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Research Note

Effects of Mebendazole and Albendazole on Secondary Alveolar Hydatid Disease in Mongolian Gerbils with Special Reference to the Timing of Treatment

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Abstract

Mebendazole and albendazole were given orally to *Meriones unguiculatus* infected with *Echinococcus multilocularis* at single doses of 50 and 100 mg/kg/day, respectively, daily from 3 to 24, 31 to 60, 61 to 90 or 91 to 120 days post-infection (p.i.). After medication, the metacestode tissues were weighed. The results showed that the drugs suppressed the growth of metacestodes if the medications were started before 61 days p.i. On the contrary, they did not suppress the growth if the medications were started after 91 days p.i. These data suggest that the efficacy of these drugs on alveolar hydatid disease depends on the timing of the treatment.

Key words: *Echinococcus multilocularis*, mebendazole, albendazole, *Meriones unguiculatus*

Alveolar echinococcosis is one of the serious parasitic diseases in the world. Surgical treatment is thought to be the most effective therapy. However, some cases are inoperable at advanced stages of the disease. Many studies have reported that benzimidazole derivatives, mebendazole and albendazole, are effective in the treatment of alveolar hydatid disease in humans and in experimental animals (Schantz *et al.*, 1982; Eckert, 1986; Rausch, 1986; Inaoka *et al.*, 1987; Vanparijis, 1990; Wilson *et al.*, 1992). Our present experiments were conducted to clarify if the efficacy of these drugs on secondary alveolar hydatid disease in Mongolian gerbils is dependent on the timing of the treatment.

E. multilocularis, Alaskan strain, has been maintained in our laboratory using Mongolian gerbils as intermediate hosts. The animals were supplied by the Department of Veterinary Science, National Institute of Health, Tokyo. Male and female animals aged over eight weeks were used. The animals were infected by intraperitoneal inoculation with about five hundred protoscoleces. The preparation of them was described previously (Kanazawa *et al.*, 1993). Briefly, secondary alveolar hydatid cysts were digested with dispase (Godo Shusei Co. Ltd., Tokyo, Japan) and protoscoleces were collected with the use of a wire mesh. Mebendazole and albendazole, kindly supplied by Janssen-Kyowa and Smith-Kline Pharmaceutica, respectively, were suspended in distilled water containing 0.5% methylcellulose (Sigma). Each group was composed of six animals (male/female: 3/3). In the control groups, infected but not medicated, 0.5 ml of distilled water containing 0.5% methylcellulose was given orally with a metal catheter to each gerbil at a single daily dose. In the medicated groups, 50 mg/kg/day of mebendazole and 100 mg/kg/day of albendazole were administered orally to each animal at a single daily dose from three to 24 days, from 31 to 60, from 61 to 90, and from 91 to 120 days post-infection (p.i.) throughout the test period. Preliminary experiments had shown that the doses of the drugs used were thought to be maximum without causing severe damage to the animals. Slight weight loss of animals was observed in the groups given mebendazole, but those treated with albendazole

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Table 1 Weight of metacestode tissue (MT) recovered from *Meriones unguiculatus* treated with mebendazole and albendazole

Medication		Number of* surviving animals	Weight of MT (g) (Mean±SD)	Reduction† rate (%)
Drug	Treatment period			
None (control)	3– 24 days p.i.	6/6	0.35± 0.03	
	31– 60 days p.i.	6/6	12.2 ± 3.6	
	61– 90 days p.i.	6/6	21.8 ± 4.1	
	91–120 days p.i.	4/6	32.0 ± 6.9	
Mebendazole (50mg/kg/day)	3– 24 days p.i.	6/6	0.05± 0.03‖	
	31– 60 days p.i.	6/6	2.8 ± 1.9‖	77
	61– 90 days p.i.	6/6	14.7 ± 3.0§	33
	91–120 days p.i.	3/6	31.7 ± 2.8	1
Albendazole (100mg/kg/day)	3– 24 days p.i.	6/6	ND‡	
	31– 60 days p.i.	6/6	2.8 ± 2.6‖	77
	61– 90 days p.i.	6/6	16.4 ± 3.0	25
	91–120 days p.i.	4/6	48.0 ±10.5	–150

*Number of surviving animals/Number of used animals

†Reduction rate = (weight of control MT – weight of treated MT)/(weight of control MT) × 100

‡Not done.

Difference was significant from the control value (paired t test). §$P<0.05$, ‖$P<0.01$

showed no such side effect (data not shown). Necropsy was carried out immediately after the end of the treatment periods. All metacestode tissues were removed from the peritoneal cavity and the organs of each animal and were weighed individually. Two animals in a control group, three in a mebendazole-treated group and two in an albendazole-treated group died after 91 days p.i.

The results are shown in Table 1. Mebendazole and albendazole suppressed the growth of secondary alveolar hydatid cysts in the groups which received the drugs before 61 days p.i. However, in the groups which had the drugs administered after 91 days p.i., neither of the drugs suppressed the growth of secondary alveolar hydatid cysts.

After treatment, a part of the metacestode tissues were minced and inoculated into parasite-free Mongolian gerbils and examined the viability. Two or three months after inoculation, living parasite tissue was present in animals. By the microscopical examination, distinct signs of destruction were discernible in metacestodes of the groups treated with mebendazole and albendazole, but mebendazole was observed to damage metacestodes to a greater degree than albendazole.

A number of studies have reported that benzimidazoles are of high therapeutic value in the treatment of hydatid disease. Taylor *et al.* (1988) reported that albendazole treatment reduced parasite weight after the therapy for 1 month which was begun 3 months after infection, using cotton rats as experimental animals, although the data were not statistically significant. It has been well known that duration of treatment is one of the important factors in evaluating effects of these drugs (Witassek *et al.*, 1981). The treatments with mebendazole and other benzimidazole compounds is equally effective when initiated 7 days or 40 days after infection and if it is carried out for at least 60 days (Eckert, 1986). In our experiments, these drugs were administered to the animals for only one month. Therefore, we do not exclude a possibility that these drugs are effective against alveolar hydatid disease if the drugs are given more than one month even 3 months p.i. However, the present results strongly suggest that the efficacy of the drugs on alveolar hydatid disease depends on the timing of the treatment.

Although it was reported that smaller cysts were

more readily treated than larger ones in human cystic hydatid disease (De Rosa and Teggi, 1990; Todorov *et al.*, 1992), we do not find the works that pointed out such relationship in human alveolar hydatid disease. In humans it is rarely possible to ascertain when a patient's infection was first acquired. The period before onset of signs and symptoms is variable, but it takes several or many years. The results in the present work may suggest importance of early diagnosis of human alveolar hydatid disease.

We got an unexpected result. Although it was not statistically significant, the metacestode tissue of the albendazole-treated group from 3 months p.i. was heavier than the one of the control group. Further experiments should be carried out to confirm it. In addition, the mechanism involved in the time-dependent lack of effectiveness of these drugs is not clear, and further studies will be necessary to determine why the responses of longer-term infection to these drugs are unsatisfactory.

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