The pharmacokinetics of antipyrine in patients with graded severity of schistosomiasis

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1 The pharmacokinetics of antipyrine have been studied in patients with schistosomiasis. In comparison to a control group of subjects ($n = 6$), patients with early (active) schistosomiasis (passing live ova in urine or stools without clinical and laboratory evidence of liver involvement; $n = 6$) exhibited similar pharmacokinetic parameters.

2 Of seven patients with hepatosplenic schistosomiasis (exhibiting hepatic fibrosis, splenomegaly, at least one episode of haematemesis, ascites), five showed markedly enhanced antipyrine half-life and reduced clearance. Compared to controls, the mean half-life of this group was increased from 10.9 ± 2.4 to 19.9 ± 9.5 h (mean $\pm$ s.d.; $P \leq 0.05$) and clearance reduced from 3.81 ± 0.74 to 2.18 ± 0.80 l h⁻¹ ($P \leq 0.01$). There was no change in the apparent volume of distribution.

3 Liver biopsy was performed on all patients diagnosed as having hepatosplenic schistosomiasis in the 2 weeks prior to the antipyrine study.

4 The results of this study indicate that hepatic microsomal metabolism is impaired in patients with advanced hepatosplenic schistosomiasis.

Keywords antipyrine schistosomiasis inhibition of metabolism

Introduction

Schistosomiasis is a major endemic health problem in Egypt. It is known to produce histological and pathological changes in the different host organs, especially the liver. *Schistosoma* infection is an important cause of chronic liver disease and can lead to hepatic fibrosis and portal hypertension with congestion of the gastrointestinal mucosa (Ramos *et al.*, 1964).

Hepatic disease may alter drug pharmacokinetics through reduced metabolic capacity and through changes in hepatic blood flow (reviewed by Blaschke, 1977; Branch & Shand, 1976; Sultatos *et al.*, 1980; Vesell, 1978; Wilkinson & Schenker, 1975; Williams & Mamelok, 1980). Previous studies have indicated that the clearance of antipyrine is either unaltered (Homeida *et al.*, 1978) or reduced (Brant & Prata, 1979) in

hepatosplenic schistosomiasis. The pharmacokinetics of two other low clearance drugs, metronidazole and oxamniquine were not significantly altered (Daneshmend *et al.*, 1982; Daneshmend & Homeida, 1983). In contrast, hepatosplenic schistosomiasis markedly altered the pharmacokinetics of labetalol (Daneshmend *et al.*, 1982), the finding being consistent with reduced flow dependent drug clearance in schistosomiasis.

Data from an experimental model of hepatic schistosomiasis in the mouse has indicated that the disease can markedly reduce drug metabolism (Cha & Edwards, 1976). We have recently shown (El-Raghy & Back, unpublished observations), a graded inhibitory effect on hepatic microsomal enzyme activity in mice dependent on the degree of infection.

The present study was designed to examine the effect of two distinct stages of the disease on antipyrine kinetics in man, namely early (active) schistosomiasis without liver involvement and advanced disease with hepatic fibrosis, splenomegaly, ascites and with a history of haematemesis.

Methods

Subjects

The study was carried out in 19 subjects recruited from rural health units around Assiut. The aims of the study were carefully explained and written consent obtained. All subjects were from a similar socio-economic background and underwent a thorough clinical examination and a battery of clinical laboratory tests including careful urine and stool examination for parasites, haemoglobin, haematocrit, red blood cell and platelet count, white cell and differential count, and serum levels of transaminases, alkaline phosphatase, total proteins, bilirubin, albumin and globulins.

Subjects were divided into three groups. Group 1 comprised a control group of six healthy volunteers (all male; aged 25–33 years; weight 65–75 kg) who had no history of schistosomiasis or evidence of schistosomal ova in their urine or stools. Group 2 comprised six subjects (four male, two female; aged 18–30 years; weight 65–77 kg; four with *Schistosoma mansoni* and two with *Schistosoma haematobium*) who were passing live schistosomal ova in their urine or stools. There was no evidence in this group of hepatosplenomegaly or any clinical evidence of liver involvement. Group 3 comprised seven subjects (all male; aged 27–42 years; weight 53–70 kg) with hepatosplenic schistosomiasis. The liver was palpable two fingers below the costal margin in five patients, but not in the other two. Splenomegaly of moderate (2–5 fingers below costal margin) to severe degree (down to umbilicus) was present in four and three patients respectively. All had ascites. All group 3 patients had at least one episode of haematemesis. Portal hypertension was evidenced by the demonstration of oesophageal varices on oesophagoscopy. Liver biopsy was performed within the period 0–2 weeks before the commencement of the study. All patients showed the known histopathological lesions of schistosomal hepatic fibrosis.

Subjects in group 1 and 2 were not receiving any drug therapy but patients in group 3 were on diuretics and vitamin supplements.

Procedure

Following an overnight fast, subjects received antipyrine (300 mg) by mouth. Saliva samples were obtained immediately before and at 2, 4, 6, 8, 12, 24 and 48 (Group 3 only) h after antipyrine. Saliva samples were transported frozen to Liverpool for assay by high performance liquid chromatography (h.p.l.c.) as previously described (Back *et al.*, 1983).

Pharmacokinetic analysis

Antipyrine half-life ($t_{1/2}$) was calculated from the elimination rate constant obtained by least squares regression analysis of saliva drug concentrations. Clearance (CL) was calculated from the dose divided by the area under the saliva concentration time curve (AUC) extrapolated to infinity. AUC was calculated by the trapezoidal rule.

The apparent volume of distribution (V) was calculated from the equation:

$$V = \frac{CL \cdot t_{1/2}}{0.693}$$

for statistical analysis a non-paired Student's t -test was used.

Results

In patients with early schistosomiasis, antipyrine saliva kinetics were similar to controls (Table 1). In contrast, mean data from patients with advanced schistosomiasis were significantly different from controls. The half-life was increased from 10.9 ± 2.4 to 19.9 ± 9.5 h (mean $\pm$ s.d.) and clearance decreased from 3.81 ± 0.74 to 2.18 ± 0.80 l h⁻¹. There was no change in the apparent volume of distribution, although there was a greater range of values (0.57 – 1.16 l kg⁻¹).

Two patients (17 and 18) had values for half-life and clearance which fell within the control range. There was no obvious correlation between the severity of disease, as judged by clinical examination and clinical laboratory tests, and the degree of inhibition of antipyrine metabolism. There were two patients (13 and 14) with serum albumin levels of less than 30 g l⁻¹ and both showed antipyrine half-lives of greater than 20 h. However, the remaining patients had albumin levels greater than 30 g l⁻¹ and half-lives ranging from 7.7 to 28.3 h.

Table 1 Pharmacokinetic parameters of antipyrine in control subjects and patients with active (early) schistosomiasis and advanced schistosomiasis.

Subject	$t_{1/2}$ (h)	CL ($l\ h^{-1}$)	AUC ($\mu g\ ml^{-1}\ h$)	V ($l\ kg^{-1}$)
<i>Controls</i>				
1	11.6	4.15	72.4	0.90
2	13.2	3.85	77.9	1.09
3	11.1	3.75	80.0	0.86
4	11.6	4.15	72.4	0.96
5	6.3	4.56	65.8	0.61
6	11.8	2.42	123.8	0.63
Mean $\pm$ s.d.	10.9 $\pm$ 2.4	3.81 $\pm$ 0.74	82.1 $\pm$ 21.0	0.84 $\pm$ 0.18
<i>Early schistosomiasis</i>				
7	9.0	4.71	63.7	0.79
8	11.0	3.63	82.7	0.83
9	14.1	3.22	93.3	1.00
10	9.5	3.85	77.9	0.75
11	10.1	4.22	71.1	0.81
12	10.3	4.49	66.8	0.98
Mean $\pm$ s.d.	10.7 $\pm$ 1.8	4.02 $\pm$ 0.56	75.9 $\pm$ 11.0	0.86 $\pm$ 0.10
<i>Advanced schistosomiasis</i>				
13	32.6	0.81	371.7	0.63
14	20.3	2.57	116.7	1.16
15	28.3	1.56	192.5	0.91
16	16.8	2.70	110.9	1.13
17	8.7	2.96	101.2	0.57
18	7.7	2.83	106.1	0.59
19	25.0	1.82	164.6	1.01
Mean $\pm$ s.d.	19.9 $\pm$ 9.5*	2.18 $\pm$ 0.80**	166.2 $\pm$ 96.8*	0.86 $\pm$ 0.26

* $P \leq 0.05$; ** $P \leq 0.01$; Significantly different from controls, Student's *t*-test.

Discussion

Brant & Prata (1979) examined the pharmacokinetics of antipyrine in three groups, controls, intestinal schistosomiasis only and hepatosplenic schistosomiasis but without ascites or encephalopathy. Compared to controls, antipyrine clearance remained unchanged in group 2 but was decreased by 39% in the patients with hepatosplenic disease. In contrast to this finding, the study from Sudan (Homeida *et al.*, 1978) found no difference in antipyrine kinetics between controls and those with compensated hepatosplenic schistosomiasis. The results of our study concur with that of Brant & Prata (1979) and indicate that hepatic microsomal metabolism is impaired in patients with advanced schistosomiasis who exhibit clear evidence of liver involvement with fibrosis, splenomegaly and ascites.

The clearance values we report in this study for control subjects are higher than we (Back *et al.*, 1983) and many others have previously found, although Dossing & Andreason (1981) have reported similarly high values. With hindsight, we should have also taken some plasma samples to

determine the saliva:plasma ratio of antipyrine in our subjects.

Branch *et al.* (1973) have indicated that in patients with liver disease, the impairment of antipyrine elimination is greatest when hepatocellular function is severely compromised. Patients with hypoalbuminaemia or hypoproteinaemia showed the greatest prolongation of half-life. It is recognized that a low serum albumin level is a feature of failing function of the liver parenchyma and represents a failure of protein synthesis. In the present study only two patients in group 3 had hypoalbuminaemia (i.e. $\leq 30\ g\ l^{-1}$); the remaining five patients having low-normal albumin levels. Three of these five patients, however, had significantly reduced antipyrine clearance values.

Inter-individual variation in severity of schistosomiasis has been discussed by Dunn & Kamal (1981). The standard explanation for the variation is the wide range of intensity and duration of tissue egg deposition. In addition, there are data (the determination of histocompatibility types) to suggest differences in susceptibility to the disease (Abdel Salem *et al.*, 1979). The lack of

clear-cut, consistently abnormal biochemical tests even in advanced disease, apparently indicates that in most patients functional integrity of liver cells is maintained. It is difficult to explain why in our group 3 patients, who all had severe clinical changes, antipyrine half-lives ranged from 7.7 to 32.6 h. It is possible that some

patients had additional pathological changes which contributed to the disturbance of hepatic enzyme activity.

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