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Chemotherapeutic Effects of Praziquantel, Niclosamide, Mebendazole and Bithionol on Larvae and Adults of *Hymenolepis nana* in Mice

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Abstract

Praziquantel, niclosamide or mebendazole was orally administered to mice harbouring adult *Hymenolepis nana* 12 or 12—16 days post-infection. Praziquantel (25 mg/kg) was completely effective at the single administration, similar to the result of Thomas and Gönnert (1977). Worm reduction by niclosamide was about 25—50% at a single dose of 100 or 500 mg/kg and at five successive doses of 100 mg/kg/day. Worm reduction due to mebendazole was about 10—20% at a single dose of 100 or 500 mg/kg while the drug completely eliminated adult worms at five successive doses of 100 mg/kg/day.

Praziquantel (25 mg/kg/day), niclosamide (500 mg/kg/day), mebendazole (500 mg/kg/day) or bithionol (500 mg/kg/day) was administered to mice harbouring cysticercoids of *H. nana* in the intestinal villi for 3 consecutive days (1—3 days post-infection). None of these drugs had larvicidal effect. However, praziquantel (25 mg/kg) was completely effective against larval *H. nana* in the intestinal lumen when the single dose was given 5 days post-infection or later.

Key words: praziquantel, niclosamide, mebendazole, bithionol, *Hymenolepis nana*

Introduction

Recently, praziquantel, niclosamide, benzimidazoles, bithionol, paromomycin sulphate and other drugs have been used to treat human cestode infections. The previous communication by Maki and Yanagisawa (1985) reported that out of the four drugs, mebendazole, flubendazole, bithionol and paromomycin sulphate, mebendazole was found to be most effective for elimination of adult *H. nana*. However, relative effectiveness of praziquantel, niclosamide and mebendazole still remains to be clarified, though praziquantel was reported to be more effective than niclosamide against adult *H. nana* (Gupta and Katiya, 1983).

Another problem in the treatment of this cestode infection is that some patients are concurrently infected with not only adult *H. nana* in the lumen but also cysticercoids of *H. nana* in the villi. To treat *H. nana* infection completely, cysticercoids as well as adults should be eliminated. To the best of the present authors' knowledge, however, no data have been presented so far indicating the possibility of successful chemotherapeutical treatment of cysticercoids in the villi.

Praziquantel has been reported to be effective against some tissue-parasitic larval stages of cestodes, *Taenia fasciolaris, T. pisiformis, T. tenuicollis* and *T. bovis* (Thomas and Gönnert, 1978). Mebendazole has been reported to be effective against hydatids of *Echinococcus granulosus,* cysticerci of *T. pisiformis* and tetrathyridia of *Mesocestoides corti* (Heath *et al.*, 1975). It is interesting to investigate whether these drugs, and niclosamide and bithionol *in* addition have effectiveness against *H. nana* cysticercoids in host intestinal villi.

In succession to the previous report by Maki and Yanagisawa (1985), we describe in this paper relative effects of some anticestode drugs on adult and other stages of *H. nana* in mice.

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Materials and Methods

Drugs examined are tablets containing 600 mg pure praziquantel per tablet (Bayer AG) and pure powders of niclosamide (Bayer AG Leverkusen), mebendazole (Janssen Pharmaceutica, Belgium) and bithionol (Tanabe Pharmaceutical Co. Ltd).

All studies were carried out in the following procedures. Female ICR-strain mice (about 5 weeks old) were each inoculated with 100 shell-removed eggs prepared by the method by Maki *et al.* (1983) via a stomach tube, and the mice randomly divided into experimental and control groups of 6—7 animals each. The drugs were suspended in 1% (v/v) Tween 80 to give the specified concentration in 0.1 ml of the suspension per 10 g body-weight. The concentration of praziquantel refers to pure praziquantel in the tablet. Each of the drug suspensions was given orally with a stomach tube to infected mice harbouring mature or immature worms. Praziquantel was administered at a single dose of 25 or 50 mg/kg 12 days post-infection for the evaluation of efficacy of the drug against adult worms, at three consecutive doses of 25 mg/kg/day (1—3 days post-infection) for the evaluation of efficacy of the drug against larvae or at a single dose of 25 mg/kg 1, 2, 3, 4, 5, 6, 7, 9, or 14 days post-infection for the evaluation of efficacy of the drug against larvae and adults. Niclosamide or mebendazole was each administered at a single dose of 100 or 500 mg/kg 12 days post-infection or at five successive doses of 100 mg/kg/day (12—16 days post-infection) for the evaluation of efficacy of the drugs on adult worms, or at three successive doses of 500 mg/kg/day (1—3 days post-infection) for the evaluation of efficacy of the drugs against larvae. Bithionol was administered at 500 mg/kg/day for three successive days (1—3 days post-infection) for the evaluation of efficacy of the drug against larvae. Control mice received vehicle alone. All the medicated and control mice were killed 14—19 days post-infection and the scolices in the intestine were counted as described by Maki and Yanagisawa (1983). Data were analyzed statistically using Student's *t*-test. P values less than 0.05 were considered significant.

Results and Discussion

Effects of praziquantel, niclosamide and mebendazole against *H. nana* adults was comparatively examined and the data are summarized

Table 1 Comparison of anthelmintic effects of praziquantel, niclosamide and mebendazole on adult *Hymenolepis nana* in mice

Experiment number	Drugs used	Doses mg/kg/day ×days	Worms recovered Mean±S.E. (No. of mice examined)	Reduction in mean number of worms (%)
I	Praziquantel	50×1 (day* 12)	0 (5)	100†
	Praziquantel	25×1 (day 12)	0 (6)	100†
	Niclosamide	100×1 (day 12)	39.0± 7.7 (6)	25
	Control	1% Tween 80×1 (day 12)	52.0±11.6 (6)	——
II	Niclosamide	500×1 (day 12)	30.9± 2.9 (7)	48.2†
	Niclosamide	100×1 (day 12)	44.9± 3.3 (7)	24.8†
	Niclosamide	100×5 (day 12-16)	40.0± 6.2 (7)	33.3
	Mebendazole	500×1 (day 12)	50.3±12.6 (6)	15.7
	Mebendazole	100×1 (day 12)	54.4± 3.7 (7)	8.9
	Mebendazole	100×5 (day 12-16)	0 (7)	100†
	Control	1% Tween 80×1 (day 12)	59.7± 5.3 (7)	——
	Control	1% Tween 80×5 (day 12-16)	60.0± 2.3 (7)	——

* Days after infection on which a drug was given

† Statistically significant ($p<0.05$)

in Table 1. Praziquantel given at 25 and 50 mg/kg 12 days post-infection were completely effective against adult *H. nana*. This result is similar to that of Thomas and Gönnert (1977). Worm reduction by niclosamide was about 25—50% at a single dose of 100 or 500 mg/kg (12 days post-infection) and at five successive doses of 100 mg/kg/day (12—16 days post-infection) (Table 1). Worm reduction due to mebendazole was about 10—20% at a single dose of 100 or 500 mg/kg (12 days post-infection). However, mebendazole administered at five successive doses of 100 mg/kg/day (12—16 days post-infection) eliminated adult worms completely (Table 1). It was clearly shown in the present study that mebendazole was much more effective in divided administration (100 mg/kg/day for 5 successive days) than in a single administration (500 mg/kg). The effectiveness of niclosamide in the present study was not so high as that in Gupta and Katiya (1983). They reported that in three out of four mice infected with adult *H. nana* were free of worms 48 hours after medication with niclosamide at a single dose of 400 mg/kg.

No drugs were effective in elimination of cysticercoids in the intestinal villi (Table 2) despite our assumption that some of the drugs examined would affect tissue-parasitic cysticercoids of *H. nana* in view of the previous reports on eliminating effects of other types of larval cestodes. Worm reduction rates of 42% and 19% by praziquantel and bithionol were not significant statistically (Table 2).

Fig. 1 shows the effects of praziquantel at a single dose of 25 mg/kg given at varying days post-infection against *H. nana*. Effect was complete when the single dose was given 5 days post-infection or later. However, this result was different from that by Thomas and Gönnert (1978) who reported almost complete effect of the drug administered 3 days post-infection. There may be difference among various strains of mice in days after egg-inoculation when cysticercoids migrate from the mouse villi into the intestinal lumen.

Gupta and Katiya (1983) reported complete elimination of cysticercoids of *H. nana* by 3 successive doses of praziquantel (25 mg/kg/day) or niclosamide (400 mg/kg/day) 3—5 days post-infection. Most of the larvae of *H. nana* are found in the lumen of mouse intestine 5 days post-infection onwards (Novak and Evans, 1981: Maki and Yanagisawa, unpublished). As Fig. 1 shows, at 25 mg/kg 5 days post-infection, praziquantel eliminated *H. nana* completely. Thus the remarkable effects of praziquantel and niclosamide against cysticercoids (Gupta and Katiya, 1983) was probably ascribable to elimination of larvae in the lumen by the drugs.

In view of reports of Thomas and Gönnert (1977, 1978), Maki *et al.* (1983), Maki and Yanagisawa (1985) and the present communication, a conclusion can be drawn as follows: Adult and larval *H. nana* in the lumen of the intestine can be completely eliminated with a single administration of praziquantel and Ma-Klua or with a divided administration of mebendazole while

Table 2 Comparison of anthelmintic effects of praziquantel, niclosamide, mebendazole and bithionol on larval *Hymenolepis nana* in mice

Drugs used	Doses mg/kg/day ×days	Worms recovered Mean±S.E. (No. of mice examined)	Reduction in mean number of worms (%)
Praziquantel	25×3 (day* 1-3)	35.4± 5.2 (7)	41.6†
Niclosamide	500×3 (day 1-3)	70.4± 8.8 (7)	0
Mebendazole	500×3 (day 1-3)	66.2±13.1 (7)	0
Bithionol	500×3 (day 1-3)	49.2±10.6 (6)	18.8†
Control	1% Tween 80×3 (day 1-3)	60.6±12.9 (7)	——

* Days after infection on which a drug was given

† None of these are significant

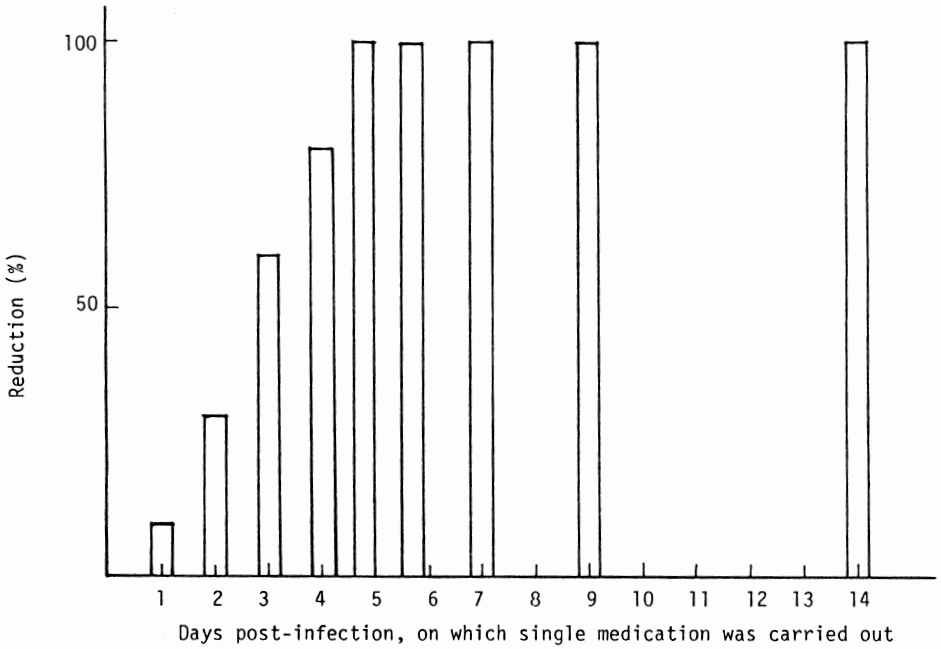

Fig. 1 Chemotherapeutic effect of praziquantel on *Hymenolepis nana* at an oral single dose of 25 mg/kg on varying days post-infection
Mice inoculated with 100 shell-removed eggs were administered with a single dose of praziquantel (25 mg/kg) at varying days post-infection and dissected 14-19 days post-infection.

H. nana cysticercoids in mouse-intestinal villi are resistant to all the drugs examined. To eliminate *H. nana* infection completely, it is therefore recommended to administer the drug again 5 days after termination of the first treatment or later.

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