ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1986, p. 953–954
0066-4804/86/120953-02$02.00/0

Vol. 30, No. 6

Comparative Efficacy of Ketoconazole and Mebendazole in Experimental Trichinosis

JOHN A. HESS,[1]* PRANATHARTHI H. CHANDRASEKAR,[2] MARK MORTIERE,[3] AND JOHN A. MOLINARI[3]

Departments of Anatomy[1] and Microbiology and Biochemistry,[3] School of Dentistry, University of Detroit, Detroit, Michigan 48207, and Department of Internal Medicine, Division of Infectious Diseases, Wayne State University School of Medicine, Detroit Receiving Hospital, Detroit, Michigan 48201[2]

Received 23 December 1985/Accepted 15 September 1986

The therapeutic efficacy of ketoconazole and mebendazole was studied in ICR/CD-1 mice infected with *Trichinella spiralis* for 17 to 20 weeks. Efficacy of both drugs was over 70% when compared with results in control mice. This study indicates that both ketoconazole and mebendazole should be considered in the treatment of trichinosis in humans.

The benzimidazoles are considered the agents of choice in treating the muscle phase of trichinosis (2). Although thiabendazole has been in use for several years, it has now been replaced by the more effective drug mebendazole (methyl 5-benzoyl-2-benzimidazole carbamate (12). Several recent reports documented the efficacy of mebendazole in experimental and human trichinosis (3, 9, 11, 14). However, the effectiveness of drug therapy during the late muscle stages (several months after ingestion of the parasite) of trichinosis has not been adequately examined. Successful treatment with prolonged, high-dose mebendazole in chronic human trichinosis has been reported in one instance (7).

The present preliminary investigation concerned the therapeutic activity of mebendazole in experimental trichinosis during the fully encysted chronic phase and compared its anthelminthic activity with that of another imidazole, ketoconazole. Ketoconazole is a well-known antifungal agent; however, its anthelminthic activity has heretofore not been investigated.

The ICR/CD-1 mice were 8 to 10 weeks old and weighed 30 to 33 g at the time of exposure to infection. The *Trichinella spiralis* larvae were harvested, and the animals were infected with a modification of the pepsin-hydrochloric acid digestion method described by Larsh and Kent (6).

Mice harboring the infection for 17 to 20 weeks were randomly divided into three groups, with one group receiving ketoconazole, another receiving mebendazole, and the third serving as the control group. Each drug was given orally in three regimens (Table 1). Suspensions of commercial formulations of ketoconazole (200 mg of ketoconazole per Nizoral tablet [Janssens Pharmaceutica, Beerse, Belgium]) and mebendazole (100 mg of mebendazole per Vermox tablet [Janssens]) were used for inoculation. Each animal received the specified dose of 0.1 ml/10 g of body weight (Table 1).

Necropsy of mice was carried out 4 days after completion of therapy. *T. spiralis* infection was established by examination of the diaphragm from each animal prior to nematode isolation. The number of larvae present was estimated by sampling and adjusted with distilled water to the appropriate dilution. Larval counts from each group of infected mice (each mouse weighed approximately 35 g) were pooled and reported in Table 1 as the total worm burden per group. During the larval count, the size, appearance (coiled or uncoiled), and motility of the larvae also were recorded.

Tissue samples from the diaphragm and psoas muscles were fixed in 10% neutral buffered Formalin, embedded in paraffin, and cut in 6-μm sections. These sections were stained with Harris hematoxylin and eosin.

Table 1 shows the relative efficacies of different regimens of mebendazole and ketoconazole for mice with chronic trichinosis. The number of larvae in the groups of mice treated with either drug was considerably less than that noted in control mice. Marked reduction in the mean worm burden was noted in group 1 mice treated with 12.5 mg of mebendazole or ketoconazole per kg pf body weight twice daily for 4 days. A similar reduction in the worm burden was noted when the same dose of either drug was given only once orally (group 2) but for a longer period (8 days). With a larger dose (group 3; 25 mg/kg), reduction in worm burden was slightly less than that seen in groups 1 and 2 but not significantly different.

The microscopic appearance of the diaphragms taken from the infected control animals showed that the larvae were normal in size and were tightly coiled in well-developed cysts between the muscle fibers. The capsules were surrounded by a mild inflammation consisting mainly of lymphocytes, mononuclear phagocytes, and foreign-body giant cells. Most of the larvae from the drug-treated mice were less than normal in size, loosely coiled or arclike, and motionless. However, the viability of larvae from either control or drug-treated mice was not determined. In the infected ketoconazole-treated mice, the inflammatory reaction appeared moderate, whereas in the infected mebendazole-treated mice, the reaction was considered intense when compared with the reaction in control mice. Histologically, there did not appear to be any differences between those mice receiving 12.5 mg and those receiving 25 mg of the same drug per kg.

Mebendazole is considered the most effective anthelminthic agent for the muscle phase of trichinosis. Mebendazole given at a dose of 12.5 mg/kg of body weight twice daily for 3 days significantly reduced the number of encysted larvae in mice after 28 days of infection (9). Our study showed similar efficacy with the same dose of mebendazole given twice daily for 4 days in mice after several months of infection. Drug efficacy was not diminished by an 8-day regimen of mebendazole given once daily (group 2). Although the dose employed in the study is higher than the recommended dose

* Corresponding author.

TABLE 1. Number of *T. spiralis* larvae recovered from the musculature of control mice and mice treated with various regimens of mebendazole or ketoconazole

Group	Dose (mg/kg)	Length of therapy (days)	No. of mice	Mean no. of worms (% efficacy)[a]/group treated with:		
				Control	Mebendazole	Ketoconazole
1	12.5, Twice daily	4	4	8,166	1,000 (87.7)	981 (88.0)
2	12.5, Once daily	8	6	13,150	1,533 (88.3)	2,283 (82.6)
3	25, Once daily	8	6	9,666	2,700 (72.1)	2,417 (75.0)

[a] % Efficacy = [(number of larvae in control group − number of larvae in treated group)/number of larvae in control group] × 100.

of 5 mg/kg for trichinosis in humans (12), a case report of a patient receiving 22 mg of mebendazole per kg for extended treatment periods has shown that the drug was tolerated with minimal side effects (7).

Ketoconazole has been used extensively in humans as an oral broad-spectrum antifungal agent (10). In addition, it has been shown to possess activity against many protozoa, as noted by its antimalarial activity in vitro (13) and antileishmanial and antitrypanosomal activity both in vitro and in vivo (1, 8, 15). In the present investigation, 12.5 mg of ketoconazole per kg given once or twice daily was shown to be as effective as mebendazole in chronic trichinosis. The slight decrease in efficacy of the high-dose regimen may be related to host toxicity to higher levels of imidazoles.

Mebendazole is thought to act on the polymerization of tubulin and to block microtubule assembly in helminths (4). Ketoconazole may have a similar binding affinity with larval tubulin. Both mebendazole and ketoconazole may bind sterols of helminths as ketoconazole binds the sterols of fungi, thereby interfering with the formation of cell membrane (5). Thus, both drugs may exert their effect on helminths by two mechanisms. The advantages of ketoconazole include ease of administration, broad range of activity, and patient tolerance. It should be considered for use in the treatment of trichinosis.

LITERATURE CITED

1. **Berman, J. D.** 1981. Activity of imidazoles against *Leishmania tropica* in human macrophage cultures. Am. J. Trop. Med. Hyg. **30**:566–569.
2. **Campbell, W. C., and D. A. Denham.** 1983. Chemotherapy, p. 335–366. *In* W. C. Campbell (ed.), Trichinella and trichinosis. Plenum Publishing Corp., New York.
3. **Fernando, S. S. E., and D. A. Denham.** 1976. The effects of mebendazole and fenbendazole on *Trichinella spiralis* in mice. J. Parasitol. **62**:874–876.
4. **Friedman, P. A., and E. G. Platzer.** 1980. Interaction of anthelminthic benzimidazoles with *Ascaris suum* embryonic tubulin. Biochem. Biophys. Acta **630**:271–278.
5. **Halevy, S., and L. Avivi.** 1966. Sterols of *Trypanosomidae*. Ann. Trop. Med. Parasitol. **60**:439–444.
6. **Larsh, J. E., and D. E. Kent.** 1949. The effect of ethanol on acquired immunity to infection with *Trichinella spiralis*. J. Parasitol. **35**:45–53.
7. **Levin, M. L.** 1983. Treatment of trichinosis with mebendazole. Am. J. Trop. Med. Hyg. **32**:980–983.
8. **McCabe, R. E., F. G. Araujo, and J. S. Remington.** 1983. Ketoconazole protects against infection with *Trypanosoma cruzi* in a murine model. Am. J. Trop. Med. Hyg. **32**:960–962.
9. **McCracken, R. O., and D. D. Taylor.** 1980. Mebendazole therapy of parenteral trichinosis. Science **207**:1220–1222.
10. **Negroni, R., A. M. Robles, A. Arechavala, M. A. Tuculet, and R. Galimberti.** 1980. Ketoconazole in the treatment of paracoccidioidomycosis and histoplasmosis. Rev. Infect. Dis. **2**:643–649.
11. **Ozeretskovsaya, N. N., T. M. Morentets, E. V. Pereverezeva, A. M. Bronstein, N. L. Veretennikova, M. O. Kolosova, A. M. Poverenny, V. K. Podgorod-Nichenko, and D. A. Kagorodin.** 1981. Therapeutic properties of benzimidazoles in trichinellosis and the side effects of the treatment, p. 287–290. *In* C. W. Kim, E. J. Ruitenberg, and J. S. Teppema (ed.), Trichinellosis. Reedbooks, Chertsey, England.
12. **Pawlowski, Z. S.** 1981. Trichinellosis, p. 84. *In* H. F. Conn (ed.), Current therapy. The W. B. Saunders Co., Philadelphia.
13. **Pfaller, M. A., and D. J. Krogstad.** 1981. Imidazole and polyene activity against chloroquine-resistant *Plasmodium falciparum*. J. Infect. Dis. **144**:372–375.
14. **Sonnet, J. J., and D. Thienpont.** 1977. The treatment of trichinosis with mebendazole. Acta Clin. Belg. **32**:297–302.
15. **Urcyo, F. G., and N. Zaias.** 1982. Oral ketoconazole in the treatment of leishmaniasis. Int. J. Dermatol. **21**:414–416.