Chemotherapy of experimental *Echinococcus multilocularis* in jirds

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**Abstract.** A total of 50 jirds (*Meriones unguiculatus*) were infected by intraperitoneal implantation of 0.20 g metacestode tissue of *Echinococcus multilocularis*. The feed of 4 groups of 10 animals each was treated for 35 days with 500 ppm albendazole, flubendazole, mebendazole or praziquantel; 1 group of 10 jirds served as unmedicated controls. At autopsy 2 weeks after the end of medication, the transplants had increased in size and weight, reaching a total weight of 78.11 g in the control group, 21.60 g in the albendazole-treated group, 3.63 g in the flubendazole-treated group, 7.00 g in the mebendazole-treated group and 68.91 g in the praziquantel-treated group. The percentage in reduction of parasitic tissue weight as compared with control values was 72%, 95%, 91% and 12%, respectively. The calculated daily drug intake was approximately 48 mg/kg body weight. Drug-related side effects were not observed.

Benzimidazole derivatives are known to be highly active against gastrointestinal helminths and tissue-stage larvae. Mebendazole (Vermox: Janssen; Beerse, Belgium) is one of the drugs selected by the World Health Organisation (WHO) for worldwide use as an anthelmintic. This drug is also highly effective against trichinellosis in man and animals (Thienpont et al. 1974; Sonnet and Thienpont 1977). Flubendazole (Fluvermal: Janssen; Beerse, Belgium), the fluorine analogue of mebendazole (Thienpont et al. 1978), and albendazole (Valbazen: Smith Kline – R.I.T.; Genval, Belgium) (Theodorides et al. 1976) are also commercially available agents against gastrointestinal nematodes. Praziquantel (Biltricide: Bayer; Leverkusen, FRG) is an iso-chinolin derivative with high activity against schistosomiasis (Gönnert and Andrews 1977) and tapeworms (Thomas and Gönnert 1978).

Literature on the chemotherapy of cystic and alveolar hydatid disease in man and animals, reviewed by Schantz et al. (1982) and Eckert (1986), has demonstrated the successful use of benzimidazoles. Marshall and Edwards (1982) demonstrated the efficacy of praziquantel against the development of protoscolices of *Echinococcus granulosus* in mice by the implantation of sustained-release silicone-rubber discs. Alveolar echinococcosis in man, caused by the larval stages (metacestodes) of *E. multilocularis*, is primarily an infection of the liver. The spread of the parasite from the liver to other organs plays an important role in the clinical course of the disease, and the prevention of parasite spread is one important aim of chemotherapy with benzimidazole compounds (Schantz et al. 1982).

In the present study, the efficacy of four different drugs, i.e. albendazole, flubendazole, mebendazole and praziquantel, was studied by feed medication in jirds artificially infected by the implantation of metacestode tissue of *E. multilocularis*.

**Materials and methods**

**Animals.** A total of 50 female jirds (*Meriones unguiculatus*) aged 10 weeks old and weighing about 60 g were used in the study. Based on their body weight, they were divided into five comparable groups of ten jirds each. The groups were kept in Makroon cages and were given water and pelleted standard feed ad libitum.

**Parasite material.** An isolate of *E. multilocularis* (kindly provided by Prof. Dr. Eckert of Zurich) has been maintained in jirds for several years. Metacestode tissue material was isolated from the peritoneal cavity of an animal infected for several months. The metacestode mass was washed in Ringer’s solution with antibiotics (400 IU penicillin and 400 μg streptomycin/ml) and cut into pieces weighing 0.20 g before use (Eckert et al. 1983).

**Infection.** The jirds were euthanized by subcutaneous injection of 0.2 ml neuroleptanalgesic (Thalamonal: Janssen; Beerse,
Belgium). The anaesthetized rodents were infected by a minor surgical intervention for the implantation of about 0.20 g metacestode tissue in the peritoneal cavity (Eckert and Pohlenz 1976). Thereafter, virginiamycin-neomycin powder (Spitalen: Smith Kline-R.I.T.; Genval, Belgium) was applied to the wound and the skin was closed with metal Michel clamps.

**Medication.** The four test drugs albendazole, flubendazole, mebendazole and praziquantel were added as pure substances to standard mouse feed at 500 ppm before the pelleting process. The medicated feed was given ad libitum for 35 consecutive days, beginning 7 days post-infection (p.i.).

**Experimental design.** Each of four groups of ten jirds was treated with one of the test drugs, and one group served as infected, unmedicated controls. Necropsy was carried out 2 weeks after the end of medication (day 56). All parasitic material was removed from the peritoneal cavity of each animal and weighed individually. The data were statistically analysed by means of the Mann-Whitney U-test (two-tailed probability). The feed consumption per group was recorded to calculate the mean daily drug intake (mg/kg).

**Results and discussion**

None of the jirds died during the experimental period. In some groups, the transplants had increased in weight and size during the 56-day period from an initial weight of 0.20 g to a large metacestode mass that infiltrated the whole peritoneal cavity. The total metacestode tissue weights are summarized in Table 1. A total of 78.11 g parasitic material was dissected from the peritoneal cavity of the ten infected controls. All groups medicated with the three benzimidazoles showed significantly reduced (P < 0.001) metacestode tissue weight as compared with control values. However, the proliferation of the transplants was particularly inhibited by flubendazole and mebendazole, reaching a metacestode weight reduction of 95% and 91%, respectively. In the flubendazole-treated group, slight proliferation of the 0.20 g implanted metacestode tissue was observed in four of ten jirds, with a maximum of 1.21 g tissue weight.

In the mebendazole-treated group, the transplant had slightly proliferated in five of ten jirds, with a maximum of 3.90 g tissue weight. The average daily feed intake for 35 days was comparable in all treated groups, reaching about 6 g/day per animal. The mean body weight of the rodents at the end of the experiment was 62 g, and the calculated daily drug intake was approximately 48 mg/kg body weight. The 500-ppm medication with the four drugs over 35 days was well tolerated. Praziquantel had little or no inhibitory effect on the proliferation of the transplant (12% reduction). The relative inactivity of praziquantel in this study has been confirmed in jirds by Thomas and Gönnert (1978) and, recently, in cotton rats (Sigmodon hispidus) by Taylor et al. (1988).

In a study with *E. multilocularis* in jirds, Eckert et al. (1978) revealed that mebendazole given at 500 ppm damaged the protoscolices after 20 days of medication and destroyed them completely after 60 days. In the present study, the reduced proliferation of the transplant in jirds medicated for 35 days with mebendazole and flubendazole may have been completely inhibited had medication continued.

These data confirm the findings of Davis et al. (1986), described in a WHO study on the efficacy of mebendazole in patients infected with *E. multilocularis*. These authors concluded that mebendazole therapy may arrest the development of the lesions and is therefore indicated in most cases of alveolar echinococcosis, irrespective of surgery. The efficacy of long-term treatment with mebendazole in 60 patients with alveolar echinococcosis was recently reported by Ammann et al. (1988); the cumulative survival of the patients was 96% at 5 years and 84% at 10 years. Compared with a historical control mortality of >90% within 10 years, the mortality in the mebendazole-treated patients was only 16% within the same period.

A reduction in parasitic weight after albendazole treatment (72%) was also observed by Taylor et al. (1988) in cotton rats (*Sigmodon hispidus*) with a viable infection that persisted after treatment. Evidence of a beneficial response with albendazole in human hydatid disease has been reported by many workers (Morris et al. 1985; Okelo 1986; Saimot et al. 1983). Wilson et al. (1987) reported favorable results in two patients with active alveo-

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**Table 1.** Total metacestode tissue weight of 10 jirds in each of the treated groups and the percentage of reduction as compared with unmedicated controls

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total tissue weight (g)</th>
<th>Reduction (%)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>78.11</td>
<td>0</td>
</tr>
<tr>
<td>Albendazole</td>
<td>21.60 ± 7.23</td>
<td>72</td>
</tr>
<tr>
<td>Flubendazole</td>
<td>3.63 ± 0.12</td>
<td>95</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>7.00 ± 0.34</td>
<td>91</td>
</tr>
<tr>
<td>Praziquantel</td>
<td>68.91 ± 3.39</td>
<td>12</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate the range of metacestode tissue weight

* *P < 0.001*