-life of the drug. However, after 8 h there is a third phase of slower disappear-

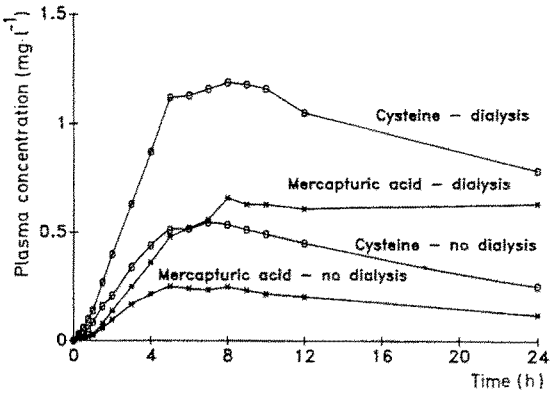

Fig. 4. Mean plasma concentrations of cysteine and mercapturic acid conjugates of paracetamol following an oral dose of 1.0 g in 7 patients with moderate renal failure not on dialysis and 6 patients on regular haemodialysis

Table 4. Mean 24-h urinary recovery of paracetamol and its major metabolites in healthy volunteers and patients with moderate renal failure

	Fractional urinary recovery %					
	Paracetamol	Glucuronide conjugate	Sulphate conjugate	Cysteine conjugate	Mercapturate conjugate	% of dose recovered in 24 h
Healthy volunteers	4.1 (1.4)	60.7 (7.5)	28.1 (5.1)	3.0 (1.7)	4.1 (1.7)	82.5 (6.1)
Moderate renal failure patients	2.4 (1.1)	61.0 (6.8)	30.8 (6.1)	3.0 (0.9)	2.8 (1.4)	56.9 (17.1)

Table 5. Renal clearance (ml · min^{-1}) of paracetamol and its conjugates in healthy volunteers and patients with moderate renal failure

	Paracetamol	Glucuronide conjugate	Sulphate conjugate	Cysteine conjugate	Mercapturic acid conjugate	24-h urine volume (l)
Healthy volunteers	15.7 (6.0)	137 (31)	172 (39)	-	-	1.81 (0.69)
Moderate renal failure patients	5.9 (2.5)	14.5 (6.6)	14.8 (7.6)	35.4 (45)	80.2 (45)	2.08 (0.64)

ance in which the half-life is increased to 4 to 5 h [13]. This late elimination phase was greatly extended in the patients with renal disease and possible rate-limiting mechanisms include slow transfer of residual drug from peripheral tissues back to the circulation and augmented enterohepatic circulation of paracetamol conjugates with regeneration of the parent drug. The latter is more likely since similar unexpected impairment of elimination of drugs such as oxazepam, diflunisal and clofibric acid has been described in patients with chronic renal failure [14–16]. Like paracetamol, these drugs are extensively metabolized by glucuronide conjugation. In patients with renal failure there may be enterohepatic circulation of the retained glucuronide conjugates with regeneration of the parent drug by hydrolysis and subsequent reabsorption [3]. This effect is probably greatest with drugs which form labile ester glucuronides [17]. Paracetamol is converted to a more stable ether glucuronide which is normally excreted into bile to only a limited extent [18]. Although the residual plasma concentrations of paracetamol observed in the present single dose study were low and clinically insignificant, higher concentrations might be expected with the extensive cumulation of conjugates which would occur during long-term treatment in patients with severe renal failure.

The overall metabolic fate of paracetamol in the patients with moderate renal failure and the healthy volunteers was similar as judged by the fractional urinary recovery of the drug and its major metabolites. In particular, the recovery of glutathione-derived conjugates was not increased and there was no evidence of enhanced conversion to potentially toxic metabolites. In the patients with moderate renal failure the renal clearances of paracetamol glucuronide and sulphate were greatly reduced and correlated with the plasma creatinine concentration. In contrast, the renal clearance of unchanged paracetamol was unrelated to the plasma creatinine and in proportion it was reduced much less than the renal clearances of the conjugates. Indeed, the mean renal clearance of paracetamol was within the normal range of 5 to 20 $ml \cdot min^{-1}$, and as in healthy subjects its clearance (but not those of the glucuronide and sulphate conjugates) was dependent on the urine flow rate [8]. The polar glucuronide and sulphate conjugates are excreted primarily by active tubular secretion but the renal clearance of paracetamol depends on glomerular filtration with extensive passive tubular reabsorption [9, 19]. The strikingly disproportionate decrease in the clearance of the conjugates implies much greater reduction in the capacity for active tubular transport than for passive reabsorption. It is also possible that competition or saturation of tubular transport by retained endogenous anions contributes to the very low clearance of the conjugates in patients with renal failure.

Plasma concentrations of the cysteine and mercapturic acid conjugates were very low and the disappearance of the former in the haemodialysis patients indicates a route of elimination other than renal excretion. In the patients with moderate renal failure the renal clearances of both metabolites were considerably greater than the glomerular filtration rate, raising the possibility of their formation from precursors in the kidney. The findings are consistent with renal acetylation of cysteine to form the mercapturic acid conjugate. The volumes of distribution of the individual glucuronide and sulphate conjugates of paracetamol have not been reported previously. Similar values of about 0.27 $ml \cdot kg^{-1}$ were obtained for both conjugates in the patients with moderate renal failure, and these are of the same order as reported previously for the two metabolites combined [9, 11].

The glucuronide and sulphate conjugates of paracetamol appear to be eliminated almost entirely by renal excretion, and marked cumulation would occur with continued use of the drug in patients with renal failure. Predictions based on the clearance of these metabolites by haemodialysis [10] indicate that the average maximum plasma concentrations of glucuronide and sulphate conjugates would exceed 500 and 400 $mg \cdot l^{-1}$ respectively during regular therapy with 1 g of paracetamol 4 times daily in patients with end stage renal disease on twice weekly maintenance haemodialysis. Further studies with multiple doses should be carried out in patients with renal disease and similar cumulation may be expected with other drugs that are extensively converted to polar metabolites which depend on renal excretion for their removal from the body.

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