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Therapeutic Effects of Praziquantel (Embay 8440) against *Hymenolepis nana* Infection

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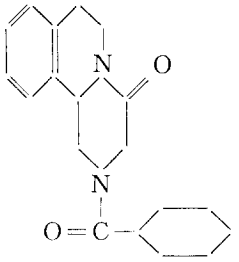
INTRODUCTION

Hymenolepis nana is a common tapeworm found in the small intestine of man and is diagnosed in about 0.6 per cent of fecal examinations made in Korea (1978). It is more common in children than in adults. The clinical symptoms of this infection are usually slight or almost absent. While a large number of *H. nana* attached to the wall of the small bowel may produce considerable irritation of the intestinal mucosa. There may be troubles in the gastro-intestinal region, i.e., abdominal pain, diarrhea and other non-characteristic symptoms.

H. nana is one of the more difficult worms to eliminate from the human intestine. Except for niclosamide (Yomesan) no other available anthelmintic is considered to be satisfactory in the treatment of this cestode infection. The use of filix mas, acridine compounds, carbon tetrachloride, hexylresorcinol, bithionol and dichlorophen etc. are usually followed by relapse, and the cure rate is not satisfactory. Since 1960 niclosamide is currently the drug of choice in cestodiasis. Numerous trials have demonstrated the high curative efficacy of niclosamide in infestations due to *Taenia saginata*, *T. solium*, *Diphyllobothrium latum* and *H. nana*. In the treatment of *H. nana* infection, however, a single dose of niclosamide gave usually relapse after treatment, but the extended course of treatment gave a good result (Nagaty et al., 1962). According to Cavier (1966) who summarized the results of treatment in 8 trials conducted against *H. nana* with a general regimen of six days' treatment with niclosamide, 160 cases were treated with a mean cure rate of 84 per cent.

Recently, a new broad spectrum anthelmintic, praziquantel (EMBAY 8440) has been shown an excellent activity against all species of schistosomes and cestodes in men and animals. Praziquantel is 2-cyclohexylcarbonyl-1, 3, 4, 6, 7, 11 b-hexahydro-2H-pyrazino [2, 1-a] isoquinolin-4-one and its structural formula is as follow:



Praziquantel is a derivative of a new heterocyclic system, an isochinolin-pyrazin-derivative. The active substance is a colourless, almost odourless crystalline powder having a bitter taste.

The present study was undertaken to determine the efficacy of praziquantel at two different doses in cases with proven infection of *Hymenolepis nana*, and also to determine the incidence and severity of side effects at the dosage used.

MATERIALS AND METHODS

A total of 60 proven cases of *Hymenolepis nana* infection were treated with two different dose levels of praziquantel. Twenty-nine cases (10~18 years; 24 males and 5 females) received a single dose of 15 mg of praziquantel per kg of body weight, and 31 cases (8~17 years, 23 males and 8 females) received a single dose of 25 mg/kg body weight of praziquantel.

Fecal examinations consisted of formalin-ether sedimentation method and Stoll's egg counting method. These tests were performed in three aliquots of one feces sample at before treatment, and in each time the feces of three consecutive days on one, two and three weeks after treatment. The evaluation of efficacy was based upon the egg reduction rate or the absence of eggs in the feces. Complete cure was determined by the absence of *H. nana* eggs in the feces, which was confirmed by at least two further examinations by the formalin-ether sedimentation method.

The patients were carefully observed to ascertain the type and severity of side effects. The following laboratory examinations were carried out in all patients immediately before and 24 hours after the medication: clinical hematology for hemoglobin, blood cell counts, differential counts; blood biochemistry for such as bilirubin, SGOT, SGPT and BUN, and urinalysis for glucose, protein and microscopical examinations for deposits.

RESULTS

A total of 60 patients harboring *Hymenolepis nana* were treated with praziquantel in two different dose levels. As shown in Table 1, 29 cases with an average EPG of 10,762(100~120,800) were treated with praziquantel in a single dose of 15 mg/kg body weight. In the result complete cure was obtained. Both in the egg reduction rate and cure rate on the 19th to 21st day after the treatment was 100 per cent. On the other hand, 31 patients with an average EPG of 3,641 (100~54,400) received a single dose of 25 mg/kg body weight. Thirty cases of 31 had negative egg counts and cured completely in each tests on the 19th to 21st day after treatment, but only one case had counts of 200 eggs per gram of feces in each tests on the 20th and 21st day after treatment. Therefore the average egg reduction rate after treatment was 99.8 per cent, and the cure rate shows 96.8 per cent.

The patients were carefully screened in order to determine the type and severity of side effects. Side effects were observed in both the dosage groups. As shown in Table 2, 7 (24.1%) of the 29 patients who received 15 mg

Table 1. Therapeutic effects of praziquantel (Embay 8440) against *Hymenolepis nana*

Doses	No. of treated cases	Pre-Tx. mean EPG (range)	No. of positive cases in follow-up exam. (days)			Egg reduct. rate (%)	No. of cases cured	Cure rate (%)
			5~7	12~14	19~21			
15 mg/kg×1	29	10,762 (100~120,800)	1	0	0	100.0	29/29	100.0
25 mg/kg×1	31	3,641 (100~54,400)	0	0	1 (EPG:200)	99.8	30/31	96.8

/kg body weight single dose of praziquantel complained of some side effects——5 cases with abdominal pain, 1 case with diarrhea and 2 cases with vertigo. But all of symptoms were mild and transitory and occurred within the first 24 hours after dosing. Similar mild and transitory side effects were observed in 13(41.9 %) of the 31 cases who received praziquantel 25 mg/kg body weight at a single dose. These were abdominal pain in 5 and vertigo in 8 cases and 3 cases with headache.

Clinical hematology, biochemistry and urinalysis were performed immediately before and the next day after treatment in all 60 cases. There were no significant differences between the pre- and post-treatment examinations. No abnormalities were detected in all these tests.

Some of the patients in both the trials had concurrent *Ascaris lumbricoides*, hookworm, *Trichuris trichiura* infections. A single doses of 15 and 25 mg/kg of praziquantel had very little effect in these worms.

Table 2. Incidence of side effects

Dose	15 mg/kg	25 mg/kg
No. of treated cases:	29	31
No. of cases with symptoms	7 (24.1%)	13 (41.9%)
Symptoms		
Abdominal pain (mild)	5	5
Vertigo	2	8
Headache	0	3
Diarrhea	1	0

DISCUSSION

Hymenolepis nana is the smallest tapeworm found in the small intestine of man. It is estimated that over 43.5 million persons throughout the world are infected (De Carneri and Vito, 1973). Surveys reveal an incidence by countries of 0.2 to 3.7 per cent, although in certain areas 10 per cent of the children are infected (Brown, 1975). Kim et al. (1971) reported that the incidence of *H. nana* in Korean population was 0.7 per cent and the highest incidence was 2.5% from Cheju Do. The most of cases were found in children. Except for niclosamide, no other drug is considered satisfactory in the treatment of *Hymenolepis nana* infection. Niclosamide is current drug of choice for the treatment of *Taenia saginata* and *Diphyllobothrium latum* in a single dose treatment, and *H. nana* in an extended course for 5 to 7 days. Numerous trials have demonstrated the high curative efficacy of niclosamide in infection of *H. nana* (Nagaty et al., 1962; Shafel and Abaza, 1962; Yokogawa and Yoshimura, 1962; Garin et al., 1964; Cavier, 1966; Perera et al., 1970; Most et al., 1971). In *H. nana* infections man acts at the same time as the definitive and the intermediate host. Since onchospheres develop in the jejunal villi and cercocyst emergence into the intestinal lumen occurs about 4 days later, there exists a stage in the life cycle where the onchospheres are beyond any drug contact. (Davis, 1972). The niclosamide probably has no effect in the cercocystic stages embedded between the villi. Therefore treatment of this infection for seven days is necessary. However, Ahkami and Hajian (1970) using a high dosage regimen with a single dose of niclosamide, successfully treated 25 patients with *H. nana* infection in Iran. Children were given a dose of 100~130 mg/kg and adults were given 70~80 mg/kg. All patients were apparently cured and no side effects were noted.

According to Thomas (1977), praziquantel, a new type of acylated isoquinole-pyrazine is highly active against cestodes and well tolerated in animals. A single, low oral or subcutaneous dose is reliably effective against immature and mature *Hymenolepis nana* in mice, various *Taenia* species in cats and dogs and other

cestodes in mice, rats, cats, dogs and sheep. Furthermore, praziquantel is effective on experimental cysticercosis, e.g. *Cysticercus bovis* in cattle. Cansonieri et al. (1977) gave a single oral dose of praziquantel to the 43 cases harboring *H. nana*. In the results, 80.8 and 93.3% of cure rates were obtained in the groups taken the drug of 13.5~16.0 mg/kg and 25 mg/kg respectively. On the other hand, Espejo (1977) treated 25 cases infected *H. nana* using a single dose of 15 mg/kg body weight of praziquantel, and he obtained 100% of cure rate. Again, Groll (1977) noted a total of 392 patients with cestode infections were tested with a single oral dose of praziquantel. Infection with *Taenia* species and *Diphyllobothrium pacificum* treated with 10 mg/kg, *Hymenolepis nana* and *D. latum* treated with 25 mg/kg produced a 100% cure rate. Baranski(1977) treated 16 hymenolepiasis patients with a single oral dose of 15 or 20 mg/kg of praziquantel. He noted the higher dosages were 100 per cent effective in all patients. The drug showed a high degree of cestocidal activity and according to the dosage used it yielded cure rates of 80~100 % in hymenolepiasis. Similarly Schenone et al. (1977) reported that a single oral dose of 10, 15 and 25 mg/kg of praziquantel showed cure rates of 77.3%, 94.7% and 100 per cent respectively in 71 *H. nana* infected children. Therefore they suggest that the optimal curative dosage should be in between 15 and 25 mg/kg body weight.

In the present trial, a single oral dose of 15 mg/kg body weight of praziquantel cured completely in all cases, however 30 (96.8%) of 31 cases who received a single oral dose of 25 mg/kg body weight were cured completely, but only one case was treated incompletly, while the EPG of *H. nana* was lowered from 5,280 EPG at before treatment to 200 EPG at the 20th and 21st days after treatment. This was considered to be relapsed or reinfected. It is generally accepted that the first appearance of *H. nana* eggs in the feces is about 30 days after ingestion of infective stage of eggs. In this connection, this case would be most probably considered as relapse.

Very good effectiveness of praziquantel in the treatment against *H. nana* infection in this study together with its excellent toleration suggest this drug may become the drug of choice for *Hymenolepis nana* as well as other cestode infection.

Intensive studies on toxicology and pharmacology have shown a very good tolerance for all animal species tested (Steiner et al., 1976; Steiner and Garbe, 1976; Diekmann and Bühring, 1976; Obermeier and Frohberg, 1977; Machemer and Lorke, 1978). Carefully monitored studies in healthy volunteers with dosage scheme supposed to be therapeutically effective also did not reveal any signs of toxicity and/or intolerability (Leopold, 1977). However, praziquantel has no significant effect against intestinal nematodes such as *Ascaris lumbricoides*, hookworms and *Trichuris trichiura* infections.

SUMMARY

A total of 60 patients with *Hymenolepis nana* infection were treated with a single oral dose of praziquantel in two different dose levels. Twenty-nine cases treated with praziquantel in a single dose of 15 mg/kg body weight produced a 100% cure rate. On the other hand, 30 out of 31 patients who received a single dose of 25 mg/kg body weight cured completely, but only one case had counts of 200 EPG of feces in each tests on the 20th and 21st days after treatment. The cure rate was 96.8% and the mean egg reduction rate of 99.8 per cent was obtained.

Side effects were mild and transitory. In a few cases, abdominal pain, vertigo, headache

and diarrhea were complained in a few hours after medication. Clinical hematology, serum biochemistry and urinalysis were performed immediately before and the next day after treatment in all cases. There were no significant abnormalities detected in these tests.

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=國文抄錄=

矮小條蟲症에 對한 Praziquantel(Embay 8440)의 治療效果

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最近 새로 開發된 Praziquantel (Embay 8440), 2-cyclohexylcarbonyl-1, 3, 4, 6, 7, 11 b-hexahydro-2H-pyrazino [2, 1-a] isoquinolin-4-one을 使用하여 60例의 矮小條蟲感染에 對한 驅蟲效果와 副作用에 對하여 檢討하였다.

29例의 矮小條蟲感染者(10~18歲, 男子 24名 및 女子 5名)에 對하여 Praziquantel 15 mg/kg를 單回 投藥하여 1, 2, 3週에 各各 3日間 連日 採便하여 糞便檢査를 하여 治療效果를 判定하였다. 投藥前의 平均 E.P.G.가 10,762 (100~120,800)이던 것이 投藥後에는 全例가 糞便檢査에서 蟲卵陰性으로 나타나 100%의 治療率을 얻었다.

한편 31名의 矮小條蟲感染者(8~17歲, 男子 23名 및 女子 8名)에 對하여 Praziquantel 25 mg/kg을 單回投藥하였다. 投藥前의 平均 E.P.G.는 3,641(100~54,400)인데 治療後 19~21日에 採便한 糞便檢査에서는 單一例에서만 蟲卵이 陽性이었다. 即 治療前 E.P.G.는 5,280에서 治療後 E.P.G. 200으로 減少하여서 平均蟲卵減少率은 99.8%이었고, 96.8%의 治療率을 얻었다.

副作用에 있어서 Praziquantel 15 mg/kg 投藥群 29名中 7名(24.1%)에서 輕微한 腹痛, 眩氣症 및 泄瀉 等을 呼訴하였고 25 mg/kg 投藥群 31名中 13名(41.9%)에서 亦是 輕한 腹痛, 眩氣 및 頭痛을 呼訴하였다. 投藥直前과 投藥 24時間 後에 血液像, 血液生化學 및 尿檢査를 全例에서 實施한 바 投藥前後에 있어서 顯著한 差異가 없었다.