The treatment of *Fasciolopsis buski* infection in children: a comparison of thiabendazole, mebendazole, levamisole, pyrantel pamoate, hexylresorcinol and tetrachloroethylene*

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Abstract

Four relatively new broad spectrum anthelmintics (thiabendazole, mebendazole, levamisole and pyrantel pamoate) were compared with two older anthelmintics, (tetrachloroethylene and hexylresorcinol) to treat heavy *Fasciolopis buski* infections in 17 children aged 4-13 years in hospital. Tetrachloroethylene was the most effective drug in these 17 children and another 49. Large numbers of worms were expelled and faecal egg counts were markedly reduced (99%). The mean number of worms per child was 122 with a range of 7 to 818. All the other anthelmintics tested were ineffective; no worms or only a few were expelled after treatment. However, the oral administration of tetrachloroethylene and hexylresorcinol were associated with severe anaphylactic reactions which were prevented by prior treatment with antihistamines.

Introduction

Fasciolopsis buski, the giant intestinal fluke of man and pigs, is found mainly in China and the Far-east (BARRETT-CONNOR, 1981; STOLL, 1947). Heavy infections are associated with diarrhoea, oedema and malnutrition, which may lead to severe prostration and sometimes death (BARLOW, 1925; SADUN & MAIPHOOM, 1953; VIRANUVATTI *et al.*, 1953). In the past the infection was treated with relatively toxic substances such as oil of chenopodium, beta naphthol, thymol, carbon tetrachloride and hexylresorcinol (BARLOW, 1925). Tetrachloroethylene (TCE) is an effective drug but can also produce unpleasant effects.

In the last 20 years, new "broad-spectrum" anthelmintics such as thiabendazole, mebendazole, pyrantel pamoate and levamisole have been developed which are highly effective against intestinal nematodes (KEYSTONE, 1982) and, in some instances, against cestodes (GOLDSMITH, 1980). However, the effect of these new agents on intestinal trematode infections has not apparently been reported. We evaluated the therapeutic effect of these new drugs against *F. buski* and compared their efficacy with two of the older drugs, tetrachloroethylene and hexylresorcinol.

Methods

Subjects

The study was conducted at the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh. 66 children aged 4 to 13 years were recruited from the village of Nandipara (one mile south of Dhaka) if their mothers had seen flukes in their child's faeces and if ova were observed by microscopical examination of direct faecal smear. 16 children had mild gastrointestinal symptoms while the remaining 50 were asymptomatic. Before admission to hospital for a week for chemotherapy, the children and their parents were told of the nature and purpose of the study and written consent was obtained. The protocol for this trial had been approved by the ethical review boards of Johns Hopkins University, Baltimore, USA, the Bangladesh Medical Research Council and the Cholera Research Laboratory (now ICDDR,B), Bangladesh.

Laboratory investigations

On admission to hospital, a physical examination was performed and specimens of blood and faeces were taken for laboratory investigations. To assess liver function, serum levels of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvate transaminase (GPT) were determined one day before treatment, and 3 and 30 days after treatment in 10 children who received tetrachloroethylene (TCE).

Parasitology

To determine the concentration of *F. buski* eggs in faeces, at least three separate faecal specimens were examined in duplicate on the day of admission and on fourth and seventh days after treatment. About 2 mg of faeces were placed in merthiolate-iodine-formalin (MIF) and emulsified and eggs counted as described by DUNN (1968) using a multiplication factor of 500 to give eggs per gram of faeces.

Treatment with anthelmintic agents

17 children were arranged in different treatment groups depending upon the availability of the drugs in hospital pharmacy: a random allocation was not possible due to a lack of hospital bed space. Thiabendazole (Mintezol, Merck, Sharp and Dohme, USA) was given to five children as an oral suspension (0·5 g/5 ml) at a dose of 0·25 ml/kg body-weight twice daily for two consecutive days. Mebendazole (Vermox, Janssen Pharmaceuticals, Belgium) was given to four children as a tablet chewed and swallowed with water at a dose of 100 mg/child, twice daily for two or three days. Pyrantel pamoate suspension (Combantrin, Pfizer Laboratories, USA) was administered to three children as one oral dose of 10 mg/kg body-weight. Levamisole (Ketrax, ICI, Bangladesh) was administered to four children as one oral dose in liquid form (80 mg for the 5 to 15 years age group) after a light meal. For five days after treatment all bowel movements were collected in a bucket and the contents were sieved through a tea strainer and the worms recovered and counted.

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Treatment with tetrachloroethylene (TCE) and hexylresorcinol.
The children were prepared by giving them a light, low-fat meal in the evening before treatment; the drug (TCE) was given in a soft gelatin capsule (Neam worm capsule, Parke Davis, USA) at a dose of 0·1 mg/kg body-weight on an empty stomach next morning. The child was kept as a non-ambulant patient on a cholera cot which has a central hole to facilitate collection of stool and the worms. Four to five hours after TCE administration, purging was induced by the oral administration of an aqueous suspension of 5 to 10 g of magnesium sulphate. To prevent dehydration, 5% dextrose saline solution was infused intravenously. All bowel movements were collected for the next five days and the number of flukes expelled was counted. The first four children treated with TCE developed an anaphylactic reaction. Therafter, as a preventive measure, antihistamine injections (15 mg promethazine HCL, Phenergen, May & Baker, Bangladesh) were given to all children immediately before administering TCE.

Hexylresorcinol was given to one child only at a dose of 0·1 mg/kg. The anaphylatic reaction was so severe that the treatment was not repeated again.

Results

Effects on worms and eggs

The effects of six different anthelmintics in 66 children are shown in Table I. None of the broad-spectrum anthelmintics (thiabendazole, mebendazole, levamisole, pyrantel pamoate) was effective against *F. buski*, except where the worm burden was large and then only a few worms were expelled. There was no significant drop in egg counts.

TCE was the most effective trematocidal drug tested. In the 49 children treated with TCE alone, the mean number of eggs/g of faeces before and after treatment were 52·3 and 0·6 respectively; in the 17 children given anthelmintic treatment before TCE, the corresponding figures were 48·5 and 0·8.

Hexylresorcinol was also effective; the only child who received the drug expelled 115 worms and the egg count dropped from 45·6 to 0·3.

By regression analysis, a moderate degree of correlation was found between the worm load and the concentration of eggs in MIF samples ($r = 0{\cdot}66$, $p<0{\cdot}05$, $n = 43$).

Side-effects

Although TCE and hexylresorcinol were both effective, they were very poorly tolerated by the children. Four of six children treated without the prior administration of antihistamine developed severe allergic reactions, three cases after treatment with TCE and one after treatment with hexylresorcinol. The reaction to the latter drug was so severe that further treatment with this agent was discontinued, so only one child received this drug. Shortly after the administration of TCE, the children developed toxic manifestations such as restlessness, vomiting, hurried respiration, salivation, abdominal pain, skin rash and confusion. Radial pulse was rapid (130/min), feeble, and the blood pressure was too low to be recorded with the sphygmomanometer. The reaction was stabilized by the intravenous infusion of 5% dextrose saline, an intramuscular antihistamine injection (promethazine hydrochloride, 15 mg) and bed rest. Thereafter each child was similarly pretreated with antihistamine and no further instances of allergic reaction were seen in 60 children who were subsequently treated with TCE.

The broad-spectrum anthelmintics were well tolerated by the children and no instances of adverse reaction were seen.

There was a transient elevation of the average serum GOT level ($\bar{x} \pm$ S.D., $n = 10$) three days after TCE administration (33·3 ± 20·0 international units to 59·3 ± 21·0 I.U.), the level however had returned to the pre-treatment value 30 days later (38·6 ± 11·0 I.U.). There was no appreciable change in the serum level of GPT before (26·0 ± 2·0 I.U.) and three days after (29·0 ± 10·0 I.U.) treatment with TCE.

Discussion

The four so-called "broad-spectrum" anthelmintics were not found to be effective against *F. buski*. These drugs are known to be most active against intestinal nematodes, although mebendazole is claimed to treat *Taenia* species (GOLDSMITH, 1980). The few trematodes expelled after treatment with thiabendazole and levamisole were from children who were subsequently found to have large worm burdens. In comparison, a single dose of TCE resulted in the expulsion of large numbers of worms and a 99% fall in egg counts. However, after the administration of TCE a significant number of the first six children treated developed a severe anaphylactic reaction which was prevented subsequently by prior administration of antihistamine. The severity of the reaction appeared to be related to the number of worms expelled by the child. The mechanism of this reaction is however unknown.

Tetrachloroethylene is a powerful irritant to tissues and causes chemical burns and ulceration (SWINYARD, 1975). After oral administration, TCE is not thought to be absorbed in any appreciable amount from the normal gastrointestinal tract and systemic

Table I—Results of the treatment of *Fasciolopsis buski* infections in 66 children using either four "broad spectrum" anthelmintics followed by tetrachloroethylene (TCE), hexylresorcinol or TCE alone

No. of children	Age (yrs) Mean ± SD	First treatment drug	No. of flukes expelled Mean (range)	Follow-up treatment drug	No. of flukes expelled Mean (range)
4	7·5 ± 2·5	mebendazole	2 (1-3)	TCE	73 (6-172)
5	8·6 ± 1·8	thiabendazole	7 (1-19)	TCE	100 (26-280)
4	9·2 ± 2·1	levamisole	32 (2-86)	TCE	203 (3-723)
3	7·2 ± 1·6	pyrantel pamoate	3 (1-8)	TCE	61 (25-103)
1	5·0	hexylresorcinol	115	none	—
49	8·15 ± 2·8	none	—	TCE	107 (20-210)

effects are rare, although liver damage may occur (*Pharmaceutical Codex*, 1979). However, the flukes are likely to damage the epithelium and protective mucus layer of the gut by their mode of attachment and feeding, perhaps making the gut mucosa more permeable to TCE which results in an anaphylactic reaction. However, in 10 of our subjects, the serum level of GPT was unaltered, while a transient elevation of GOT was seen before and after treatment with TCE. Another alternative cause of the anaphylatic reaction may be the sudden release and absorption of large amounts of antigen from the injured flukes. However, in contrast to our study, two studies have reported negligable side effects after treatment with TCE and hexylresorcinol (BROWN *et al.*, 1959; PLAUT *et al.*, 1969) though this may be due to the smaller number of flukes present in these subjects; mean burdens of 13 and 18 were recorded compared with our mean of 122. This suggests that heavily infected children are more prone to develop allergic reactions.

The mechanism of the anthelmintic action of TCE has not been established. TCE has been used to treat hookworm infections, where the drug was found to cause a reversible paralysis of the worms (GOLDSMITH, 1980). In *F. buski* infections, a similar mechanism may be responsible for their detachment from the mucosa. Resorcinol compounds are derivatives of phenols and possess toxic properties similar to TCE.

In our study, the child who developed severe reactions after taking hexylresorcinol might have been atypical, but for reason of safety this treatment was not used again. Praziquantel, a relatively safe drug, has been successfully used in the treatment of all species of schistosomes (DAVIS & WEGNER, 1979). However, only limited data is available for its use against *F. buski*, (see BUNNAG *et al.*, 1983) which is an intestinal rather than systemic infection, and further evaluation is needed.

We therefore conclude that the four broad-spectrum anthelminthic agents are not effective in the treatment of *F. buski* infections. Tetrachloroethylene, in the recommended doses is an effective drug, but because of its potential for causing anaphylactic reactions, especially where there are heavy worm burdens, the drug should be administered under clinical supervision, preferably with prior antihistamine treatment.

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