Adverse Events from a Randomized, Multi-Arm, Placebo-Controlled Trial of Mebendazole in Children 12–24 Months of Age

Serene A. Joseph,^{1,2} Antonio Montresor,³ Martín Casapía,⁴ Lidsky Pezo,⁴ and Theresa W. Gyorkos^{1,2*}

¹Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada; ²Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montréal, Québec, Canada; ³Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland; ⁴Asociación Civil Selva Amazónica, Iquitos, Peru

Abstract. Large-scale deworming interventions, using anthelmintic drugs, are recommended in areas where the prevalence of soil-transmitted helminth infection is high. Anthelmintic safety has been established primarily in school-age children. Our objective was to provide evidence on adverse events from anthelmintic use in early childhood. A randomized multi-arm, placebo-controlled trial of mebendazole, administered at different times and frequencies, was conducted in children 12 months of age living in Iquitos, Peru. Children were followed up to 24 months of age. The association between mebendazole administration and the occurrence of a serious or minor adverse event was determined using logistic regression. There was a total of 1,686 administrations of mebendazole and 1,676 administrations of placebo to 1,760 children. Eighteen serious adverse events (i.e., 11 deaths and seven hospitalizations) and 31 minor adverse events were reported. There was no association between mebendazole and the occurrence of a serious adverse event (odds ratio [OR] = 1.21; 95% confidence interval [CI] = 0.47, 3.09) or a minor adverse event (OR = 0.84; 95% CI = 0.41, 1.72). Results from our trial support evidence of safety in administering mebendazole during early childhood. These results support World Health Organization deworming policy and the scaling up of interventions to reach children as of 12 months of age in endemic areas.

INTRODUCTION

The administration of anthelmintic drugs (i.e., deworming) on a large scale is recommended in areas where soil-transmitted helminth (STH) infections are of public health importance.^{1,2} Treatment with the single-dose benzimidazoles, albendazole and mebendazole, is considered safe in both infected and noninfected individuals³; therefore, deworming interventions targeted to high-risk groups, without prior screening, is both cost-effective and efficient. Safety has been evaluated mainly in studies of school-age children: adverse events are rare and are mainly related to the elimination of heavier worm burdens after treatment.^{4,5} When symptoms do occur, they are mild and transitory, consisting primarily of gastrointestinal symptoms.⁶

In preschool-age children, knowledge of anthelmintic safety is largely based on data from children 24 months of age and older. This is partly due to the inclusion of children 12–24 months of age in deworming recommendations only as of 2002, after a World Health Organization (WHO) Informal Consultation reviewed evidence on anthelmintic use in this younger age group.⁵ One trial conducted in preschool-age children in Tanzania provided age-disaggregated information on adverse effects specifically in children under 2 years of age.⁷ Similar incidences of fever, cough, difficulty breathing, diarrhea, respiratory illness, dysentery, and seizure were reported in each trial arm, 1 week after administration of mebendazole (500 mg) or placebo. However, as some children in the trial had difficulty swallowing the chewable tablet, WHO included the recommendation that anthelmintic drugs be crushed and mixed with liquid before administration in young children.⁵

Other trials that have included children in the second year of life in their study populations have generally reported only on mortality, with similar rates between intervention and

control groups.^{8–10} A cluster-randomized controlled trial, designed specifically to assess the effect of albendazole on reducing early childhood mortality, found similar mortality rates in the intervention and control groups.¹¹ The reporting of other serious or minor adverse events has been limited, and age-disaggregated data are not widely available. To provide further evidence for deworming recommendations in the preschool-age group, for whom coverage still remains low,¹² we report on adverse events that occurred during a trial examining the effect of mebendazole in children 12–24 months of age.

MATERIALS AND METHODS

Study design. Detailed information on trial procedures, including copies of the protocol and CONSORT checklist, is described elsewhere.^{13,14} In brief, we conducted a double-blind, multi-arm, block-randomized, placebo-controlled trial on the effect of different timings and frequencies of mebendazole administration (500 mg, single-dose tablet, crushed and mixed with fruit juice) on growth and development in early childhood (ClinicalTrials.gov NCT01314937). Children were enrolled at 12 and 13 months of age during routine growth and development (“Crecimiento y Desarrollo” [CRED]) visits in 12 participating study health centers in Iquitos, Peru. Children were followed up every 6 months for 1 year at their 18- and 24-month CRED visits. If a child was suffering from a health condition that affected the assessment of primary or secondary outcomes of the trial during enrollment or follow-up, the trial visit was postponed until the child was considered to be healthy.

At the 12-month CRED visit (i.e., baseline visit), children were randomly assigned to one of four interventions:

1. Group 1: mebendazole at the 12-month visit and placebo at the 18-month visit.
2. Group 2: placebo at the 12-month visit and mebendazole at the 18-month visit.

*Address correspondence to Theresa W. Gyorkos, Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Royal Victoria Hospital, V Building, 687 Pine Avenue West, Montréal, QC, Canada. E-mail: theresa.gyorkos@mcgill.ca

3. Group 3: mebendazole at the 12- and 18-month visits.
4. Group 4: placebo at the 12- and 18-month visits.

Children in all groups received mebendazole at the end of the study (i.e., at the 24-month visit).

A total sample size of 1,760 children (i.e., 440 children per group) was estimated based on detecting a difference in the primary outcome of weight gain among intervention groups after 1 year of follow-up.¹⁴ Additional outcomes that were ascertained were length (i.e., height in children under 2 years of age), cognitive, language and fine motor development, and STH infection prevalence and intensity. The main results of the trial are published elsewhere.^{14,15}

Mebendazole tablets were donated by INMED Peru (originator drug from Janssen-Cilag, manufactured for Janssen Pharmaceutica, Beerse, Belgium). The placebo tablets were manufactured by Laboratorios Hersil (Lima, Peru), and were identical in appearance to the mebendazole tablets. Because of the age of the children, the randomly assigned mebendazole or placebo tablet was crushed, mixed with a fruit juice, and administered to the child by trained research assistants (e.g., nurses and nurse midwives) in the health center. All participating children and their parents, research assistants, and other research personnel were blinded to intervention status. Children remained under observation in the health center for 30 minutes after administration of the treatment, in case of immediate side effects.

The research team did not actively question parents on adverse event occurrence during the course of the trial. Parents were instructed to advise the research assistant of any adverse event as soon as possible after it occurred, regardless of the type or timing of the event or the potential likelihood of its association with participation in the trial. We used WHO guidelines for classification of these reported adverse events.¹ Serious adverse events were considered to be one of the following: 1) death, 2) life-threatening condition, 3) hospitalization or prolongation of hospitalization, 4) persistent or significant incapacity, 5) cancer, or 6) accidental or intentional overdose. All other adverse events that were reported and that did not meet the definition of a serious adverse event were considered to be minor adverse events. We describe all serious adverse events that were reported (irrespective of the time interval between administration and event), and minor adverse events reported to have occurred within 1 week of administration of the treatment. Details on all reported adverse events were obtained by interviewing the parents and, if available, through a review of hospital or health center medical records. Diagnoses were made by independent health personnel not associated with the research project.

All serious adverse events were reported within 48 hours of knowledge of the event to the ethics committees of the Universidad Peruana Cayetano Heredia and the Instituto Nacional de Salud, in Peru, and the McGill University Health Centre in Canada. Minor adverse events were reported on a twice-yearly basis to the ethics committees. At three time points during the study, data were sent to the trial's Data Safety and Monitoring Committee (DSMC), to make an independent assessment of any association between adverse events and anthelmintic administration.

Statistical analysis. After the trial concluded, intervention groups were unblinded. To comment on the adverse event

experience of the study population, *a posteriori*, we made two comparisons:

1. The occurrence of adverse events by intervention group, with groups 1, 2, and 3 each compared with group 4 (i.e., the control group). In this instance, the denominator was equivalent to the number of participants. In this analysis, no distinction was made as to when the adverse event occurred.
2. The occurrence of adverse events by treatment received, with mebendazole compared with placebo. In this instance, the denominator was equivalent to the number of treatment administrations at the 12- and 18-month visits combined. This latter analysis was done as treatment occurred at more than one time point. This allowed for appropriate classification of adverse events in groups that received mebendazole and placebo at different visits. In group 1, treatment was classified as mebendazole at the 12-month visit and placebo at the 18-month visit. In group 2, treatment was classified as placebo at the 12-month visit and mebendazole at the 18-month visit. In group 3, treatment was classified as mebendazole at both 12- and 18-month visits. In group 4, treatment was classified as placebo at both 12- and 18-month visits.

Logistic regression was used to calculate unadjusted and adjusted odds ratios (ORs) for the association between mebendazole and serious and minor adverse events, respectively. Where the number of treatment administrations was used as the denominator, clustering of observations by child was taken into account using a generalized estimating equation. Multivariable analyses were adjusted for age, sex, health center, district, and socioeconomic status. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 1,760 children were enrolled between September 2011 and June 2012 and randomly assigned to one of the four intervention groups. At baseline, 880 children received mebendazole (i.e., groups 1 and 3) and 880 children received placebo (i.e., groups 2 and 4). At the 18-month visit, there were 806 administrations of mebendazole (i.e., 401 in group 2 and 405 in group 3) and 796 administrations of placebo (i.e., 401 in group 1 and 395 in group 4). A total of 1,563 children (i.e., 88.8% of the baseline study population) attended the 24-month visit between September 2012 and July 2013, all of whom then received mebendazole. The prevalence of any STH infection rose from 14.5% at baseline to 28.5% at the 18-month visit. At the 24-month visit, 42.6% of participants suffered from infection with at least one STH species. At baseline, there was no heavy-intensity infection of any STH species. Less than 2% suffered from moderate-intensity *Ascaris* infection, and 0.3% suffered from moderate-intensity *Trichuris* infection. Hookworm infection was negligible (less than 1% prevalence) and was all of light intensity. At the 24-month visit, 9.5% and 0.6% of participants suffered from moderate-intensity *Ascaris* and *Trichuris* infections, respectively. Heavy-intensity infection was only found with *Ascaris*, and affected only 0.6% of participants. Hookworm infection remained negligible and only of light intensity.

TABLE 1

Number of serious and minor adverse events in children aged 12–24 months participating in an anthelmintic trial in Peru (2011–2013), by intervention group

	MEB/PBO*	PBO/MEB†	MEB/MEB‡	PBO/PBO§
Serious adverse events	7	1	5	5
Death	5	1	3	2
Hospitalization	2	0	2	3
Minor adverse events	5	9	9	8
Total adverse events	12	10	14	13

*Group 1 (MEB/PBO): mebendazole at the 12-month visit and placebo at the 18-month visit.

†Group 2 (PBO/MEB): placebo at the 12-month visit and mebendazole at the 18-month visit.

‡Group 3 (MEB/MEB): mebendazole at the 12- and 18-month visits.

§Group 4 (PBO/PBO): placebo at the 12- and 18-month visits.

There were 18 serious and 31 minor adverse events reported during the trial. The numbers of adverse events by intervention group are given in Table 1. Similar numbers of serious, minor, and total adverse events were observed in each group, with the exception of only one serious adverse event occurring in group 2, receiving mebendazole once at the 18-month visit. There was no statistically significant difference in the number of serious adverse events in any of the intervention groups compared with the control group (group 1: OR = 1.41, 95% confidence interval [CI] = 0.44, 4.47; group 2: OR = 0.20, 95% CI = 0.02, 1.70; and group 3: OR = 1.00, 95% CI = 0.29, 3.48). There was also no statistically significant difference in the number of minor adverse events in any of the intervention groups compared with the control group (group 1: OR = 0.77, 95% CI = 0.29, 2.10; group 2: OR = 1.11, 95% CI = 0.45, 2.77; and group 3: OR = 1.34, 95% CI = 0.56, 3.22).

Details on each serious adverse event are provided in Table 2. The mean time between treatment administration and occurrence of a serious adverse event was 117.7 days (standard deviation [SD] = ± 70.3). All serious adverse events occurred at least 6 days (range = 6–227 days) after mebendazole administration, well after the complete clearance of the drug, which occurs in less than 24 hours.¹⁶

The majority of serious adverse events (72.2%) were reported before the 18-month visit. There was a range of diagnoses

reported, none of which were deemed to be related to anthelmintic use before unblinding (i.e., based on the symptoms or the timing at which the event occurred) by the research team, ethics committees, or the DSMC.

A total of 10 serious adverse events occurred after treatment with mebendazole and a total of eight serious adverse events occurred after treatment with placebo. The occurrence of a serious adverse event was not found to be statistically significantly associated with mebendazole in unadjusted (OR = 1.24, 95% CI = 0.49, 3.15) or adjusted analyses (OR = 1.21, 95% CI = 0.47, 3.09).

Details on minor adverse events are provided in Table 3. Minor adverse events occurred, on average, 1.6 days (SD = ± 1.5 ; range = 0.125–6 days) after administration of the tablet. Similar to what was observed with serious adverse events, most minor adverse events (83.9%) were reported before the 18-month visit. The most common minor adverse event was acute diarrheal disease (71.0%). Fewer minor adverse events were reported after administration of mebendazole compared with placebo (e.g., 14 versus 17). This was not a statistically significant difference, either in unadjusted analysis (OR = 0.82, 95% CI = 0.40, 1.67) or in adjusted analysis (OR = 0.84, 95% CI = 0.41, 1.72).

DISCUSSION

We provided detailed information on adverse events in a large study population of preschool-age children (between 12 and 24 months of age) participating in a trial of mebendazole. Our results indicate that treatment with mebendazole was not associated with the occurrence of either serious or minor adverse events. Although this was an *a posteriori* analysis, for which the trial was not specifically designed, our results are consistent with previous studies that have demonstrated anthelmintic safety in school-age and preschool-age children.^{3,4,17–19}

Although there are limitations to the validity of passive reporting of adverse events, we believe that we were able to capture the majority of serious adverse events because we

TABLE 2

Details on SAEs in children aged 12–24 months participating in an anthelmintic trial in Peru (2011–2013)

No.	Intervention group	SAE	Diagnosis	Study visit before SAE	Days between intervention and SAE	Intervention received before SAE
1	MEB/PBO	Hospitalization	Acute bronchial obstruction, ADD	Baseline	6	Mebendazole
2	MEB/PBO*	Death	Acute dehydration	Baseline	19	Mebendazole
3	MEB/MEB†	Hospitalization	Thrombocytopenia	Baseline	23	Mebendazole
4	MEB/PBO	Death	Respiratory insufficiency	Baseline	26	Mebendazole
5	MEB/MEB	Death	Multi-organ dysfunction	18-month	55	Mebendazole
6	MEB/PBO	Death	Hypovolemic shock	Baseline	86	Mebendazole
7	PBO/PBO	Death	Pneumonia	Baseline	92	Placebo
8	MEB/PBO	Death	Pneumonia	18-month	98	Placebo
9	MEB/PBO	Hospitalization	Cervical neuropathy	18-month	106	Placebo
10	PBO/PBO‡	Death	Multisystem failure	Baseline	137	Placebo
11	MEB/PBO	Death	Respiratory distress	Baseline	163	Mebendazole
12	MEB/MEB	Hospitalization	Convulsions	Baseline	169	Mebendazole
13	PBO/PBO	Hospitalization	Dysentery, amebiasis, giardiasis	18-month	172	Placebo
14	PBO/MEB§	Death	Pyelonephritis	Baseline	177	Placebo
15	PBO/PBO	Hospitalization	Pneumonia	Baseline	183	Placebo
16	MEB/MEB	Death	Information unavailable	Baseline	187	Mebendazole
17	PBO/PBO	Hospitalization	Dengue, malaria, leptospirosis	18-month	193	Placebo
18	MEB/MEB	Death	Probable dehydration from CDD	Baseline	227	Mebendazole

ADD = acute diarrheal disease; CDD = chronic diarrheal disease; SAE = serious adverse events.

*Group 1 (MEB/PBO): mebendazole at the 12-month visit and placebo at the 18-month visit.

†Group 3 (MEB/MEB): mebendazole at the 12- and 18-month visits.

‡Group 4 (PBO/PBO): placebo at the 12- and 18-month visits.

§Group 2 (PBO/MEB): placebo at the 12-month visit and mebendazole at the 18-month visit.

TABLE 3
Details on MAEs in children aged 12–24 months participating in an anthelmintic trial in Peru (2011–2013)

No.	Intervention group	MAE	Study visit before MAE	Days between intervention and MAE	Intervention received before MAE
1	MEB/MEB*	Acute urticaria	Baseline	0.13	Mebendazole
2	PBO/MEB†	Emetic syndrome	Baseline	0.13	Placebo
3	PBO/PBO‡	Acute pharyngitis, urticaria	Baseline	0.25	Placebo
4	PBO/PBO	ADD	Baseline	0.25	Placebo
5	PBO/PBO	ADD with dehydration	Baseline	0.33	Placebo
6	PBO/MEB	ADD	Baseline	0.42	Placebo
7	PBO/PBO	Allergic reaction	18-month	0.42	Placebo
8	MEB/PBO§	ADD, urinary tract infection	18-month	0.46	Placebo
9	MEB/PBO	ADD	Baseline	0.5	Mebendazole
10	MEB/MEB	ADD without dehydration	Baseline	0.67	Mebendazole
11	PBO/MEB	Acute pharyngitis	Baseline	1	Placebo
12	PBO/MEB	ADD with dehydration	Baseline	1	Placebo
13	PBO/PBO	Suspected dysentery	Baseline	1	Placebo
14	MEB/PBO	ADD without dehydration	Baseline	1	Mebendazole
15	PBO/MEB	ADD with dehydration	Baseline	1	Placebo
16	MEB/MEB	ADD without dehydration	Baseline	1	Mebendazole
17	PBO/PBO	ADD with dehydration	Baseline	1	Placebo
18	MEB/MEB	ADD, bronchial hyperactivity	Baseline	1	Mebendazole
19	PBO/PBO	ADD	Baseline	2	Placebo
20	MEB/PBO	ADD	Baseline	2	Mebendazole
21	MEB/PBO	Allergic reaction	Baseline	2	Mebendazole
22	MEB/MEB	ADD without dehydration	Baseline	2	Mebendazole
23	MEB/MEB	ADD without dehydration	Baseline	2	Mebendazole
24	MEB/MEB	ADD without dehydration	Baseline	2	Mebendazole
25	MEB/MEB	ADD without dehydration	18-month	3	Mebendazole
26	MEB/MEB	Conjunctivitis	18-month	3	Mebendazole
27	PBO/MEB	Febrile syndrome	18-month	3	Mebendazole
28	PBO/MEB	Acute rhinopharyngitis	Baseline	3	Placebo
29	PBO/MEB	ADD with dehydration	Baseline	4	Placebo
30	PBO/MEB	Common cold, ADD without dehydration	Baseline	5	Placebo
31	PBO/PBO	ADD with dehydration, febrile syndrome	Baseline	6	Placebo

ADD = Acute diarrheal disease; MAE = minor adverse events.

*Group 3 (MEB/MEB): mebendazole at the 12- and 18-month visits.

†Group 2 (PBO/MEB): placebo at the 12-month visit and mebendazole at the 18-month visit.

‡Group 4 (PBO/PBO): placebo at the 12- and 18-month visits.

§Group 1 (MEB/PBO): mebendazole at the 12-month visit and placebo at the 18-month visit.

followed up the participants every 6 months, and our trial was integrated within health centers. As children regularly attend routine CRED visits every 2 months from 12 to 24 months of age, health center or research personnel would likely have been made aware of any child who died or was hospitalized during the course of the trial.

The number of minor adverse events reported is likely an underestimation of the true incidence. In a study in Tanzania with active reporting of adverse events 1 week after anthelmintic treatment of children under 24 months of age, the total number of episodes reported was much higher, with 216 of a total of 653 administrations.⁷ With passive reporting, factors related to health center, research assistant, and participant could all have contributed to the events which were brought to our attention. Parents and/or research assistants may have been more aware of changes in child health status at the start of the study, and more likely to associate the changes with participation in the trial. Over the course of the trial, parents may have been less likely to associate morbidity of their child with the study treatment. Consistent with this premise, the majority of adverse events were reported after treatment administration at the baseline visit. Although we attempted to maintain consistency in reporting, and to have a continual presence in the health centers and communities over the 2 years of data collection in the trial, a change in behavior may have led to a decrease in adverse event reporting over the course of the trial. It is also possible that the decrease in adverse events over time is explained by a true decrease in

morbidity over the course of the second year of life. Seasonality could also be a factor in adverse event incidence, particularly with communicable disease events; however, we believe that any underestimation or change in reporting over time would have had a nondifferential effect among the intervention groups, in part, due to the blocked randomization strategy used. In addition, adverse events associated with the elimination of worms from children having moderate- to heavy-intensity infections would have been unlikely as the majority of infections in our trial were of light intensity.

The true incidence of adverse events in our study population may be lower than in other study populations or in the broader population of children in Iquitos. Our mortality rate was, indeed, lower than in the study region, which has an under-five mortality rate of 40 per 1,000 live births and a mortality rate of 11 per 1,000 children in children under-five who have reached their first birthday.²⁰ Our attempt to enroll children only when they were healthy, so as not to affect other study outcomes, may have led to lower morbidity in the trial's study population. As we conducted the trial within existing health infrastructure, we may have also enrolled a healthier study population who has easier access to health services compared with nonenrolled children living in the study area. However, we had conducted a pretrial canvassing of the study area before commencing the trial to identify and enroll children who may not have been regularly attending their CRED visits to increase the generalizability of our results.¹³

A concern regarding anthelmintic use in children in this younger age group is the risk of choking on the tablet.⁵ As recommended by WHO, we eliminated this risk by crushing the tablet and mixing it with a fruit juice. This was found to be acceptable in this age group, and no episodes of choking were reported; however, it did require extra time for crushing and mixing the tablet and assistance from parents. This should be taken into account in large-scale deworming programs where administration may be more rapid and not always performed by health personnel. Although available in some countries, a liquid suspension of mebendazole is, on average, 10 times the cost of an equivalent 500 mg mebendazole tablet.²¹ As with all liquid suspensions, doses can be inconsistent without proper mixing of the liquid before each administration, so alternative strategies may be needed in large-scale deworming programs.³

Overall, the results of this study support evidence of safety of administration of a 500-mg, single-dose tablet of mebendazole (crushed and mixed with fruit juice) to children 12–24 months of age. Our results also demonstrate the feasibility of passive adverse event reporting in a large study of children. We believe that it is important to better define the symptoms and time frame of adverse events that should be recorded in anthelmintic studies in preschool-age children. This will help to provide more accurate and comparable results, particularly when active adverse event reporting is not possible. The results of our study will contribute to the evidence base on anthelmintic safety and provide support for international policies and scaling-up of deworming interventions in preschool-age children.

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Authors' addresses: Serene A. Joseph and Theresa W. Gyorkos, Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada, E-mails: serene.joseph@mail.mcgill.ca and theresa.gyorkos@mcgill.ca. Antonio Montresor, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland, E-mail: montresora@who.int. Martín Casapía and Lidsky Pezo, Asociación Civil Selva Amazónica, Iquitos, Peru, E-mails: mcasapia@acsaperu.org and lpezo@acsaperu.org.

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