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LOW EFFICACY OF MEBENDAZOLE AGAINST HOOKWORM IN VIETNAM: TWO RANDOMIZED CONTROLLED TRIALS

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Abstract. Vietnam is participating in a global de-worming effort that aims to treat 650 million school children regularly by 2010. The treatment used in Vietnam is single dose oral mebendazole (Phardazone®) 500 mg. We tested the efficacy of single dose mebendazole 500 mg in the therapy of hookworm infection in a randomized double-blind placebo-controlled trial among 271 Vietnamese schoolchildren. The treatment efficacy of single dose mebendazole in children did not differ significantly from placebo, with a reduction in mean eggs per gram of feces relative to placebo of 31% (95% CI –9 to 56%, $P = 0.1$). In light of these findings we then carried out a similar randomized trial comparing triple dose mebendazole, single dose albendazole, and triple dose albendazole against placebo in 209 adults in the same area. The estimated reduction in mean post-treatment eggs per gram of feces relative to placebo was 63% (95% CI 30–81%) for triple mebendazole, 75% (47–88%) for single albendazole, and 88% (58–97%) for triple albendazole. Our results suggest that single dose oral mebendazole has low efficacy against hookworm infection in Vietnam, and that it should be replaced by albendazole. These findings are of major public health relevance given the opportunity costs of treating entire populations with ineffective therapies. We recommend that efficacy of anti-helminth therapies is pilot tested before implementation of national gut worm control programs.

INTRODUCTION

Worldwide more than 2 billion people are chronically infected with soil-transmitted helminths (STH): *Ascaris lumbricoides*, the hookworms (*Ancylostoma duodenale* and *Necator americanus*), or *Trichuris trichiura*.[1] Especially in children, anemia, growth impairment, poor school attendance, and delay in intellectual development are established consequences of STH infection, resulting in a significant burden on health care and financial resources in low-income countries.[1–7] Ill health secondary to intestinal helminth infection is said to be preventable through regular deworming.[2–7] As a consequence, the World Health Assembly urged the international community to take firm action against STH infections in 2001. Since then, the 'Partners for Parasite Control' (WHO member states, the World Food Program, UNICEF, the World Bank, research institutions, and non-governmental organizations) set out to deworm 650 million school-aged children at risk of STHs and schistosomiasis regularly by 2010.[1] In Vietnam, where an estimated 6 million school-aged children are infected with a STH, the recommended STH control campaign comprises periodic mass treatment with single dose oral mebendazole (Phardazone® 500 mg), given either once a year in areas with STH prevalences between 20% and 50%, or twice a year in areas with STH prevalences above 50%.[8,9] During the 2005–2006 school year, the National Institute of Malariology, Parasitology, and Entomology (NIMPE) in collaboration with WHO will be treating 2.5 million schoolchildren in Vietnam, and the plan is to gradually extend the program.[10]

As part of a randomized placebo-controlled trial of the effect of treating hookworm infection on the occurrence and severity of allergic disease,[11] we assessed the effectiveness of single dose Phardazone® 500 mg in hookworm-infected Vietnamese children. In the light of our findings, we carried out a further randomized double-blind placebo-controlled trial, comparing the effectiveness of multiple dose mebendazole with single or multiple dose albendazole in Vietnamese adults.

METHODS

Study 1. We invited all 309 6- to 11-year old children attending two primary schools in a rural commune in Khanh Hoa province, central Vietnam. Those who were not systemically ill or known to be allergic to the trial intervention were eligible to take part. The children and their parents were visited by local health care workers, specifically trained for the project, and given a disposable container with clear instructions on how to provide a fresh stool sample the next day together with an information leaflet and consent form. The following day, provided informed consent was granted, the sample was collected and the child assigned at random in permuted blocks of 10 and stratified by school, to receive either single dose mebendazole (Phardazone®) 500 mg or matching placebo (Pharbaco [Central Pharmaceutical Company No. 1], Hanoi, Vietnam). The randomization code was generated independently at the Oxford University Clinical Research Unit in Ho Chi Minh City, and the randomization sequence was subsequently concealed from study participants, health care workers administering the treatments, and those assessing the main outcomes by ensuring that all treatments were packaged by the Oxford University Clinical Research Unit in sealed opaque consecutively numbered envelopes. Both mebendazole and placebo were manufactured for the study with the same equipment. Administration of the tablets was done under direct supervision of the field workers to ensure complete adherence. Placebo tablets were identical in shape, smell, and color to the active treatments, and neither the study participants nor those administering the treatments knew which was the active treatment. Two weeks after ad-

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ministration of the study medications, a second stool sample was collected from each child. All stool samples were transported to the local district hospital, where they were examined for parasite eggs both qualitatively and quantitatively in terms of eggs per gram (epg) feces by salt flotation method with McMaster counting chambers within a maximum of 6 hours after collection. For negative slides a second slide was examined. All laboratory technicians were blind to treatment allocation. The trial mebendazole (Phardazone®) and mebendazole placebo were independently quality tested by the Bureau of Food and Drugs, Department of Health, Republic of the Philippines, to assess whether they met international quality standards.

Study 2. All 247 adults aged 16 and older living in one village in the same geographical area were invited to participate in our second study. The same methods were used as in the first study but this time, there were four comparison groups: single dose mebendazole placebo, mebendazole (Phardazone®) 500 mg daily for three days, albendazole 400 mg single dose (Mekozetel®, Mekophar Chemical Pharmaceutical Joint Stock Company, Ho Chi Minh City, Vietnam), or albendazole 400 mg daily for three consecutive days. Randomization was generated and concealed as in the first study, and permuted blocks of 20 were used. Although field workers and study participants could tell whether they were allocated to the one of the two groups receiving single treatment or triple treatments, those assessing the stool analysis outcomes were masked to the intervention groups throughout the study. Villagers with a systemic illness, who were pregnant, or were known to be allergic to one of the intervention drugs were excluded. Fecal egg counts were carried out just before and 2 weeks after therapy, as in Study 1. We also performed a validation study, comparing McMaster salt flotation in the field with ether sedimentation as gold standard. Ether sedimentation was done independently on 151 samples from the adult study. Fresh stool samples were preserved in 10% formalin and then transported to IMPE Ho Chi Minh City. The laboratory technicians at IMPE Ho Chi Minh City were blind to the results with salt flotation.

All data were double entered using SPSS Data Entry Station 4.0. The primary endpoint for both studies was parasite intensity as measured by percent decline in arithmetic mean epg after treatment, relative to arithmetic mean post-treatment placebo.[12] A secondary endpoint was cure from hookworm infection (i.e., loss of hookworm eggs from feces in those infected at baseline). Cure rate was analyzed as a binary variable by logistic regression. To control for any change in mean epg in the placebo group, reduction in egg count was calculated as the percentage mean reduction compared with post-treatment egg counts in the placebo group. Egg counts were highly overdispersed, and were therefore analyzed by generalized negative binomial regression. This approach assumes a negative binomial error structure for the dependent variable and a log link, and allows both the mean and the negative binomial parameter ($\ln\alpha$) to be dependent on the explanatory variable (treatment group). The dependent variable was the number of eggs counted, with the weight of feces examined included as an offset. Post-treatment egg counts were analyzed in those with pre-treatment egg count above zero. Differences between treatment and placebo groups were analyzed by simple linear contrasts. For analysis of the effect of pretreatment burden on efficacy in the second study, pretreatment burden was coded as 0 = light (<2000 epg), 1 = medium (2000–3999 epg) or 2 = heavy (>3999 epg), according to WHO guidelines.[1] The analysis was then repeated, including burden class as a continuous covariate, to examine for interaction between burden class and treatment. All analysis was performed using Stata 9.1. An intention-to-treat analysis was planned in the event of study dropouts. Ethics approval for the two studies was granted by the University of Nottingham Research Ethics Committee and the Scientific Committee of Khanh Hoa Provincial Health Service, Vietnam. Local doctors and community leaders were involved in the design and conduct of the study throughout.

RESULTS

Study 1 was carried out in June 2005. Of the 309 eligible children, 271 (88%) participated, of whom 134 received placebo and 137 mebendazole; 38 children did not participate due to absence from school on the relevant date. The overall prevalence of hookworm infection in the study group at baseline was 62%, and the mean intensity was 175 epg (range 0–3800 epg). The species of hookworm present was not identified, but previous studies have shown that *Necator americanus* is the predominant species in our study area (see Hoang Thi Kim, Nguyen Thi Viet Hoa, Marchand R, 1995. Intestinal worms, malaria, and anemia in Khanh Phu. Unpublished report NIMPE, Hanoi). Other baseline characteristics of participants are summarized in Table 1. In addition, we found 16 children (6%) with *Ascaris lumbricoides* infection, but numbers in each treatment group were too small to reliably analyze treatment efficacy. No participants were lost to follow-up and all were included in the final analysis. As shown in Table 1, there was no significant difference between treatments in the proportion of infected children cured at 2 weeks (33% (26/78) in the placebo group and 38% (34/90) in the mebendazole group. Efficacy in terms of percentage reduction in arithmetic mean eggs per gram feces relative to placebo was also not significantly different (31%, 95% CI −9 to 56%).

Study 2 was carried out in August 2005. Of the 247 eligible adults, 209 (85%) took part in the second study, of whom 54 received three doses of mebendazole over 3 days, 54 single dose albendazole, 47 three doses of albendazole, and 54 single dose mebendazole placebo tablets. Reasons for non-participation were refusal ($N = 26$), absence from the village ($N = 5$), illness ($N = 5$), and pregnancy ($N = 2$); 91% of participants were infected with hookworm at baseline, with a mean intensity of 1283 epg (range 0–17850 epg). Fourteen individuals had heavy infections (>3999 epg).[1] Six participants (3%) were infected with either *Ascaris* or *Trichuris* as well as hookworm infection. No participants were lost to follow-up and all were included in the analysis. At the end of the 2-week period, the cure rates were 26% (13/50) for three dose mebendazole, 45% (21/47) for single dose albendazole, 79% (34/43) for three dose albendazole, and 35% (18/51) for placebo. Only the triple dose albendazole course was significantly superior to placebo in terms of cure ($P < 0.001$). The estimated reduction in arithmetic mean post-treatment eggs per gram of feces relative to placebo was 63% (95% CI 30–81%), 75% (47–88%), and 88% (58–97%) for triple dose mebendazole, single dose albendazole, and triple dose albendazole, respectively.

TABLE 1

Baseline characteristics and baseline and post treatment hookworm eggs per gram (egp) by treatment group, and estimated percentage efficacy relative to placebo for both trials

	Study 1 (children)			Study 2 (adults)				
	Placebo	Single dose Mebendazole	*P* value	Placebo	3 dose Mebendazole	Single dose Albendazole	3 dose Albendazole	*P* value†
N treated	134	137		54	54	54	47	
Male/female	57/77	65/72		25/29	25/29	25/29	28/19	
Mean age	9	9		37	35	37	33	
Age range	7–11	7–11		18–68	16–75	16–65	17–65	
Hookworm positive at baseline	58% (78/134)	66% (90/137)	0.2	94% (51/54)	93% (50/54)	87% (47/54)	91% (43/47)	0.6
Cure rate (95% CI) (n neg/pos at baseline)	33% (23–45) (26/78)	38% (28–49) (34/90)	0.5	35% (22–50) (18/51)	26% (15–40) (13/50)	45% (30–60) (21/47)	79%¶ (64–90) (34/43)	< 0.001
Baseline mean hookworm epg*	306	263	0.3	1068	2210‡	1120	1173	0.004
Posttreatment mean hookworm epg*	181	126	0.11	930	342‡	230¶	109¶	0.0004
Reduction in mean epg relative to pretreatment epg	41%	52%		13%	85%	79%	91%	
Reduction in mean epg relative to placebo (95% CI)		31% (−9, 56)			63% (30, 81)	75% (47, 88)	88% (58, 97)	

* Arithmetic mean in those positive for hookworm at baseline.
† Test for difference between groups.
‡ Significantly different from placebo ($P < 0.005$); ¶($P < 0.001$).

Adjustment for age and sex did not alter any of these findings. When the analysis was repeated including the interaction between pretreatment burden class (light, medium, or heavy) and treatment, there was a non-significant increase in efficacy with increasing pretreatment burden (Likelihood ratio test, $\chi^2 = 4.32$, df = 3, $P = 0.23$). All drugs, single or triple dose were equally well tolerated. No adverse events were reported in either study.

Comparison of egg counting techniques showed that 88.7% of samples (134/151) were positive by salt flotation, compared with 90.7% (137/151) by ether sedimentation, and 95.4% (144/151) by either method. Arithmetic mean egg counts were 1332 epg for salt flotation and 1723 epg for ether sedimentation. In addition, the Bureau of Food and Drugs, Department of Health, Republic of the Philippines, confirmed that our mebendazole met international quality criteria as set out in the US Pharmacopoeia.

DISCUSSION

Main findings. The first study demonstrated that single dose generic mebendazole (Phardazone®) was not significantly superior to placebo against hookworm in rural Vietnamese children, with an estimated cure rate 5% greater than placebo and a mean reduction of egg intensity 31% better than placebo. For mass treatment programs, the most important measure is reduction in intensity, as programs aim to reduce rather than eliminate parasites. Because single oral dose Phardazone® is currently being used for the 'Partners for Parasite Control' campaign in Vietnam, the low efficacy of this regimen is of major public health concern. As albendazole has a higher efficacy against hookworm infection than mebendazole, we also compared single and triple dose albendazole with triple dose mebendazole in our second study.[13,14] We found that all three treatments were better than placebo in terms of reduction of fecal egg count, with triple dose albendazole being the most efficacious. Although our study suggests that albendazole used on three consecutive days has the highest efficacy and despite the relatively low efficacy of single dose albendazole (75%) compared with other studies worldwide, single dose albendazole might be a reasonable compromise between efficacy and costs for mass treatment in Vietnam.[13,14] Three-day treatment regimens are not appropriate for mass control programs, and were only included in the current study as possible regimens for our asthma study.

Study strengths and limitations. Strengths of our two related studies include the randomized controlled design, blinding of the outcome assessment, use of placebos, high participation rates, and complete follow-up of all those randomized. Although participant numbers were modest, resulting in relatively wide confidence intervals, the upper 95% confidence limit for the observed 31% efficacy of single dose mebendazole relative to placebo was only 56%, which is unlikely to be clinically useful for a national helminth control program. Fecal helminth egg counts are known to be highly variable.[15] Although variability can be reduced by performing repeated egg counts over a number of days, such variation should not lead to differential bias. Egg counts may also vary over time in untreated individuals, as shown by the decline in egg counts post-treatment in the placebo group. This may reflect both regression to the mean and real variation in egg count through time. Similar observations have been made in other studies, emphasizing the importance of comparing efficacy to a control group.[16,17] Another potential limitation in generalizing our findings is that the second study was conducted among adults.[14] This was a necessity because by that time all children in the study area had already been enrolled in our main clinical trial on hookworm-allergy links. Moreover, the pretreatment burden was much higher in the second study. The effect of pretreatment burden on efficacy is unclear, with both increases and decreases in efficacy with increasing burden reported.[13,14] Here, we found a slight, but non-significant, increase in efficacy with increasing burden, although the statistical power to detect such an effect was small. Thus it is possible that efficacy of mebendazole was underestimated in the first study, compared with higher intensity populations. In contrast to other reported studies of drug efficacy, which typi-

cally use Kato-Katz thick smears to quantify egg counts, we used a salt-flotation technique. This is unlikely to have affected the results, as salt flotation showed similar sensitivity to the more widely used formol-ether sedimentation. Formol-ether has been shown to have similar, or reduced, sensitivity to Kato-Katz.[18,19]

Possible reasons for low efficacy. Drug quality or manufacturer has been reported to affect mebendazole efficacy in some, but not other, studies.[20,21] However, the tablets we used were independently quality tested and met international standards. Efficacy may also vary geographically.[13] The reasons for this are unclear, but it highlights the importance of testing the effect of anthelmintic treatment locally *prior to* the launch of large control campaigns.[22] There is now also growing concern about resistance to benzimidazoles.[23,24] Resistance has been widely reported in livestock parasites after frequent de-worming, and although benzimidazole resistance has so far not been conclusively demonstrated in human hookworms, drug resistance may explain the apparent decline in mebendazole efficacy seen after repeated mass treatment with mebendazole.[25,26] Lack of mebendazole treatment efficacy in a previously untreated population has also been reported from Mali.[16] To our knowledge, there are no previous published reports of mebendazole efficacy against hookworm in Vietnam, though a recent study from neighboring Cambodia reported a significant decline in hookworm egg counts after twice-yearly mebendazole.[27] Although drug resistance as a consequence of drug selection pressure seems very unlikely in our study population without a history of previous mass treatments and very limited availability of over-the-counter anthelmintics, further monitoring of the parasite population for resistance using egg hatch assays or molecular genetics may be prudent.[28,29]

Study implications. Single dose mebendazole 500 mg and single dose albendazole 400 mg are recommended by the 'Partners for Parasite Control' initiative for hookworm control. Of the two, mebendazole is often chosen due to its slightly lower price.[30] Our findings suggest that single dose mebendazole may lack suitable efficacy for the intended purpose in Vietnam, and continued use of mebendazole should depend on further studies of treatment efficacy in high intensity populations in Vietnam. In contrast, the higher efficacy of single dose albendazole would make this a suitable alternative. There are considerable opportunity costs associated with well-intentioned widespread use of insufficiently effective antihelmintic treatments, underlining the need for local testing of anthelmintic efficacy prior to the implementation of national control programs. More generally, the low efficacy reported here and in some other studies highlights both the need for monitoring of drug efficacy and possible drug resistance, and the urgent need for research and development of novel anthelmintic drugs, combination chemotherapy, and alternative methods of control, such as vaccination.[24,31–33]

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