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Side effects of praziquantel in the treatment of *Schistosoma mansoni* in Maniema, Zaire

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Summary

In a small community in Maniema, Zaire, heavily infected with *Schistosoma mansoni*, direct observations were made of the side effects of praziquantel in the hours immediately after treatment. Intense abdominal discomfort and the production of bloody diarrhoea were observed in more than half of the treated population. These effects were seen both in children and in adults and the onset of the symptoms was registered within 30 min of treatment. The frequency of the side effects was correlated with the intensity of the infection. No satisfactory explanation could be given why the side effects in Maniema appear to be so intense compared with the general experience elsewhere.

Introduction

The use of praziquantel in population-based chemotherapy of *Schistosoma mansoni* in some villages in Eastern Zaire resulted in frequent and intense side effects (Polderman *et al.*, unpublished data). In these villages a modification of Bayer's protocol for investigational phase II-B clinical trials in schistosomiasis was used and side effects were registered at 24 hours after treatment. The immediate effects, occurring in the few hours immediately following treatment, tend to be underestimated when inquiries are made only then. In Maniema, the most intense side effects were seen shortly after treatment. The population rapidly developed quite a positive attitude towards this new drug and appears to accept the intense and immediate episodes of abdominal pains and bloody diarrhoea ("You can feel that this drug works"). Routine questioning, 24 hours after treatment showed a high rate of abdominal side effects. In our opinion, however, answers to these question—asked 24 hours after administration of the drug—are likely to underestimate the real dimensions of abdominal discomfort and the production of bloody diarrhoea as a side effect of treatment, in this particular area of Zaire. In the present work the course of events in the hours directly after praziquantel treatment have been closely observed and is described and discussed.

Methods and Population

The investigation was carried out in the village of Mususano, 40 km east of Kalima. 91 of a total population of about 100 persons participated in the study (49 males, 42 females). Three different stool specimens were received from 77 persons and two from 14 persons. With the exception of one 37-year-old woman, all persons excreted eggs at least once. This woman was not included in the subsequent observations. All samples were examined by two different microscopists, each counting eggs in Kato smears of 25 mg of faeces. All stool samples were collected in the week before treatment.

In the third stool sample, received and examined just before treatment, the presence of occult blood was recorded with the use of Hema-test^{R} tablets. On the day of treatment, all persons were called together at the dispensary and everybody was treated with a single dose of praziquantel, 40 mg/kg. The tablets were swallowed with a glass of water and the exact hour of the drug administration was recorded. Everybody was kept under observation until four hours after treatment. During these four hours events as physically observed by us were recorded. Moreover, before sending the patients home, a verbal inquiry was made into the side effects experienced by each of the patients.

Results

The age-specific geometric mean egg counts per g faeces (epg) are given in Table I.

In Table II the most prominent side effects are listed. The "entity" of "abdominal discomfort"

Table I—Age specific egg output per g faeces in Mususano

Age class	N	epg
1-5	9	173
6-10	12	1206
11-20	15	1581
21-40	38	775
41-60	17	886

N.B. The data refer to the arithmetic mean egg counts of 4 to 6 Kato smears prepared from 2 to 3 stool samples from each individual.

Table II—Side effects recorded during an observation period of four hours after treatment with praziquantel (40 mg/kg) in Mususano, Eastern Zaire

Type of Side effects	Frequency of side effects
Bloody diarrhoea	50 (56%)
Colicky abdominal pain without production of bloody diarrhoea	21 (23%)
vomiting	12 (13%)
"other complaints" (general discomfort and "vertigo")	14 (15%)
No. of persons treated and followed up for 4 hrs.	90

Table III—Bloody diarrhoea in males and females and in different age groups

	Age Groups				
Males	1-10	11-20	21-40	41-60	Total
Number of males producing a macroscopic bloody diarrhoea	6	2	14	5	27
Mean number of portions of bloody diarrhoea	1·7	2·5	1·6	2·4	1·8
N	10	5	21	13	49
Females					
Number of females producing a macroscopic bloody diarrhoea	7	4	8	3	23
Mean number of portions of bloody diarrhoea	2·7	2·5	2·6	3·5	2·8
N	11	10	16	4	41

Table IV—The occurrence of occult blood in the stools before treatment related to the production of bloody diarrhoea after treatment

HEMA^{R}-test reading before treatment	No. of persons with bloody diarrhoea after treatment	N
Negative	9	18
Weakly positive	24	43
Strongly positive	16	27

(except the production of bloody diarrhoea) was bound to be unreliable since all treated persons could observe each other's problems. Vomiting was observed in 10 patients (seven of whom were observed to vomit twice or thrice), whereas it was admitted by 11 patients on verbal inquiry. No further attention has been paid to the other complaints ("general discomfort" and "vertigo") because they are ill defined. The occurrence of diarrhoea which could be seen to be bloody was the most frequent and the most impressive observation. It was usually accompanied by an intense colicky abdominal pain. The numbers of bloody stools that were passed during the observation period of four hours varied from one to six. The appearance of the stools varied from mushy or thin diarrhoea streaked with blood to deep red liquid or mucoid mixtures of blood and faeces. The quantities of bloody stools could not be determined; they varied from small to fairly large (over 0·25l).

Regarding the reliability of the answers to our inquiry as compared to our personal observation, six persons said they had not passed bloody stools although we saw them being produced. In seven persons we did not observe the production although they claimed to have passed bloody stools. In the other 77 persons, our actual observations agreed with the patients' statements. Only the bloody stools which we observed are considered in tables III, IV and V.

Bloody stools were observed in both sexes and in all age groups (Table III). The mean numbers of bloody stools was higher in females than in males.

The first production of bloody diarrhoea or colicky abdominal pains were observed soon after swallowing praziquantel: within half an hour in 30% of the cases, and within one hour in more than two thirds of the cases in whom these effects were recorded.

It is conceivable that the high proportion of persons passing bloody diarrhoea following treatment is a reflection of similarly high rates of blood loss before treatment. Visually only one pre-treatment stool specimen contained some blood. According to the Hema-tests^{R} carried out just before treatment, 70 of 88 cases were positive. However, no correlation was observed between the Hematest^{R} reading before treatment and the presence and frequency of bloody diarrhoea after treatment (Table IV).

Among those who passed bloody stools, the pre-treatment egg counts were higher than among the others. This holds true for males and for females, for children and for adults ($p<0·05$; Rank test of Wilcoxon), see Table V.

Discussion and Conclusions

The observations on the frequent occurrence of abdominal discomfort and the production of several portions of bloody diarrhoea shortly after treatment were considered to merit publication because of their unexpected intensity and sudden onset. No serious and long-lasting or fatal complications were seen. On the day after treatment, two women who suffered from side effects as described above, still felt tired as a result of the intense abdominal pains they had experienced on the day of treatment but these had faded altogether by the next day. Short-lasting but often intense intestinal side effects, similar to these described in Mususano, have been seen frequently among approximately 2000 people who have been treated with praziquantel in the area up to the present.

It is remarkable that intense intestinal side effects as described here have not been reported earlier and seem to be unknown in the ± 25,000 well-monitored treatments that were given in Bayer's Multicentre trial (Wegner, personal communication). The intestinal side effects and production of bloody diarrhoea are correlated with the intensity of infection as expressed by egg excretion (Table V) but although the egg counts are high in Mususano, reports on others' experience with praziquantel also include treatments

Table V—The recorded side-effects in relation to the pre-treatment egg counts*

Type of Complaints	Males		Females	
	epg	n	epg	n
No complaints registered	554·3	(5)	141·6	(8)
Abdominal complaints or vomiting but no bloody diarrhoea observed	583·4	(17	845·8	(10)
Bloody diarrhoea observed	1494·0	(27)	1222·4	(22)
	Children		Adults	
No complaints registered	200·8	(4)	243·6	(10)
Abdominal complaints or vomiting but no bloody diarrhoea observed	495·0	(19)	886·0	(14)
Bloody diarrhoea observed	1414·9	(19)	1334·8	(30)

*The egg counts were calculated as the arithmetic means from six Kato counts done on three different stool samples produced on three different days in the week before treatment.

of heavily infected subjects (e.g. COUTINHO *et al.*, 1983). The level of egg excretion in itself cannot explain the unexpected frequency and intensity of side effects in Maniema.

Existing lesions of the intestinal wall due to whichever reason, are likely to bleed as a result of the purging effect and shifting calcium balance caused by the drug (JIM & TRIGGLE, 1979). Again it is unexpected that this effect would be so intense here, and almost absent elsewhere: hookworm and *Trichuris* infections are common but not particularly intense and *Entamoeba histolytica* is rare in the area.

It can be concluded that the side effects become manifest very soon after swallowing the drug, that they are more intense in Maniema than described elsewhere (e.g. KATZ *et al.*, 1981; MCMAHON, 1981; KARDAMAN & AMIN, 1983), and that they are particularly pronounced in heavy infections. The causes for the unusual intensity of the side effects remain obscure. Nutritional factors, concomitant other disease and characteristics of the local strain of the parasite could all be postulated as possible and partial explanations. In view of the important role of praziquantel in population-based chemotherapy, a better understanding of these causes is highly desirable.

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