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ALTERED DRUG METABOLISM IN HEPATOSPLENIC SCHISTOSOMIASIS

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SUMMARY

The purpose of the present study was to assess the effect of the intrahepatic vascular lesions of schistosomiasis mansoni on drug metabolism. Plasma antipyrine half-lives ($T_{\frac{1}{2}}$) and metabolic clearance rates (MCR) were measured after a single oral dose of antipyrine (18 mg/kg/b.w.) in 20 controls, Group 1; in 9 subjects with intestinal schistosomiasis, Group 2; and in 15 subjects with the compensated hepatosplenic form of the disease, Group 3; The mean values of plasma antipyrine half-lives and metabolic clearance rates were found to be significantly different in the Group 3 as compared to Groups 1 and 2.

Group 1 — $T_{\frac{1}{2}}$ 13.55 ± 3.10 hours, MCR 28.46 ± 9.61 ml/min;

Group 2 — $T_{\frac{1}{2}}$ 11.33 ± 3.35 hours, MCR 30.08 ± 12.82 ml/min;

Group 3 — $T_{\frac{1}{2}}$ 22.00 ± 8.5 hours, MCR 17.45 ± 6.84 ml/min.

Changes in antipyrine metabolism did not correlate with changes in other metabolic functions of the liver, suggesting that the cause for these changes was not defective cellular fuction. This study indicates that these changes in antipyrine metabolism could be due to increased systemic bioavailability of the drug. Possibility of drug toxic reaction is suggested.

INTRODUCTION

Schistosomiasis mansoni is endemic in the northeastern region of Brazil and in other parts of the world, where it constitutes the major cause of portal hypertension [8]. The hepatosplenic form of the disease is characterized by portal fibrosis, intrahepatic portal vascular obstruction, portal hypertension with or without a collateral circulation. Although flow studies on human hepatosplenic schistosomiasis are few, pressure determinations and angiograms have shown evidence of a decrease in portal blood flow. However, when total hepatic blood flow was measured it remained within the normal range, suggesting that the deficit in portal venous flow may be compensated for by an increase in the arterial flow [16].

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As the liver is the major site for drug metabolism, obstruction to portal blood flow might be expected to alter this function. When hepatosplenic schistosomotic patients were treated with niridazole they showed greater incidence of side effects than those with the intestinal form of the disease treated with the same drug at similar dosage. These symptoms were related to higher blood levels of the drug [10].

In cirrhosis of the liver several studies have demonstrated that the metabolism of antipyrine was significantly correlated with the serum albumin and the prothrombin values, therefore to the functioning mass of the liver [2]. Hepatosplenic schistosomotic patients, when compensated, have normal liver function tests [7].

There is scanty information on how these patients metabolize drugs. Our study was undertaken to investigate the effect of the intrahepatic lesions of schistosomiasis mansoni on drug metabolism.

Antipyrine was selected as a drug test because its plasma decay curve in normal subjects reflects microsomal metabolism, since antipyrine administration orally in solution is completely absorbed from the gastrointestinal tract, distributed evenly in the total body water and less than 10% of the drug excreted unchanged by the kidneys [5].

PATIENTS AND METHODS

44 Subjects of both sexes were studied and divided into three groups.

Group 1 — 20 Normal volunteers. There were 14 males and 6 females. The mean age of the group was 31 years (range 21-60 years). Each volunteer was carefully examined and found to be in good health. They had not been on drugs for the last three weeks prior to the study.

All had skin test and stool examinations negative for viable ova of **Schistosoma mansoni**.

Group 2 — 9 Subjects with intestinal schistosomiasis. There were 6 males and 3 females. The mean age was 30 years (range 20 — 56 years). All had skin test and stool examinations positive for viable ova of **Schistosoma mansoni**.

None had hepatosplenomegaly — nor had been on any drug.

Group 3 — 15 Subjects with hepatosplenic schistosomiasis. There were 8 females and 7 males. The mean age was 36 years (range 18 — 53 years). Skin test and stool examinations were positive for viable ova of **Schistosoma mansoni** in all subjects. All had hepatosplenomegaly. Portal hypertension was evidenced by the demonstration of oesophageal varices on oesophagoscopy or on selective splenic arteriography. Liver biopsy was performed in all subjects. Its characteristic feature was: Symmers fibrosis, preserved hepatic lobular architeture, mononuclear portal infiltrates, absence of regenerative nodules and of signs of cholestasis. Neither ascites nor signs of encephalopathy were found in any subject of this group. They had not been on any drug. Routine biochemical liver function tests were performed in all subjects.

Antipyrine test

A single oral dose of 18 mg/kg/b.w. of antipyrine (crystals Merck) was dissolved in tap water and administered at 7.00 a.m., after a fasting blood sample was obtained. Further blood samples were taken at 3, 6, 9 and 24 hours after antipyrine administration. The plasma was separated and frozen until assayed in duplicate by the method of BRODIE et al.[6]. The values were plotted against time on semilog paper. A straight line was drawn graphically if a nearly perfect fit could be obtained with at least three of the four points, and the $T_{\frac{1}{2}}$ and C_o was read off the graph.

The apparent volume of distribution was calculated from the equation.

$$aVD = \frac{\text{Dose administered}}{C_o}$$ where C_o is the theoretical plasma concentration at zero time. The metabolic clearance rate (MCR) was calculated from the equation $MCR = \frac{0.693 \times aVD}{T_{\frac{1}{2}}}$ (ml/min).

The elimination rate constant expressed as a percentage of time was calculated from equa-

tion $K = \frac{0.693}{T_{\frac{1}{2}}}$

Statistical analyses were performed using the Student's T test.

RESULTS

Table I shows the mean values and S. D. of the quantitative liver function tests and plasma antipyrine half-lives for the group 3. Changes in antipyrine $T_{\frac{1}{2}}$ did not correlate with any of the given parameters. However, as a group, the subjects had low leucocyte and low platelet counts, suggesting hypersplenism. Even though there was no correlation between changes in antipyrine metabolism and the number of leucocytes and platelets. The biochemical parameters show undoubtedly that the subjects were compensated. Mean albumin value of 39.7 g/l and prothrombin time of 13.87 sec are in agreement with published data for the compensated form of the disease.

TABLE I

Comparison of the pharmacokinetics of antipyrine with the biochemical parameters in 15 subjects with hepatosplenic schistosomiasis. Mean values and S. D. are given.

		Albumin g/1	Globulin g/1	SGPT IU/1	Bilirubin μmol/1	Alkaline Phosphatase IU/1	Prothrombin Time s	Platelet Count x/10⁹/1	Leucocyte Count x/10⁹/1	Antipyrine T1/2 —n—
S I	Mean	39.7*	37.3*	12.10*	15.56*	153.58*	13.85*	129,666*	4,178*	22,00
Unit	S D	6.3	11.3	7.11	5.13	113.75	1.25	90,108	1,519	8.52
Trad.		g%	g%	URF	mg%	UK.A.	s	mm³	mm³	—h—
Unit	Mean	3.97	3.73	12.10	0.91	21.94	13.85	129,666	4,178	22.00
	S D	0.63	1.13	7.11	0.30	16.25	1.25	90.108	1,519	8.52

Table II shows the pharmacokinetic data of antipyrine for the all three groups of subjects. The mean values of the plasma half-lives of antipyrine for the group 3 were 22.00 hours ± 8.52 S.D. and for the group 1 were 13.55 hours ± 3.10 S. D. ($p < 0.005$) and for the small group 2 were 11.33 hours ± 3.35 S. D. ($p < 0.005$). Statistically significant differences were also found between group 3 and groups 1 and 2, with respect to the mean values of the metabolic clearance rate and elimination rate constant. The mean apparent volume of distribution for the group 3 of 27.34 1 ± 8.64 S.D. was not significantly different from that of the group 1 (31.52 1 ± 5.67 S.D.) and that of the group 2 (27.06 1 ± 6.94) p = n.s.

TABLE II

Pharmacokinetic data of antipyrine in all three groups. Mean values and S.D. are given.

	Controls n = 20		Hepato-intestinal Group n = 9		Hepato-splenic Group n = 15		t test
	Mean	S.D.	Mean	S.D.	Mean	S.D.	P
Antipyrine T1/2 Hours	13.55	3.10	11.33	3.35	22.00	8.52	< 0.005
Antipyrine clearance ml/min	28.46	9.61	30.08	12.82	17.45	6.84	< 0.005
Apparent vol. of distribution 1	31.52	5.67	27.06	6.94	27.34	8.64	n.s.
Elimination rate constant %	0.092	0.032	0.109	0.029	0.060	0.028	< 0.005

Figure 1 — shows the individual values of the antipyrine $T_{1/2}$ in all three groups. The antipyrine $T_{1/2}$ was 13.55 hours ± 3.10 S. D. (range 6 — 18 hours) which is consistent with previously published data [9]. The small group of subjects with intestinal schistosomiasis had a similar values 11.33 hours ± 3.55 S.D. (range 9 — 18 hours). The 15 subjects with hepatosplenic schistosomiasis showed a significant increase in the $T_{1/2}$ of antipyrine, 22.00 hours ± 8.52 S. D. (range 8 — 43 hours) $p < 0.005$. However 5 subjects had antipyrine $T_{1/2}$ within the normal range.

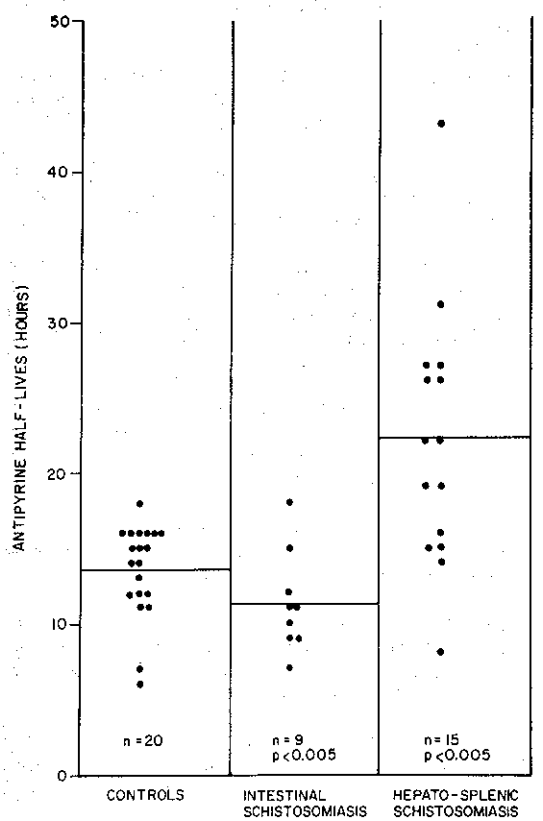

Fig. 1 — Antipyrine half-lives in normal subjects and in patients with intestinal and hepatosplenic schistosomiasis. Each enclosed circle represents values for a single individual. Horizontal lines indicate means.

DISCUSSION

Our results indicate that the hepatosplenic form of schistosomiasis mansoni significantly decreases antipyrine metabolism. Changes in the basal plasma half-life of antipyrine occur after administration of drug that induce[18] or inhibit[19] hepatic microsomal metabolism. Genetic factors [17], nutritional state [1], race [11], age, and sex [14], smoking habits [15] exposure to environmental factors [13] and disease state [3] have also been shown to alter drug metabolism.

Changes in antipyrine half-life that occurred in our patients are similar to those found in patients with cirrhosis of the liver, where the greatest changes seemed to be correlated with low albumin and prothrombin levels.

However, our results could not be correlated with changes in those parameters. Interestingly enough all patients had a similar degree of histologic lesions. In cirrhosis of the liver three possible explanations for the prolonged $T_{1/2}$ of antipyrine have been accepted, i.e. altered drug distribution, altered liver blood flow and decreased rate of metabolism. Antipyrine is distributed in the total body water and this is known to increase in chronic liver disease. Our patients had neither ascites nor oedema. Furthermore there was not significant changes in the apparent volume of distribution in the three groups. The metabolism of some drugs might be dependent on liver blood flow [4]. Hepatic blood flow in hepatosplenic schistosomiasis has been shown to be in the normal range, however, portal blood flow has not been measured. As portal hypertension is a common feature in this form of the disease, this may decrease blood flow in the portal vein consequently the drug blood supply to the liver. This may be an explanation for our results. Contrary to the cirrhosis of the liver our hepatosplenic patients had nearly normal liver function tests, therefore, the changes in antipyrine $T_{1/2}$ could not be attributed to changes in the metabolic functions of the liver. Other factors may be involved. Increased systemic bioavailability of the drug may well be another explanation for

our results. It has been shown in dogs that systemic bioavailability of antipyrine is greater after surgical portacaval shunting [12]. This would suggest that spontaneous portacaval shunting that occur in patients with portal hypertension may lead to higher drug blood levels. Although we cannot conclude from our study that this is so, patients with the greatest changes in antipyrine $T_{\frac{1}{2}}$ were those with oesophageal varices. Preliminary results of antipyrine metabolism before and after splenectomy and ligature of oesophageal varices indicate that antipyrine metabolism is in fact influenced mainly by the shunting of the blood from the liver. This study is in progress. Based on our results we would caution physician to adjust the doses of antischistosomal agents downwards since the systemic availability of these agents may be increased and could cause toxic reactions. This may be relevant once schistosomiasis needs field mass treatment. Special attention should be paid to those subjects with signs of collateral circulation even when compensated.

RESUMO

Alteração do metabolismo de drogas em pacientes com a forma hepatesplênica da esquistossomose mansoni

O presente estudo foi realizado para avaliar o efeito das lesões vasculares hepáticas da esquistossomose mansônica no metabolismo de drogas. A vida média de antipirina ($T_{\frac{1}{2}}$) e seu clearance metabólico (MCR) foram determinados em três grupos de pacientes: grupo 1 — Controle — 20 indivíduos, grupo 2 — 9 indivíduos com a forma intestinal, grupo 3 — 15 pacientes com a forma hepatesplênica compensada da esquistossomose mansônica. Os valores médios encontrados foram significativamente diferentes no grupo 3 quando comparados com os dos grupos 1 e 2. As alterações no metabolismo da antipirina não se correlacionaram com nenhuma função metabólica do fígado, sugerindo que a causa para essas alterações não era falência celular, e sim maior concentração da droga no organismo.

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