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THERAPEUTICAL EVALUATION OF DIFFERENT DOSE REGIMENS OF PRAZIQUANTEL IN SCHISTOSOMIASIS MANSONI, BASED ON THE QUANTITATIVE OOGRAM TECHNIQUE.[1]

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SUMMARY

A clinical trial involving 80 patients of both sexes, from ages 15 to 55, with chronic intestinal or hepatointestinal schistosomiasis mansoni, was carried out to evaluate the therapeutical efficacy of different dose regimens of praziquantel.

The patients were randomly allocated into four groups with an equal number of cases and were then treated with one of the following dosages: 60 mg/kg for 1 day; 60 mg/kg daily for 2 days; 60 mg/kg daily for 3 days; and 30 mg/kg daily for 6 days.

The assessment of **para**sitological cure was based on the quantitative oogram technique through rectal mucosa biopsies which were undertaken prior to, as well as, 1, 2, 4 and 6 months post-treatment. Concurrently, stool examinations according to the qualitative Hoffman, Pons & Janer (HPJ) and the quantitative Kato-Katz (K-K) methods were also performed.

The best tolerability was observed with 30 mg/kg daily for 6 days whereas the highest incidence of side-effects (mainly dizziness and nausea) was found with 60 mg/kg daily for 3 days. No serious adverse drug reaction has occurred.

The achieved cure rates were: 25% with 60 mg/kg for 1 day; 60% with 60 mg/kg daily for 2 days; 89.5% with 60 mg/kg daily for 3 days; and 90% with 30 mg/kg daily for 6 days. At the same time there has been a downfall of 64%, 73%, 87% and 84% respectively, in the median number of viable **S. mansoni** ova per gram of tissue. Thus, a very clear direct correlation between dose and effect could be seen.

The corresponding cure rates according to stool examinations by HPJ were 39%, 80%, 100% and 95%; by K-K 89%, 100%, 100% and 100%. This discrepancy in results amongst the three parasitological methods is certainly due to their unequal accuracy. In fact, when the number of viable eggs per gram of tissue fell below 5,000 the difference in the percentage of false negative findings between HPJ (28%) and K-K (80%) became significative. When this number dropped to less than 2,000 the percentage of false negative results obtained with HPJ (49%) turned significant in relation to the oogram as well.

In conclusion, it has been proven that praziquantel is a highly efficacious agent against **S. mansoni** infections. If administered at a total dose of 180 mg/kg divided into either 3 or 6 days, it yields a 90% cure rate. Possibly, one could reach 100% by increasing the total dose to 240 mg/kg. Furthermore, it was confirmed that the quantitative oogram technique is the most reliable parasitological method when evaluating the efficacy of new drugs in schistosomiasis mansoni.

KEY WORDS: Schistosomiasis; Praziquantel; Oogram.

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INTRODUCTION

Praziquantel, an isoquinoline-pyrazino derivative, is a broad spectrum antihelminthic agent[36] which has proven in experimental studies to be a remarkable active compound against all schistosome species pathogenic to man[18, 34, 45, 46], including **Schistosoma mansoni** strains resistant to oxamniquine[13, 14]. It has also shown to bear a quite safe toxicological profile[17].

In human schistosomiasis mansoni, using single oral doses from 40 to 60 mg/kg BWT, cure rates higher than 80% have been reported in Brazil in accordance with parasitological assessments by Kato-Katz stool examinations[10, 26, 40, 43]. Inclusively, double-blind trials applying the same parasitological methodology to compare the efficacy of praziquantel and oxamniquine failed to disclose significant differences between the two drugs[8, 15, 25, 39].

In a recent double-blind trial based on the quantitative oogram technique, we also found no significant difference in the efficacy of both drugs administered in a single dose, praziquantel 65 mg/kg and oxamniquine 18 mg/kg[12]. However, contrary to the previously reported findings, the achieved cure rates, 29% and 23% respectively, were rather low. These divergent results can be explained by the unequal accuracy of the methods applied for parasitological evaluation since, in the same trial, the correspondent cure rates according to stool examinations by Kato-Katz were 92% and 86%, and by Hoffman, Pons & Janer 50% for either drug. In addition, it has been demonstrated that a single dose of praziquantel induces in practically all patients a complete interruption of the egg-laying capacity of the parasites during the first four weeks following the treatment. Thereafter, in non-cured cases a sharp fall (83%) in the mean number of living ova per gram of tissue is maintained.

Nevertheless, an explanation for the divergence between the remarkable antischistosomal activity observed experimentally and the frequent recurrence rate we have found clinically with a single dose administration by means of the oogram, requires further considerations.

When schistosomes are exposed to praziquantel they exibit an almost instantaneous tetanic contraction of the musculature[32] and rapid structural damage to the syncytial tegument such as vacuolization and surface blebbing[6, 31]. Tegumental injury (basal vacuolization) can be induced by oxamniquine as well, but the lesion becomes apparent only after hours or days[27] whilst with praziquantel its onset is extremely rapid[32, 38]. As early as 15 minutes after treating mice, schistosomes were found contracted, paralysed and translocated from mesenteric veins to the liver and their tegument had developed typical lesions[29]. In vitro exposure to 30 μg/ml for 60 minutes resulted in severe injury[44]. Evidence for the rapidity of praziquantel action was equally denoted by the reduction of 63% in the titer of circulating worm antigen 72 hours following the treatment of mice infected with **S. mansoni**[47].

Nonetheless, using sub-curative doses in mice the worms recovered and seemed to be almost normal within three days, although the initial appearence of the tegumental lesion was indistinghishable from that caused by a curative dose[28, 37]. This indicates that complete recovery from the drug effect may take more than 24 hours. Actually, observations in mice revealled that on the 4th day subsequent to a single sub-curative dose, **S. mansoni** have either recovered or were dying in the liver[1, 30]. Thus, a certain degree of injury or of drug exposure can be tolerated by the parasites and can be repaired, but if the limit of such repairing capacity is exceeded then irreversible fatal damage occurs[3].

In fact, tegumental vacuolization itself is not lethal to schistosomes since parasites in mice have recovered completely within 3 days after a sub-curative dose. Death of worms occurred as soon as the injury became severe enough[2]. In this circumstance, neutrophils and eosinophils were seen attached to the schistosome surface already 4 hours after the drug administration. Soon afterwards the worms became fixed to the walls of blood vessels by fibroblasts. Invasion of schistosome's body by phagocyte cells was in full progress 14 hours post-treatment leading to the lysis of the parasite tissues within 7 days. Finally, the dead worms had disintegrated ra-

pidly, enclosed in a granulomatous reaction within two weeks after therapy[29]. The rapid aggregation of granulocytes around drug-affected parasites insinuates that immunological processes may be involved[1]. Indeed, exposure of previously disguised **S. mansoni** antigens as a result of contact with praziquantel has happened in vitro[19]. The drug engenders membrane instability which exposes antigenic determinants leading granulocytes to congregate onto the worm. The partial destruction of the tegument opens doors for entry of phagocytic cells that then lyse the schistosome tissues[1]. In addition, the release of antigenic component from injuried parasite tegument may not only sensitize the host but possibly confer some degree of resistance to subsequent reinfection[44].

Consequently, the main question rests in the definition of the optimal praziquantel concentration and duration of exposure in vivo, which is necessary to inflict irreversible fatal damage to the worms.

In vitro, experiments have revealed that with concentrations of 3.2×10^{-6}M to 3.2×10^{-4}M of praziquantel the observed injury to the parasites was a time function of exposure to the drug, rather than of its concentration[4, 5, 6]. Apparently, the antischistosomal effect of praziquantel is not so entirely related to the absolute height of its maximal plasma level as to the length of exposure to the drug[2]. Praziquantel at a concentration of 0.6 μM produces a good chemotherapeutical effect, provided that the total period of exposure ranges from 6 to 10 hours[2].

In animals and man alike, following an oral intake, the drug reaching the liver via portal vein is extensively metabolized at a fast rate so that within 1 hour only 5 to 7% are still unmetabolized praziquantel (the biologically active principle) and its half-life is just 90 minutes[28]. This first-pass effect, which varies from individual to individual, is more effective in smaller doses than in larger ones[28]. Peak serum concentration of unchanged praziquantel, 4.1 μM, is reached in about 2 hours and may prevail for approximately 4 hours after an oral dose of 50 mg/kg, 20% (0.8 μM) being the active protein unbound fraction[28].

Therefore, the effectively available drug is only a small percentage of the total administered dose and lasts for a relatively short time.

Actually, the same dose has been more effective in killing late rather than early developmental stages of **S. mansoni** in vivo, but no such difference in susceptibility was observed in vitro. This apparent resistance might result from these immature forms found in the peripheral systemic circulation being exposed to lower concentrations of praziquantel than the mature parasites located in the liver and mesenteric veins[44].

The drug bioavailability, however, can be improved by changing its dosage schedule. In mice the total amount of praziquantel required per os to produce a reduction of 95% in the number of parasites could be decreased by more than 70% by administering multiple doses (10 x 18.5 mg/kg) instead of only one (1 x 685 mg/kg)[18]. A single oral dose of 50 mg/kg diminished the number of **S. mansoni** in mice by 12% whilst 5 doses given at daily intervals killed 82% of the worms[18].

Based upon: (a) our previous therapeutical trial[12] in which it has been proven, through serial rectal mucosa biopsies, that a single dose of praziquantel leads to a marked decrease of the worm burden in human **S. mansoni** infection; (b) the experimental evidence that, depending on the concentration and time of exposure, this drug is able to cause the death of this parasite; we have designed the present clinical trial to investigate whether dose regimens other than a single day treatment would yield higher cure rates.

PATIENTS AND METHODS

Children, elderly patients, pregnant or lactating women, and those cases having concomitant acute or serious chronic diseases, severe anemia or nutritional deficiency, cardiac, pulmonar, hepatic or renal insufficiency, were excluded from the trial.

A total of 80 patients free from previous specific therapy, 41% male and 59% female, from 15 to 55 years old with a mean age of 27, weighing 57.8 kg in the average, with chronic intestinal (64%) or hepatointestinal (36%) schistosomiasis mansoni had voluntarity been enrolled in the trial. All of them were living in Belo Horizonte, state capital of Minas Gerais, away from endemic areas.

The worm burden as measured by the number of viable eggs per gram of tissue taken by rectal mucosa biopsy ranged from 1,173 up til 12,875 with a mean of 3,410 and a median of 3,025. Nine percent had more than 5,000, 45% from 3,001 to 5,000, 32% from 2,001 to 3,000 and 14% from 1,001 to 2,000. These figures shape a skewed distribution curve with most of the patients, as it would be expected, lodging a worm burden lower than the mean. Consequently, non-parametric tests (chi-square and Fisher exact probability tests) were applied for the statistical analysis of the results.

The patients were treated at an out-patient clinic and instructed not to get in touch with any focus of schistosoma infection at least during the six-month period subsequent to the therapy. Following a randomized distribution they were allocated into four groups having an equal number of cases and were then treated with different dose regimens: 60 mg/kg for 1 day; 60 mg/kg daily for 2 days; 60 mg/kg daily for 3 days; and 30 mg/kg daily for 6 days. As shown in Table I the four groups were homogeneous in regard to the relevant factors that could influence the therapeutical response, particularly the age range of the patients and the intensity of their worm burden.

TABLE I

Distribution of patients with schistosomiasis mansoni in accordance with the dose regimen of praziquantel, sex, age, body weight, clinical form of the disease and worm burden based on the quantitative oogram.

Treated patients		20	20	20	20
Praziquantel dosage		60 mg/kg 1 day	60 mg/kg daily 2 days	60 mg/kg daily 3 days	30 mg/kg daily 6 days
Sex	Male	45%	20%	50%	50%
	Female	55%	80%	50%	50%
Age (Years)	Mean	30	24	27	26
	Range	15 — 55	15 — 45	18 — 44	18 — 40
Weight (kg)	Mean	59.8	55.8	56.0	59.6
	Range	42 — 79	38 — 79	41 — 66	42 — 84
Clinical form	Intestinal	65%	70%	65%	55%
	Hepatointestinal	35%	30%	35%	45%
Number of viable eggs/g of tissue	Mean	3340	3640	3382	3278
	Median	3025	2463	3195	3315
	Range	1823 — 6879	1653 — 12875	1910 — 5657	1173 — 5333
	> 5000	10%	15%	5%	5%
	3001 — 5000	50%	15%	50%	65%
	2001 — 3000	30%	50%	35%	15%
	1001 — 2000	10%	20%	10%	15%

Praziquantel was presented in tablet form containing 300 mg. The total daily dose was administered per os, in the morning, divided into two intakes 4 hours apart, under nurses' close supervision. During the days of treatment the patients remained under clinical observation for a few hours after the drug administration in order to look for any occurrence of adverse reactions.

Prior to the therapy all patients underwent a thorough physical examination and were submitted to rectal mucosa biopsy in order to have a quantitative oogram performed[9, 11], as well as, to stool examinations by both the qualitative Hoffman, Pons & Janer[20] and the quantitative Kato-Katz[24] methods. A kit (vermi-fec®) from Boehringer Mannheim was used for the latter examination and for each patient the result was expressed by the arithmetic mean of three slides. All these parasitological examinations were repeated on the same day, at the end of the 1st., 2nd., 4th. and 6th. month post-treatment.

RESULTS

The occurrence of untoward effects is demonstrated in Table II. The best tolerated dose regimen was 30 mg/kg daily for 6 days whereas the higher incidence of complaints was associated with the administration of 60 mg/kg daily for 3 days. Actually, the respective frequencies

refering to: total incidence of side-effects (40% vs. 80%); dizziness (15% vs. 65%); and nausea (15% vs. 55%). were significantly ($p < 0.05$) lower with the former dosage. The inverse holding true for light severity of symptoms (67% vs. 32%). On the other hand, there was neither any significant difference in regard to overall tolerability amongst the four groups nor any occurrence of serious adverse drug reaction. With the majority of the patients the side-effects appeared within the first four hours (98%) subsequent to the drug intake, did not last longer than 12 hours (75%), and their intensity was light to moderate (94%).

TABLE II

Occurrence (%) of side-effects with different dose regimens of praziquantel

Evaluated patients		20	20	20	20
Praziquantel dosage		60 mg/kg 1 day	60 mg/kg daily 2 days	60 mg/kg daily 3 days	30 mg/kg daily 6 days
Total incidence		40.0	65.0	75.0	35.0
Intensity	Light	37.0	35.0	32.0	63.0
	Moderate	52.0	62.0	63.5	31.0
	Severe	11.0	3.0	4.5	6.0
Dizziness		15.0	45.0	65.0	15.0
Nausea		20.0	20.0	55.0	15.0
General malaise		20.0	20.0	10.0	5.0
Heart-burn		15.0	—	15.0	20.0
Headache		5.0	15.0	25.0	5.0
Drowsiness		5.0	—	35.0	10.0
Abdominal pain		—	25.0	10.0	—
Vomiting		—	—	5.0	—
Skin rash		—	5.0	—	—
Fever		—	—	5.0	—
Anorexia		—	—	—	5.0
Overall tolerability	Good	65.0	55.0	40.0	75.0
	Regular	30.0	40.0	50.0	20.0
	Poor	5.0	5.0	10.0	5.0

The assessment of therapeutical efficacy in accordance with the quantitative oogram technique, as shown in Table III, revealed the following cure rates, i. e., no single viable **S. mansoni** egg in all rectal mucosa biopsies performed during the 6-month parasitological follow-up: 25% with 60 mg/kg for 1 day; 60% with 60 mg/kg daily for 2 days; 89.5% with 60 mg/kg daily for 3 days; and 90% with 30 mg/kg daily for 6 days. The last two regimens did not differ one from the other, but there had been a highly significant difference between either one and 60 mg/kg daily for 2 days ($p < 0.01$) or 60 mg/kg for 1 day ($p < 0.001$). Inclusively these two last dosages also differed significantly ($p < 0.01$) one from the other. Furthermore, a marked reduction in the median number of viable eggs per gram of tissue in non-cured patients was observed in all four groups. However, this reduction was more noticeable with either 60 mg/kg daily for 3 days (minus 87%) or 30 mg/kg daily for 6 days (minus 84%) and less with 60 mg/kg for 1 day (minus 64%).

TABLE III

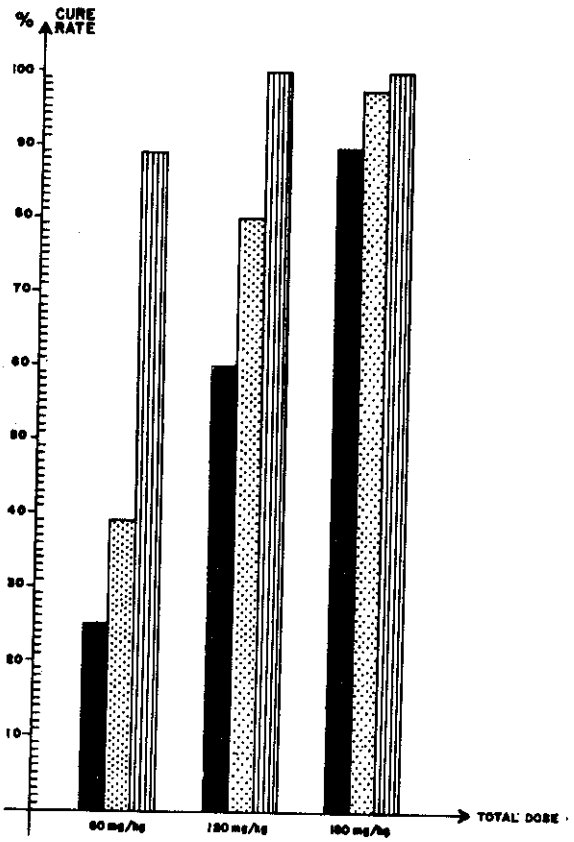
Therapeutical efficacy of different dose regimens of praziquantel according to the quantitative oogram performed 1, 2, 4 and 6 months after treatment

Praziquantel dosage		60 mg/kg 1 day	60 mg/kg daily 2 days	60 mg/kg daily 3 days	30 mg/kg daily 6 days
Controlled patients		20	20	19	20
Cured patients		5 (25%)	12 (60%)	17 (89,5%)	18 (90%)
Median number of viable eggs/g of tissue in non-cured cases	Before treatment	3023	2662	4191	3348
	After treatment	1099	715	562	542
	Reduction	63.6%	73.1%	86.6%	83.8%

Considering the cure rates in relation to the stool examinations by Hoffman, Pons & Janer and Kato-Katz methods, the corresponding figures were: 39% and 89% with 60 mg/kg for 1 day; 80% and 100% with 60 mg/kg daily for 2 days; 100% and 100% with 60 mg/kg daily for 3 days; 95% and 100% with 30 mg/kg daily for 6 days. When confronted with the oogram findings these percentages are quite divergent particularly the data pertaining to Kato-Katz as seen in Table IV and Graphic 1.

TABLE IV
Comparison of cure rates attained according to the quantitative oogram and stool examinations by Hoffman, Pons & Janer (HPJ) and Kato-Katz (K-K) methods

Praziquantel dosage			60 mg kg 1 day	60 mg kg daily 2 days	60 mg kg daily 3 days	30 mg kg daily 6 days
Cure rate	Quantitative oogram		25.0%	60.0%	89.5%	90.0%
	Stool examination	HPJ	39.0%	80.0%	100.0%	95.0%
		K-K	89.0%	100.0%	100.0%	100.0%



Graphic 1 — Correlation between the cure rates of variable doses of praziquantel and different parasitological methods (■ oogram, ▨ Hoffman, Pons & Janer, ▥ Kato-Katz).

The discrepancy amongst the three parasitological methods derives from their variable accuracy. In fact, when the number of viable eggs per gram of tissue fell below 2,000 the difference (20%) in the positivity by Hoffman, Pons & Janer in relation to the oogram became statistically significant ($p < 0.01$). Moreover, the difference (43%) between the positivity of Kato-Katz and Hoffman, Pons & Janer already turned significative when that number was inferior to 5,000. These results are displayed in Table V and Graphic 2.

TABLE V
Correlation between the quantitative oogram findings and the positivity of stool examinations by Hoffman, Pons & Janer (HPJ) and Kato-Katz (K-K) methods

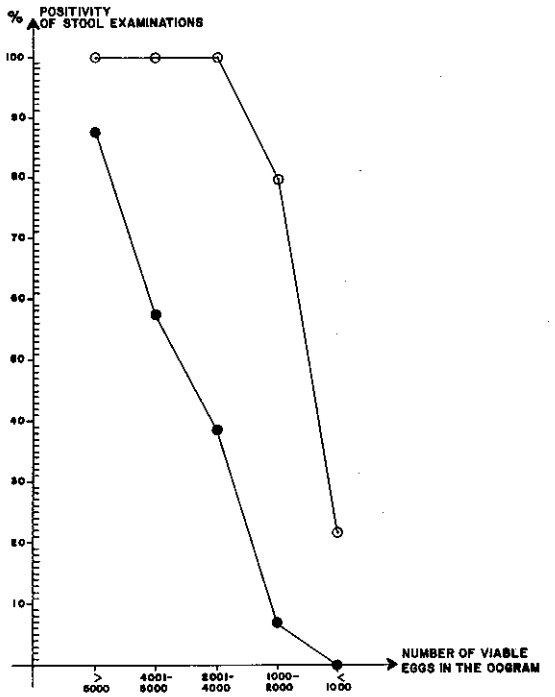
Number of viable eggs/g of tissue	Nº of exams	Positive stool examinations	
		HPJ (%)	K-K (%)
> 5000	8	100.0	87.5
4001 — 5000	14	100.0	57.1
2001 — 4000	52	100.0	38.5
1000 — 2000	44	79.5	6.8
< 1000	42	21.4	0.0
TOTAL	160	73.7	23.7

DISCUSSION

Praziquantel, a novel schistosomicidal agent which nowadays is regarded as the first choice medication for human schistosomiasis[22, 23, 33], has proven according to the quantitative oogram technique, to be highly efficatious in **S. mansoni** infection if used in an adequate dose regimen.

In this trial, when administering 60 mg/kg for 1 day the cure rate was just 25%, however

it rose up to 90% when the same daily dose was taken for 3 consecutive days. Parallelly, there had been a corresponding downfall of 64% and 87% in the median number of **S. mansoni** ova per gram of feces in non-cured patients, confirming both the superior efficacy of the latter dosage and the sensitivity of the applied parasitological methodology.



GRAPHIC 2 - CORRELATION BETWEEN THE QUANTITATIVE OOGRAM FINDINGS AND THE POSITIVITY OF THE STOOL EXAMINATIONS BY HOFFMAN, PONS & JANER (O) AND KATO-KATZ (●) METHODS

Graphic 2 — Correlation between the quantitative oogram findings and the positivity of the stool examinations by Hoffman, Pons & Janer (⊗) and Kato-Katz (●) methods.

In the treatment of other human trematodiases with praziquantel, analogous therapeutical responses were reported[21]: in **Opisthorchis viverrini** infections cure rates of 44% or 88% were achieved with 1 or 2 days administration of 25 mg/kg daily and with 30 mg/kg daily for 3 days 91% was reached; with infections caused by **Clonorchis sinensis,** another liver fluke, 50 mg/kg daily yielded 47% cure rate if given for 1 day but 80% if given for 2 days, yet more 75 mg/kg for 1 day resulted in 81% cure rate and 100% when this daily dose was extended for 2 days; in **Paragonimus westermani** infections, a lung fluke, 75 mg/kg daily taken during 1, 2 or 3 days ensued cure rates of 71%, 86% and 100%, respectively.

The reason for attaining parasitological cure in some patients with just a single day treatment whereas in others, solely if the drug administration is prolonged for two or more days, most probably relies on the distinct patterns of individual pharmacokinetics. Those who convert praziquantel quickly and extensively into hydroxylated and conjugated metabolites, that are inactive or considerably less potent, will require higher doses and/or lengthned therapeutical courses than those who do not eliminate the drug from plasma so efficiently. In this context, with a single dose of 30 mg/kg a relatively high cure rate (76.7%) has been obtained in hepatosplenic schistosomiasis mansoni[10] in comparison to the quite low figure (33.3%) attained in intestinal or hepatointestinal cases[35], using the same parasitological control of cure (Kato-Katz stool examination). Perhaps, patients presenting hepatosplenic forms metabolize praziquantel at a slower pace or the drug by-passes the liver via portosystemic shunts allowing higher plasma concentrations of the active principle for longer periods of time.

Certainly, as it was demonstrated in vivo, the antiparasitic efficacy of praziquantel against **S. mansoni** is due to its ability to produce tegumental damage, an effect that depends on the drug concentration and on the duration of the parasite exposure to it[44]. Both are a function of the peak level and time course of unmetabolized praziquantel in the serum which are known to vary greatly from patient to patient[28, 42]. Therefore, ideally an individual dose regimen should be established for every patient based on the monitoring of the drug serum concentration, but in practice this is unfeasible. Possibly, a simple way to secure a cure rate very close to 100% in all case would have to consist of augmenting the total dose up to 240 mg/kg (either 40 mg/kg daily for 6 days or 80 mg/kg daily for 3 days). Actually, total doses of 1,000 mg/kg or even higher (100 mg/kg daily during 10 days[7], 50 mg/kg daily during 3 weeks[41], 75 mg/kg daily during 15 days[7]) have been well tolerated by patients with neurocysticercosis.

Another relevant aspect to be considered is the disparity amongst the results accomplished with the different procedures employed for assessment of parasitological cure. In fact, the accuracy of the stool examination methods have varied in direct correlation with the number of viable ova per gram of tissue in the oogram: below 5,000 the Kato-Katz already showed a significant lower sensitivity in comparison to the Hoffman, Pons & Janer, which for its turn was significantly inferior to the oogram when that number was less than 2,000. In connection to this, we have already commented on similar findings achieved in a previous clinical trial[12]. Likewise, other investigators have demonstrated the superiority of the rectal mucosa biopsy in proving the presence of schistosoma ova in respect to stool filtration and MIF concentration methods, which still yield more reliable results than a direct fecal smear[16]. Furthermore, they also have pointed out that the positivity of fecal examinations diminishes in direct correlation with the decrease in the number of viable eggs per 20 mm^2 of tissue in the biopsy[16].

In conclusion, it has been proven that a 90% cure rate can be attained in schistosomiasis mansoni with praziquantel when administering either 60 mg/kg daily during 3 days or 30 mg/kg daily during 6 days. The former dosage is more convenient but the latter has been associated with milder and lower incidence of untoward effects. The ideal dose regimen should be fixed individually by virtue of the variable intestinal absorption rate, extent of hepatic metabolization and plasma protein-binding capacity, main factors that influence the serum concentration of the unchanged praziquantel and its half-life. However, since it is unfeasible to establish a specific dosage for every patient, perhaps the administration of a total dose of 240 mg/kg divided into 3 or 6 days would lead to 100% cure rate.

Finally, it has been confirmed that the quantitative oogram technique is the most accurate method for assessing the therapeutical efficacy of antischistosomal agents in mansoni schistosomiasis so that it should be applied at the earliest phases of the clinical study of all new drugs.

RESUMO

Avaliação terapêutica de diferentes esquemas posológicos do praziquantel na esquistossomose mansônica, baseada na técnica do oograma quantitativo.

Uma pesquisa clínica compreendendo 80 pacientes de ambos os sexos, de 15 a 55 anos de idade, portadores de esquistossomose mansônica crônica, formas intestinal ou hepatintestinal, foi efetivada para avaliar a eficácia do praziquantel em diferentes esquemas posológicos.

Os pacientes foram distribuídos aleatoriamente em quatro grupos, com igual número de casos, sendo tratados com uma das seguintes dosagens: 60 mg/kg em um dia, 60 mg/kg diários por dois dias, 60 mg/kg diários por três dias e 30 mg/kg diários por seis dias.

A avaliação da cura parasitológica baseou-se na técnica do oograma quantitativo mediante biópsias da mucosa retal, realizadas antes, bem como um, dois, quatro e seis meses após o tratamento. Concomitantemente, efetuaram-se exames de fezes segundo os metódos qualitativo de Hoffman, Pons & Janer e quantitativo de Kato-Katz.

A melhor tolerabilidade foi verificada com 30 mg/kg diários durante seis dias, enquanto a maior incidência de efeitos colaterais, em especial tontura e náusea, ocorreu com 60 mg/kg diários durante três dias. Nenhuma reação adversa grave foi observada com o medicamento.

Alcançaram-se os seguintes índices de cura: 25% com 60 mg/kg em um dia; 60% com 60 mg/kg diários por dois dias; 89,5% com 60 mg/kg diários por três dias e 90% com 30 mg/kg diários por seis dias. Paralelamente houve uma queda de, respectivamente, 64%, 73%, 87% e 84% no número mediano de ovos viáveis de **S. mansoni** por grama de tecido. Assim, constatou-se uma correlação direta entre dose e efeito.

Os correspondentes índices de cura, segundo os exames de fezes, foram 39%, 80%, 100% e 95% com o método de Hoffman, Pons & Janer e com o de Kato-Katz 89%, 100%, 100% e 100%.

A discrepância encontrada nos resultados entre os três métodos parasitológicos decorre da desigualdade na precisão dos mesmos. Quando o número de ovos viáveis por grama de tecido caiu abaixo de 5000, a diferença no percentual de achados falso-negativos entre Hoffmann, Pons & Janer (28%) e Kato-Katz (80%) tornou-se significativa. Quando esse número baixou para menos de 2000, a percentagem de resultados falso-negativos encontrada com Hoffman, Pons & Janer (49%) também passou a ser significativa em relação ao oograma.

Em conclusão, ficou provado que o praziquantel é altamente eficaz na infecção pelo **S. mansoni.** Administrado na dose total de 180 mg/kg, dividida em três ou seis dias, o praziquantel proporcionou 90% de cura. Provavelmente, poderia atingir 100% se a dose total fosse aumentada para 240 mg/kg. Ademais, confirmou-se que o oograma quantitativo consiste no método mais fidedigno para avaliar a eficácia terapêutica de novas drogas na esquistossomose mansônica.

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