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Drug metabolism in hepatosplenic schistosomiasis in the Sudan: a study with antipyrine

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SUMMARY The disposition of antipyrine following oral administration of 1200 mg has been investigated in 10 patients with histologically confirmed hepatosplenic schistosomiasis and 11 normal subjects living in Sudan. Drug metabolising activity as assessed by antipyrine clearance was similar in patients when compared with normal controls. We conclude that antipyrine disposition is normal in patients with clinically compensated hepatosplenic schistosomiasis.

In recent years the prevalence of infection with *Schistosoma mansoni* has been increasing resulting in large numbers of young patients presenting with hepatosplenomegaly (Omer *et al.*, 1976). Although the hepatosplenic form of schistosomiasis has the reputation of being a relatively benign disease compared with alcohol induced cirrhosis (Reboucas, 1975), it can induce portal hypertension in a proportion of patients who are heavily infected (Ramos *et al.*, 1964), and, rarely, may induce ascites and hepatic decompensation. Patients with hepatosplenomegaly due to schistosomiasis are increasingly often being treated for both their parasitic disease and also for intercurrent diseases. Therefore, it is of importance to know whether hepatic drug metabolism is maintained in such patients or whether it is impaired.

Recent evidence derived from an experimental model of hepatic schistosomiasis in the mouse suggests that this disease can markedly reduce drug metabolising activity (Cha and Edwards, 1976). However, it has not been ascertained in man whether there is a significant impairment of drug metabolism which might be of therapeutic importance.

Accordingly, we have compared the pharmacokinetics of antipyrine in patients with hepatosplenic schistosomiasis to age, race-matched normal subjects.

Methods

SUBJECTS

Sudanese patients with schistosomiasis

Ten patients from the Gezira district in the Sudan, who had histologically proven hepatosplenic schistosomiasis, were studied. All subjects had evidence of *Schistosoma mansoni* infection and one subject also had *Schistosoma haematobium*. No subject was on medication or had other intercurrent disease. None of the subjects had ascites or a prior history of haematemesis. Clinical details of these patients are provided in Table 1.

Normal Sudanese subjects in Sudan

Eleven normal Sudanese subjects of the same socioeconomic class from the Gezira district who had no history of disease, were drug free, and had no schistosomal ova in a faecal examination participated in the study. All subjects were non-smokers.

PROCEDURE

Antipyrine (1200 mg) was administered orally after an overnight fast. Subsequently, blood samples were drawn at three, six, nine, 12, and 24 hours. Plasma was separated by centrifugation and stored at $-20°C$. Samples were transported frozen to Bristol, England, for assay. All samples were assayed by the method of Brodie *et al.* (1949). Antipyrine half-life ($T_{\frac{1}{2}}$) was estimated by least square regression analysis of log plasma concentration with respect to time. Assuming complete absorption, negligible first-pass elimination, and a one compartment system (Andreasen and Vesell, 1974), apparent volume of distribution (Vd) was estimated as:

$$Vd = \frac{Dose}{C_{po}} \qquad \text{Eq. 1}$$

where C_{po} is the back extrapolated plasma concentration at time zero. Clearance (Cl) was calculated from:

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Table 1 *Clinical details of patients with bilharzia*

Subject — *Liver histology*	*Age (yr), sex*	*Weight (kg)*	*Serum albumin (g/l)*	*Serum globulin (g/l)*	*Alkaline phosphatase (IU)*	*Bilirubin (μmol/l)*	*Aspartate amino transferase (1 unit/l)*
1 Periportal fibrosis	28 M	38	43	42	329	12	20
2 Lymphocytic infiltration in sinuses	29 M	45	46	28	84	10	10
3 Numerous granuloma and ova	16 M	40	40	42	147	7	8
4 Dense chronic inflammatory Foci	17 M	45	46	32	70	5	13
5 Periportal fibrosis	15 M	68	44	44	392	5	15
6 Granulamata and ova	16 M	40	52	54	196	3	22
7 Periportal fibrosis	16 M	40	46	41	168	11	13
8 Dense fibrous tissue, moderate inflammatory infiltrate	17 M	60	38	39	147	4	8
9 Periportal fibrosis	55 M	87	56	42	49	5	13
10 Periportal fibrosis	35 F	45	50	29	28	9	13

$$Cl = Vd \times \frac{0{\cdot}693}{T_{\frac{1}{2}}} \qquad \text{Eq. 2}$$

Group values were compared using Student's unpaired *t* test.

Results

Eight of the patients with hepatosplenic schistosomiasis who were selected for this study had histological evidence of advanced periportal fibrosis and the other two had granuloma formation with ova present in their liver biopsies. However, no patient had had ascites or a haematemesis in the past and serum albumin and bilirubin values were normal (Table 1).

Although there was no statistically significant difference in body weight between the two groups of subjects, patients with schistosomiasis tended to be lighter than normal subjects (Table 2). Antipyrine clearance was not significantly different between groups, however, when normalised for body weight, there was a trend for an increase in the mean clearance by 27% ($P = 0{\cdot}15$). The volume of distribution was significantly lower in patients with schistosomiasis and in comparison with controls. However, the volume of distribution of antipyrine correlated significantly with body weight ($r = 0{\cdot}60$, $P < 0{\cdot}004$), so that when volume of distribution was normalised for body weight there was no difference between the two groups. Antipyrine half-life was significantly reduced by 30% in patients with hepatic schistosomiasis.

Discussion

The major observation of this study has been that patients with clinically compensated, but histologically proven hepatosplenic schistosomiasis had a normal ability to eliminate antipyrine. Antipyrine was investigated in this study because it has several characteristics that result in it being a suitable model drug for studies investigating drug metabolising potential *in vivo*. It is completely absorbed, extensively metabolised by the liver with a slow rate of metabolism, and has negligible protein binding (Brodie and Axelrod, 1950). As a consequence its clearance reflects only drug metabolising ability (Wilkinson and Shand, 1975). In order to reduce intersubject variation between subjects due to size, the most precise estimate of drug metabolising ability is clearance normalised for body weight. Using this estimate, drug metabolising ability in hepatosplenic schistosomiasis was not significantly different from controls. There was even a trend for clearance per kilogram to be increased in liver disease patients; however, the patients in the present study were lighter than controls, so that total clearances were numerically similar. It is interesting to note that the percentage reduction in mean antipyrine half-life, which was statistically significant, was similar to the percentage increase in mean clearance normalised for body weight. Half-life is a variable dependent on both distribution and elimination making interpretation of differences in half-lives difficult. However, in the present study, the correlation of body weight with volume of distribution suggests that half-life was, in fact, an estimate of clearance normalised for body weight. Thus, in contrast with Caucasian patients with cirrhosis (Branch *et al.*, 1973; Andreasen *et al.*, 1974), it is possible that the metabolic activity in hepatosplenic schistosomiasis increases rather than decreases. This is possibly in relationship to the hepatomegaly observed in these patients.

Normal drug metabolising activity in patients with compensated schistosomal liver disease contrasts with marked reductions in hepatic concentrations of the drug metabolising enzymes, cytochrome P_{450} and cytochrome P_{450} reductase, and of drug metabolising activity in hepatic schistosomiasis in mice (Cha and Edwards, 1976). However, in this

Table 2 *Comparison of antipyrine pharmacokinetics in normal Sudanese subjects and patients with hepatosplenic schistosomiasis*

	Normal (n = 11)	*Hepatosplenic schistosomiasis (n = 10)*	*Difference between means (%)*
Age (yr)	31·2 ± 4·6	23·2 ± 4·4	− 26
Wt (kg)	58·6 ± 4·4	50·8 ± 5·1	− 13
Antipyrine volume of distribution (L)	44·3 ± 1·8	34·7 ± 2·4*	− 22
(l/kg)	0·79 ± 0·05	0·71 ± 0·04	− 10
Antipyrine clearance (ml/min)	27·2 ± 2·7	30·6 ± 3·5	+ 12
(ml/min Kg^{-1})	0·49 ± 0·05	0·62 ± 0·07	+ 27
Antipyrine half-life (h)	20·4 ± 1·9	14·3 ± 1·6*	− 30

Mean ± SEM *P<0·05. Unpaired Student's *t* test in comparison with normal Sudanese subjects.

experimental model these reductions were found to be dependent on the degree of infection with the parasite. This suggests that patients with excessive parasitic loads who develop hepatic decompensation might have a reduction in drug metabolising potential, but in the more typical case of hepatosplenic schistosomiasis drug metabolism remains within the normal range.

In the Gezira area of the Sudan, as in many other areas of the world, large-scale irrigation schemes have been associated with a dramatic increase in the prevalence of *Schistosoma mansoni*, so that approximately 80% of teenagers and 40% of adults currently excrete ova (Omer *et al.*, 1976). With this high prevalence, increasing efforts have been made to treat such patients, including all 10 patients in the present study. The two drugs hycanthone and niridazole are the most widely prescribed. Hycanthone is thought to be extensively and slowly metabolised initially by hydroxylation followed by conjugation to metabolites which are predominantly excreted in bile (Rosi *et al.*, 1965). Hycanthone therapy has been associated in a few patients with the development of acute hepatic necrosis which has been attributed to either the production of a toxic metabolite or failure to conjugate a toxic metabolite (Dennis and Kobus, 1974). Furthermore, metabolites of hycanthone are strongly mutagenic in experimental animals (Batzinger and Bueding, 1977). Thus, an inference of this study is that the potential of producing toxic intermediate metabolites remains and, if anything, is slightly increased in hepatosplenic schistosomiasis. In contrast, niridazole is a drug with a high intrinsic clearance; it is rapidly metabolised by reduction of the heterocyclic nitro group contained in its molecule with the result that, in normal subjects, there is a high hepatic extraction of drug on its route from the gut to the systemic circulation resulting in a low systemic availability. If portosystemic vascular anastomoses develop as a consequence of portal hypertension, then this drug will be absorbed from the gut, pass directly into the systemic circulation, and be present in higher concentrations, even though drug metabolising activity remains unchanged. This could explain the high plasma concentrations observed with chronic oral administration in patients with hepatosplenic schistosomiasis (Faigle and Keberle, 1969). The importance of the potential for high clearance drugs to have increased plasma concentrations even if drug metabolising activity is normal is emphasised by the fact that, at high plasma levels, niridazole can cause acute neuropsychiatric disorders (Bradley and Davis, 1972).

In conclusion, the normal antipyrine clearance observed in the subjects investigated in the present study suggests that the elimination of drugs which have a low hepatic extraction ratio will be normal in clinically compensated hepatosplenic schistosomiasis. However, drugs with a high hepatic extraction ratio may have abnormal pharmacokinetic disposition because of anatomical changes in blood flow rather than changes in intrinsic clearance.

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