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Use of Benzimidazoles in Children Younger than 24 Months for the Treatment of Soil-Transmitted Helminthiasis

A Montresor¹, S Awasthi², and DWT Crompton³

¹Communicable Diseases Control, Prevention and Eradication, World Health Organization, 1211 Geneva 27, Switzerland ²Institute of Clinical Epidemiology, King George Medical College UP, India ³WHO Collaborating Centre for Soil-transmitted Helminthiasis, Graham Kerr Building, University of Glasgow, Glasgow G12 8QQ, Scotland

Abstract

Considerable experience and limited quantitative evidence indicate that infections with the soil-transmitted helminths *Ascaris lumbricoides* and *Trichuris trichiura* usually start to become established in children aged 12 months and older. Since children living in countries where the infections are endemic are at risk of morbidity, even those as young as 12 months may need to be considered for inclusion in public health programmes designed to reduce morbidity by means of regular anthelmintic chemotherapy. This situation raises the question as to whether such young children should be given anthelmintic drugs. Systems for the absorption, distribution, metabolism and elimination of drugs do not fully develop until children are in their second year of life. Current knowledge, however, reveals that the incidence of side effects linked to benzimidazole drugs in young children is likely to be the same as in older children. Accordingly, we conclude that albendazole and mebendazole may be used to treat children as young as 12 months if local circumstances show that relief from ascariasis and trichuriasis is justified.

Keywords

Benzimidazole derivatives; drug safety; infants; soil-transmitted helminthiasis

1 Introduction

The public health significance of soil-transmitted helminth infections is now widely accepted, especially in children. For example, in 1993 the World Development Report considered that these infections are a major cause of morbidity in children aged 5-14 years (World Bank, 1993). More recently, the Fifty-fourth World Health Assembly, meeting in Geneva in May 2001, urged Member States to take action to control morbidity due to soil-transmitted helminth infections by ensuring regular administration of anthelmintic drugs to school-age children living in endemic areas (World Health Assembly Resolution

Corresponding author: Dr Antonio Montresor, Strategy Development and Monitoring for Parasitic Diseases and Vector Control, Communicable Diseases Control, Prevention and Eradication, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland, Tel: (+41) 22 7912621, Fax: (+41) 22 7914869, montresora@who.int.

WHA54.19). Such conclusions and recommendations have arisen following decades of clinical work, the assessment of the results of numerous community investigations and the widespread use of anthelmintic drugs (Albonico et al., 1998; Stephenson et al., 2000).

In this article we explore three important primary questions regarding soil-transmitted helminth infections (*Ascaris lumbricoides* [roundworm], *Ancylostoma duodenale* and *Necator americanus* [hookworms] and *Trichuris trichiura* [whipworm]) in children under 24 months of age. Are these infections regularly found in this age group? If present, what is the severity of the morbidity caused by these infections in this age group? Should albendazole and mebendazole, benzimidazoles recommended by WHO for controlling morbidity due to these infections (WHO, 2000) be used to treat children in this age group? Satisfactory answers are needed to several supplementary questions. Have children under 24 months been excluded for reasons of safety? Have albendazole and mebendazole been tested in children younger than 24 months? If not, why not? Is there any experience of these drugs having been used in children under 24 months in a public health setting? What would be the outcome of an analysis of the risks of treatment to the health of the child to the benefits of relief from the burden of disease?

1.1 Soil-transmitted helminth infections in children under 24 months of age

Given the estimated scale of numbers of infections worldwide with soil-transmitted helminths (Crompton, 1999), a sizeable number of children under 24 months might be expected to be infected. Epidemiological surveys reveal that the prevalence and intensity of *A. lumbricoides* and *T. trichiura* rise rapidly during early childhood and tend to reach peak values in children around 10 years of age (Anderson et al., 1992). Infections with *A. duodenale* and *N. americanus* usually reach peak prevalence and intensity values in older children or young adults. Accordingly, since this review is focused on young children, most attention will be paid to infections with *A. lumbricoides* and *T. trichiura*.

The transmission of soil-transmitted helminths depends mainly on people acquiring infective stages from their contaminated environment. It is generally assumed that when children are about 12 months old they will begin crawling and toddling in and around the home and eating solid foods; both activities are likely to expose them to infective eggs of *A. lumbricoides* and *T. trichiura* (see Crompton, 1994). Investigations have shown that infections such as *A. lumbricoides* tend to be distributed in family clusters (Williams et al., 1974; Forrester et al., 1988) thereby increasing the chances of younger members becoming infected.

Despite the numbers of surveys undertaken to assess the distribution and abundance of soil-transmitted helminths in communities worldwide, comparatively few provide detailed information about the infections specifically in children under 24 months. Typically, results are expressed as prevalence or intensity in relation to host age, with host age being displayed in classes of 0-4 years, 5-9 years, 10-14 years and so on. It is not possible from such displays to extract the data about children under 24 months. Results from a few surveys based on stool examinations of this age group are shown in Table 1. The comments in these publications indicate that the infections are usually acquired in children older than 12

months (see Kan et al., 1989); the same observation occurs in the many papers whose results are expressed in the 0-4 year-old age class.

The reasonable conclusion from this brief discussion is that children over 12 months may need to be included in public health programmes designed to control morbidity due to soil-transmitted helminthiasis. There may be no case for including younger children; their treatment should be left to a physician on a case by case basis.

1.2 Morbidity due to soil-transmitted helminthiasis in children under 24 months of age

Much evidence has been obtained to show that the health and growth of pre-school and school-age children improves following appropriate anthelmintic treatment to reduce the intensity of soil-transmitted helminth infections (Crompton et al., 2002). Reduced food intake (Hadju et al., 1996), reduced iron status and the onset of iron deficiency anaemia (Stoltzfus et al., 1996), impaired nutritional status (Thein Hlaing et al., 1991), decreased physical fitness (Stephenson et al., 1993), interference with digestion and absorption (Carrera et al., 1984; Taren et al., 1987; Jalal et al., 1998) and reduced cognitive performance (Nokes et al., 1992; Stoltzfus et al., 2001) are known to accompany soil-transmitted helminthiasis. The evidence for this pathology is usually obtained by comparing infected with uninfected children and measuring improvements following anthelmintic treatment (Stephenson, 1987; Stoltzfus et al., 1997). The severity of the morbidity is directly related to the intensity of infection.

There is every reason to suppose that children under 24 months must experience similar morbidity if infected with soil-transmitted helminths. Few studies have been carried out with this age group, perhaps because of the reluctance of investigators to use anthelmintic drugs on young children unless constant medical supervision was available. Awasthi et al., (2001a), carried out a major investigation involving 2,010 children aged 6-12 months (mean 9.5 months) recruited from poor communities in Lucknow, India. In the follow-up examinations, significant improvement in weight gain was detected in children given doses of albendazole (600 mg powder) and vitamin A when measurements were made 18 months after the intervention. Treatment with a placebo (calcium powder) and vitamin A was not accompanied by this effect. In an earlier pilot study in the same area, involving children under 12 months at the start, Awasthi et al., (1995) had compared the growth of 85 such children given albendazole (400 mg in syrup form) and vitamin A with that of 54 similar untreated children and had found significant growth improvements in those who had been dewormed ($p < 0.01$).

Several other studies have included children under 24 months and have attempted to evaluate the impact of soil-transmitted helminthiasis on their health (see Pamba et al., 1987; Awasthi et al., 2001b; Tanumihardjo et al., 1996; Kloetzel et al., 1982). The results are not always conclusive; improvements are found in some cases and benzimidazole drugs appear to be well tolerated. The life-threatening consequences of infection with *A. lumbricoides* such as intestinal obstruction should not be overlooked when the health of young children in relation to this infection is under review (Crompton, 1994). Fewer worms may cause an obstruction in a child of 12 months as compared with one of 10 years.

1.3 Safety of benzimidazole compounds in children under 24 months

The discussion so far is leading to the view that there is a reasonable case for including children as young as 12 months in community programmes designed to control morbidity due to soil-transmitted helminthiasis by means of benzimidazole compounds. In this case, the correct dose of WHO-recommended albendazole or mebendazole would be the relevant control measure and the drugs must be known to be of good quality. However, despite the perceived benefits of relieving young children from the burden of soil-transmitted helminthiasis, parents, programme managers and health workers must be convinced that such drugs are 'safe' with the minimum occurrence of transient side-effects.

The treatment of young children with drugs presents specific problems since drug absorption, distribution and metabolism tend to be different in this age group compared with older children and adults (O'Flaherty et al., 1994). Accordingly, new drugs are not routinely tested in children under 24 months with the result that drug manufacturers may omit or exclude them from prescribing instructions. The European Commission estimates that over half of the medicinal products currently used on European children have never been specifically evaluated for use in children under 24 months (European Commission, 2002). Children living in developing countries may be excluded from prescribing information because their inclusion would have little commercial significance in the pharmaceutical market (Troullier, 2000).

1.4 Pharmacokinetics of benzimidazole compounds in children

Pharmacokinetics for any drug in young children differ from those in adults for a variety of factors linked to the immaturity of the systems responsible for drug absorption, distribution, metabolism and elimination. A simple dosage adjustment such as correcting doses according to weight or to body surface area is not sufficient to guarantee appropriate therapeutic action and minimal side effects. However, in the case of benzimidazole compounds, the active ingredient does not need to be absorbed or metabolized by the liver in order to be effective against intestinal nematodes. On oral administration, it passes directly to the worms and kills them. Consequently, the reduced drug absorption and the weak liver metabolism of drugs in young children do not represent a problem in the case of benzimidazoles.

1.5 Drug absorption

Absorption is the translocation of a drug from its site of administration into the bloodstream. According to Milsap et al., (1994) the absorption of a drug administered orally depends on its physico-chemical properties and on a variety of factors in the patient (see Table 2). The available data indicates that in children aged 8 months and older, benzimidazole toxicity is not enhanced by the stage of development of factors involved in drug absorption (Table 2).

1.6 Drug distribution

After absorption, a drug may be distributed in both interstitial and cellular fluids. This distribution of most drugs is influenced by age-dependent factors (Besunder et al., 1988; Milsap et al., 1994). According to the available data summarized in Table 3, the risk of benzimidazole toxicity in children older than 12 months is not increased by the stage of development of the determinants of drug distribution.

1.7 Drug metabolism

The pathway for benzimidazole metabolism depends on oxidation by hepatic cytochrome P450. After birth, the cytochrome system matures rapidly (Ryan, 1993) but the rate by which different enzymes reach adult levels varies considerably (eg metabolism of caffeine reaches adult levels at about 6 months, while metabolism of midazolam may still be impaired in children approaching 3 years). Although children metabolize drugs at different rates from adults, in the case of benzimidazoles this seems to be a minor problem from the toxicological point of view, since these drugs are known to be well tolerated at high and prolonged dosages in laboratory animals (JECFA, 1989).

1.8 Drug elimination

The clearance of drugs from the blood usually occurs through two mechanisms: renal filtration which is reduced in neonates and infants and biliary excretion which performs similarly in little children as in adults (Jackson et al., 1998). In the case of benzimidazoles, most of the drug is not absorbed and is discharged directly in the faeces. Such drug that is absorbed is eliminated through the bile.

1.9 Experience of using albendazole and mebendazole in children under 24 months

A large amount of experience has been gained concerning the use of albendazole and mebendazole in children and adults of all ages. Both drugs act by selectively binding to nematode tubulin, inhibiting tubulin polymerase and so blocking the formation of microtubules essential for cell division (see Albonico et al., 1998). Since their introduction hundreds of millions of oral doses have been given to people of all ages resulting in the highly successful treatment of soil-transmitted helminth infections.

A summary of literature reports concerning the use of benzimidazoles in children under 24 months is presented in Table 4. In total, 17 articles report on the treatment of over 2,189 children. For 1,209 treatments reported in group A (Table 4), there was no mention of active investigation and no side-effects were documented. In the case of 979 treatments reported in group B, side-effects were actively searched for but were not found. The only report of side-effects concerns one episode of convulsion reported from Dubai (el Kalla, 1990). In this case the infant treated with mebendazole was 7 weeks old and the problem may have been caused by increased drug absorption (see Table 2). However, considering the fact that seizures continued for 2 days, a period beyond the drug elimination time and the fact that this symptom has not been reported as a side-effect of benzimidazoles, we suggest that the symptoms may not have been related to the mebendazole treatment.

The incidence of adverse effects in the treatment and control groups reported by Montresor et al., (2002) after investigation of 653 treatments with mebendazole (500mg) in 212 children aged under 24 month during a double-blind, placebo-controlled, randomized trial is presented in Table 5. No statistically significant difference was observed in the incidence rate of side effects in the two groups. The three reports of dysentery recorded in the treatment group were not likely to be related to the treatment since in two cases the episode was associated with fever starting before the drug administration. In one case dysentery occurred 6 days after the drug administration.

At an Informal Consultation convened by the World Health Organization in Geneva in April, 2002 to review the treatment of children under 24 months for soil-transmitted helminthiasis, information was provided by Dr J Horton and by Professor P Folb (personal communications to the authors based on presentations to a WHO Informal Consultation, Geneva, 2002) about the use of albendazole and mebendazole in this age group. Information about the safety profile of albendazole in children under 24 months, as determined from spontaneous reporting systems, fell within the expected pattern of events seen in older children and adults, namely a range of transient minor side-effects which are rarely reported (Horton, 2002 - personal communication) such effects, including epigastric pain, nausea, diarrhoea, vomiting and headache, disappear after 48 hours (Rossignol et al., 1984). Similar effects have been reported when mebendazole has been used to treat soil-transmitted helminthiasis (Albonico et al., 1998). Horton also pointed out that adverse events linked to albendazole use concerned high doses such as those given for the treatment of opportunistic infections in AIDS patients and not the doses used for the treatment of intestinal nematodes. Folb (2002 – personal communication), after a thorough scrutiny of published literature, found no reports of serious adverse events in young children, including those under 24 months, given the appropriate dose of either albendazole or mebendazole.

2 Conclusion

Since soil-transmitted helminth infections are widespread and begin to be established in children aged 12 months and since these infections are harmful to the development, growth and health of such children, there is a case for offering them anthelmintic treatment with WHO-recommended drugs of proven quality. Available evidence indicates that albendazole and mebendazole (benzimidazole compounds) may be used for treatment of soil-transmitted helminthiasis in children aged 12 months and older provided that the case for their use is established. The health benefits of treatment appear to override any risks associated with the correct administration of the drugs.

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Table 1

Summary of available epidemiological data on prevalence of soil-transmitted helminthiasis in children under 24 months

Country	Sample size	Age-range (Months)	Parasites *	Prevalence % 13-24 months	Reference
China	329	0-48	A / T / H	80 / 20 / 0	Yu et al., 1989
Sierra Leone	191	0-12	A	2	Wilson et al., 1991
Malaysia	4	0-12	A + T + H	25	Kan, 1993
Philippines	544	1-24	A + T	25-75	Cabrera et al., 1997
Nicaragua	372	0-24	A / T	23 / 12	Oberhelman, 1998
Laos	24	0-24	A / T / H	37 / 12 / 4	Phetsouvannh, 2001
Indonesia	30	6-60	A / T / H	73 / 63 / 6	Prihartono, 1986
Philippines	91	0-48	A / T / H	77 / 77 / 14	Cabrera et al., 1989
Malaysia	37	0-12	A + T + H	68	Mohammod et al., 1989
Sri Lanka	63	0-48	A / T / H	62 / 50 / 7	Ismail et al., 1993
Kenya	100	8-24	A / T / H	62 / 52 / 39	Pamba et al., 1987
Zaire	100	9-23	A / T / H	66 / 48 / 7	Mbendi et al., 1988
Brazil	8	12-23	A / T	NA	Barbieri et al., 1993
Tanzania	42	6-24	A / T / H	54 / 81 / 64	Albonico et al., 1994
Tanzania	317	6-24	A / T / H	49 / 69 / 41	Montresor et al., 2002

* A = *Ascaris lumbricoides* T = *Trichuris trichiura* H = Hookworms

Table 2

Patient factors affecting drug absorption and performance in children under 24 months

Factor	Role in drug absorption	Performance in children < 24 months	Increased risk benzimidazoles toxicity		Reference
			<12	<24	
Gastric and duodenal pH	Affects drug solubility and ionization	In children under 1 month Increased basal acid output resulting in increased drug absorption	Yes	No	Hyman, 1983
Gastric emptying times	Determines the rate and the extent of drug absorption	In children under 8 months Prolonged gastric emptying times results in increased drug absorption	Yes	No	Heimann, 1980
Surface area available for absorption	Determines the rate and the extent of drug absorption	Reduced * drug absorption in case of underlying diseases states (eg short bowel syndrome, diarrhoeal disease)	No	No	Parson, 1977
Bile salt pool size	Essential for absorption of lipid and lipid-soluble drugs	Reduced * in Infant compared to adults	No	No	Watkins, 1973
Bacterial colonisation	Important for hydrolysis of drug conjugates that are excreted in bile	Reduced * in Infant compared to adults	No	No	Yoshioka, 1983

* Reduced absorption does not represent a problem for benzimidazole activity

Table 3

Patient factors affecting drug distribution and their performance in children under 24 months

Factor	Role in drug distribution	Performance in children <24 months	Increased risk benzimidazoles toxicity		Reference
			<12	<24	
Protein binding	Drug transport in plasma	Normal adult levels reached at 10 –12 months	Yes	No	Ecobichon, 1973
Body compartments size	Relevant for the relationship between the amount of drug in the body and its plasma concentration	In order to achieve plasma and tissue concentration similar to the one in adult, higher doses per Kg body-weight must be given to infants	No	No	Boreus, 1978
Membrane permeability	Protects CNS from toxic effects	Permeability of the blood-brain barrier is similar to the one of adult since foetal period	No	No	Saunders, 1999

Table 4

Summary of experiences of anthelmintic in children under 24 months.

Group	Country	Sample size	Age-range (Months)	Drug given*	Side effects		Reference
					Investigated	Reported	
A	Indonesia	30	6-60	PP 10 mg/kg	No	No report	Prihartono, 1986
	Philippines	91	0-48	PP and O/PP	No	No report	Cabrera, 1989
	Malaysia	37	0-12	O/PP 15mg/kg	No	No report	Mohammod, 1989
	Sri Lanka	63	0-48	MBD 100 mg b.d. 3 days	No	No report	Ismail, 1993
	India	988	6-12	ALB 400 mg	No	No report	Awasthi, 2001b
B	Malawi	30	0-24	ALB 200 mg	Yes	No	Pugh, 1986
	Kenya	100	8-24	ALB 200 mg	Yes	No	Pamba, 1987
	Zaire	100	9-23	ALB 10 mg/kg	Yes	No	Mbendi, 1988
	Dubai	1	2	MBD 50 mg b.d. 3 days	Yes	Yes	el Kalla, 1990
	Brazil	8	12-23	ALB 200 mg	Yes	No	Barbieri, 1993
	Tanzania	42	6-24	MBD 250 mg	Yes	No	Albonico, 1994
	India	382	0-24	ALB 400 mg	Yes	No	Awasthi, 1995
	Tanzania	317	6-24	MBD 500 mg	Yes	No	Montresor, 2002

* MBD = mebendazole PP = pyrantel pamoate O/PP = oxantel +pyrantel pamoate ALB = albendazole

Group A Epidemiological data

Group B Treatment experiences with no active investigation of side effects.

Table 5

Incidence of adverse effects in mebendazole-treatment and placebo groups of children aged less than 24 months, in the 1-week after treatment. (Adapted from Montresor et al., 2002)

Adverse events	Mebendazole Treatment (n=317)		Placebo (n=336)	
	Number of episodes ¹	IR ²	Number of episodes ¹	IR ²
ARI-1 *	3	0.009	3	0.009
ARI-2 **	2	0.006	1	0.003
Cough	32	0.100	37	0.110
Difficult breathing	5	0.015	6	0.017
Diarrhoea	18	0.056	12	0.035
Dysentery	3	0.009	0	0
Fever	45	0.141	49	0.145
Seizure	0	0	0	0

¹ Incident episodes of side effects in the week following the treatment

² IR: incidence rate per treatment episode

* Acute Respiratory Illness-1: cough episode with one or more days of rapid or difficult breathing

** Acute Respiratory Illness-2: cough episode with one or more days of rapid or difficult breathing and one or more days of fever