Tropenmedizin und Parasitologie

Organ der
Deutschen Tropenmedizinischen
Gesellschaft

1981
Georg Thieme Verlag
Stuttgart · New York

32. Band 1981

143 Abbildungen
in 206 Einzeldarstellungen
und 113 Tabellen

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Tropenmed. Parasit. 32 (1981) 234–236

Praziquantel in Clonorchiasis and Opisthorchiasis

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Summary

A single stool examination revealed pathogenic intestinal parasites in 462 (58%) of 796 vietnamese and cambodian refugees. 56 (7.0%) were infected with Clonorchis sinensis and/or Opisthorchis viverrini.
These patients received Praziquantel in a dosage of 20 mg/kg bwt. p.day on 3 consecutive days. Parasitological controls were completed after 12 months. No further excretion of eggs could be detected in 88% of the patients.
Concurrent infections with other trematodes and cestodes were also cured. Nematode infections remained uninfluenced. No change of haematological and biochemical parameters could be observed during therapy.
Diarrhea and epigastric pain were common side effects, which are probably not effects of the drug itself. They rather seem to be due to the release of parasitic antigens. This is also indicated by a further increase of circulating Ig E after therapy.

Praziquantel in der Behandlung von Clonorchiasis und Opisthorchiasis

Eine einmalige Stuhluntersuchung ergab bei 462 (58%) von 796 vietnamesischen und kambodschanischen Flüchtlingen einen Befall mit pathogenen Intestinalparasiten. 56 (7.0%) waren mit Clonorchis sinensis und/oder Opisthorchis viverrini infiziert. Diese Patienten erhielten Praziquantel in einer Dosierung von 20 mg/kg KG tgl. über 3 Tage. Nachkontrollen wurden bis 12 Monate nach Behandlung durchgeführt und zeigten bei 88% der Patienten eine vollständige Heilung. Begleitinfektionen mit anderen Trematoden und mit Zestoden waren ebenfalls nicht mehr nachweisbar, während gleichzeitiger Nematodenbefall unbeeinflußt blieb. Veränderungen hämatologischer und biochemischer Parameter wurden während der Behandlung nicht beobachtet.
Diarrhoe und Oberbauchbeschwerden waren die häufigsten Nebenwirkungen. Diese scheinen weniger direkte Wirkungen des Praziquantel zu sein, sondern eher die Folge der Freisetzung von Wurmantigenen. Dem entspricht auch ein weiterer Anstieg des zirkulierenden Ig E nach Therapie.

Introduction

The therapy of infestations with liverflukes used to be difficult: most of the drugs tested were either to toxic or of poor effect (Rim et al. 1975). Niclofolan showed the best efficacy compared to toxicity; but cure rate is still unsatisfactory and during therapy there are frequent side effects, especially biochemical signs of liver damage. Praziquantel, a newly developed compound, is now well known for its excellent effect on cestodes and schistosomes (Seubert et al. 1977). It is well tolerated and has a low toxicity (Leopold et al. 1978). Rim (1979) first reported promising results of Praziquantel in the treatment of Clonorchiasis with an efficacy superior to Niclofolan.

Patients and Methods

A single parasitological stool examination was routinely done in 796 vietnamese and cambodian refugees with methods previously described (Löscher et al. 1980). In 462 (58%) of the refugees pathogenic intestinal parasites were found. 56 persons (7.0%) passed eggs of *Clonorchis sinensis* and/or *Opisthorchis viverrini*. It is not possible to distinghish *C. sinensis* and *O. viverrini* by their eggs (Sadun 1955). In one of the heavily infected vietnamese patients a saline purgation during therapy revealed partly damaged adult flukes who could be determined as C. sinensis by their finely branched testes. Nevertheless, from an epidemiological point of view it is most probable, that some of the "*C. sinensis*" – diagnosed infections are actually caused by *O. viverrini* and that even in some cases there might be mixed infections (Sadun 1955, Wykoff et al. 1965).

The age of the 56 patients treated varied between 10 and 61 years (average 27 y.), 31 were male, 25 female.

In 42 patients there was an additional infection with other trematodes, cestodes and nematodes (Table 1). Praziquantel was given in a daily dosage of 20 mg per kilogramm body-weight (divided in 3 postprandial doses) on 3 consecutive days. All patients were hospitalized during therapy.

Tab. 1 Patients treated with Praziquantel: additional helminth infestations

56 Clonorchis sinensis/Opisthorchis viverrini	
14 single infections	
42 multiple infections:	
20	Trichuris trichiura
18	Hookworm
10	Ascaris lumbricoides
9	Strongyloides stercoralis
3	Hymenolepis nana
1	Fasciolopsis buski
1	Taenia saginata
1	Trichostrongylus spp.

Severity of infection was classified according to the number of eggs per gram of faeces (EPG) as an average of 3 examinations by the quantitative method of Stoll (1926). Parasitological controls with the MIFC method (Blagg et al. 1955) were done 3 days and 1, 2, 4, 12, 24 and 50 weeks after beginning of the treatment.

Routine parameters (haemogram, SGOT, SGPT, γ-GT, LDH, CK, alk. phosphatase, bilirubin, creatinine, urea, glucose, serum electrophoresis, Quick-test, PTT, urinanalysis) were controlled before, during and 1, 2, 4, and 24 weeks after therapy. Serum concentrations of Immunoglobulin E were determined by a Paper-Radio-Immuno-Sorbent-Test (Kjellman et al. 1976).

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Tab. 2 No. of positive stool examinations before and after treatment with Praziquantel in 56 patients with Clonorchiasis/Opisthorchiasis

EPG	before	3rd	1w	2w	3w	3m	6m	12m
> 30000	1	1	1	1^+	–	–	–	–
< 30000	7	4	1	2^+	0	0	0	0
< 10000	11	4	0	1^+	0	1^+	0	0
< 1000	37	9	3	2^+	0	0	0	0
Total:	56	18	5	6^+	0	1^+	0	0

+ = not further controlled, but treated once more

Results

Parasitological controls are summarized in Tab. 2: at the third day of therapy, excretion has already stopped in most cases – particularly in minor infections. In 18 patients, still passing eggs, there was a markedly reduced excretion with unfertilized eggs seen in a high percentage. 2 weeks after treatment, stool examination was still positive in 6 patients with C. sinensis/O. viverrini-infection; in 4 of them being temporarily negative after 1 week. These 6 patients were not further controlled, but treated once more.

One patient showed a renewed excretion of eggs, as late as 3 months after treatment.

In the remaining 49 patients no control (the last one after 12 months) revealed an output of eggs. The cure rate was therefore 88%.

The 7 patients, who were not cured during the first course, were treated once again, with a dosage of 3-times 25 mg Praziquantel per kg bwt. daily on 2 consecutive days. Controls have been negative in all patients so far (follow up 8–12 months).

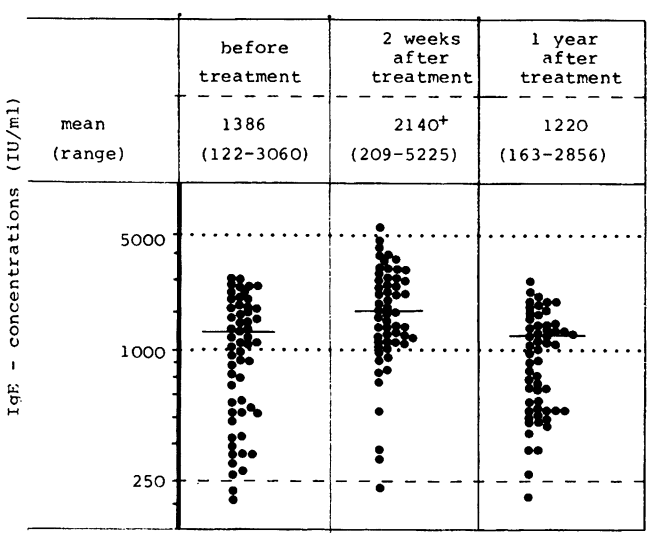

Fig. 1 Serum IgE concentrations in 56 patients with Clonorchiasis and Opisthorchiasis before and after treatment with Praziquantel. + = significant difference to levels before treatment (paired t-test $p < 0.01$)

Tab. 3 Side effects of Praziquantel (20 mg/kg bwt./daily/3 days)

No. of patients treated	56
epigastric pain	19
diarrhea	17
nausea	3
headache	1
dizziness	1
No. of patients with side effects	29 (52%)

All additional infections with large and small intestinal flukes and with cestodes (Table 1) were also cured. Infections with nematodes remained uninfluenced. Side effects (Table 3) were registered in 29 (52%) patients, with diarrhea and epigastric pain being the most common. No significant changes of biochemical or haematological parameters could be observed during therapy.

Serum IgE concentrations (Fig. 1) were raised (> 250 IU/ml) in 54 of 56 patients at the time of diagnosis (mean 1386 IU/ml, range 122–3060). Determination of IgE 2 weeks after therapy showed a further increase in all patients (mean increase 754 IU/ml, range 87–2722), which proved to be significant when pre- and post-treatment data (log transformed) were compared by paired t-test ($p < 0.01$). At the end of the follow up (12 months) the mean serum IgE level has decreased slightly below pre-treatment value (1220 IU/ml, range 163–2856), but without following such an uniform pattern again: the majority showed a clearcut decrease, whereas in some cases IgE levels were in the same range or even still higher compared to pretreatment values.

Discussion

At present, Praziquantel is the most promising drug in Clonorchiasis and Opisthorchiasis, with superior efficacy and low toxicity compared to all other drugs used. However, the optimal therapeutic regimen is still somewhat controversial: single dose therapy – desirable especially for mass treatment – results in low cure rates, even if high doses (50 mg/kg bwt.) are given (Rim et al. 1979). Better results are attained, if the regimen is extended and Praziquantel is administered in several doses.

With the rather low daily dosage of 20 mg/kg bwt. (divided in 3 daily doses), given over the prolonged period of 3 days, we obtained a high cure rate, equally to that of 75 mg/kg bwt. (divided in 3 doses) on a single day (Rim et al. 1979). The only 100%-cure rate could be achieved

in 15 patients with Clonorchiasis with 75 mg/kg bwt./daily for 2 days (Rim et al. 1979). This dosage was also used in our study for the repeated therapy without a failure so far. However, the optimal regimen has to be confirmed in larger comparative trials.

Increased serum IgE concentrations in Clonorchiasis and Opisthorchiasis have not been reported hitherto, but are not unexpected, since raised serum IgE levels have been found in a variety of helminth infestations, especially those with a tissue invading stage (Löscher et al. 1978). The further increase of circulating IgE after treatment with Praziquantel, which occurred in a completely uniform pattern, obviously demonstrates the release of helminth antigens leading to an augmented IgE-synthesis. This parallels the transient increase of circulating IgE in Schistosomiasis after treatment with Metrifonate and Hycanthone (Löscher et al. 1978).

Diarrhea and epigastric pain were common side effects in our patients. Similar observations have been made in trials of Praziquantel in Schistosomiasis and were designated such as "abdominal syndrome" (Wegner et al. 1980). These symptoms have not been registered in healthy volunteers, not even in high doses (Leopold et al. 1978). Therefore these "abdominal" side effects should not be considered as intrinsic effects of Praziquantel. It is more likely, that they are a consequence of the release of parasitic antigens during treatment. This is also indicated by the increase of circulating IgE after therapy. Moreover these symptoms would be consistent with immediate typ hypersensitivity reactions mediated by IgE-antibodies.

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