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SCHISTOSOMA MANSONI: EFFECTS OF ANESTHETICS AND ANTIMONIAL DRUGS ON WORM SHIFT IN THE MOUSE

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SUMMARY

Mice experimentally infected with **Schistosoma mansoni** were injected with sodium thiopental or sodium antimonyl gluconate (Triostib R), or submitted to halothane inhalation, with or without a previous injection of thiopental.

Data obtained showed that halothane and thiopental induce worm shift to the liver (99 and 76%, respectively). Sodium gluconate and antimonium (Triostib R) shifted 52% of worms towards the liver.

These results seem to indicate that the use of antimonium would be unnecessary, when surgical removal of schistosomules is carried out through the extracorporeal filtration technique, in patients with portal hypertension.

KEY WORDS: Manson schistosomiasis — Experimental disease in mice — Antimonial drugs — Worm shift

INTRODUCTION

Extracorporeal worm filtration [8,9] has been proposed based on the hypothesis that the simultaneous displacement of a great number of dead worms towards the liver, after treatment, could induce an extensive inflammatory reaction in this organ. Nowadays, it is assumed that this problem is not as bigger as it was thought to be at the seventies [17]. However, a significant amount of immunecomplexes is known to be formed stimulated by parasite residues. Considering the daily egg laying by female worms of about 400, from which 60% are accumulated in the tissues [16] and depending on the opportunity offered by a patient, who suffering from bilharziasis portal hypertension has to have an operation done, the withdrawal of worms throughout an extracorporeal filtration, in the same surgical act, sounds desirable. The process of filtration was proposed in 1967 [9] and it is only considered justifiable if there is a clear indication for surgical treatment of patients with portal hypertension. The technique described included the administration of pentavalent antimony, which acting against the parasites would facilitate their filtration. Nevertheless, the antimony toxicity to the patient constitutes a great inconvenient of the technique.

In our experience with this procedure it was observed that the anesthesia by itself was effective in dislodging the worms towards the liver and distal portal vein lumen, facilitating in that way their remotion by means of a cannula put in the portal system through the splenic vein and connected to a filter system. Should that occur the antimonial injection with the same purpose was dispensable.

The present work was carried out in order to experimentally test this hypothesis using **Schistosoma mansoni** infected mice.

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MATERIALS AND METHODS

1. First experiment

Female albino mice were subcutaneously infected with about 80 cercariae of **Schistosoma mansoni**, LE strain, Belo Horizonte. Forty-six days later the animals were submitted to tests with the drugs. Sodium thiopental (CEME, Rio de Janeiro) was injected intraperitoneally (i.p.) in doses of 1.25 (Group I) and 2.5 mg/kg (Group II). A third group was composed by mice injected i.p. with the same doses of thiopental plus expositian to halothane (Fluothane, Wellcome Lab., S.A.) in a transparent glass reservoir. The 4th group of animals was exposed to an atmosphere of halothane in the glass reservoir in the same way described for Group III, but without any previous injection of thiopental, until loss of consciousness. The anesthesia was maintained by means of a funnel containing an halothane embedded cotton which allowed an increase or decrease in halothane concentration in the respiratory surroundings of the animals, depending on the anesthetic necessity. Ten animals were maintained as a control group in which there was no drug injection nor inhalation (Group V).

After 60 min of anesthesia the animals were sacrificed by cervical compression and, immediately after, perfused according to the method described elsewhere [13]. The worms were counted separately in two portal regions: the first one the liver and distal portion of portal vein and its bifurcation, the second corresponding to the mesenteric veins. The control group (Group V) was submitted to the same procedures.

2. Second experiment

A second experiment was performed in female albino mice after 46 days of a transcutaneous infection with 120 cercariae, LE strain, Belo Horizonte. Eleven of those animals (Group VI) were injected with sodium antimonyl gluconate (Triostib R, Burroughs Wellcome & Co., London), 4 mg/kg i.v., and five of them were maintained as a control group (Group VII).

Statistical analysis in the first experiment was done by analysis of variance and Scheffé-test for comparison between means and in the second by Studentés t-test, with $P < 0.05$ indicating significance.

RESULTS

The first experiment (Table I) clearly showed a shift of worms towards the liver in the thiopental-treated group (2.5 mg/kg) and in animals which had received halothane associated or not to thiopental. In the control group only 40% of worms were found in the upper portal vein and liver ($P < 0.01$). The group treated with a smaller dose of thiopental (1.25 mg/kg) showed a shift of 64.6% of worms to the liver, but this was not statistically significant when compared to the control group.

TABLE I

Effect of anesthetics on the shift of adult **Schistosoma mansoni** worms to the upper region of portal vein and liver, in mice. Worm recovery (mean ± SEM) = 32.75 ± 5.4

Mice (n)	Treatment	% recovered worms	
		Liver and upper portion of portal vein	Mesenteric veins
6	Thiopental (1.25 mg/kg)	64.6	35.4
6	Thiopental (2.5 mg/kg)	76.1	23.9
7	Thiopental (1.25 mg/kg) + halothane	98.8	1.2
7	Halothane	98.5	1.5
10	Control	40.0	60.0

Some mice died due to anesthetic effect. In the halothane plus thiopental (1.25 mg/kg) treated group four out of eleven died. The same incidence of deaths was observed in group treated with halothane. The animals dead during the experiment were not used for worm recovery.

Table II shows that in the second experiment the pentavalent antimonial (Triostib R) shifted 52% of worms towards the liver and upper portion of portal vein. The control experiment showed a shift of 29.3% of worms to the same regions. The difference between these two groups was shown to be statistically significant ($P < 0.05$), indicating that the antimonial was responsible for shift of worms but in smaller proportion than halothane or sodium thiopental.

T A B L E II

Effect of sodium antimonyl gluconate (Triostib) on the shift of adult **Schistosoma mansoni** worms to the upper region of portal vein and liver, in mice. Worm recovery (mean ± SEM) = 76.1 ± 9.0

Mice (n)	Treatment	% recovered worms	
		Liver and upper portion of portal vein	Mesenteric veins
11	Sodium antimonyl gluconate (4 mg/kg)	52.0	48.0
5	Control	29.3	70.7

DISCUSSION

The practice of extracorporeal schistosome filtration can only be justified when there is a clear clinical indication to operate upon a patient with the aim to treat the portal hypertension caused by those worms. The technique of extracorporeal filtration was experimentally developed in baboons by GOLDSMITH & KEAN, in 1966 [8]. These authors have posteriorly tested with success the technique in Brazilian human volunteers [9]. Since then the technique has been used many times with good results. However, the utilization of antimonial is not devoid of adverse effects amongst which it can be cited: cough, joint pain, bradycardia, headache, fainting, dyspnea, facial edema, abdominal pain, vascular collapse and cutaneous rashes. Hemolytic anemia may occasionally occur during the course of chronic treatment. On the other hand, the use of antimonials is contraindicated in patients with hepatic, cardiac or renal failures as well as in massive schistosome infestation [10]. As the parasitic charge is not usually determined it is very difficult to know which patients are massively infected. Furthermore, patients presenting schistosomotic portal hypertension have, as a rule, different degrees of liver damage and occasionally renal lesions induced by the disease itself.

Some authors discuss the real benefit of the technique to the patient. WARREN [17] commented that the effects of adult worms dead by schistosomicidal drugs, in the general findings of pathology, would not be a significant feature. This author quoted the results from an experiment done by CHEEVER et al. [6], in which mice massively infected by worms and submitted to chemotherapy did not present rough hepatic lesions around the dead worms. He made a relationship between the number of dead worms per kg/body weight in humans and concluded that the mice infection corresponded to a charge of 100.000 worms in a human adult patient. His work put in question the reasons for applicability of the extracorporeal filtration technique. Nevertheless, an important aspect may be considered, as besides the gross hepatic lesions caused by dead worms, one must remember immunecomplexes formation resulting from simultaneous desintegration of innumerable worms. These immunecomplexes might deposit in distant tissues, inducing lesions in important organs, such as lungs and basal membrane of the kidneys [1,2,11,12,14,15]. In this way, the mechanical recovery of schistosomes from the portal blood by means of extracorporeal filtration would be advantageous by preventing the formation of those immunecomplexes secondary to dead worms.

Concerning the results of the present paper, the mortality observed after halothane associated or not to thiopental might be explained either by: an overdosage, due to the rudimentary process used for drug administration, in which the concentrations the animals inhaled could not be determined, or by a decrease in the hepatic metabolism produced by schistosomiasis. The infected animal has a small capacity of drug metabolization since several enzymes of the hepatic microsomal system are depressed [3,4,5,7]. So, it is postulated that animals with schistosomiasis would be more susceptible to the action of halothane.

Our results clearly showed that the effects of thiopental or halothane, drugs routinely employed as anesthetics in general surgical practice, might be sufficient to shift the most of the adult worms facilitating, in this way, the extracorporeal filtration process and eliminating the need of antimonial administration to perform that technique.

The present data reinforce the advantages that extracorporeal worm filtration could bring to the human host, namely: a) avoidance of formation of a great number of circulating immunecomplexes in tissues from worms dead by chemotherapy; b) with mechanical parasites erradication it would be unnecessary the use

of drugs that, in spite of the advances in therapeutics, are still biological poisons, which even having a high specificity against the parasite could induce damage against host tissues.

Finally, it must be reinforced that the proposed therapeutic process of surgical removal of parasites only could be justifiable in the presence of a clear indication to submit the patient to an abdominal surgery to treat his portal hypertension or its complications such as bleeding esophageal varices of hypersplenism.

RESUMO

Schistosoma mansoni: **efeitos de anestésicos e antimonial (Triostib R) sobre o deslocamento de vermes no camundongo.**

Camundongos experimentalmente infectados com **Schistosoma mansoni** foram injetados com tiopental sódico ou antimonial (Triostib R), ou submetidos à inalação de halotano, com ou sem uma injeção prévia de tiopental. Os resultados mostraram que o halotano e o tiopental induzem, respectivamente, o deslocamento de 99 e 76% dos vermes para o fígado. Gluconato de sódio e antimônio (Triostib R) deslocou 52% de vermes. Estes resultados parecem indicar que o uso de antimonial seria desnecessário quando se faz a remoção cirúrgica de esquistossomos pela técnica de filtração extracorpórea em pacientes com hipertensão portal.

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