ORIGINAL ARTICLE

Oxantel Pamoate–Albendazole for *Trichuris trichiura* Infection

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ABSTRACT

BACKGROUND

Infections with soil-transmitted helminths (*Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) are widespread and often occur concomitantly. These parasitic-worm infections are typically treated with albendazole or mebendazole, but both drugs show low efficacy against *T. trichiura*. Albendazole is the drug of choice against hookworm.

METHODS

In this double-blind trial conducted on Pemba Island, Tanzania, we randomly assigned children, 6 to 14 years of age, to receive one of four treatments: oxantel pamoate at a dose of 20 mg per kilogram of body weight, plus 400 mg of albendazole, administered on consecutive days; oxantel pamoate at a single dose of 20 mg per kilogram; albendazole at a single dose of 400 mg; or mebendazole at a single dose of 500 mg. We assessed the efficacy and safety profile of oxantel pamoate–albendazole when used in the treatment of *T. trichiura* infection (primary outcome) and concomitant soil-transmitted helminth infection (secondary outcome). Efficacy was determined by means of assessment of the cure rate and egg-reduction rate. Adverse events were assessed four times after treatment.

RESULTS

Complete data were available for 458 children, of whom 450 were infected with *T. trichiura*, 443 with hookworm, and 293 with *A. lumbricoides*. The cure rate of *T. trichiura* infection was significantly higher with oxantel pamoate–albendazole than with mebendazole (31.2% vs. 11.8%, P=0.001), as was the egg-reduction rate (96.0% [95% confidence interval {CI}, 93.5 to 97.6] vs. 75.0% [95% CI, 64.2 to 82.0]). The cure rate with albendazole (2.6%) and the egg-reduction rate with albendazole (45.0%; 95% CI, 32.0 to 56.4) were significantly lower than the rates with mebendazole (P=0.02 for the comparison of cure rates). Oxantel pamoate had low efficacy against hookworm and *A. lumbricoides*. Adverse events (mainly mild) were reported by 30.9% of all children.

CONCLUSIONS

Treatment with oxantel pamoate–albendazole resulted in higher cure and egg-reduction rates for *T. trichiura* infection than the rates with standard therapy. (Funded by the Medicor Foundation and the Swiss National Science Foundation; Current Controlled Trials number, ISRCTN54577342.)

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Soil-transmitted helminthiasis is caused by chronic infection with nematode worms, *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*.[1] More than 1 billion people are infected with one or several species of soil-transmitted helminths. Infection with *T. trichiura*, a roundworm commonly known as whipworm, causes a global burden of 638,000 disability-adjusted life-years.[1-3]

The periodic administration of anthelmintic drugs (i.e., albendazole or mebendazole) to at-risk populations is the global strategy for controlling morbidity due to soil-transmitted helminth infection.[4] The goal of control programs is to eliminate childhood illness caused by soil-transmitted helminth infection — that is, to decrease the prevalence of moderate and heavy infection intensity among school-age children to less than 1%.[5]

Treatment with albendazole or mebendazole, in a single-dose regimen, results in high cure rates against infection with *A. lumbricoides*; only albendazole is associated with a satisfactory cure rate against hookworm. Both drugs are associated with a low cure rate against *T. trichiura* infection.[6-10] Although *T. trichiura* infection is not highly pathogenic unless the infection intensity is high, there is a growing recognition of the public health effects of trichuriasis.[11] Hence, there is a need to develop new, effective, and broad-spectrum anthelmintic drugs.[12]

Oxantel is the m-oxyphenol analogue of pyrantel and has been marketed as a veterinary drug since 1974. It shows high trichuricidal activity.[13-15] A number of exploratory trials showed that oxantel pamoate was effective when given as a single dose of 10 to 20 mg per kilogram of body weight.[16-20]

The aim of the present study was to assess the efficacy and safety profile of a combination of oxantel pamoate and albendazole (Zentel, GlaxoSmithKline) in children infected with *T. trichiura* (primary outcome). We also studied the effect of this combination therapy on concurrent infections with hookworm and *A. lumbricoides* (secondary outcome). Monotherapies with oxantel pamoate, albendazole, and mebendazole (Vermox, Johnson & Johnson) served as comparators.

METHODS

STUDY DESIGN AND PATIENTS

We conducted this randomized, controlled, double-blind trial from September through November 2012 in two primary schools, Mchangamdogo and Shungi, on Pemba Island, Tanzania. Children 6 to 14 years of age were invited to provide two stool samples, and children who were positive for either *T. trichiura* or hookworm were considered eligible for inclusion in the trial. Children presenting with *T. trichiura*–hookworm coinfection were enrolled with highest priority. A medical history was obtained from children who met the inclusion criteria, and each child underwent a physical examination. Children who had any systemic illness (e.g., clinical malaria or hepatosplenic schistosomiasis), as assessed by a medical doctor at the initial clinical assessment, were excluded from the trial.

STUDY OVERSIGHT

Ethical approval was obtained from the Ministry of Health and Social Welfare of Zanzibar, Tanzania, and from the ethics committee of Basel, Switzerland. Written informed consent was obtained from all the parents or guardians, and all the children provided verbal assent. All the authors take full responsibility for the study design; the collection, analysis, and interpretation of the data; and the fidelity of the report to the study protocol (available with the full text of this article at NEJM.org).

RANDOMIZATION

Children were randomly assigned, with the use of block sizes of four, to receive one of four treatments: oxantel pamoate at a dose of 20 mg per kilogram, plus 400 mg of albendazole; oxantel pamoate at a dose of 20 mg per kilogram; 400 mg of albendazole; or 500 mg of mebendazole. Children, study-site investigators, and laboratory technicians were unaware of the study-group assignments.

Each child received tablets on 2 consecutive days. On the first day, children were given either oxantel pamoate or, in the study groups that did not include therapy with oxantel pamoate, identical placebo tablets. Oxantel pamoate and identical matching placebo were given to the nearest half tablet according to the calculated dose per kilogram of body weight. On the second day, children were administered two tablets. Participants in the two treatment groups that included albendazole received albendazole and a placebo matching mebendazole, children in the mebendazole group received mebendazole plus a placebo matching albendazole, and children in the

oxantel pamoate monotherapy group received a placebo matching albendazole plus a placebo matching mebendazole.

There was no industry involvement; the drugs were purchased. Placebos exactly matching albendazole and mebendazole were purchased from Fagron. Oxantel pamoate and the matching placebo were manufactured at the University of Basel.[21] Drug quality was assured for all products used.

STUDY PROCEDURES

We explained the purpose and procedures of the study, including potential benefits and risks, to the parents or guardians of the children. At baseline, children who were willing to participate provided us with the informed-consent form signed by a parent or guardian and with two stool samples obtained over consecutive days. Stool samples were transferred to the Public Health Laboratory–Ivo de Carneri. From each sample, duplicate Kato–Katz thick smears were prepared and examined for soil-transmitted helminth eggs by one of six experienced laboratory technicians (all of whom were unaware of the treatment assignments).[22] For quality control, 10% of the slides were randomly chosen and reexamined; the agreement was more than 95%.

Before treatment, children were asked about clinical signs and symptoms, and their weight and height were measured. Adverse events were assessed and graded by means of active questioning at four time points after treatment — at 3 hours and 24 hours after the first and second treatments (for details about judging the severity of adverse events, see the study protocol).

Treatment efficacy was assessed 18 to 23 days after treatment, after children had submitted an additional two stool samples. At the end of the study, all school-going children were offered albendazole (at a dose of 400 mg) according to national guidelines.[4,23]

SAMPLE SIZE

We calculated that with a sample of 70 children infected with *T. trichiura* per treatment group the study would have 80% power to test the primary hypothesis that the oxantel pamoate–albendazole combination would result in a higher cure rate than the current drug of choice (i.e., mebendazole). Our calculations were based on an estimated cure rate against *T. trichiura* of 35% with mebendazole[6] and an estimated cure rate of 60% with oxantel pamoate–albendazole. To account for loss to follow-up, we increased the sample in each treatment group to 95 participants, resulting in a total of 380 school-age children with *T. trichiura* infection in the four treatment groups.

To provide the study with sufficient power to determine the efficacy of the combination therapy against concomitant hookworm infection (secondary outcome, with the prevalence of hookworm infection expected to be 60%), the sample was increased to 500 children. We also performed analyses to determine whether oxantel pamoate–albendazole was superior to its single components with respect to the primary and secondary outcomes. No adjustment was made for multiple testing.

STATISTICAL ANALYSIS

Data were double-entered into a database (Excel 2010, Microsoft), cross-checked, and analyzed with the use of Stata software, version 10.1 (StataCorp). The multiple imputation sensitivity analysis was performed with the use of R software, version 3.0.0 (www.r-project.org).

Potential imbalances in the baseline characteristics of the enrolled children (i.e., age, sex, school, weight, height, and log geometric-mean soil-transmitted helminth egg counts) were compared with the use of logistic and linear regression models, as appropriate. In the between-group comparisons, the mebendazole group was the reference group.

An available case analysis[24] was performed, which included all children with primary outcome data. A sensitivity analysis that used an intention-to-treat approach was performed for the primary hypothesis with the use of several different methods for imputation of missing data (i.e., best-case and worst-case scenarios and a multiple-imputation approach with the use of an iterative regression imputation, with age, sex, weight, height, treatment group, and log-transformed soil-transmitted helminth egg counts at baseline as predictors).

The cure rate, which was our primary outcome measure, was calculated as the percentage of the children who became egg-negative after treatment among those who had had eggs in their stool at baseline. The number of eggs per gram of stool was assessed by adding up the egg counts from the quadruplicate Kato–Katz thick smears and multiplying this number by six. Infection intensity was classified according to World Health

Organization (WHO) cutoffs.[25] Cure rates were further stratified according to infection intensity before treatment.

In addition, we calculated the number of children with moderate or heavy infection before treatment who had no infection or only light infection after treatment — a key goal of the WHO global program for control of soil-transmitted helminthiasis.[5] Crude logistic regressions (including all four treatment groups) and adjusted logistic regressions (with adjustment for age, sex, and school) were used to calculate differences in cure rates among treatment groups.

To test the primary hypothesis, logistic regression was used to compare the cure rates with oxantel pamoate–albendazole and with mebendazole among children with *T. trichiura* infection. Monotherapy comparators (i.e., oxantel pamoate and albendazole) were compared with mebendazole to assess which of the two drugs (oxantel pamoate or albendazole) was more efficacious. Adverse events were evaluated descriptively as the difference in the proportion of children reporting adverse events before and after treatment.

Geometric-mean soil-transmitted helminth egg counts were calculated for the treatment groups before and after treatment to assess the corresponding egg-reduction rate, an equally important variable for drug efficacy and therefore our secondary outcome; the egg-reduction rate was equal to $100 \times (1 - [\text{mean at follow-up} \div \text{mean at baseline}])$. (For arithmetic means, which have been recommended recently as a methodologic alternative,[26] see Table S1 in the Supplementary Appendix, available at NEJM.org.) A bootstrap-resampling method with 10,000 replicates was used to calculate 95% confidence intervals of the geometric means for the egg-reduction rates.[27] The differences in egg-reduction rates were determined under the assumption that nonoverlapping confidence intervals indicated statistical significance.

RESULTS

PARTICIPANTS AND BASELINE DATA

Of 900 children who were invited to participate, 798 had complete baseline data (Fig. 1). Of these, 774 children (97.0%) were positive for *T. trichiura*, 464 (58.1%) were infected with hookworm, and 461 (57.8%) had an *A. lumbricoides* infection. Triple-species infections were diagnosed in 316 children (39.6%).

Since we were interested in the efficacy of the drugs against *T. trichiura* infection (primary outcome) and concomitant soil-transmitted helminth infection (secondary outcome), we included all children with a *T. trichiura*–hookworm coinfection (456 of the 774 children with *T. trichiura* infection). In addition, to reach our overall estimated sample size, we included 16 children with single *T. trichiura* infection and 8 with single hookworm infection. Among these 480 children, 309 were coinfected with *A. lumbricoides*.

No significant between-group differences were observed with regard to any of the baseline characteristics ($P>0.05$). On average, children at the Mchangamdogo school, as compared with those from the Shungi school, had a lower baseline *T. trichiura* infection intensity, which was associated with lower cure rates (Table S2 in the Supplementary Appendix). A total of 4 children were absent during treatment and the follow-up survey. A total of 18 children were lost to follow-up after treatment because they did not provide two stool samples (14 children) or because identification materials were mislabeled (4). Hence, no primary-outcome data were available for 22 children.

Demographic and baseline laboratory characteristics of the 480 children included in the analysis are summarized in Table 1. Treatment groups were well balanced with respect to age, sex, weight, and height. Classifications of infection intensities according to WHO cutoffs are presented in Table 1.

EFFICACY AGAINST *T. TRICHIURA*

Cure rates and egg-reduction rates among 450 children with *T. trichiura* infection are shown in Table 2. Treatment with oxantel pamoate–albendazole resulted in a significantly higher cure rate among children with *T. trichiura* infection than did mebendazole (31.2% vs. 11.8%, $P=0.001$). Oxantel pamoate alone was associated with a significantly higher cure rate than mebendazole (26.3% vs. 11.8%, $P=0.01$). Albendazole monotherapy resulted in a significantly lower cure rate than mebendazole monotherapy (2.6% vs. 11.8%, $P=0.02$). Adjustment for school, sex, and weight did not influence these estimates. Stratification according to infection intensity showed that in both treatment groups that received oxantel pamoate, the cure rate among lightly infected children was approximately 39% (39.0% with oxantel pamoate–albendazole and 39.3% with oxantel pamoate monotherapy), whereas the cure rates

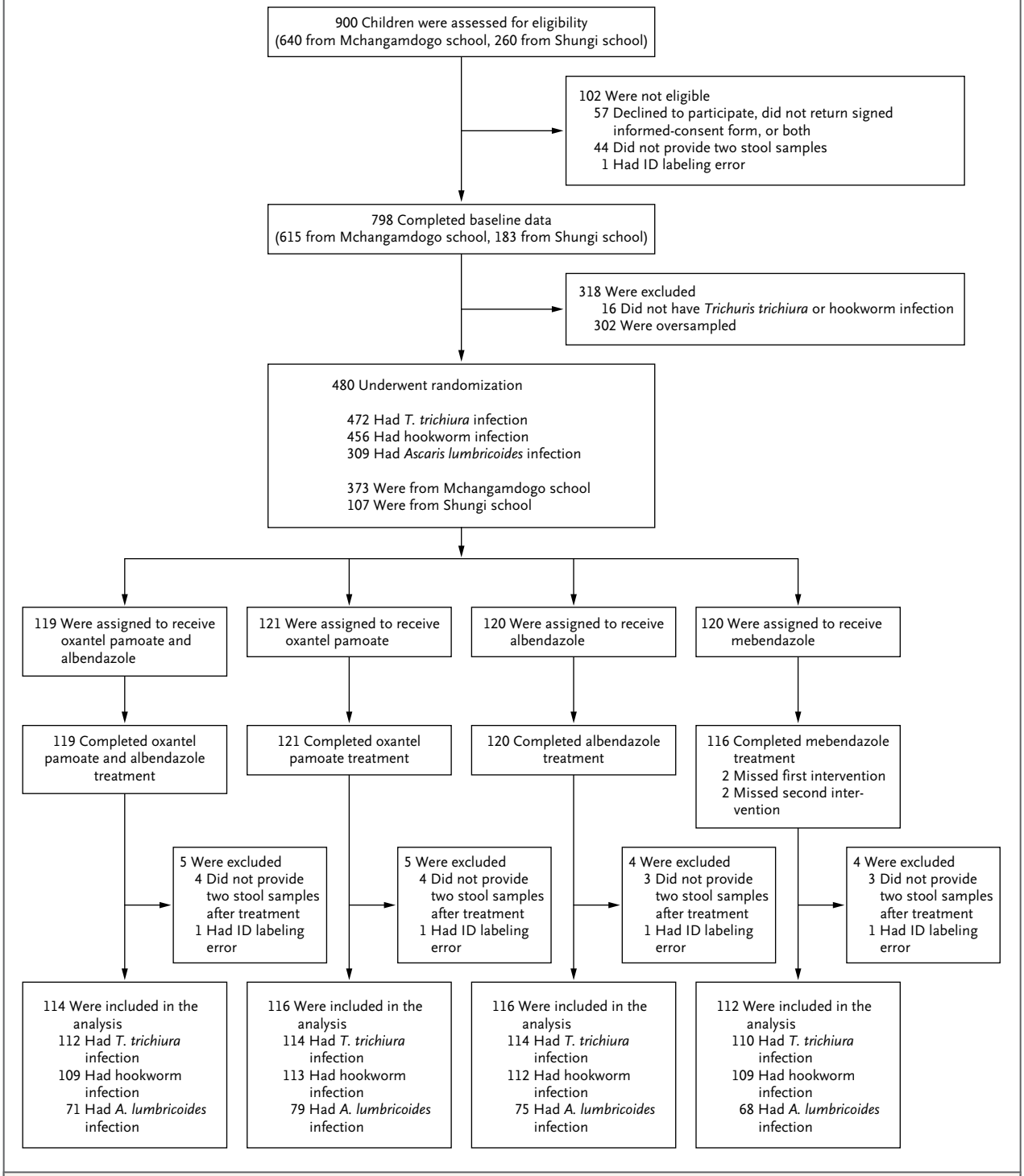

Figure 1. Study Enrollment, Randomization, and Follow-up.
ID denotes identification.

Table 1. Characteristics at Baseline.*

Characteristic	Oxantel Pamoate–Albendazole (N=119)	Oxantel Pamoate (N=121)	Albendazole (N=120)	Mebendazole (N=120)	Total (N=480)
Age — yr	9.6±1.6	9.9±1.8	9.9±1.7	9.6±1.6	9.7±1.7
Sex — no.					
Girls	58	59	55	61	233
Boys	61	62	65	59	247
School — no.					
Mchangamdogo	92	94	94	93	373
Shungi	27	27	26	27	107
Weight — kg†	25±4	26±5	25±5	25±4	25±5
Height — cm‡	128±12	128±17	129±13	128±8	128±13
Trichuris trichiura infection					
Children infected — no. (%)	117 (98.3)	119 (98.3)	118 (98.3)	118 (98.3)	472 (98.3)
Geometric mean no. of eggs/g of stool	807	885	883	847	855
Infection intensity — no. (%)§					
Light	61 (52.1)	59 (49.6)	67 (56.8)	61 (51.7)	248 (52.5)
Moderate	54 (46.2)	58 (48.7)	49 (41.5)	52 (44.1)	213 (45.1)
Heavy	2 (1.7)	2 (1.7)	2 (1.7)	5 (4.2)	11 (2.3)
Hookworm infection					
Children infected — no. (%)	113 (95.0)	118 (97.5)	116 (96.7)	117 (97.5)	464 (96.7)
Geometric mean no. of eggs/g of stool	133	122	108	112	118
Infection intensity — no. (%)¶					
Light	111 (98.2)	117 (99.2)	115 (99.1)	114 (97.4)	457 (98.5)
Moderate	0	0	1 (0.9)	2 (1.7)	3 (0.6)
Heavy	2 (1.8)	1 (0.8)	0	1 (0.9)	4 (0.9)
Ascaris lumbricoides infection					
Children infected — no. (%)	74 (62.2)	82 (67.8)	79 (65.8)	74 (61.7)	309 (64.4)
Geometric mean no. of eggs/g of stool	1920	3126	2366	2143	2368
Infection intensity — no. (%)‖					
Light	38 (51.4)	38 (46.3)	43 (54.4)	41 (55.4)	160 (51.8)
Moderate	35 (47.3)	44 (53.7)	33 (41.8)	32 (43.2)	144 (46.6)
Heavy	1 (1.4)	0	3 (3.8)	1 (1.4)	5 (1.6)

* Plus–minus values are means ±SD. There were no significant between-group differences.
† Data were missing for four children in the mebendazole group.
‡ Data were missing for two children in the albendazole group and four in the mebendazole group.
§ The intensity of *T. trichiura* infection was categorized as light (1 to 999 eggs per gram of stool), moderate (1000 to 9999 eggs per gram of stool), or heavy (≥10,000 eggs per gram of stool).
¶ The intensity of hookworm infection was categorized as light (1 to 1999 eggs per gram of stool), moderate (2000 to 3999 eggs per gram of stool), or heavy (≥4000 eggs per gram of stool).
‖ The intensity of *A. lumbricoides* infection was categorized as light (1 to 4999 eggs per gram of stool), moderate (5000 to 49,999 eggs per gram of stool), or heavy (≥50,000 eggs per gram of stool).

Table 2. Cure Rates and Egg-Reduction Rates.*

Variable	Oxantel Pamoate–Albendazole	Oxantel Pamoate	Albendazole	Mebendazole
T. trichiura				
No. of children positive for infection				
Before treatment	112	114	114	110
After treatment	77	84	111	97
Cure rate — % (95% CI)	31.2 (22.5–40.0)	26.3 (18.1–34.5)	2.6 (0.0–5.6)	11.8 (5.7–17.9)
No. of children cured/total no. with infection (%)				
From light infection	23/59 (39.0)	22/56 (39.3)	3/67 (4.5)	12/57 (21.1)
From moderate infection	12/52 (23.1)	8/57 (14.0)	0/45	1/49 (2.0)
From heavy infection	0/1	0/1	0/2	0/4
Geometric mean no. of eggs/g of stool				
Before treatment	769	874	853	813
After treatment	31	59	469	203
Egg-reduction rate — % (95% CI)	96.0 (93.5–97.6)	93.2 (90.0–95.7)	45.0 (32.0–56.4)	75.0 (64.2–82.0)
Moderately or heavily infected children with no or light infection after treatment — % (95% CI)†	84.9 (74.9–94.9)	77.6 (66.5–88.6)	46.8 (32.0–61.1)	58.5 (44.8–72.2)
Hookworm‡				
No. of children positive for infection				
Before treatment	109	113	112	109
After treatment	53	101	45	90
Cure rate — % (95% CI)	51.4 (41.8–60.9)	10.6 (4.9–16.4)	59.8 (50.6–69.0)	17.4 (10.2–24.7)
Geometric mean no. of eggs/g of stool				
Before treatment	136	127	108	109
After treatment	6	78	4	45
Egg-reduction rate — % (95% CI)	95.6 (92.8–97.3)	38.6 (19.5–55.3)	96.3 (93.9–97.6)	58.7 (42.6–71.6)
A. lumbricoides				
No. of children positive for infection				
Before treatment	71	79	75	68
After treatment	4	71	6	6
Cure rate — % (95% CI)	94.4 (88.9–99.9)	10.1 (3.3–16.9)	92.0 (85.7–98.3)	91.2 (84.3–98.1)
No. of children cured/no. with infection (%)				
From light infection	36/36 (100.0)	6/35 (17.1)	36/40 (90.0)	38/40 (95.0)
From moderate infection	31/34 (91.2)	2/44 (4.5)	31/32 (96.9)	24/28 (85.7)
From heavy infection§	0/1	—	2/3 (66.7)	—
Geometric mean no. of eggs/g of stool				
Before treatment	1967	3452	2426	1876
After treatment	<1	2472	1	1
Egg-reduction rate — % (95% CI)	99.98 (99.96–100.00)	28.4 (0.0–54.2)	99.97 (99.91–99.99)	99.94 (99.82–99.98)
Moderately or heavily infected children with no infection or light infection after treatment — % (95% CI)†	97.1 (91.3–100.0)	13.6 (3.1–24.2)	97.1 (91.3–100.0)	89.3 (77.1–100.0)

* CI denotes confidence interval.
† The goal of the World Health Organization global program for the control of soil-transmitted helminthiasis is to reduce the rate of illness from infection with soil-transmitted helminths in school-age children to below a level that would be considered a public health problem (i.e., to reduce soil-transmitted helminth infection of moderate and high intensity among school-age children to <1%).[5]
‡ Most hookworm infections (>95%) were classified as light.
§ No children in the oxantel pamoate or mebendazole monotherapy group had heavy infection.

Table 3. Adverse Events and Related Symptoms Assessed at Five Time Points.*

Time Point	Oxantel Pamoate–Albendazole	Oxantel Pamoate	Albendazole	Mebendazole	Total
	number/total number (percent)				
Before treatment	12/119 (10.1)	21/120 (17.5)	13/120 (10.8)	13/115 (11.3)	59/474 (12.4)
After first treatment					
3 hr	9/119 (7.6)	16/121 (13.2)	15/120 (12.5)	8/116 (6.9)	48/476 (10.1)
24 hr	18/119 (15.1)	20/121 (16.5)	12/120 (10.0)	21/116 (18.1)	71/476 (14.9)*
After second treatment					
3 hr	15/119 (12.6)	15/121 (12.4)	11/120 (9.2)	6/116 (5.2)	47/476 (9.9)
24 hr	15/117 (12.8)	25/118 (21.2)	15/115 (13.0)	11/110 (10.0)	66/460 (14.3)

* One child in the oxantel pamoate–albendazole group was observed with moderate episodes of diarrhea and fever 24 hours after treatment. All other adverse events were characterized as mild.

with mebendazole and albendazole were 21.1% and 4.5%, respectively, among lightly infected children. Cure rates based on different intention-to-treat approaches are shown in Table S3 in the Supplementary Appendix.

Oxantel pamoate–albendazole and oxantel pamoate monotherapy were associated with high egg-reduction rates among children with *T. trichiura* infection (96.0%; 95% confidence interval [CI], 93.5 to 97.6, and 93.2%; 95% CI, 90.0 to 95.7, respectively). A significantly lower egg-reduction rate was observed in the group that received mebendazole than in either treatment group that received oxantel pamoate (75.0%; 95% CI, 64.2 to 82.0), and the egg-reduction rate with albendazole was significantly lower than the rate with mebendazole (45.0%; 95% CI, 32.0 to 56.4).

A total of 84.9% of the children with moderate or heavy *T. trichiura* infection at baseline had either no infection or a light infection after treatment with oxantel pamoate–albendazole (Table 2). In contrast, considerably fewer children receiving mebendazole or albendazole had no infection or a light infection after treatment (58.5% and 46.8%, respectively).

EFFICACY AGAINST HOOKWORM

A total of 443 children infected with hookworm were included in the analysis. Albendazole monotherapy resulted in a significantly higher cure rate against hookworm than any other applied treatment (59.8%, vs. 17.4% with mebendazole; P<0.001). Adding oxantel pamoate did not increase the efficacy (59.8% with albendazole alone vs. 51.4% with oxantel pamoate–albendazole; P=0.21) (Table 2). High egg-reduction rates against hookworm were observed with albendazole (96.3%; 95% CI, 93.9 to 97.6) and with albendazole combined with oxantel pamoate (95.6%; 95% CI, 92.8 to 97.3). As compared with the rates after treatments that included albendazole, the egg-reduction rates were significantly lower after treatment with mebendazole (58.7%; 95% CI, 42.6 to 71.6) and after oxantel pamoate monotherapy (38.6%; 95% CI, 19.5 to 55.3).

EFFICACY AGAINST *A. LUMBRICOIDES*

Complete data were available for 293 children infected with *A. lumbricoides*. Treatment with albendazole and mebendazole resulted in high cure rates among children with *A. lumbricoides* infection (92.0% and 91.2%, respectively) (Table 2). The cure rate with oxantel pamoate–albendazole was 94.4% (95% CI, 88.9 to 99.9). All the children infected with *A. lumbricoides* who were treated with albendazole or mebendazole had egg-reduction rates close to 100%. Monotherapy with oxantel pamoate resulted in low cure and egg-reduction rates among children with *A. lumbricoides* infection.

SAFETY

Adverse events were assessed in 476 children, but not all children were available at all time points after treatment (Table 3). No serious adverse events were noted during the study. Before treatment, 59 children (12.4%) had mild symptoms. When we pooled the children in the two treatment groups that included oxantel pamoate, we found that 13.8% of the children had mild symptoms before treatment. At 3 hours and 24 hours

after the administration of oxantel pamoate, mild adverse events were observed in 10.5% and 15.8% of the children, respectively, in the pooled group. The proportions of children with mild adverse events in the groups that received the placebo matching oxantel pamoate on the first day were 11.1% before treatment and 9.7% and 14.0% at 3 hours and 24 hours after treatment, respectively. Similarly, the number of mild adverse events after the administration of albendazole and mebendazole differed only slightly from the levels observed before treatment (maximum increase, 2.7 percentage points).

The highest number of adverse events was observed 48 hours after the administration of oxantel pamoate monotherapy (24 hours after the administration of placebo), occurring in 25 children (21.2%), as compared with 21 children with adverse events (17.5%) before treatment. The largest increase in the proportion of mild adverse events was seen in the mebendazole group 24 hours after administration of the placebo matching oxantel pamoate (increase from before treatment, 6.8 percentage points). Children receiving oxantel pamoate were not absent more often during the assessment of adverse events than were those who received standard treatments.

Abdominal cramps and headache were the most frequently reported adverse events (in 15.1% and 12.4% of children, respectively) that were observed at one or more of the four time points after treatment. However, these were also the most frequently observed clinical signs and symptoms before treatment (Fig. 2, and Table S4 in the Supplementary Appendix). Overall, 147 children (30.9%) had a total of 349 adverse events, all of which were mild except for 2 moderate episodes observed in 1 child.

DISCUSSION

Given the trichuricidal properties of oxantel pamoate,[13-20] we assessed this drug in a randomized, controlled trial in a highly endemic area.[7,10] Because the geographic distribution of *T. trichiura* and other soil-transmitted helminth infections overlap,[1,2,28] we combined oxantel pamoate with albendazole to further the spectrum of activity against multiple soil-transmitted helminths. We chose albendazole because it shows the highest activity among the anthelmintic drugs currently on the market against hookworm infection.[6]

We found that oxantel pamoate (with or without albendazole) was significantly more efficacious against *T. trichiura* than was albendazole or mebendazole monotherapy. Furthermore, egg-reduction rates were more than 90% in the two treatment groups that included oxantel pamoate. As we had anticipated, oxantel pamoate showed little effect against hookworm infection.[15] In addition, little effect was observed with oxantel pamoate against *A. lumbricoides*.

As expected, albendazole showed high efficacy against hookworm and *A. lumbricoides* infections, whereas mebendazole showed only low-to-moderate activity against hookworm but high efficacy against *A. lumbricoides*.[6] The low cure and egg-reduction rates with albendazole and mebendazole among children with *T. trichiura* infection corroborate findings from prior studies.[7,10,29] Particularly low cure rates were observed among children with moderate- or high-intensity *T. trichiura* infection, regardless of whether albendazole or mebendazole was administered.

In addition, only approximately half the children presenting with moderate or heavy infection at baseline received a diagnosis of no infection or light infection after treatment with albendazole or mebendazole. These are worrying findings, because the WHO recommends the periodic administration of albendazole and mebendazole for control of morbidity due to soil-transmitted helminthiasis, but clearly, the stated goal — to reduce illness from infection with soil-transmitted helminths in school-age children to below a level that would be considered a public health problem (i.e., to reduce soil-transmitted helminth infection of moderate and high intensity among school-age children to <1%) — was not met in our study.

Adverse events, most of which were mild, were observed in approximately 30% of the children. The number of clinical symptoms observed before treatment was similar to that after treatment. The somewhat higher frequencies of symptoms in the two groups that received oxantel pamoate, as compared with the groups that received albendazole or mebendazole, had been observed even before administration of the drug. Hence, there is no indication of an increase in adverse events in the treatment groups that received oxantel pamoate, as compared with the groups that received a standard treatment. Given the limited absorption of oxantel pamoate from

Figure 2. Clinical Symptoms and Adverse Events.

Spider plots indicate the percentage of observed clinical symptoms (before treatment) and adverse events (after treatment) in the four treatment groups. Oxantel pamoate was administered on the first day of treatment, whereas albendazole and mebendazole were administered on the second day of treatment.

the gastrointestinal tract, as reported in the veterinary health literature, our findings seem reasonable.[30] Nevertheless, the safety of oxantel pamoate warrants further scientific inquiry. Drug interaction between albendazole and oxantel pamoate should be studied in particular, because it would be operationally more convenient to administer both drugs simultaneously.

In conclusion, the combination of oxantel pamoate and albendazole had significantly higher efficacy against *T. trichiura* than did albendazole or mebendazole. Moderate and heavy *T. trichiura* infection intensities were cleared in a large proportion of the children after the administration of oxantel pamoate (with or without albendazole) — results that contrast with findings after standard treatments. Hence oxantel pamoate, particularly in combination with albendazole, could be useful in the global strategy for the control of soil-transmitted helminthiasis.

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