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PHARMACOKINETICS AND DISPOSITION

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Single-dose pharmacokinetics of paracetamol and its conjugates in Chinese non-insulin-dependent diabetic patients with renal impairment

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Abstract *Objective*: A single oral dose of paracetamol (20 mg · kg^{-1}) was given to 38 Chinese patients with non-insulin-dependent diabetes mellitus (NIDDM) who had either normal renal function or varying degrees of renal impairment, with creatinine clearances ranging from 4 to 123 ml · min^{-1} · 1.73 m^{-2}. The plasma and urinary concentrations of paracetamol and its major metabolites were measured by high-performance liquid chromatography (HPLC).
Results: The absorption and elimination of paracetamol were unaffected by renal impairment. However, the area under the plasma concentration time curve and the elimination half-life of paracetamol metabolites increased significantly with worsening renal insufficiency. Mean renal clearances of paracetamol and its conjugates were significantly reduced in these subjects. There was no evidence of altered metabolic activation with renal impairment.
Conclusion: The results demonstrate that paracetamol disposition is minimally affected by diabetic nephropathy; however, extensive accumulation of conjugates may occur.

Key words Paracetamol, Renal failure; polar conjugates, non-insulin-dependent diabetes mellitus (NIDDM), pharmacokinetics

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Introduction

Paracetamol undergoes both oxidation and conjugation reactions to non-toxic metabolites, making it an ideal drug for the study of inhibition or activation of these pathways and the factors which may affect the elimination of conjugated metabolites, such as renal disease. The effects of hepatic dysfunction [1, 2] and renal impairment [3, 4] on the disposition of paracetamol have been examined in Caucasians. However, reports regarding the effects of diabetes on the pharmacokinetics of paracetamol remain conflicting [5, 6]. In this study, we examined the effects of varying degrees of diabetic renal disease on the pharmacokinetics of paracetamol.

Subjects and methods

Thirty-eight Chinese patients diagnosed as having non-insulin-dependent diabetes mellitus (NIDDM) for more than 2 years were recruited from the Diabetes Clinic at the Prince of Wales Hospital, Hong Kong. Glycaemic control was assessed by glycosylated haemoglobin, plasma fructosamine and glucose concentrations using standard methods. Renal function was determined from the mean 24 h creatinine clearance (CL_{CR}) based on an average of three values from individually measured 24 h urine collections over a period of 2 weeks and calculated as ml · min^{-1} · 1.73 m^{-2}. The coefficient of variation (CV) of CL_{CR} was 12.3%. Patients were divided into four groups accordingly:

Group 1: normal renal function, CL_{CR} > 90 ml · min^{-1} · 1.73 m^{-2}, $n = 6$
Group 2: mild renal impairment, CL_{CR} 60–90 ml · min^{-1} · 1.73 m^{-2}, $n = 8$
Group 3: moderate renal impairment, CL_{CR} 30–60 ml · min^{-1} · 1.73 m^{-2}, $n = 11$
Group 4: severe renal impairment, CL_{CR} < 30 ml · min^{-1} · 1.73^{-2}, $n = 13$

The study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, The Chinese University of Hong Kong. Informed consent was obtained from all patients. All patients abstained from taking paracetamol-containing drugs for 2 weeks prior to the study. Following overnight fasting, an oral dose of paracetamol syrup (Panadol, Sterling-Winthrop) 20 mg · kg^{-1} was administered with 100 ml water. Patients remained sedentary

for 2 h, after which their usual medications and diabetic diet were given. Blood was taken into heparinised tubes before and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 24 and 48 h following paracetamol administration. Urine was saved from 0–4, 4–8, 8–24, and 24–48 h with chloroform as preservative.

Plasma and urine concentrations of paracetamol and its metabolites (glucuronide, sulphate, cysteine and mercapturic acid conjugates) were measured by high performance liquid chromatography (HPLC) [7]. The concentrations of the conjugates were calculated as paracetamol equivalents.

Pharmacokinetic parameters were estimated using the SIPHAR pharmacokinetic modelling programme (Simed, Centre d'Etude et de Recherches en Statistique et Informatique Médicales, Cedex, France). The data were fitted to a one-compartment model with first-order absorption. The elimination half-life ($t_{1/2}$) the peak plasma concentration (C_{max}), the time to reach the peak (t_{max}) and the area under the plasma concentration time curve from 0 to infinity (AUC_{∞}) were calculated using standard methods [8]. The renal clearances (CL_R) of unchanged paracetamol and the individual conjugates were calculated as AUC (0–48 h)/urinary recovery (48 h) of unchanged paracetamol or its conjugates.

Plasma paracetamol concentrations were fitted between 0 and 8 h and then extrapolated to 24 and 48 h using the coefficients of the terminal elimination phase. This approach excludes paracetamol which has undergone enterohepatic circulation from the calculation of the pharmacokinetic parameters. The extrapolated concentrations and the measured concentrations can then be compared.

The pharmacokinetic data from the four groups of patients were compared by a one-way analysis of variance (ANOVA) with the Scheffé test for post hoc comparisons. Results are expressed as means with (SD) or medians with (range) where appropriate. The 95% confidence intervals are given for normally distributed endpoints. A P value of less than 0.05 was considered significant.

Results

Of the 38 patients, 20 were male. Mean age was 58 (11) years (range 34–75 years). The mean duration of diagnosed diabetes was 8.1 (3.9) years. There were no significant differences in age, sex and body mass index between the four groups. Mean fasting plasma glucose was 9.61 (3.47) $mmol \cdot l^{-1}$, HbA_{1c} was 8.07 (1.46) (%) and fructosamine was 332 (71) $\mu mol \cdot l^{-1}$. Known duration of illness, glycaemic control and serum albumin concentration were similar in all groups. Mean creatinine clearances in the four groups were 106 (92–120), 78 (69–86), 46 (40–51) and 16 (13–20) $ml \cdot min^{-1}$, respectively.

The mean plasma paracetamol concentration vs time curves for the four groups are shown in Fig. 1 and the pharmacokinetic parameters for paracetamol and the metabolites are presented in Table 1. There were no between group differences for the paracetamol t_{max}, AUC or $t_{1/2}$. CL_R values were significantly lower in the moderate to severe renal failure groups when compared to the normal renal function and mild impairment

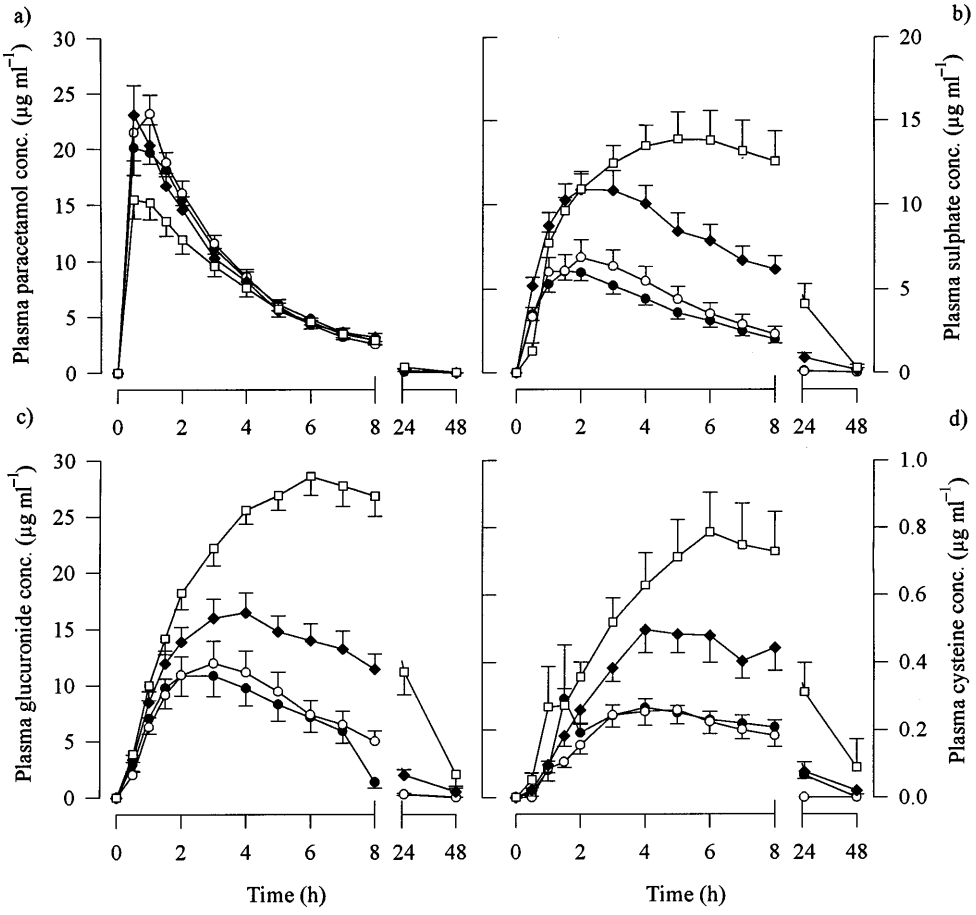

Fig. 1 Mean (SEM) plasma concentrations of: (a) paracetamol, (b) sulphate conjugate, (c) glucuronide conjugate and (d) cysteine conjugate in NIDDM patients with normal renal function (group 1, ●), mild renal impairment (group 2, ○), moderate renal impairment (group 3, ◆), and severe renal impairment (group 4, □)

Table 1 Mean pharmacokinetic parameters for paracetamol and its conjugates in patients with normal renal function (group 1) and mild (group 2), moderate (group 3) and severe (group 4) renal failure. Data are presented as the means (95% confidence interval) or medians (range)[a]

Parameter	Group 1 ($n = 6$)	Group 2 ($n = 8$)	Group 3 ($n = 11$)	Group 4 ($n = 13$)
Paracetamol				
C_{max} ($\mu g \cdot ml^{-1}$)[a]	22.5 (20.3–28.5)	25.4 (15.6–30.7)	20.1 (9.80–36.4)	18.2 (11.3–27.6)
t_{max} (h)[a]	0.75 (0.5–1.5)	0.75 (0.5–1.0)	1.0 (0.5–1.5)	1.0 (0.5–4.0)
AUC_∞ ($\mu g \cdot ml^{-1} \cdot h$)	85.0 (72.6–97.4)	82.4 (70.3–94.5)	89.0 (70.7–107)	77.1 (64.0–90.2)
$t_{1/2}$ (h)	2.31 (1.88–2.74)	2.19 (2.00–2.37)	2.47 (2.26–2.65)	2.54 (2.29–2.79)
CL_R ($ml \cdot min^{-1}$)[a]	12.8 (9.5–16.5)*	10.2 (8.1–11.5)*	8.2 (4.3–9.5)	7.1 (3.1–9.2)
Actual conc. at 24 h	0.18 (0.10–0.27)	0.11 (0.04–0.17)	0.26 (0.12–0.40)	0.54 (0.31–0.77)
Extrapolated conc. at 24 h	0.04 (0.00–0.07)	0.02 (0.00–0.03)	0.04 (0.01–0.07)	0.05 (0.02–0.07)
Cysteine				
$t_{1/2}$ (h)[a]	11.3 (5.68–19.7)	5.61 (3.64–50.2)	6.00 (3.60–55.1)	8.01 (5.50–23.3)
AUC_∞ ($\mu g \cdot ml^{-1} \cdot h$)[a]	4.54 (3.32–8.54)	3.16 (1.30–23.5)	8.18 (4.94–29.6)	17.2 (8.30–39.5)
C_{max} ($\mu g \cdot ml^{-1}$)[a]	0.30 (0.21–0.36)**	0.24 (0.18–0.52)**	0.51 (0.18–1.12)**	0.73 (0.39–1.91)
CL_R ($ml \cdot min^{-1}$)[a]	18.2 (9.1–20.4)**	10.5 (7.9–16.2)**	5.2 (2.3–7.6)	2.8 (0.6–4.1)
Glucuronide				
$t_{1/2}$ (h)[a]	3.40 (2.63–9.41)**	3.40 (2.15–4.25)**	5.07 (2.55–9.14)**	7.29 (4.25–13.4)
AUC_∞ ($\mu g \cdot ml^{-1} \cdot h$)[a]	73.5 (60.3–142)*	64.6 (57.0–169)*	612 (94.7–808)	652 (180–910)
C_{max} ($\mu g \cdot ml^{-1}$)[a]	8.9 (7.50–18.4)**	9.6 (6.80–19.7)**	15.2 (11.8–31.7)**	29.9 (18.8–37.7)
CL_R ($ml \cdot min^{-1}$)[a]	108 (70–123)**	82 (47–124)**	48 (25–61)**	17 (10–35)
Sulphate				
$t_{1/2}$ (h)[a]	4.05 (2.55–5.11)**	2.99 (1.69–4.18)**	4.58 (3.38–7.33)**	7.93 (3.66–18.0)
AUC_∞ ($\mu g \cdot ml^{-1} \cdot h$)[a]	44.5 (23.9–57.3)**	39.7 (30.7–66.3)**	107 (84.0–141)**	290 (134–580)
C_{max} ($\mu g \cdot ml^{-1}$)[a]	6.35 (4.54–7.42)**	6.26 (4.24–13.6)**	10.8 (5.41–16.9)**	13.6 (5.80–28.3)
CL_R ($ml \cdot min^{-1}$)[a]	160 (92–194)**	102 (80–127)**	58 (22–95)**	26 (11–45)

*$P < 0.05$, **$P < 0.01$ vs group 4

groups and correlated significantly with creatinine clearance, $r = 0.461$, $P < 0.005$. CL_R was also significantly lower in the mild renal impairment group when compared to those with normal renal function, $P < 0.05$. The extrapolated plasma paracetamol concentration at 24 h was less than 0.05 $\mu g \cdot ml^{-1}$ in all four groups; however, the actual concentration was 5 times greater in the normal group, 6 times greater in the mild and moderate renal failure groups, and 11 times greater in the severe renal failure group (see Table 1).

The mean plasma concentration vs time profiles for the paracetamol conjugates (glucuronide, sulphate and cysteine) are shown in Fig. 1 and the pharmacokinetic parameters are given in Table 1. There was accumulation of all the polar metabolites, and in general the poorer the renal function the higher the C_{max}, the longer the t_{max}, and the greater the AUC_∞. Conjugates were still detectable at 48 h in some of these patients. CL_R for all conjugates fell significantly as renal function deteriorated. Mercapturic acid was not detectable in the plasma of any of the subjects.

The mean total 48 h urinary recovery of the administered dose as unchanged paracetamol and its conjugates in patients with severe renal failure was significantly reduced when compared to those with normal renal function, 98% (71–101%) vs 61% (49–72%), $P < 0.002$. The 48 h recoveries of sulphate and cysteine conjugates were similarly reduced 35% (29–40%) vs 24% (17–26%), $P < 0.05$, and 3.5% (2.4–4.6%) vs 1.9% (1.5–2.1%), $P < 0.05$, respectively. The glucuronide conjugates accounted for 39–51% of the recovery of the dosing in the four groups. Only 3–5% of the total urinary recovery was as unchanged paracetamol. However, the 48 h recovery of the mercapturic acid conjugate was not significantly reduced (2.6–2.9%) in contrast with the cysteine conjugates.

Discussion

The pharmacokinetic parameters of paracetamol itself in all these diabetic patients were comparable to those reported in healthy subjects [3, 9, 10] and no delay in gastric emptying was seen. Paracetamol elimination based on 0–8 h plasma data was not significantly affected by renal function. The renal clearance of paracetamol tended to decrease with deteriorating renal function but this did not result in a significant increase in plasma paracetamol $t_{1/2}$ or AUC. The discrepancy between the paracetamol concentration extrapolated to 24 h from the 0–8 h data and the measured concentration (see Table 1) suggests that paracetamol is undergoing enterohepatic circulation, and/or is being systemically resynthesised from its conjugates. If this is the case, significant accumulation of conjugates in renal failure could potentially cause higher than normal paracetamol plasma concentrations with repeated dosing [4]. However, the data show that even after repeated

dosing the amount recirculated, while possibly prolonging therapeutic efficacy, would not be of toxicological significance.

In Caucasians, both mercapturate and cysteine conjugates accumulate in plasma with increasing severity of renal impairment and are excreted in similar amounts in the urine [3]. However, in our patients, only the cysteine conjugate was detectable in the plasma despite similar amounts of both conjugates being found in the urine. The HPLC assay would have detected mercapturate conjugate concentrations as low as one-tenth of those measured for cysteine in the same samples. These findings therefore suggest that acetylation of the cysteine conjugate to mercapturate may occur predominantly in the kidney in these patients.

With the exception of the mercapturate conjugate, there was marked accumulation of the polar metabolites in patients with poor renal function, and renal clearance was positively associated with creatinine clearance. Diffuse nodular sclerosis of the glomeruli in diabetic renal disease reduces the effective surface area for ultrafiltration, explaining the marked reduction in the renal clearance of paracetamol conjugates.

In conclusion, sulphate and glucuronide conjugation remain the predominant metabolic pathways in renal failure without evidence of a significant increase in metabolic activation. In severe renal failure there is gross accumulation of paracetamol conjugates and possibly systemic/intestinal deconjugation reactions resulting in significant regeneration of free paracetamol. As all the conjugates are inert, their accumulation has no clinical implications. However, for agents with active metabolites, the accumulation of potentially toxic substances in diabetic renal disease could lead to serious adverse reactions.

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