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Paracetamol pharmacokinetics in patients with hepatosplenic schistosomiasis

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Summary

Plasma concentrations and AUCs of paracetamol 1.5 g in patients with schistosomiasis and various degrees of periportal fibrosis were greater than in control subjects. As the toxic metabolite of paracetamol is a product of oxidation and as oxidative capacity is possibly reduced in patients with schistosomiasis, they may be less likely to exhibit paracetamol toxicity.

Schistosomiasis (bilharziasis) is associated with periportal fibrosis and in the later stages of the disease, reduced liver blood flow and hepatocyte dysfunction. Studies with drugs which are mainly metabolised in the liver such as labetalol and propranolol demonstrate prolonged plasma elimination half-lives and greater areas under the curve (Daneshmend et al., 1982; Homeida et al., 1987). Paracetamol is a widely used analgesic and antipyretic which is rapidly metabolised in the liver. The major metabolites are the sulphate (25%) and glucuronide (75%). In overdose the capacity of the conjugating mechanism is exceeded, and a reactive oxidative metabolite is formed which can produce hepatocellular damage leading to a prolonged plasma elimination half-life and acute liver failure.

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The present study investigated the pharmacokinetics of paracetamol in 8 Sudanese patients (mean age 28.5 ± 12.7 years, mean weight 50.1 ± 6.5 kg; (Table 1) with schistosomiasis and various degrees of periportal fibrosis, (Homeida et al., 1988) and in 8 Sudanese controls (mean age 26.5 ± 2.1 years, mean weight 58.4 ± 7.6 kg). Both patients and controls were administered paracetamol 1.5 g as a single oral dose. Blood samples for assay of paracetamol were collected before and at 30, 60, 90, 120, 150 min and 3, 5 and 8 h after administration. Plasma levels of paracetamol were measured by HPLC, using a method modified from that of Sood and Green (1987). Paracetamol and internal standard, 2-acetamidophenol, were extracted into ethyl acetate. After evaporation, the compounds were injected onto a 15 cm Spherisorb 5 ODS column, using 30% methanol in 0.015 M phosphate buffer as eluent.

In the control group the maximum plasma paracetamol concentration $C_{p_{max}}$ and time at which it occurred t_{max} were 21.0 ± 2.0 μg/ml; 0.9 ± 0.2

TABLE 1

Clinical and biochemical characteristics of 8 Sudanese patients with periportal fibrosis

Patient no.	Age (years)	Sex	Weight (kg)	Liver (cm BCM)	Spleen (cm BCM)	Grade of P.P.F.	S. Bile (mg/dl) normal (0.5–1.2)	S. alb. (g/l) (35–50 years)	S. glob (g/l) (30–50 years)	S. alk. Phos. KAU/dl (4–14)
1	18	M	56	5	12	III	0.6	44	50	7
2	30	M	55	0	10	I	0.6	36	6	8
3	55	M	60	0	14	I	1.5	30	35	3
4	16	M	45	5	10	II	1.5	38	51	15
5	20	M	40	0	14	I	0.8	44	42	8
6	32	F	45	4	12	III	0.6	39	42	7
7	22	M	48	4	6	II	0.8	50	39	10
8	35	M	52	2	18	I	1.5	40	70	5

BCM = below the costal margin; P.P.F. = periportal fibrosis; S. bile = serum bilirubin; S. alb. = serum albumin; S. glob. = serum globulin; S. alk. Phos. = serum alkaline phosphatase.

h compared with 24.2 ± 2.1 μg/ml; 1.3 ± 2.0 h in the patient group. The plasma concentration/time profile for paracetamol demonstrated (Fig. 1) no significant difference at any time interval (Mann–Whitney U-test) between patients and controls. Similarly there were no significant differences between area under the curves (AUC), plasma elimination half-lives ($t_{1/2}$), clearance Cl) and volume of distribution V_{d_β} (Table 2). The mean plasma paracetamol concentrations according to grade of periportal fibrosis were: Grade I = 21.6 μg/ml ($n = 4$), Grade II = 20.3 μg/ml ($n = 2$) and Grade III = 27.9 μg/ml ($n = 2$) compared with the control values 21.0 ± 2.0 μg/ml ($n = 8$), demonstrating a trend towards higher concentrations with Grade III fibrosis.

Previous studies in patients with pre-existing liver diseases have not shown increased hepatotoxic effects during short-term use of therapeutic doses of paracetamol (Andreasen and Hutters, 1979; Forrest et al., 1979; Neuberger et al., 1980). In patients with marked hepatic dysfunction doubling of paracetamol half-life following 1.5 g paracetamol (Forrest et al., 1979) did not compromise the conjugation of paracetamol with glutathione as the proportions excreted as cysteine and mercapturic acid conjugates were normal. In another study, Andreasen and Hutters (1979) gave paracetamol 1 g three times a day for 3–5 days to patients with chronic liver disease and demonstrated no accumulation of paracetamol or increase in half-life.

TABLE 2

Paracetamol pharmacokinetic parameters in Sudanese patients with hepatosplenic schistosomiasis and in Sudanese controls. Results are expressed as the mean ± S.E.M. (n = 8)

	Age (years)	Wt. (kg)	AUC μg/ml · h	$t_{1/2}$ (h)	Cl (L/h)	V_{d_β} (L)	$C_{p_{max}}$ (μg/ml)	t_{max} (R)
Patients	28.50 ±4.51	50.50 ±2.30	92.41 ±12.70	2.40 ±0.15	0.35 ±0.03	59.43 ±4.36	24.11 ±2.09	1.31 ±0.21
Controls	26.50 ±2.14	58.38 ±2.47	71.97 ±9.82	2.07 ±0.12	0.40 ±0.05	67.14 ±5.92	21.00 ±2.02	0.88 ±0.21

AUC = area under the plasma concentration time curve; $t_{1/2}$ = plasma elimination half-life; Cl = clearance; V_{d_β} = volume of distribution, (Bioavailability assumed to be 1); $C_{p_{max}}$ = maximum plasma concentration; t_{max} = time to maximum plasma concentration.

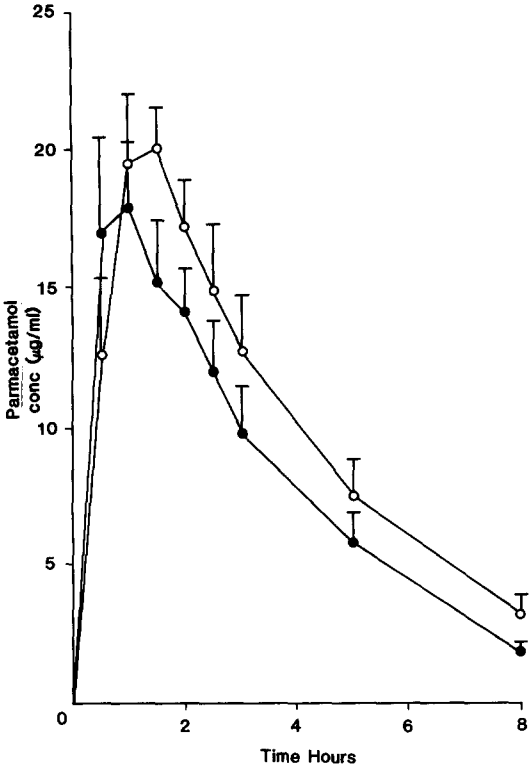

Fig. 1. Plasma concentration (μg/ml) of paracetamol in patients with hepatosplenic schistosomiasis (○) and in controls (●) following a single oral dose (1.5 g). Results expressed as mean ± S.E.M. ($n = 8$).

In the present study, the AUC and ($t_{1/2}$) were not significantly higher in the patients with periportal fibrosis compared with controls. As the major pathway of paracetamol metabolism is conjugation and the patients were not jaundiced, they could obviously cope with the endogenous substances requiring glucuronidation and were able to cope with the addition of a small amount of paracetamol. As the toxic metabolite is a product of oxidation and oxidative capacity may be reduced in patients with schistosomiasis (El-Raghy et al., 1985) although this fact is contentious (Homeida et al., 1978), they may be less likely than normal to have the reactive oxidative metabolite and to get acute liver failure after overdosage.

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