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Is the Exclusion of Children under 24 Months from Anthelmintic Treatment Justifiable?

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Abstract

There are no reports documenting toxicity or adverse effects after treatment of children under 24 months of age with benzimidazole derivative and there is an urgent need to clarify this point in light of the potential detrimental effect that soil-transmitted helminthiasis have on this age group.

A total of 653 treatments (317 mebendazole 500 mg; 336 placebo) were administered to 212 children under 24 months of age as part of 1 year anthelmintic drug study conducted among pre-school age children in Tanzania. Data on fever, cough, diarrhoea, dysentery and acute respiratory illness were collected one week following the treatment.

No differences between the occurrence of adverse effects in the two groups were observed. In light of the potential nutritional benefit achieved by regular deworming in this young age group, the policy that excludes children under 24 months of age from treatment should be re-considered.

Keywords

Mebendazole; adverse effects; children under 2 years

Introduction

Children under 24 months of age who are infected with helminths are presently excluded from treatment with mebendazole and other anthelmintics (WHO 1995) on the basis of the prescribing information given by the producers of the drugs.

We investigated with the original producers and several national regulatory authorities the reasons for such exclusion and concluded that it is due to a lack of information on the treatment of this age group and not on any reports documenting, or suggesting, toxicity or adverse effects. On the other hand, the documented poor absorption of the drug by the

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The study has been conducted in Pemba, Zanzibar, United Republic of Tanzania from June 1996 to June 1997

gastrointestinal tract [Dawson and Watson 1985] and the report of only rare, mild and transient side effects in all the other age groups [WHO, 1996] were, in our view, good predictors for the absence of significant side effects in this age group. As suggested for other drugs by Trouiller *et al* [2000], the lack of information on children under 24 months of age results in large part from the limited commercial interest that young children in developing countries represent for pharmaceutical companies. In Pemba, the great majority of children under 24 months is already infected by soil-transmitted helminths [Stoltzfus *et al.* 2000] and this is probably the case in other endemic countries. In addition, the hypothesis that soil-transmitted helminthiasis in very young children could have a serious negative impact on motor development [Stoltzfus *et al.* 2001] and in nutrition due to the modulation of the immune response toward a Th2 type [Cooper *et al.* 2000], requires urgent clarification on the safety of anthelmintic treatment in this age group.

Method

The data presented in this report, were collected in year long double blind randomised trial conducted in Kengeja, Pemba Island, Zanzibar, United Republic of Tanzania from August 1996 to August 1997. Pre-school children were studied to determine the nutritional gain of deworming and/or iron supplementation in a hookworm and malaria endemic population. Details of the study methodology are reported elsewhere [Stoltzfus *et al.* 2001]. 614 children 6-59 months of age were identified by a census in the 451 households of Kengeja and invited to enter the trial. Parents of all children who participated in the study gave their informed consent. Each child in the study received chewable mebendazole 500 mg (or placebo) every three months and syrup containing 10 mg of iron as ferrous sulphate (or placebo) daily for 12 months in a 2 x 2 factorial design. Informed consent was obtained from children parents or guardian and the human experimentation guidelines of the US Department of Health and Human services were followed in the conduct of the clinical trial. The study received approval from the ethical committees of the Ministry of Health of Zanzibar, Johns Hopkins University and of the World Health Organization.

The age of each child was calculated from a formal birth certificate or from his or her "Road-to-Health Card". The data reported here refer to the 653 treatments given to 212 different children that were under 24 months of age at the time of any of the four drug administrations.

At baseline (September 1996), the sample was composed of 212 children less than 24 months of age. With the progression of the study and the ageing of the children, the number of children less than 24 months of age was reduced to 176 at the second treatment (December 1996), to 151 children at the third round of treatment (March 1997) and to 114 children at the fourth and final round of treatment (June 1997).

During the one year study, the daily presence of common morbidity symptoms was assessed weekly with questionnaires administered to the mothers by trained village monitors. Presented here are the questionnaire results of the first week following treatment. In addition, the health workers in the village dispensary were trained to respond and record any serious adverse effects.

Data on the following adverse effects were collected : fever, cough, diarrhoea (defined as four or more loose stool episodes in a day), dysentery (defined as a diarrhoea episode with blood on the stools in one or more days), Acute Respiratory Illness-1 (defined as a cough episode with one or more days of rapid or difficult breathing) and Acute Respiratory Illness-2 (defined as a cough episode with one or more days of rapid or difficult breathing and one or more days of fever). In total, 653 treatments (317 mebendazole; 336 placebo) were administered to 212 different children under 24 months of age. Data on 4275 days of post treatment observation (mean 6.5 days/treatment) are presented in this report.

Results

Only minor problems were observed in children less than 2 years related to the swallowing of the chewable tablets. In these cases the tablet was crushed between two spoons and administered with water.

No adverse effects were reported by the health workers in the village dispensary.

The incidence of adverse effects in the mebendazole and placebo groups in the week after treatment and the Relative Risk (RR) are presented in Table 1.

There was no statistically significant differences in Incidence Rate (IR) between the two groups. For dysentery it was not possible to calculate a Relative Risk in the week after treatment because no cases were reported in the placebo group during this period. To place the observed Incidence Rates in context, we calculated a “Daily Incidence Rate” (DIR = number of episodes / days at risk) for the year-long study period in the placebo group of children under 24 months ($DIR = 2.88 \cdot 10^{-4}$), representing, in our view, the expected occurrence of these symptoms in this age group. We compared this “expected rate” with the Daily Incidence Rate of dysentery in the week after treatment in the mebendazole group ($DIR = 1.35 \cdot 10^{-3}$). A significant DIR ratio was calculated in this case (DIR ratio = 4.69 IC: 1.29-17.07).

Discussion

The absence of mebendazole in a liquid form was easily overcome.

We consider the absence of side effect reports from the village dispensary and the absence of significant differences in the incidence rate an important indication for the use of anthelmintics in this age group. Moreover, a review of the case-reports of the three cases of dysentery showed that in one case the three days dysentery episode started 6 days after mebendazole administration, this is unlikely in relation with the drug since mebendazole is largely excreted unchanged through the faeces within 24 hours [WHO, 1996]. The second report referred to one dysentery episode for two days following a period of two weeks of fever, cough and diarrhoea that started three weeks before the administration of mebendazole. In the third case dysentery followed a fever period that started two days before mebendazole administration. We are therefore convinced that the slightly statistically significant DIR ratio calculated is due to chance and not to any side effect of the drug.

The results of this study with mebendazole 500 mg confirm, in a larger sample and with a higher dose, the absence of side effects of benzimidazole derivative drugs in children less than 24 months of age that was reported after the use of mebendazole 250 mg by Albonico *et al* (1994) [n=41] and of albendazole 200 mg by Pugh *et al.*(1986) [n=30], Mbendi *et al* (1988) [n=37] and Pamba *et al.* (1989) [n=100]. Children under 2 years of age are presently excluded from treatment in case of infection with soil-transmitted helminths, this is largely due to the belief that intensity of infection in this age group was low and therefore morbidity was assumed to be irrelevant. However, in light of the hypothesis that important nutritional benefits could be obtained from regular deworming in this age group and from the lack of any adverse effects, this policy should be re-considered. Clear recommendations for treatment of children of this age group need to be developed.

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References

- Albonico M, Renganatan E, Bosman A, Uledi UM, Alawi KS, Savioli L. Efficacy of a single dose of mebendazole on prevalence and intensity of soil-transmitted nematodes in Zanzibar. *Tropical and Geographical Medicine*. 1994; 3:142–146.
- Cooper PJ, Chico ME, Sandoval C, Espinel I, Guevara A, Kennedy MW, Urban JF Jr, Griffin GE, Nutman TB. Human infection with *Ascaris lumbricoides* is associated with a polarized cytokine response. *Journal of Infectious Diseases*. 2000; 182:1207–13. [PubMed: 10979919]
- Dawson M, Watson TR. The effect of dose form on the bioavailability of mebendazole in man. *British Journal of Clinical Pharmacology*. 1985; 19:87–90. [PubMed: 3978024]
- Mbendi M, Mashako MN, Lukini M, Ndogola ZL. Mebendazole dans le traitement des nématodoses intestinales chez les enfants agé de 1 à 2 ans. *Medicine et Chirurgie Digestive*. 1988; 17:213–215.
- Pamba HO, Bwimbo NO, Chungue CN, Estambale BBA. A study on efficacy and safety of albendazole (Zentel) in the treatment of intestinal helminthiasis in Kenyan children less than 2 years of age. *East African Medical Journal*. 1989; 66:197–202. [PubMed: 2591328]
- Pugh RN, Teesdale CH, Burnham GM. Albendazole in children with hookworm infection. *Annales of Tropical Medicine and Parasitology*. 1986; 80:565–7.
- Stoltzfus RJ, Chwaya HM, Montresor A, Albonico M, Savioli L, Tielsch JM. Malaria, hookworms, and recent fever are related to anemia and iron status indicators in Zanzibari children 0-5 years and these relations change with age. *Journal of Nutrition*. 2000; 130:1724–1733. [PubMed: 10867043]
- Stoltzfus RJ, Kvalsvig JD, Chwaya HM, et al. Effects Of Iron Supplementation and Anthelmintic Treatment on Motor and Language Development of Zanzibari Preschool Children. *British Medical Journal*. 2001; 323:1384–1396.
- Trouiller P, Rey JL, Bouscharain P. Pharmaceutical development concerning diseases predominating in tropical regions: the concept of indigent drugs. *Annales Pharmaceutiques Francais*. 2000; 58:43–6.
- WHO. Drugs used in parasitic diseases. Second edition. Model Prescribing Information. World Health Organization; Geneva: 1995.
- WHO. Report of the WHO informal consultation on the use of chemotherapy for the control of morbidity due to soil-transmitted nematodes in humans. 1996. WHO/CTD/SIP/96.2

Table 1

Incidence of adverse effects in mebendazole treatment and placebo group in the 1 week period after treatment.

Adverse effects	Mebendazole (n=317)		Placebo (n=336)		RR (95% CI)
	Total episodes ¹	IR ²	Total episodes ¹	IR ²	
Fever	45	0.141	49	0.145	0.97 (0.63-1.50)
Cough	32	0.100	37	0.110	0.91 (0.55 – 1.50)
Difficult breathing	5	0.015	6	0.017	0.88 (0.27 – 2.92)
Diarrhoea	18	0.056	12	0.035	1.63 (0.77 – 3.43)
ALRI-1 [*]	3	0.009	3	0.009	1.06 (0.21 – 5.29)
ALRI-2 ^{**}	2	0.006	1	0.003	2.13 (0.19 – 23.57)
Dysentery	3	0.009	0	0	----
Seizure	0	0	0	0	NA

¹ Incident episodes of adverse effect 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