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STABILITY OF SCHISTOSOMA MANSONI PROGENY TO ANTISCHISTOSOMAL DRUGS (*)

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SUMMARY

The susceptibility of the MAP Brazilian strain (F_1 to F_5 progenies) of **S. mansoni** to four antischistosomal drugs has been reported in a previous study. In the present investigation, progeny F_{14} of the same strain, was tested for stability to the same 4 drugs. A new medication, Oltipraz (35,972 RP), was added to the study. Five groups of 12 mice infected with cercariae by tail immersion were treated with hycanthone, oxamniquine, niridazole, praziquantel and Oltipraz. An untreated group was used as control. Schistosomal activity was assessed by the localization of worms in the portal vein system, by oogram changes, and percentage of parasite reduction. The stability of the susceptibility of progeny F_{14} did not change in relation to generations F_1 to F_5; the progeny was resistant to hycanthone and oxamniquine, but sensitive to niridazole, praziquantel and Oltipraz. We emphasize the importance of the phenomenon of resistance of the worm in view of the fact that oxamniquine has been widely used in Brazilian areas where mansonic schistosomiasis is endemic.

INTRODUCTION

The occurrence of resistant **S. mansoni** strains has been reported by several investigators [2,3,6]. In a study on the behavior of a Brazilian strain (MAP) of the worm towards schistosomicidal drugs, were observed that progenies F_1 to F_5 were resistant to oxamniquine and hycanthone but sensitive to niridazole and praziquantel [3]. The patient (MAP) from whom the strain was isolated was treated once with hycanthone and twice with oxamniquine, with no parasitologic cure.

To evaluate the stability of the susceptibility of the MAP strain, an experimental therapeutic trial was carried out with the F_{14} progeny.

In the present study we utilized a new drug, Oltipraz (35,972 RP), a new schistosomicidal drug that has been already tested in clinical trials [7,8].

MATERIAL AND METHODS

After a previous study, we have been maintaining the MAP strain in our laboratory without exposure to schistosomicidal drugs by the following transfer scheme: **Biomphalaria glabrata** — mice — **Biomphalaria glabrata.**

F_{14} Cercariae obtained from **B. glabrata** snails were used to infect female albino mice (Swiss), by the tail immersion technique [9]. Each mouse was exposed to 100 cercariae. Drug treatment was carried out as follows 45 days after cercarial infection: 1 x 80 mg/kg hycanthone, intramuscularly; 1 x 100 mg/kg oxamniquine; 5 x 100 mg/kg/day niridazole; 5 x 100

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mg/kg/day praziquantel, and 5 x 125 mg/kg/day Oltipraz, orally. Each drug was applied to a different group of 12 mice. An untreated control group was formed to obtain miracidia for the next generation.

The mice were killed with a blow on the neck 10 days after treatment and the worms recovered by perfusion [9]. The schistosomicidal action was evaluated by the distribution of worms in the mesenteric vessels, percentage of mice with oogram changes and percentage of parasite reduction [1,4,9].

RESULTS

We noticed that there was a high percentage of male worms in almost all groups, specially in that treated with oxamniquine. We could also observe (Table I) the existence of two different patterns obtained by the therapeutic evaluation.

TABLE I

Antischistosomal activity of drugs in mice experimentally infected with MAP strain of **Schistosoma mansoni** (progeny F_{14})

Drugs	Number of animals		Mean worm burden	(%) males	Distribution of schistosomes (%)		% of mice with oogram changes	% parasite reduction
	Treated	Examined			Liver and portal vein	Mesenteric vessels		
Hycanthone	12	10	24.3	62.6	26.7	73.3	0.0	2.9
Oxamniquine	12	12	32.4	93.7	63.7	36.3	0.0	2.6
Praziquantel	12	12	14.2	85.9	98.9	1.1	100.0	97.0
Niridazole	9	9	9.2	85.5	92.8	7.2	100.0	44.6
Oltipraz	10	9	16.6	75.2	100.0	0.0	100.0	100.0
Control	12	10	38.7	74.7	44.2	55.8	0.0	0.0

In the first pattern, represented by the groups treated with praziquantel, niridazole and Oltipraz we found a low percentage of worms in the mesenteric veins, 100% of altered oograms, and a high percentage of parasite reduction.

In the second pattern, showed by the groups treated with hycanthone and oxamniquine, the findings consisted by a greater amount of worms in the mesenteric veins, no alterations in the oograms, and a low percentage of parasite reduction.

The data of the first pattern have demonstrate some susceptibility to the antischistosomal used against those groups of worms, by the other hand the results obtained in the second pattern were very similar to the control group, confirming the worm resistance to the oxamniquine and hycanthone.

One of the most important criteria to be evaluated in experimental analysis of susceptibility, in relation to antischistosomal drugs against **S. mansoni** is the percentage of parasite reduction, since the surviving worms are the responsable by the therapeutic failure and potentially able to produce resistance progenies to this drugs [5,10].

Although cercarian infection was performed on groups of 12 mice, it was not always possible to treat the same number of animals because of mortality during the 45-day period proceeding drug administration.

Worm mortality was not detected in the control group.

DISCUSSION

In the 14th progeny of the MAP strain, worm resistance remained stable when compared to the 1st to 5th progeny with respect to hycanthone and oxamniquine. The strain also showed stability of the susceptibility to niridazole and praziquantel.

In the present study, Oltipraz, which was being used for the first time against the MAP strain, showed clear activity. No cross-resistance with the other drugs studied here was shown by Oltipraz.

An interesting fact occurred in the present experiment. A relatively high percentage of male worms occurred in the infections espe-

cially in the group of mice treated with oxamniquine. Some investigators demonstrated that in infections by males only, most worms tend to be localized in the liver and portal vein [11,12]. In the present study, although most of the worms were located in the liver and portal vein, in the animals treated with oxamniquine it could be seen that, when other parameters were utilized, the worms were resistant to the drug. However, the importance of well-balanced bisexual infections should be emphasized for the correct analysis of susceptibility to schistosomicidal drugs when the criterion of worm distribution is used.

CONCLUSIONS

In conclusion, our results show that: (a) the resistance and susceptibility to four drugs of an **S. mansoni** strain were stable in the F_{14} progeny when compared to generations F_1 to F_5; (b) a new drug, Oltipraz, tested only on progeny F_{14}, was shown to be effective, with no cross-resistance with hycanthone and oxamniquine.

RESUMO

Estabilidade de progênie de Schistosoma mansoni **a drogas esquistossomicidas**

A suscetibilidade de linhagem brasileira (MAP), nas gerações F_1 a F_5 de **S. mansoni** a quatro drogas esquistossomicidas foi descrita em trabalho anterior. Na presente pesquisa os Autores testam a estabilidade da progênie F_{14} da referida linhagem às quatro drogas e a um novo medicamento, Oltipraz (35,972 RP). Cinco grupos de 12 camundongos infectados com cercárias por meio da imersão da cauda, foram tratados com hycanthone, oxamniquine, niridazole, praziquantel e Oltipraz. Foi utilizado um grupo controle de camundongos infectados e não tratados. A atividade esquistossomicida das drogas foi avaliada pela localização dos vermes no sistema porta, pelas alterações no oograma e percentagem de redução de vermes. A suscetibilidade dos vermes da geração F_{14} mostrou-se estável em relação àquelas observadas nas progênies F_1 a F_5; a progênie F_{14} de vermes foi resistente ao hycanthone e oxamniquine; todavia, foi sensível ao niridazole, praziquantel e Oltipraz. Os Autores enfatizam a importância do fenômeno de resistência do verme em vista do fato do oxamniquine ser largamente utilizado em áreas do Brasil onde a esquistossomose mansônica é endêmica.

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