There is no consensus on the benefits of treatment with any specific anthelminthic compound on muscle-stage trichinosis. A double-blind, placebo-controlled comparison was done of 3 antiparasitic drugs during an outbreak of trichinosis in Chiangrai Province, northern Thailand. Forty-six adults were randomized to receive 10 days of oral treatment with mebendazole (200 mg twice a day), thiabendazole (25 mg/kg twice a day), fluconazole (400 mg initially, then 200 mg daily), or placebo. All patients received treatment to eradicate adult intestinal worms. Trichinella spiralis infection was proved parasitologically in 19 (41%) of 46 patients and by serodiagnosis in all cases. Significantly more patients improved after treatment with mebendazole (12/12) and thiabendazole (7/7) than after treatment with placebo (6/12; \( P < .05 \)) or fluconazole (6/12). Muscle tenderness resolved in more patients treated with thiabendazole and mebendazole than in those treated with placebo (\( P < .05 \)). However, 30% of volunteers could not tolerate the side effects of thiabendazole. In summary, Trichinella myositis responds to thiabendazole and to mebendazole.

Human trichinellosis, more commonly called trichinosis, is most common in Asia, Latin America, and Central Europe. The prevalence of Trichinella spiralis in domestic swine ranges from 0.001% in the United States to >25% in parts of China. After ingestion of Trichinella-contaminated meat, larvae are released in the stomach and mature into adults in the small bowel. Mature female parasites release newborn larvae that are carried by lymph and blood throughout the body and may enter striated muscle.

There is no consensus on how best to manage the muscle-invasion phase of trichinosis. Comparative studies have failed to demonstrate a clear-cut advantage of one anthelminthic compound over another [1, 2], and no specific chemotherapeutic agent has proved beneficial. Some authorities believe that corticosteroids play a greater role in the management of severe muscle disease than do antiparasitic drugs [3]. We compared the efficacy of 3 drugs with that of a placebo during a trichinosis outbreak in a village in Chiangrai Province, northern Thailand, where ~200–600 cases occur annually during communal feasts celebrating the Thai New Year. Mebendazole and thiabendazole are the most widely used anthelminthics for trichinosis. The third drug evaluated was fluconazole, a better-absorbed derivative of ketoconazole that has known antitrichinella properties [4]. Fluconazole’s efficacy against muscle larvae in mice is as effective as that of mebendazole (authors’ unpublished data). The newer benzimidazole, albendazole, has been used to treat trichinosis [5, 6] but was not chosen because it is less active than mebendazole on muscle-stage parasites in mice [7].

Patients and Methods

Patients. A study team (2 physicians, 4 nurses, and 5 technicians) from the Armed Forces Research Institute of Medical Sciences, Bangkok, was notified when an index case was identified and traveled the same day to the outbreak site. Villagers who shared the infective meal were traced. Febrile males and nonpregnant females >18 years old were eligible if there was myalgia and/or muscle tenderness plus eosinophilia and/or elevated serum creatinine phosphokinase (CPK) concentration. Patients with life-threatening complications were not enrolled.
Patients were randomized to receive 1 of 4 oral regimens: (A) mebendazole, 200 mg twice a day for 10 days; (B) thiabendazole, 25 mg/kg twice a day for 10 days; (C) fluconazole 400 mg on day 1 then 200 mg/day for 9 days; or (D) placebo (1 multivitamin twice a day) for 10 days. Medication for each patient was dispensed in a prelabeled vial coded only with a study number and a letter (A, B, C, or D). Patients who vomited within 1 h were redosed. All patients received treatment to eradicate adult worms from the small intestine. The treatment of groups A and B was adequate for this purpose [8]; groups C and D were given pyrantel, 11 mg/kg for 5 days [9]. Salicylates and acetaminophen were dispensed to control headache, myalgia, and fever. Patients with severe muscle pain refractory to analgesics were given 40–60 mg per day of prednisolone [8].

**Trichinosis diagnosis.** Venous blood samples (5 mL) taken on days 0 and 3 were passed through a 3-µm-pore filter that was examined under direct microscopy for migrating L1 larvae [8]. Muscle biopsies were performed on 8 randomly selected volunteers 4 months after study enrollment. Indirect ELISA and Western blot analysis using crude somatic antigens [10] were done on serum samples obtained on the first treatment day (day 0) and 2 and 4 months later.

**Treatment response.** Treatment was considered to be effective if myositis resolved more quickly than it did in placebo-treated controls. Therapy was judged ineffective if myositis worsened. The severity of myositis was measured objectively prior to, during, and after treatment, by the presence of muscle tenderness and by raised serum concentrations of CPK and lactate dehydrogenase (LDH). Symptoms and signs were recorded, by medical personnel who were blinded as to treatment group, twice daily for the first 10 days, then on days 14, 21, and 28 and once monthly for an additional 3 months. Patients in whom severe myositis or fever >39.0°C persisted after completing therapy were classified as treatment failures; the study code was broken, and a 10-day course of mebendazole was administered. Patients unable to tolerate study medication were excluded and treated with mebendazole, the routine treatment for trichinosis in Thailand.

**Statistical analyses.** Findings in the 3 treatment groups were compared with the placebo group by the Mann-Whitney U test for median values, by 2-sample t test for mean values, and by Fisher’s exact test for proportions. Corticosteroid requirements for the 3 treatment groups were compared with placebo by the χ2 test with Yates’s correction. Median serum CPK and LDH concentrations on days 3 and 7 were compared with baseline values by paired Wilcoxon signed rank test. Two-sided significance testing was done in all cases. Differences were considered significant at P < .05.

### Results

**Patients.** Two pigs illegally imported from Burma were the probable source of *Trichinella*-contaminated pork. Forty-six volunteers from the same village (Phasak Noi) were enrolled in the study over a 5-day period. Twelve patients each were randomized to receive placebo, fluconazole, and mebendazole; 10 were given thiabendazole. Subjects in the 4 treatment arms were comparable with respect to age, sex, admission temperature, eosinophil count, and serum albumin level. Median serum CPK and LDH concentrations were significantly higher than placebo group values only in thiabendazole-treated patients (CPK, 371 vs. 165 U/mL, P = .02; LDH, 374 vs. 210 U/mL; P = .03, Mann-Whitney U test). The most frequent clinical manifestations at admission were myalgia (100%), periorbital edema (72%), muscle tenderness (72%), and headache (61%).

Presenting clinical manifestations did not differ significantly between groups. During treatment, 70% of patients had fever of >40.0°C, and both pruritus and ocular signs were common (table 1).

**Diagnosis.** Parasitologic proof of trichinosis was obtained in 19 patients (41%), and circulating larvae were detected in 14 of 46 patients. Indirect ELISA and Western blot immunoassays were reactive with 81% and 92% of admission serum samples, respectively, and with 100% of serum samples taken 2 and 4 months later.

**Treatment response.** Three of 10 patients who were given thiabendazole had intolerable dizziness, were retreated with mebendazole, and were excluded from further evaluation. Treatment failed in half the patients randomized to receive fluconazole or placebo. These patients were given mebendazole and were not followed long-term. None of the 7 patients who completed thiabendazole and none of the 12 mebendazole-treated patients had treatment failure (P = .04 and .01, respectively, compared with placebo). Muscle tenderness resolved in significantly more patients treated with thiabendazole and mebendazole (P = .04 and .01, respectively) than in those treated with placebo. All patients were ambulatory at the time of study entry, but half the placebo-treated volunteers became unable to walk because of increasing muscle pain and weakness. Significantly fewer patients in the thiabendazole and mebendazole groups became unable to walk (table 2). No thiabendazole-treated subjects had lower serum albumin concentrations on day 7 than

### Table 1. Symptoms and signs during treatment.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo (n = 12)</th>
<th>Fluconazole (n = 11)</th>
<th>Mebendazole (n = 12)</th>
<th>Thiabendazole (n = 7)</th>
<th>Total (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;40.0°C</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Urticaria</td>
<td>17</td>
<td>27</td>
<td>33</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Ocular signs</td>
<td>33</td>
<td>46</td>
<td>42</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Pruritus</td>
<td>75</td>
<td>55</td>
<td>67</td>
<td>86</td>
<td>69</td>
</tr>
<tr>
<td>Rash</td>
<td>42</td>
<td>9</td>
<td>0</td>
<td>57</td>
<td>24</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % of patients, by treatment group.
on day 0 (P = .03 vs. placebo). Thiabendazole-treated patients had significantly lower CPK levels on days 3 and 7 and significantly lower LDH levels on day 3, compared with placebo-treated subjects. There was a nonsignificant trend for CPK and LDH levels to be higher on day 7 than at baseline in the placebo group.

Each patient could receive prednisolone for a maximum of 9 days. Placebo group volunteers received prednisolone on 54 of 108 possible days. Mebendazole-treated subjects were given corticosteroids less often than were placebo-treated subjects (38 of 108 days, P = .04). Prednisolone use was not reduced in thiabendazole-treated (30 of 63 days, P = .89) or fluconazole-treated subjects (49 of 108 days, P = .59), compared with placebo-treated subjects. Only 10 of the 43 volunteers were never given prednisolone—3 each in the mebendazole, fluconazole, and placebo groups and 1 in the thiabendazole group.

Fifteen patients were not followed long-term: 1 died, 11 had treatment failures, and 3 were unable to tolerate thiabendazole. Of the remaining 31 eligible patients, 29 (94%) were monitored successfully for 4 months. Of the 6 placebo group volunteers followed long-term, 17% were working and were myalgia-free at 1 and 2 months, 33% at 3 months, and 50% at 4 months. For 6 fluconazole-treated persons, these percentages at 1–4 months were 17%, 83%, 83%, and 100%, respectively. Half the 12 mebendazole-treated patients were working and were myalgia-free at 1 and 2 months; 67% and 100% were myalgia-free at 3 and 4 months, respectively. Of the 5 thiabendazole-treated subjects, 4 were working and were myalgia-free at 1 and 2 months; all were free of muscle symptoms at 3 and 4 months. There were no significant differences in the percentages of patients free of muscle pain and able to work in the 3 treatment arms, compared with the placebo group. Gastrocnemius muscle biopsies were performed at 4 months on 3 placebo group patients; there were no cysts in 1 specimen, 23 cysts/g in the second, and 446 cysts/g in the third. The 2 biopsy specimens from fluconazole-treated subjects contained 53 and 118 cysts/g, respectively. No cysts were found in the 1 specimen from a subject treated with mebendazole or in the 2 specimens from thiabendazole-treated subjects.

**Discussion**

This study provides the first proof that any anthelminthic drug is effective for muscle-stage trichinosis. Myositis worsened in half the subjects who received either placebo or fluconazole but was alleviated by both thiabendazole and mebendazole therapy. Thiabendazole and mebendazole, but not fluconazole, halted disease progression so that patients remained ambulatory (P < .05, compared with placebo; table 2). Compared with baseline values, there were significant reductions in muscle enzyme concentrations on days 3 and 7 and significant increases in day 7 albumin levels in the thiabendazole group only (table 2). Hypoalbuminemia is a marker of severe trichinosis and is thought to be related to protein use by larvae growing in muscle [11]. The possible therapeutic advantages of thiabendazole, however, were offset by its side effects. Thiabendazole was no more effective than placebo if the 3 patients intolerant of the drug were classified as having failed treatment.

Volunteers randomized to receive fluconazole or placebo were given pyrantel to eradicate adult parasites from the intestine. The efficacy of pyrantel against intestinal trichinellae has not been compared with that of mebendazole or thiabendazole in controlled human trials. Study volunteers were given a high dose of pyrantel [8, 9], but larvae produced during treatment could have invaded muscle. Our results, therefore, might reflect drug activity against intestinal and migrating parasites as well as against muscle parasites. Prednisolone was dispensed significantly less often to thiabendazole-treated subjects only, but corticosteroid use is a less-objective marker of treatment response than either raised muscle enzyme levels or muscle tenderness. No statistically significant long-term benefits could be demonstrated for any drug compared, with placebo. However, only two-thirds of the original cohort was followed for 4 months; one-third required retreatment with mebendazole and was excluded from further evaluation. By 4 months, all patients treated with thiabendazole, mebendazole, and fluconazole were free of muscle pain and could work compared, with 3 of 6 placebo recipients.

Disease manifestations were more severe than anticipated.
Patients often required home visits because they were unable to walk, and 1 patient randomized to receive fluconazole died. However, it is difficult to link the fatality to fluconazole. This subject was referred to hospital before complications began, deteriorated during 5 days of mebendazole therapy, and then died of ventilatory failure. Another villager not enrolled in the study also died of ventilatory failure and had been treated with mebendazole from the outset. Fatal cases of trichinosis are not unusual and occur during most large outbreaks [10, 12–14].

Both thiabendazole and mebendazole were effective against muscle larvae; however, thiabendazole was poorly tolerated, and mebendazole was perhaps less active. Albendazole was not chosen for our study because of its reported effectiveness [10] and merits further evaluation. Investigations to optimize treatment regimens for extraintestinal disease are urgently required. Trichinosis remains a major public health problem in some areas [12], and improvements in the therapy of severe cases could be lifesaving.

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