

Praziquantel Treatment in Trematode and Cestode Infections: An Update

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Status and emerging issues in the use of praziquantel for treatment of human trematode and cestode infections are briefly reviewed. Since praziquantel was first introduced as a broad-spectrum anthelmintic in 1975, innumerable articles describing its successful use in the treatment of the majority of human-infecting trematodes and cestodes have been published. The target trematode and cestode diseases include schistosomiasis, clonorchiasis and opisthorchiasis, paragonimiasis, heterophyidiasis, echinostomiasis, fasciolopsiasis, neodiplostomiasis, gymnophalloidiasis, taeniasis, diphyllbothriasis, hymenolepiasis, and cysticercosis. However, *Fasciola hepatica* and *Fasciola gigantica* infections are refractory to praziquantel, for which triclabendazole, an alternative drug, is necessary. In addition, larval cestode infections, particularly hydatid disease and sparganosis, are not successfully treated by praziquantel. The precise mechanism of action of praziquantel is still poorly understood. There are also emerging problems with praziquantel treatment, which include the appearance of drug resistance in the treatment of *Schistosoma mansoni* and possibly *Schistosoma japonicum*, along with allergic or hypersensitivity reactions against praziquantel treatment. To cope with and overcome these problems, combined use of drugs, i.e., praziquantel and other newly introduced compounds such as triclabendazole, artemisinins, and tribendimidine, is being tried.

Key Words: Praziquantel, Trematode, Cestode, Chemotherapy, Adverse reaction, Combined therapy

Introduction

The anthelmintic activity of pyrazinoisoquinoline derivatives was first discovered by E. Merck and Bayer AG, Germany, in 1972 [1]. Subsequently, in 1975, among a large number of related compounds, praziquantel, 2-cyclohexylcarbonyl (1,2,3,6,7,11b) hexahydro-4H-pyrazino (2,1-a) isoquinolin-4-one (MW 312.42), was developed as a new broad-spectrum

anthelmintic against parasitic trematodes and cestodes [1]. Praziquantel is now produced by various manufacturers around the world, including Shinpoong Pharmaceutical Company (Seoul, Korea), and is used for human and animal platyhelminth infections on a large scale.

Numerous chemotherapeutic trials have been performed to evaluate the clinical use of praziquantel in the treatment of human trematode and cestode infections, and multiple papers

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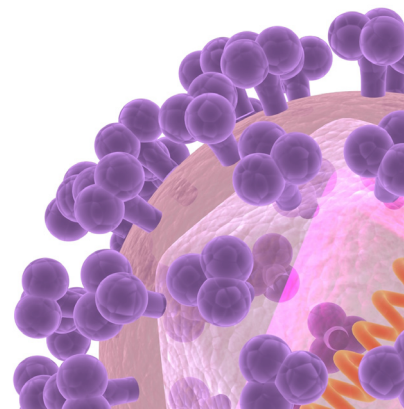
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reporting successful results have been published. It has been revealed that most of the human-infecting trematode infections, with the exception of fascioliasis (*Fasciola hepatica* or *Fasciola gigantica* infection), and most human cestode infections, except larval *Echinococcus granulosus* or *Echinococcus multilocularis* infection and sparganosis (caused by the larva of *Spirometra erinacei*), are treated successfully with recommended drug dosages and regimens, which differ by different types of trematodes and cestodes, in particular, according to the habitat in the host [2, 3].

Despite these numerous clinical reports, the basic pharmacological mechanisms of efficacy of praziquantel against helminth parasites remain poorly understood [4]. In addition, we are faced with several emerging problems that include the appearance of drug resistance in schistosomiasis [5] and possibly in clonorchiasis [6] and the occurrence of allergic and hypersensitivity reactions after praziquantel administration [7, 8]. In this context, the present paper aimed to briefly review the history of praziquantel development and clinical trials, as well as to highlight emerging problems and adverse reactions in the clinical use of praziquantel.

Pharmacokinetics

Praziquantel is rapidly taken up through the gut (in humans more than 80% of the orally administered dose is absorbed from the gastrointestinal tract) and reaches its maximal plasma concentration within 1-2 hours [2]. If a person was orally administered 20-50 mg/kg praziquantel, the peak plasma concentration would become 0.2-1.0 µg/mL [2]. The cerebrospinal fluid (CSF) concentration can be 1/7-1/5 of the plasma concentration [1]. Most of the praziquantel absorbed is metabolized in the liver by the cytochrome P450 system and becomes a hydroxylated polar metabolite form which has a lower protein binding capacity (lower helminthotoxic activity) than the unmetabolized form [1, 2]. The excretion of praziquantel occurs mainly through urine (60-80%) as well as bile and feces (15-35%) and is completed within 24 hours [1]. The elimination half-life of praziquantel in the human body is 1-2 hours [2], and after 24 hours, only a trace amount remains in the human body.

The efficacy of praziquantel on the blood, liver, and lung fluke infections is considered to be due to the polarized metabolite form, which constitutes the majority of the praziquantel in the plasma; this form has only slightly lower anthelmintic efficacy compared with its unmetabolized form [1, 2]. The efficacy of praziquantel against cerebral cysticercosis, in which the larval

cestode is located in the brain parenchyme or ventricle, is probably due to the passing of the metabolized form of the drug through the blood-brain barrier, despite the drug's overall low concentration in the CSF (only 1/7-1/5 of the plasma concentration) [2].

Helminthotoxic effects

1. Trematodes

The effects of praziquantel on helminth parasites have been studied *in vitro* and *in vivo*. *In vitro* studies were first performed on *Schistosoma mansoni*, *Schistosoma japonicum*, *Dicrocoelium dendriticum*, and *F. hepatica* from 1978-1981 [9-11]. These were followed by studies on *Clonorchis sinensis*, *Metagonimus yokogawai*, *Opisthorchis viverrini*, and *Paragonimus westermani* in 1983 [12]. The praziquantel concentrations tested were 0 (control), 1, 10, and 100 µg/mL, and the incubation times were 5, 15, 30, and 60 min [10-12]. The most prominent findings observed were rapid contraction of the worm musculature, which led to a loss of worm movement, and rapid bleb formation and vacuolization of the tegument followed by rupture of the blebs and vacuoles [9-12]. Most of these trematode species rapidly took up praziquantel, and vacuolization began to occur within a few minutes after contact with praziquantel [1]. Adult flukes of *Fibricola seoulensis* (now emended as *Neodiplostomum seoulense*) exposed *in vitro* to 0.1-100 µg/mL praziquantel solution for 5, 15, 30, and 60 min also revealed rapid contraction of the musculature and loss of movement with remarkable tegumental and subtegumental changes, in particular, bleb or blister formation followed by rupture and deformation of the tegumental integrity [13].

These *in vitro* findings induced by praziquantel were confirmed *in vivo* through studies on worms collected from experimental animals after treatment with praziquantel [11, 12, 14, 15]. Additionally, several unique findings which had not been noted by *in vitro* studies were reported. With regard to *C. sinensis*, a large balloon-shaped structural deformity occurred near the anterior end, which resulted in elongation of the distance between the oral and ventral suckers, in worms harvested from experimentally infected rats at day 4 post-treatment, and vacuoles were formed in deep parenchymal organs such as the excretory bladder [14]. Similarly, *N. seoulense* adults recovered in rats after treatment with praziquantel also showed severe vacuolization of not only the tegumental layer but also deeper parenchymal tissues, as well as narrowing of the intestines [15]. In *P. westermani*, there was some controversy regarding the *in vitro*

effect of praziquantel. In an earlier study, only a small number of vacuoles were formed in the tegument within 60 min after incubation, suggesting a weak or slow action of praziquantel on this trematode [12]. This was speculated to be due to the extremely thick (18-22 μm) tegument with numerous fortifying fibrils [12]. However, in another study, significant tegumental damage was recognized, accompanied by elongation at the anterior end of the body and vacuolization of the tegument and subtegument at 60 min after exposure to a concentration of 0.1 $\mu\text{g}/\text{mL}$ praziquantel [16]. It was further observed in the lung tissues of dogs infected with *P. westermani* that the worms with damaged tegument were invaded by host granulocytes [17] and eventually the parasite was successfully eliminated [12].

By contrast, no changes were found in the tegument of *E. hepatica* treated *in vitro* with praziquantel, possibly because *E. hepatica* possesses an exceptionally thick outer tegumental layer (up to 20 μm) with many more mitochondria than the other trematodes and its surface is much less elaborately shaped with only small surface pits [10].

2. Cestodes

The therapeutic efficacy of praziquantel in the treatment of cestode infections was first documented a little earlier than its efficacy on trematodes, in 1976-1977 [18, 19]. However, detailed *in vitro* effects on the morphological changes of worms were first studied in 1980 on *Hymenolepis nana* [20] and on *Hymenolepis diminuta*, *Hymenolepis microstoma*, *E. multilocularis*, and *Taenia taeniaeformis* in 1981 [21]. In *H. nana* tapeworms, tegumental vacuolization was exclusively observed in the neck region after 5 min incubation in a concentration of 1 $\mu\text{g}/\text{mL}$ praziquantel [20]. The vacuolization led to disruption of the syncytial layer in the apical region of the tegument; however, the tegumental microtriches and the surface coat remained unaffected [20]. The same tegumental change was observed in the neck of the adults of the other 4 tapeworm species [21]. The tegument of *Diphyllobothrium latum* adults (obtained from experimentally infected hamsters) incubated in concentrations higher than 0.1 $\mu\text{g}/\text{mL}$ for 4 hours was expanded and desquamated, and finally almost completely stripped off [22]. However, even in these specimens, the scolex and the neck region remained viable and mobile, suggesting the resistance of *D. latum* to praziquantel *in vitro* [22]. However, regardless of their *in vitro* susceptibility, human and animal infections with adult tapeworms were, with no exceptions, successfully treated *in vivo* with praziquantel. Those infections included *H. nana*, *H. diminuta*, *H. microstoma*, and *D. latum* [19, 22]. In *H. nana* and *H. diminuta* infection in mice and rats, respectively, within 10 min after praziquantel admin-

istration, the tapeworms were found apparently paralyzed, and in some cases, their tegument was distended and became dark in color, and in 30 min all the tapeworms were dislodged to the caecum [19]. In *H. microstoma* infection in mice, the adult worms were paralyzed and no longer attached to the wall of the bile duct from 8 min after the drug administration [19]. In *D. latum* infection in hamsters, the tapeworms were strongly contracted and were on their way out of the intestine within 30-35 min after the administration of the drug [22].

By contrast, the susceptibility of larval tapeworms appeared to be different by different species of tapeworms. The cysticeroid stages of *H. nana*, *H. diminuta*, and *H. microstoma* were all highly susceptible to praziquantel in infected mice or rats [19]. However, the plerocercoid larvae of *D. latum* showed no marked changes unless incubated in a very high concentration of 600 $\mu\text{g}/\text{mL}$ or more for 24 hours [22]. The protoscolices of *E. multilocularis* from praziquantel-treated animals were damaged and were not infective to dogs; however, the germinative epithelium of the cyst was not destroyed, and a parasitological cure of the infected animals with hydatid cysts could not be achieved [23]. Therefore, no consideration should be given to the use of praziquantel in the treatment of hydatid disease in humans [1]. On the other hand, praziquantel was effective against the metacestodes of *Taenia* species including *T. solium* and *T. multiceps* in animal hosts [1]. Praziquantel at a dose of 50 mg/kg/day for 10 days effectively killed cysticerci in porcine muscles, although the cysticerci in the cranial cavity were not killed by this dose [1]. The brain cysticerci in pigs could be killed by either a higher dose (100 mg/kg/day) or a higher duration of treatment (15 days \times 50 mg/kg/day) [1].

3. Mechanisms of action

The exact mechanism of action of praziquantel against trematodes and cestodes remains unclear, although there are some theories [24, 25]. A rapid influx of calcium ion (Ca^{2+}) accompanied by morphological changes of the worm, which include rapid contraction of the musculature and tegumental bleb and vacuole formation, have been among the suggested mechanisms [1, 4]. The beta subunits of voltage-gated Ca^{2+} channels have been identified as potential molecular targets of praziquantel [26]. Another proposed mechanism is the blocking of the adenosine receptors of the worms by praziquantel, causing calcium influx in the drug's antischistosomal activity [27, 28]. Although not essential for eliciting *in vitro* effects, host immune cells such as granulocytes, histiocytes, and also antibodies were reported to highly contribute to the *in vivo* effects of praziquantel in the treatment of tissue-invading helminth infections [2,

28]. In *S. mansoni*, praziquantel increases the susceptibility of the parasite to be easily attacked by host antibodies by exposing two antigens (27 kDa and 200 kDa proteins) on the surface of the worm [28].

Recommended dose and efficacy

1. Trematodes (Tables 1 & 2)

The anti-schistosome efficacy of praziquantel in human patients is generally satisfactory (Table 1), although it is effective mainly on adult fluke infections [1]. A single oral dose of 40 mg/kg, which is useful for mass treatment, is fairly effective, with cure rates of 85.7% for *S. japonicum*, 79.4-88.6% for *S. mansoni*, 83.0-88.9% for *Schistosoma haematobium*, and 75.0% for *Schistosoma mekongi* [1, 29, 30]. The cure rate can be increased to 99.5% by two doses of 40 mg/kg for *S. japonicum* [31] and to 80.8% by a single dose of 75 mg/kg for *S. mekongi* [30]. The rates

were also increased to 97.0% and 97.6% by 3×20 mg/kg/day for *S. mansoni* and *S. haematobium*, respectively [1].

The efficacy of praziquantel for treatment of liver fluke infections (except for *F. hepatica* and *F. gigantica*) is similar to that for schistosome infections (Table 1). A single dose of 40 mg/kg is useful for mass treatment, with cure rates of 87.1% for *C. sinensis*, 90.0% for *O. viverrini*, and 97.0% for *O. felineus* [32-34]. Increasing the dose to 3×25 mg/kg/day for 1 day or 2 days can increase the cure rate for *C. sinensis* to 85.7-100% [35]. In *O. viverrini* infection, a single dose of 75 mg/kg can increase the cure rate to up to 96.6% [30], and a cure rate of 100% was obtained using a regimen of 3×25 mg/kg/day for 1 day [36]. However, with regard to *F. hepatica* and *F. gigantica*, both a single dose of 40 mg/kg and a regimen of 3×25 mg/kg/day for 7 days were not effective, with 0% cure rates [37, 38]. Therefore, another kind of anthelmintic, triclabendazole, has been used for treatment of fascioliasis [39].

For treatment of *Paragonimus* species (lung flukes) infections,

Table 1. Recommended regimen and efficacy of praziquantel for treatment of human schistosome and liver fluke infections

Parasite	Regimen of praziquantel	Cure rate (%)	Egg reduction rate (%)	Reporter (year)	Reference No.
<i>Schistosoma japonicum</i>	40 mg/kg, single	85.7	NR	Andrews et al. (1983)	[1]
	40 mg/kg \times 2 times	99.5	NR	Seto et al. (2011)	[31]
	3×25 mg/kg/day \times 1 day	100.0	100.0	Andrews et al. (1983)	[1]
<i>Schistosoma mansoni</i>	40 mg/kg, single	79.4	NR	Andrews et al. (1983)	[1]
	40 mg/kg, single	88.6	96.7	Coulibaly et al. (2012)	[29]
	3×20 mg/kg/day \times 1 day	97.0	NR	Andrews et al. (1983)	[1]
<i>Schistosoma haematobium</i>	40 mg/kg, single	83.0	NR	Andrews et al. (1983)	[1]
	40 mg/kg, single	88.9	98.0	Coulibaly et al. (2012)	[29]
	3×20 mg/kg/day \times 1 day	97.6	NR	Andrews et al. (1983)	[1]
<i>Schistosoma mekongi</i>	40 mg/kg, single	75.0	96.4	Lovis et al. (2012)	[30]
	75 mg/kg, single	80.8	98.1	Lovis et al. (2012)	[30]
<i>Clonorchis sinensis</i>	40 mg/kg, single	87.1	97.6	Lee (1984)	[32]
	3×25 mg/kg/day \times 1 day	85.7	99.7	Rim and Yoo (1979)	[35]
	3×25 mg/kg/day \times 2 days	100.0	100.0	Rim and Yoo (1979)	[35]
<i>Opisthorchis viverrini</i>	40 mg/kg, single	90.9	NR	Bunnag and Harinasuta (1981)	[33]
	40 mg/kg (or 75 mg/kg), single	71.4 (96.6)	> 99.0	Lovis et al. (2012)	[30]
	2×25 mg/kg/day \times 1 day	88.5	NR	Bunnag and Harinasuta (1981)	[33]
<i>Opisthorchis felineus</i>	40 mg/kg, single	97.0	NR	Zavoikin et al. (1994)	[34]
	3×25 mg/kg/day \times 1 day	100.0	100.0	Wegner (1984)	[36]
<i>Fasciola hepatica</i>	40 mg/kg, single	0.0	0.0	Farag et al. (1986)	[37]
(<i>Fasciola gigantica</i>)	3×25 mg/kg/day \times 7 days	0.0	0.0	Farid et al. (1989)	[38]

NR, not reported.

Table 2. Recommended regimen and efficacy of praziquantel for treatment of human lung and intestinal fluke infections

Parasite	Regimen of praziquantel	Cure rate (%)	Egg reduction rate (%)	Reporter (year)	Reference No.
<i>Paragonimus westermani</i>	3 × 25 mg/kg/day × 1 day	71.4	NR	Rim and Chang (1980)	[40]
	3 × 25 mg/kg/day × 2 days	89.5	NR	Rim and Chang (1980)	[40]
	3 × 25 mg/kg/day × 3 days	100.0	NR	Rim and Chang (1980)	[40]
<i>Paragonimus heterotremus</i>	3 × 25 mg/kg/day × 1 day	76.9	NR	Wegner (1984)	[84]
	3 × 25 mg/kg/day × 2 days	90-100	NR	Andrews et al. (1983)	[1]
<i>Paragonimus uterobilateralis</i>	3 × 15 mg/kg/day × 1 day	71.1	83.2-87.3	Udonsi (1989)	[41]
	3 × 25 mg/kg/day × 1 day	97.6	90.8-96.8	Udonsi (1989)	[41]
	3 × 25 mg/kg/day × 2 days	100.0	NR	Wegner (1984)	[84]
<i>Paragonimus ecuadoriensis</i>	3 × 25 mg/kg/day × 1-2 days	100.0	NR	Wegner (1984)	[84]
<i>Fasciolopsis buski</i>	15-40 mg/kg, single	100.0	NR	Bunnag et al. (1983)	[42]
<i>Metagonimus yokogawai</i>	10-20 mg/kg, single	85-88	98.6-98.8	Rim et al. (1978)	[92]
	10 mg/kg, single	91.1	99.4	Lee et al. (1984)	[93]
<i>Heterophyes heterophyes</i>	10 mg/kg, single	60.0	NR	El-Haway et al. (1988)	[94]
	20 mg/kg, single	95.5	NR	Ata et al. (1988)	[95]
	20-40 mg/kg, single	100.0	100.0	El-Haway et al. (1988)	[94]
<i>Heterophyes nocens</i>	10 mg/kg, single	N.R.	NR	Chai et al. (1994)	[46]
<i>Haplorchis taichui</i>	40 mg/kg, single	100.0	100.0	Pungpak et al. (1998)	[96]
<i>Neodiplostomum seoulense</i>	20 mg/kg, single	N.R.	NR	Hong et al. (1984)	[43]
<i>Gymnophalloides seoi</i>	10 mg/kg, single	N.R.	NR	Lee et al. (1994)	[45]
<i>Echinostoma hortense</i>	10 mg/kg, single	N.R.	NR	Lee et al. (1988)	[44]
<i>Acanthoparyphium tyosenense</i>	10 mg/kg, single	N.R.	NR	Chai et al. (2001)	[47]

NR, not reported.

a 2-day regimen with a daily dose of 3 × 25 mg/kg is generally better than a 1-day regimen with the same daily dose (Table 2). For *P. westermani*, increasing cure rates were reported when comparing 1-day (71.4%) to 2-day (89.5%) and 3-day regimens (100%) [40]. Regarding *P. heterotremus*, a 2-day regimen was satisfactory to obtain 90-100% cure rates [1], whereas 1-day treatment revealed less satisfactory results, with only a 76.9% cure rate [36]. *P. uterobilateralis* and *P. ecuadoriensis* were more susceptible to praziquantel, showing cure rates of 97.6-100% (*P. uterobilateralis*) and 100% (*P. ecuadoriensis*) with 1-2 day regimens with daily doses of 3 × 25 mg/kg [36, 41]. Because of unsatisfactory results with 1-day treatment with praziquantel, particularly on *P. westermani* and *P. heterotremus*, an alternative drug, triclabendazole, has been tried for treatment of human paragonimiasis [39].

Various species of intestinal flukes were also reported to be highly susceptible to praziquantel with 10-40 mg/kg in a single dose (Table 2). *F. buski*, the largest of all human-infecting intes-

tinal flukes, may be successfully treated with 15-40 mg/kg in a single dose (100% cure rate) [42]. The worms recovered in the stool within 1 day of praziquantel treatment showed small to large blisters on the tegument, and several of them were seen to have ruptured [42]. Therefore, the susceptibility of *F. buski* to praziquantel is different from that of *F. hepatica* although the two species are morphologically close to each other. All of the smaller intestinal fluke species ever treated with praziquantel have been found to be highly susceptible to even lower doses, 10-20 mg/kg in a single dose (Table 2). The species tested include heterophyids (*M. yokogawai*, *Heterophyes heterophyes*, *Heterophyes nocens*, and *Haplorchis taichui*), neodiplostomum (*N. seoulense*), gymnophallid (*Gymnophalloides seoi*), and echinostomes (*Echinostoma hortense* and *Acanthoparyphium tyosenense*). Even in some species where cure rate was not reported, the drug efficacy seems to be satisfactory because numerous adult flukes were collected after treatment and purging [43-47].

2. Cestodes (Table 3)

All of the human-infecting adult tapeworm infections are successfully treated with 10-25 mg/kg praziquantel in a single dose (Table 3). *T. solium* or *T. saginata* (including *T. asiatica*) infections are highly susceptible to a low dose (10 mg/kg) of praziquantel with 96-100% cure rates [1, 48, 49]. *D. latum* infections are also successfully treated with 10-25 mg/kg praziquantel with 100% cure rates [22, 49]. However, *H. nana* infections generally need a higher dose (25 mg/kg) to obtain a satisfactory cure rate [1, 50-52]. This is because of the presence in each individual of concomitant infections with larval stages due to autoinfection, which are more or less resistant to praziquantel (as praziquantel is strong against adult helminths but not against larvae) [53]. To avoid recurrence of hymenolepiasis, a repeated treatment after 14 days is recommended.

Human cysticercosis, caused by the metacestode of *T. solium*, is the only larval cestode infection that can be successfully treated with praziquantel. A 7-day treatment with a daily dose of 3×25 mg/kg brought about highly satisfactory results, although a second treatment with the same regimen was needed in some cases [54]. Alternatively, a 15-day treatment with a daily dose of 50 mg/kg praziquantel in 3 divided doses was also effective for treatment of parenchymal brain cysticercosis [55]. However, several studies have reported better results with replacement of

praziquantel with albendazole (7-day course) or a combination of albendazole and praziquantel for treatment of subarachnoid and ventricular cysticercosis [56, 57]. In the treatment of cerebral cysticercosis, administration of corticosteroids such as dexamethasone should accompany the anthelmintic treatment in order to reduce adverse reactions such as headache, vomiting, and neurological symptoms which can occur due to elevated intracranial pressure resulting from inflammatory reactions against antigens liberated from dying cysticerci worms [2]. It is well known that cerebral cysticercosis in the ventricle or subarachnoid space and ocular cysticercosis are refractory to praziquantel or other anthelmintic treatment [2, 57, 58], probably because of the blood-brain barrier or blood-ocular barrier which can interfere with diffusion of the drug into the tissue near the cysticerci. In these cases, surgical removal is the best treatment [57]. In racemose type cysticercosis in the brain, a long course (1 month) of albendazole or combined use of albendazole and praziquantel for 1 month is recommended because complete surgical excision of all cysts in the basal cistern is usually impracticable [57].

The therapeutic efficacy of praziquantel for human sparganosis has been controversial. A human case of subcutaneous sparganosis that was treated two distinct times at an interval of 1 month, with a regimen of 3×25 mg/kg \times 5 days failed to be free

Table 3. Recommended regimen and efficacy of praziquantel for treatment of human adult and larval tapeworm infections

Parasite	Regimen of praziquantel	Cure rate (%)	Reporter (year)	Ref. no.
<i>Taenia solium</i>	5 mg/kg, single	96.2	Rim et al. (1979)	[48]
	10 mg/kg, single	100.0	Andrews et al. (1983)	[1]
<i>Taenia solium</i> or <i>T. saginata</i>	10 mg/kg, single	100.0	Rim et al. (1979), Chai et al. (1985)	[48, 49]
	10 mg/kg, single	96.0	Andrews et al. (1983)	[1]
<i>Diphyllobothrium latum</i>	10 mg/kg, single	100.0	Chai et al. (1985)	[49]
	25 mg/kg, single	100.0	Bylund et al. (1979)	[22]
<i>Hymenolepis nana</i>	10-25 mg/kg, single	76.0-98.5	Schnone (1980)	[52]
	15-25 mg/kg, single	96.8-100.0	Rim et al. (1978)	[51]
	25 mg/kg, single	95.0	Andrews et al. (1983)	[1]
<i>Cysticercus cellulosae</i>	3×25 mg/kg \times 7 days	satisfactory	Park et al. (1982)	[54]
	50 mg/kg/day \times 15 days	satisfactory	Sotelo et al. (1984)	[55]
Sparganum (<i>Spirometra erinacei</i>) ^a	3×25 mg/kg \times 5 days \times 2 times	not cured	Chai et al. (1988)	[59]
	3×25 mg/kg \times 3 days	improved	Tanaka et al. (1988), Ishii et al. (2001), Lee et al. (2011)	[61-63]
Hydatid cyst (<i>Echinococcus granulosus</i>)	50 mg/kg/day \times 30 days	IC ^b	Tekin et al. (2011)	[65]

^aAn experimental study (Sohn et al., 1993) reported failure to kill spargana treated *in vitro* in 10 μ g/mL praziquantel solution for 4 hours.

^bIC, in combination with albendazole (15 mg/kg/day \times 28 days) as a preoperative measure.

from the infection; 3 spargana survived and were surgically removed 4 months later [59]. In an *in vitro* experiment, spargana incubated in a concentration of 10 µg/mL praziquantel for 30, 60, 120, and 240 min were severely destroyed throughout their whole body except the scolex and the neck, but when mice were orally infected with these spargana, the parasites appeared to have survived and were able to be successfully recovered (76-100%) from the mice 1 month later [60]. In contrast, patients with pleural or pericardial sparganosis were successfully treated with praziquantel; a regimen of 60-75 mg/kg/day for 3 days seemed to be effective in eliminating the infection [61-63]. It is presumed that praziquantel can significantly damage and destroy the plerocercoid body *in vivo*, and the lesion (i.e., granuloma size) caused by the worm may become reduced and the patient appears to be successfully treated. However, the spargana may regenerate if their scolex and neck, which show resistance against praziquantel, remain alive [60]. This controversy should be elucidated through further studies.

Human hydatid diseases due to the metacestode (hydatid cyst) of *E. granulosus* and *E. multilocularis* are not successfully treated with praziquantel alone [1]. Therapeutic efficacy can be achieved when praziquantel is used in combination with albendazole, particularly as a pre-operative procedure [64, 65]. The regimens for praziquantel and albendazole are 50 mg/kg/day for 1 month and 10-15 mg/kg/day for 1 month, respectively [65].

3. Hookworms

It is interesting to note that with the use of 60 mg/kg praziquantel (in divided doses) in a community where schistosomiasis (*S. japonicum*) and soil-transmitted helminthiasis (hookworms, *Ascaris lumbricoides*, and *Trichuris trichiura*) were co-prevalent, the prevalence of not only schistosomiasis but also hookworm infections (not *A. lumbricoides* and *T. trichiura* infections) was decreased from 61.0% to 46.5% at 3 months after treatment [66]. Some activity of praziquantel against muscle proteins of hookworms but not of *A. lumbricoides* and *T. trichiura* was suggested [66]; however, this should be elucidated through further studies.

Recovery of tissue pathology

It has been questioned how long it will take for the tissue damage elicited by helminth infections to recover following treatment with praziquantel. In *S. mansoni* infection in mice, the eggs and worm granulomas in the liver were observed to have regressed to about a half in their original size at 5-12 weeks after

praziquantel treatment [67]. However, contradictory results were also reported; eggs and hepatic granulomas were persistent for 1 year after treatment of *S. japonicum* and *S. mansoni* with praziquantel [68, 69]. These reports mean that the liver pathology in schistosomiasis already existing at the time of treatment does not resolve quickly and may require quite a long time for recovery. Similarly, in the liver fluke infection, *C. sinensis* for example, chronic bile duct pathology in the rabbit and in guinea pigs did not recover within 9-12 weeks after praziquantel treatment [70, 71]. On the other hand, in the lung fluke (*Paragonimus iloktsuenensis*) infection in rats, the lung damage was quickly restored with the disappearance of worms after 4 weeks of praziquantel treatment, although some eggs and collagenation of the lung tissue still remained [72]. Moreover, in an intestinal fluke (*N. seoulensis*) infection, the intestinal pathology was completely restored in 3 weeks after treatment with praziquantel [73]. In the case of cysticercosis (*T. saginata*) in cattle, some remnants of cysticerci remained visible at least 20 weeks after treatment with praziquantel [74].

New trials and problems to be solved

1. New preparations of praziquantel

Trials have been done to promote the anthelmintic efficacy of praziquantel. One example is the introduction of sustained-release praziquantel (SRP) tablets [75]. The purpose of this formulation was to compensate for the disadvantage of repeated medication doses to treat, for example, *C. sinensis* and *P. westermani* infection. Praziquantel 150 (SRP150) or 300 mg (SRP300) was combined with a high-molecular-weight-matrix, hydroxypropyl methylcellulose (HPMC), and led to be released slowly over 10 hours or more. The results for treatment of *C. sinensis* infection with 50 mg/kg SRP150 were quite comparable to those obtained with conventional praziquantel in 3 separate doses (30 mg/kg, 3 times) [75]. Another example is a long-acting prevention trial by means of the insertion of praziquantel (105 mg) implants into the subcutaneous tissue of the backs of mice [76]. The praziquantel-implanted mice were challenged repeatedly with *S. japonicum* cercariae, and the results were encouraging, with nearly no worms, pairing worms, or eggs detected within 2-3 weeks in the mice [76].

2. Adverse reactions

It is generally acknowledged that praziquantel is highly effective and safe with no serious adverse reactions. Common adverse reactions are usually mild and include abdominal pain,

diarrhea, dizziness, sleepiness, and headache [77]. To avoid these reactions, it is recommended to administer praziquantel before sleep at night. However, in rare instances, praziquantel may cause allergic, anaphylactic, or hypersensitivity reactions in some individuals [7, 8, 78, 79]. A desensitization procedure was performed in a patient with paragonimiasis using small to increasing doses (30, 60, 100, 150, 300, 600, and 1,200 mg) of praziquantel at 90 min intervals, and the patient was then successfully treated with the standard dose of praziquantel (75 mg/kg daily for 3 consecutive days) [7]. In pregnant women, praziquantel treatment at a single dose of 40 mg/kg was found effective and safe for treatment of *S. mansoni* infection [80, 81].

3. Drug resistance

Possible emergence of strains (or isolates) of *S. mansoni* and *S. japonicum* resistant against praziquantel has been documented in the laboratory [82-84]. It was first reported in 1994 that *S. mansoni* subjected to drug pressure may develop resistance to praziquantel over a course of a few subcurative multiple doses of praziquantel-treated passages in mice [85]. It was also possible to induce resistance of *S. mansoni* to praziquantel by successive drug treatment of the vector snail, *Biomphalaria glabrata*, infected with the cercariae [86]. With regard to *S. japonicum*, a strain from mainland China was able to develop resistance to praziquantel under continuous drug pressure in the laboratory [83, 84].

The presence of praziquantel-resistant field isolates is well known in *S. mansoni* [84]. Resistance has been repeatedly reported in many endemic foci of *S. mansoni*, notably in African countries, such as Egypt and Senegal [84, 87, 88]. However, no evidence of tolerance or resistance to praziquantel has been detected in endemic regions of *S. japonicum* in China [31, 84]. There is no knowledge about development of resistance to praziquantel in *S. haematobium*, although it was once reported that a repeated standard treatment with praziquantel was ineffective to clear the infection with *S. haematobium* in 2 patients [89].

In other trematode species, praziquantel resistance has never been documented [90]. One small trial in clonorchiasis patients in Vietnam reported an unusually low cure rate of only 29% following praziquantel treatment with 25 mg/kg daily for 3 days [6]. This low cure rate seems to have been due to the patients receiving a low dose of the medication compared with the standard dose (40 mg/kg in a single dose or 3 × 25 mg/kg/day for 1-2 days) rather than to drug resistance of *C. sinensis* worms. In cestode infections, a few cases not successfully treated with praziquantel were reported among beef tapeworm (*T. saginata*)

infection cases [91]; however, there was no evidence of drug resistance of the parasite.

Conclusion and perspectives

Praziquantel is a broad-spectrum, highly efficacious and safe, anthelmintic against trematode and cestode infections in humans and animals. The only limitations for its use in human infections include fascioliasis, hydatid disease, and sparganosis, in which triclabendazole, a combination of praziquantel and albendazole, and surgical removal of parasites, respectively, may be used as an alternative treatment for each infection. Emerging problems include the appearance of praziquantel-resistant strains or isolates in *S. mansoni* and *S. japonicum* in the laboratory or in the field. Occurrence in some patients of allergic, hypersensitivity, or anaphylactic reactions to treatment with praziquantel is another emerging problem.

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