A randomized controlled trial comparing mebendazole and albendazole against *Ascaris*, *Trichuris* and hookworm infections

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Abstract

The efficacies and side effects of single dose treatments with 500 mg mebendazole (Janssen Pharmaceutica) and 400 mg albendazole (SmithKline Beecham) against intestinal nematodes were compared in a single-blind, randomized controlled trial among 2294 children aged 6 to 12 years on Pemba Island, Zanzibar, among whom infections with *Ascaris*, hookworms and *Trichuris* were highly prevalent. Both drugs were highly effective against *Ascaris*, with cure rates of over 97%. The cure rates for *Trichuris* were low, but both were highly effective against hookworms. Albendazole was found to be the most appropriate for mass treatment, giving similar results to a 600 mg dose and being more effective than a 200 mg dose (Janssen unpublished clinical research report, 1985). Mebendazole was introduced into human therapy against intestinal helminths in 1972 by Janssen Pharmaceutica as a single or twice daily dose of 100 mg for a maximum of 3 d. In 1980 a single dose preparation of 500 mg was developed for use in mass treatment, giving similar results to a 600 mg dose and being more effective than a 200 mg dose (Janssen unpublished clinical research report, 1985). Albendazole, a product synthesized by SmithKline Beecham Pharmaceuticals, was introduced as a single dose drug against soil transmitted nematodes in the early 1980s and its efficacy has been well documented (Hanjet & Mathias, 1991). A dose of 400 mg was found to be the most appropriate for mass chemotherapy (Fene et al., 1981).

A large trial using the recommended single dose of 500 mg mebendazole and 400 mg albendazole, against the 3 most important soil transmitted helminths.

Generic mebendazole can be manufactured in different polymorphic forms which have been reported to be less effective than the original product (Charoenlarp et al., 1992). We therefore also compared the efficacy of mebendazole (Janssen) and a generic mebendazole manufactured by Pharmamed, available through the International Dispensary Association (IDA) and UNICEF at a very low cost.

Subjects and Methods

The trial was conducted on the island of Pemba, Tanzania, by the staff of the Pemba Helminth Control Programme. Important features of the island have been described in detail elsewhere (Savioli et al., 1989).

Previous studies had indicated that the prevalence of intestinal nematode infections among schoolchildren aged 6-12 years on Pemba was likely to be in excess of 90% (Pampiglione et al., 1987). Ten schools were included in the study, the pupils of which had never before been treated against intestinal helmints. One week before starting the trial, consent for participation was sought from the parents of the children; there was no refusal. The study was designed as a single-blind, randomized controlled trial. Before the start of the trial sequentially numbered envelopes were prepared, each envelope containing a single dose of one of the 2 anthelminthic drugs. Half of the envelopes, selected using computer generated random numbers, contained albendazole 400 mg (SmithKline Beecham) and the other half mebendazole 500 mg (Janssen Pharmaceutica).

In the period from October 1992 to February 1993, containers were given to children who were asked to bring a stool sample on the following day. About 110 faecal specimens were collected each day, allocated a trial number sequentially, and whichever treatment was in the envelope with that number was administered to the child on the spot. The samples were taken to the field laboratory on the same day and examined by the Kato-Katz technique, following World Health Organization recommendations (WHO, 1993). Egg counts for hookworms were performed within one hour, before the eggs became invisible due to the glycerol treatment of the specimen. If a smear contained too many eggs to be counted reliably (more than about 10 000 eggs/g of faeces for any of the 3 parasites), the sample was processed by the modified Stoll dilution technique (De Carneri, 1992) and re-examined.

A random sample of 15% of faecal smears was re-examined by one of us (M.A.) to monitor the accuracy of the treatment of the egg counts. Most repeated examinations produced counts within 10% of the original counts.
In the initial part of the trial (the first 1360 children), children found to be relatively heavily infected with one of the helminths (>25000 eggs/g of Ascaris, or >6000 eggs/g of Trichuris, or >3000 eggs/g of the hookworms) were questioned in private by a health worker, using an open-ended questionnaire 7 days after treatment, about any problems or symptoms experienced after consumption of the drugs.

An attempt was made to collect a second stool sample from each child in the trial 21 days after treatment. If a child was absent from school or failed to produce a faecal specimen for any reason, he or she was asked to bring a sample the following day. This request was repeated up to 28 days after treatment if necessary.

In addition to the comparison of albendazole and mebendazole, a smaller trial was performed to compare the efficacies of mebendazole 500 mg (Janssen Pharmaceutica) and mebendazole 500 mg (Pharmamed). The same criteria were used for the enrolment of children in the trial and the same randomization and parasitological diagnostic techniques were followed.

Data for all children in the 2 trials were entered and analysed on a microcomputer using the EpiInfo database package. ‘Cure’ rates following drug treatment were estimated as the proportion of children excreting eggs of any particular nematode before treatment who had a zero count after treatment. Proportions were compared using standard $\chi^2$ tests. Geometric mean egg counts were estimated as $\exp[(\log_e (c+1))/n]-1$, where $c$ was the count (eggs/g) for a particular individual and $n$ the number of
samples. Geometric means were compared using t tests. Changes in egg counts within individuals were compared by calculating, for each child, $D_i = \log_{10}(c_i + 1) - \log_{10}(c_0 + 1)$, where $c_0$ was the egg count before treatment, $c_i$ the egg count after treatment and $D_i$ the difference for the $i$th child. Differences between the 2 treatments were compared using $t$ tests and the percentage egg reduction induced by treatment was estimated as $100[1 - \exp(-D)]\%$, where $D$ was the mean difference for a particular treatment.

### Results

Between October 1992 and February 1993, 2687 children brought a stool sample to the study team before entry to the trial comparing albendazole and mebendazole. Of these, 37 (1.5%) were not examined because the sample was either insufficient or too liquid. A few samples were not processed because of confusion over labelling. Altogether, 2650 children were treated with either albendazole or mebendazole and had egg counts performed on their stool samples. Two children were excluded subsequently, because they had no egg in their stool specimens of any of the 3 nematodes which were the subjects of study. Of the remaining 2648 children, second stool samples were collected from 2294 (87%) between 18 and 31 d after treatment (mean of 22.5 d); 95% of the second specimens were collected between 21 and 28 d after treatment. A second stool sample was not collected from 148 (11%) of the 1326 children treated with albendazole and from 206 (16%) of the 1326 children treated with mebendazole ($P<0.01$).

Among the children who had relatively high numbers of eggs of at least one of the parasites examined in their stool sample, 144 treated with albendazole and 118 treated with mebendazole were included in the study of possible side-effects of the drugs. The frequencies of the different symptoms reported by the children (for the 7 d following treatment) were not significantly different between the 2 treatment groups. The percentages of children reporting symptoms, other than passing worms, following albendazole and mebendazole treatment, respectively, were: headache, 9.7% and 12.7%; abdominal discomfort, 9.0% and 9.3%; diarrhoea 4.9% and 3.4%; nausea, 0.7% and 0.8%; itching, 1.4% and 0.8%; rash, 1.4% and 0.0%; fever, 0.0% and 1.7%; and vomiting, 0.0% and 0.8%.

The geometric mean egg counts (before treatment) of the children who provided a post-treatment stool sample were compared with the counts of children who did not provide a second sample. The mean counts in the 2 groups of children did not differ significantly for *Ascaris* or hookworms but, for *Trichuris*, children from whom a second sample was not obtained had lower egg counts, on average (the geometric mean counts were 658 and 525 eggs/g, $P<0.05$). A similar trend was apparent in children treated with either of the 2 drugs, though in neither case individually were the differences significant.

The Figure shows the distribution of egg counts for the 3 helminths before, and 3 to 4 weeks after, treatment. The geometric mean egg counts before and after treatment and the 'cure' rates are given in Table 1, together with the percentage reductions in the egg counts induced by the 2 treatments.

Both drugs were very effective at eliminating *Ascaris*, each inducing cure rates of $\geq 97%$. The percentage reduction in the geometric mean egg count was slightly greater for albendazole than mebendazole but this was due, at least in part, to the pre-treatment egg counts being higher among children who received albendazole ($P<0.05$). Neither drug produced a high cure rate for hookworms, but that induced by albendazole was significantly ($P<0.001$) greater than that induced by mebendazole. Similarly, the reduction in egg count produced by albendazole was significantly higher than that produced by mebendazole ($P<0.001$).

The cure rates for *Trichuris* were low for both drugs, but that among children receiving mebendazole was marginally, but significantly ($P<0.01$), higher than that among those receiving albendazole. Also, the percentage reduction in the geometric mean egg count was greater with mebendazole than with albendazole ($P<0.001$).

In the trial comparing 2 formulations of mebendazole (Table 2), 555 children provided a pre-treatment stool sample for egg counts to be assessed. A second stool sample was collected from 402 (72%) of the children between 21 and 24 d after treatment. The percentage of children from whom a second stool sample was obtained was similar for those treated with mebendazole (Pharmamed) (70%) and mebendazole (Janssen) (72%). With none of the helminths examined was there a marked or significant difference in the cure rates or percentage reductions in egg counts.

### Table 1. Pre- and post-treatment stool egg counts of *Ascaris*, hookworm and *Trichuris* among children treated with single doses of albendazole (SmithKline Beecham, 400 mg) or mebendazole (Janssen, 500 mg)

<table>
<thead>
<tr>
<th>Helminth</th>
<th>Treatment</th>
<th>No. of children</th>
<th>No. excreting eggs*</th>
<th>'Cure' rate (%)</th>
<th>Geometric mean eggs/g</th>
<th>Percentage reduction in egg counts***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before + after treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ascaris</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>1174</td>
<td>818</td>
<td>9</td>
<td>98.9</td>
<td>239</td>
</tr>
<tr>
<td></td>
<td>Mebendazole</td>
<td>1120</td>
<td>730</td>
<td>3</td>
<td>97.8</td>
<td>164</td>
</tr>
<tr>
<td><em>Hookworm</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>1174</td>
<td>1048</td>
<td>453</td>
<td>56.8***</td>
<td>391</td>
</tr>
<tr>
<td></td>
<td>Mebendazole</td>
<td>1120</td>
<td>1011</td>
<td>785</td>
<td>22.4</td>
<td>432</td>
</tr>
<tr>
<td><em>Trichuris</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>1174</td>
<td>1138</td>
<td>1018</td>
<td>10.5**</td>
<td>655</td>
</tr>
<tr>
<td></td>
<td>Mebendazole</td>
<td>1120</td>
<td>1095</td>
<td>939</td>
<td>14.2</td>
<td>658</td>
</tr>
</tbody>
</table>

*Significant differences between drug treatments are indicated thus: $*P<0.05$, $**P<0.01$, $***P<0.001$.

### Table 2. Pre- and post-treatment stool egg counts of *Ascaris*, hookworm and *Trichuris* among children treated with single doses of 500 mg of mebendazole (Pharmamed) or mebendazole (Janssen)

<table>
<thead>
<tr>
<th>Helminth</th>
<th>Source of mebendazole</th>
<th>No. of children</th>
<th>No. excreting eggs*</th>
<th>'Cure' rate (%)</th>
<th>Geometric mean eggs/g</th>
<th>Percentage reduction in egg counts***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before + after treatment</td>
<td>No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ascaris</em></td>
<td>Pharmamed</td>
<td>147</td>
<td>133</td>
<td>96.6</td>
<td>252</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Janssen</td>
<td>139</td>
<td>131</td>
<td>97.8</td>
<td>269</td>
<td>0.08</td>
</tr>
<tr>
<td><em>Hookworm</em></td>
<td>Pharmamed</td>
<td>192</td>
<td>159</td>
<td>17.2</td>
<td>514</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Janssen</td>
<td>178</td>
<td>154</td>
<td>13.5</td>
<td>472</td>
<td>128</td>
</tr>
<tr>
<td><em>Trichuris</em></td>
<td>Pharmamed</td>
<td>207</td>
<td>188</td>
<td>9.2</td>
<td>979</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>Janssen</td>
<td>190</td>
<td>167</td>
<td>12.1</td>
<td>838</td>
<td>152</td>
</tr>
</tbody>
</table>

*See note b to Table 1; no difference between the 2 drugs was significant.
duction in geometric mean egg counts resulting from the 2 treatments.

Discussion

This trial has confirmed the findings of previous smaller studies that both albendazole at 400 mg and mebendazole at 500 mg are highly effective single dose treatments of infections with Ascaris (SINNIAH et al., 1990). After administration of either drug, few eggs were found in the stools of children 3–4 weeks after treatment. Albendazole has been reported to be more effective than mebendazole against hookworms (HOLTER & FREY, 1987; ISMAIL et al., 1991), and our results confirmed this. The geometric mean egg count was reduced by 98% by albendazole, compared to 82% by mebendazole. Neither drug was very effective in clearing Trichuris infections but both reduced the egg counts by at least 50%. The follow-up rate after treatment was higher for children treated with albendazole (89%) than for those treated with mebendazole (84%), a potential source of bias in our results; the explanation is unclear. Most children who were not resurveyed after treatment had moved to another school or the school had been closed for 4 days at short notice. It is unlikely that these aspects could have affected the 2 treatment groups differentially other than by chance. Some were absent from school when the resurvey was undertaken and, although it is conceivable that such absences were related to the effectiveness of the drugs, we could find no evidence of any difference in side-effects reported by children following the 2 treatments. It seems to us most likely that the difference in follow-up rates was a chance finding.

Although the cure rates with Trichuris were low, both drugs produced substantial reductions in egg loads, with mebendazole being slightly more effective than albendazole. These levels of effect may be sufficient to control the morbidity effects of the infection. The cure rates found for Trichuris were markedly lower than those reported in other studies that used albendazole (SINNIAH et al., 1990; ISMAIL et al., 1991; P. Jongskutsungit, personal communication, 1992). A possible explanation could be related to the high prevalence of multiple nematode infections associated with Trichuris in Pemba (94% of those infected with Trichuris were also infected with Ascaris and/or hookworms). However, when we restricted comparison of the 2 drugs to the small number of children with no evidence of infection with Ascaris or hookworms, the cure rates were not markedly greater than those with all children treated (albendazole, 16% (7/44); mebendazole, 15% (7/47)). Another possible reason could be related to the high number of relatively heavy Trichuris infections. We found significant, but only small, differences in the cure rates among children with pre-treatment egg counts of less than 1000 eggs/g and those with 1000 or more; albendazole, 12.5% and 8.2% (P<0.05) and mebendazole, 17.3% and 10.5 (P<0.01), respectively.

Our results have significant implications for the use of targeted chemotherapy at the community and school level for the control of morbidity due to soil transmitted nematodes.

Mebendazole (Janssen) is about 2-5 times more expensive than albendazole (SmithKline Beecham), which costs about US$ 0.30/dose. However, mebendazole is produced in generic form at substantially lower cost and is available at 50-0.27/dose (Pharmamed). We found no material difference in the effectiveness of these 2 formulations in reducing worm burdens. Thus, although albendazole is significantly more effective against hookworms than mebendazole, the cost of the latter drug may be much lower and this may be a key consideration in choosing which drug to use in a control programme, bearing in mind the considerable reduction in hookworm egg counts that were induced by mebendazole. Of course the purchasing cost of drugs may vary according to the size of the supply and to possible special agreement with the manufacturers.

Where hookworms are the main parasite, and cost is not a critical consideration, albendazole is likely to be the drug of choice. Where mixed infections are prevalent, the choice of the cheaper alternative, in spite of a lower efficacy against the hookworms, might be considered.

The children in the study have been re-examined 4 and 6 months after treatment. Analysis of these data will indicate for how long the reduction in prevalence and intensity of infections and the treatment differences are preserved and will guide the choice of the interval between treatment for morbidity control.

Further studies using morbidity indicators, in addition to worm burden, should be conducted in order to obtain a more comprehensive insight into the impact of periodical chemotherapy with albendazole or mebendazole on the health of children in areas endemic for soil-transmitted nematodes.

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sui parassiti intestinali dell'uomo in Africa subsahariana. III.


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