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The little we know about the pharmacokinetics and pharmacodynamics of praziquantel (racemate and *R*-enantiomer)

Piero Olliaro[1,2]*, Petra Delgado-Romero[3] and Jennifer Keiser[4,5]

[1]UNICEF/UNDP/World Bank/WHO Special Programme on Research & Training in Tropical Diseases (TDR), World Health Organization, 20 Avenue Appia, CH-1211, Geneva 27, Switzerland; [2]Centre for Tropical Medicine and Vaccinology, Nuffield Department of Medicine, University of Oxford, Churchill Hospital, Oxford, UK; [3]Department of Preclinical and Medical Affairs, PharmaLex GmbH, Mannheim, Germany; [4]Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Basel, Switzerland; [5]University of Basel, Basel, Switzerland

*Corresponding author. Tel: +(41) 22 791 3734; Fax: +41 22 791 48 54; E-mail: olliarop@who.int

Praziquantel has been the mainstay of schistosomiasis control since 1984 and widely distributed since 2006 through 'preventive chemotherapy' programmes to school-aged children or at-risk populations. In addition, preschool-aged children are now recognized as a vulnerable population and a group for targeted treatment, but they may be difficult to dose correctly with the available product—a racemate, based on the biologically active enantiomer (*R*-praziquantel) and the inactive distomer (*S*-praziquantel), which contributes the bitter taste and doubles the size of the tablets. Hence, a paediatric formulation is required, possibly enantiomerically pure. Developing such a product and extending its use to younger children should be pharmacologically guided, but limited data exist on pharmacokinetics and pharmacokinetic/pharmacodynamic correlations for praziquantel. This article presents available data on the chemistry, pharmacokinetics and pharmacodynamics of praziquantel, as well as *R*-praziquantel, and points to gaps in our knowledge.

Keywords: schistosomiasis, *Schistosoma* spp., chemotherapy

Introduction

Some 779 million people are at risk of contracting schistosomiasis,[1] a neglected tropical disease accounting for 3.3 million disability-adjusted life years.[2] Praziquantel is widely used for the treatment and control of all *Schistosoma* species infecting humans and causing the intestinal (mainly *Schistosoma mansoni* and *Schistosoma japonicum*) and urinary (*Schistosoma haematobium*) forms of schistosomiasis.[3–5] Adult male–female pairs reside in the mesenteric veins and lay eggs, which sustain both the transmission and the pathology. Schistosomiasis develops over many years and is characterized by immunogenic inflammatory, granulomatous and fibrotic reactions, which are provoked by trapped schistosome eggs in the tissues.[5] Whereas treatment is directed against the adult worms, the effects of treatment are customarily assessed by counting the eggs in the excreta (stools or urine), although new methods are under development (see below).

Praziquantel has been the mainstay of schistosomiasis control since 1984. As praziquantel is effective and normally has only minor and transient side effects, it has been widely used since 2006 through 'preventive chemotherapy' programmes distributing the drug to school-aged children or at-risk populations, depending on prevalence rates. In 2010, 34 million individuals received praziquantel as part of these programmes, mostly in sub-Saharan Africa.[6] It has been estimated that in 2018 as many as 235 million people will be treated with praziquantel, equivalent to a projected use of 645 million praziquantel tablets.[6]

Recently, there has been a renewed interest in studying better formulations of praziquantel, especially for small children.[7] This stems, at least in part, from the fact that preschool-aged children are now recognized as a vulnerable population and a group for targeted treatment.[6–8]

The current product is a racemate, made of the biologically active enantiomer [*R*-praziquantel (*R*-PZQ)] and the inactive distomer [*S*-praziquantel (*S*-PZQ)], which contributes the bitter taste and unnecessarily doubles the size of the tablets (factors that render treatment less acceptable, especially to small children).[9] Hence, a paediatric formulation (e.g. orodispersible tablets) would be an improvement. There is evidence that enantiomerically pure *R*-PZQ can be synthesized economically,[10,11] which might facilitate the development of a child-friendly formulation of *R*-PZQ. It should be noted that praziquantel is registered for use in subjects aged 4 years or more,[12] which means that that this product is technically not authorized in young children. There may be safety concerns in this age group, with very limited data to support or belie them. A similar situation has been faced for the treatment of children under 24 months of age with albendazole and mebendazole; open discussions with the original producers and several national regulatory authorities concluded that the exclusion was due to a lack of information on the treatment of the age group and not to any report

documenting, or suggesting, a particular risk of toxicity.[13] In that case, a thorough review of the available pharmacokinetic and safety data concluded that benzimidazoles could be used for the treatment of soil-transmitted helminthiasis in children aged 12 months and older, and that the health benefits appear to override any potential risk associated with the administration of the drug.[14]

In order to optimize praziquantel treatment for preschool-aged children, basic information on the drug safety and pharmacology is required. However, limited data are available; only a handful of reviews on praziquantel pharmacology have been published to date[15–19] and little is known on the pharmacokinetic/pharmacodynamic correlations of praziquantel. This paper summarizes available data on the chemistry, pharmacokinetics and pharmacodynamics of praziquantel, as well as *R*-PZQ, and points to gaps in the knowledge.

Chemistry and biopharmaceutics

Praziquantel {2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one} has a molecular weight of 312.3 and is a Class II drug both according to the Biopharmaceutics Classification System [BCS; high permeability, low solubility (0.4 mg/mL)] and the Biopharmaceutics Drug Disposition Classification System (BDDCS; extensive metabolism, low solubility).[20,21] The product currently registered and distributed is a racemate containing equal proportions of *R*-(−)-PZQ (levorotatory, L-PZQ) and *S*-(+)-PZQ (dextrorotatory, D-PZQ). The structural formulae are depicted in Figure 1. While we are not aware of specific data for *R*-PZQ, neither its solubility nor its permeability (passive diffusion) are expected to differ significantly from the racemate.

Pharmacokinetics

Few pharmacokinetic studies have been performed with praziquantel in humans, and none in the main target population (school-aged children with urinary or intestinal schistosomiasis) or in preschool-aged children. Pharmacokinetic studies using *R*-PZQ have not been carried out to date. The main pharmacokinetic parameters of praziquantel after oral administration are summarized in Table 1. Studies were conducted in healthy normal volunteers (HNVs; including fasting and fed conditions), *S. mansoni*-infected adult patients with varying degrees of liver damage[22,23] and *S. haematobium*-infected subjects,[24] as well as in *S. japonicum*-infected subjects.[25,26] The doses administered ranged from 5 to 50 mg/kg in HNVs, and from 25 to 40 mg/kg in patients; the pharmacokinetics of 60 mg/kg have not been investigated, although this dose has been used to treat infected patients. Different commercial products (e.g. Distocide®, Biltricide® and Cysticide®) were used in the pharmacokinetic studies. In addition, some studies compared the main pharmacokinetic parameters of various commercial formulations.[27,28]

Few studies compared directly different doses of praziquantel: 5, 10, 20, 50 mg/kg (Cysticide®)[29] and 20 versus 40 mg/kg (Biltricide® and Distocide®).[27] Increases in AUC were not dose-proportional, which may be explained by the fact that the first-pass metabolism is dose-dependent with regard to capacity, with saturation of the metabolic routes. AUC values differed across studies and brands, which may be accounted for by interindividual variability and pharmacogenetics, as well as different dissolution profiles and bioavailability of products. Doubling the dose from 20 to 40 mg/kg produced a 2.7- and 1.4-fold net increase in AUC for Biltricide® and Distocide®, respectively.[27] The dose–response study on Cysticide® by Leopold *et al.*[29] unfortunately did not include 40 mg/kg, the current WHO-recommended dose.

Since a parenteral human formulation does not exist, the absolute bioavailability of praziquantel is not known. Studies in monogastric animals indicate a strong first-pass effect and oral mean absolute bioavailability of around 36%.

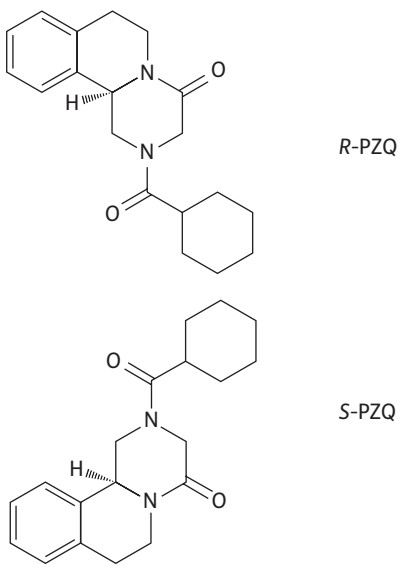

Figure 1. Structural formulae of *R*-PZQ and *S*-PZQ.

Absorption

The absorption of praziquantel is rapid (T_{max} 2–2.6 h in HNVs with Distocide®) and nearly complete (>80%) (Figure 2), but the systemic bioavailability of praziquantel is low and varies considerably between individuals. After the administration of 40 mg/kg to fasted healthy adults, the $t_{1/2}$ was reported to range from 2.2 to 8.9 h and the AUC from 2100 to 5400 ng·h/mL. Oral drugs have a greater pharmacokinetic variability than drugs administered by the intravenous route, explained by the blood flow at the absorption site, the absorptive surface area, the transit time and the gastric pH,[30] factors all influenced by concurrent food uptake.

The bioavailability of praziquantel increases with concomitant food administration. Castro *et al.*[31] showed that following the administration of a dose of 1800 mg (~25 mg/kg for a 70 kg body weight) to healthy adults, the AUC_{0-8} was 2.7-fold higher with a fatty diet (eggs, ham, orange juice, milk; ~30% lipid; ~50% carbohydrate) and ~4-fold higher with a high-carbohydrate content diet (tortillas, tomato, chicken, bread, orange juice; ~10% lipid; ~75% carbohydrate) than without food. Similarly, the administration to Sudanese adult males of praziquantel at a dose of 40 mg/kg with food (cooked beans/10% cotton seed oil/bread) resulted in a 2.6-fold increase in the $AUC_{0-\infty}$.[32] In addition, neurocysticercosis patients receiving a high-carbohydrate diet had significantly greater plasma levels than fasted patients.[33] The effect of food on the bioavailability of praziquantel may be due to changes in hepatic blood flow, altered cytochrome P450 (CYP)

Table 1. Pharmacokinetic parameters of praziquantel observed in key studies conducted in humans

Reference	Subjects (*n*)	Product	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC (ng·h/mL)
Leopold *et al.*,[29] 1978[a]	HNVs (fed) (6)	Cysticide	5	48 ± 13	2.75 ± 0.34	1.70 ± 0.14	167 ± 51
	HNVs (fed) (6)	Cysticide	10	66 ± 11	2.58 ± 0.24	1.30 ± 0.16	209 ± 55
	HNVs (fed) (6)	Cysticide	20	250 ± 25	2.08 ± 0.38	1.18 ± 0.09	645 ± 93
	HNVs (fed) (8)	Cysticide	50	1319 ± 441	1.88 ± 0.36	1.19 ± 0.10	3931 ± 1432
Castro *et al.*,[31] 2000[b]	HNVs (fast) (9)	Cysticide	25	319 ± 227	1.39 ± 0.98	2.03 ± 0.24	882 ± 417
	HNVs (fat) (9)	Cysticide	25	1095 ± 780	1.94 ± 1.09	1.72 ± 0.18	2475 ± 1166
	HNVs (carbohydrates) (9)	Cysticide	25	1962 ± 780	1.47 ± 0.64	1.66 ± 0.32	3276 ± 970
Mandour *et al.*,[22] 1990[c]	HNVs (fast) (6)	Distocide	40	978 ± 220	2.60 ± 0.30	3.30 ± 0.30	4089 ± 1594
	HNVs (fat) (6)	Distocide	40	1570 ± 328	2.70 ± 0.30	2.50 ± 0.40	5699 ± 1576
	HNVs (low fat) (6)	Distocide	40	2093 ± 382	2.00 ± 0.40	2.30 ± 0.40	7126 ± 1781
Homeida *et al.*,[32] 1994[d]	HNVs (fast) (9)	Distocide	40	1018 ± 321	1.89 ± 0.23	2.1 ± 0.29	2979 ± 825
	HNVs (fat) (7)	Distocide	40	1708 ± 297	2.47 ± 0.60	2.26 ± 0.20	7613 ± 918
Mandour *et al.*,[22] 1990[c]	HNVs (fast) (6)	Distocide	40	249 ± 41	2.10 ± 0.70	8.90 ± 1.20	2110 ± 563
	HNVs (fast) (6)	Biltricide	40	823 ± 2716	1.60 ± 0.20	6.30 ± 0.70	5409 ± 1913
Mandour *et al.*,[22] 1990[c]	HNVs (fast) (6)	Distocide	40	978 ± 220	2.60 ± 0.30	2.30 ± 0.40	3823 ± 1563
	S. mansoni patients (different grades of periportal fibrosis) (fast) (9)	Distocide	40	1618 ± 387	1.60 ± 0.30	11.90 ± 5.40	15928 ± 5489
el Guinaidy *et al.*,[23]1994[d]	*S. mansoni* patients, normal liver function (fast) (10)	Distocide	40	833 ± 519	1.48 ± 0.74	2.99 ± 1.28	3023 ± 590
	S. mansoni patients, Child A (fast) (10)	Distocide	40	931 ± 577	1.37 ± 0.61	4.66 ± 2.77	3870 ± 2435
	S. mansoni patients, Child B (fast) (10)	Distocide	40	1469 ± 739	2.21 ± 0.78	4.74 ± 2.16	10720 ± 5530
	S. mansoni patients, Child C (fast) (10)	Distocide	40	3573 ± 1296	3.20 ± 1.05	8.45 ± 2.62	45350 ± 17500
Metwally *et al.*,[27] 1995[e]	HNVs (fast) (10)	Biltricide	20	846 ± 211	1.65 ± 0.21	0.97 ± 0.19	1303 ± 276
	HNVs (fast) (10)	Distocide	20	558 ± 75	2.60 ± 0.53	1.24 ± 0.41	1562 ± 287
	HNVs (fast) (10)	Biltricide	40	1281 ± 371	2.00 ± 0.23	2.18 ± 0.29	3550 ± 883
	HNVs (fast) (10)	Distocide	40	685 ± 88	1.72 ± 0.40	2.78 ± 0.46	2133 ± 366
Kaojarern *et al.*,[28] 1989[e]	HNVs (fed) (8)	Biltricide	40	1614 ± 170	1.93 ± 0.22	NA	4830 ± 322
	HNVs (fed) (8)	brand B	40	1625 ± 207	1.72 ± 0.26	NA	4407 ± 398
	HNVs (fed) (8)	brand C	40	1247 ± 123	2.14 ± 0.22	NA	3910 ± 179
	HNVs (fed) (8)	brand D	40	1007 ± 150	2.81 ± 0.37	NA	3374 ± 366
Ofori-Adjei *et al.*,[24] 1988[b]	HNVs (fast) (6)	Biltricide	30	1213 ± 844	1.75 ± 0.30	2.7 ± 1.60	3032 ± 1443
	S. japonicum patients (fast) (5)	Biltricide	30	3124 ± 1721	1.9 ± 1.20	1.7 ± 0.70	4085 ± 3020
Watt *et al.*,[26] 1988[f,g]	*S. japonicum* patients, normal liver function (13)	Biltricide	60	2170 ± 1140	2.5 ± 1.70	1.7 ± 0.80	8940 ± 4250
	S. japonicum patients, liver moderate (9)	Biltricide	60	5010 ± 2470	1.9 ± 1.30	2.2 ± 0.64	22880 ± 15820
	S. japonicum patients, liver severe (8)	Biltricide	60	8195 ± 4860	2.6 ± 2.00	2.3 ± 1.00	37770 ± 24500

[a]Mean ± SEM; AUC_{0-24}.
[b]Mean ± SD; AUC_{0-8}.
[c]Mean ± SEM; $AUC_{0-\infty}$.
[d]Mean ± SD; $AUC_{0-\infty}$.
[e]Mean ± SEM; AUC not defined.
[f]Mean ± SD; AUC_{0-24}.
[g]Fast/fed conditions not stated.

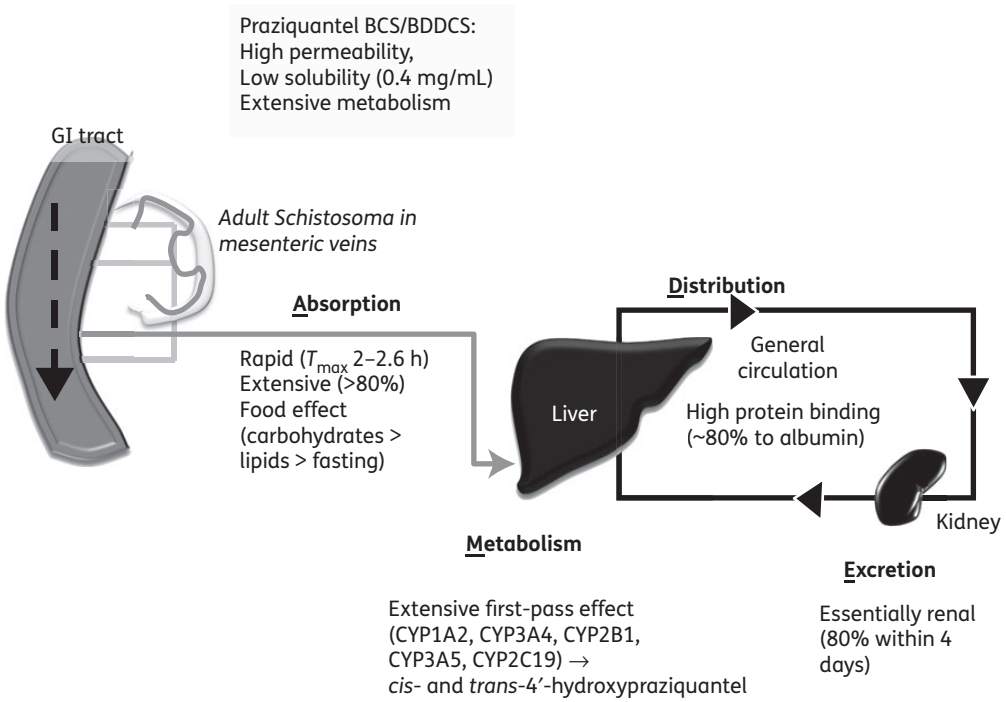

Figure 2. Schematic diagram showing the principal characteristics of praziquantel absorption, distribution, metabolism and excretion ('ADME'). GI, gastrointestinal.

expression in response to the diet or changes in the first-pass metabolism (Figure 2).[34,35]

Observed differences in the oral bioavailability might also be explained by differences in the formulation. Three studies showed a variable drug disposition following the administration of different brands to HNVs.[22,27,28] For example, Biltricide® showed a C_{max} and AUC 3.3 and 2.6 times those of Distocide®; the T_{max} and $t_{1/2}$ were shorter (0.8 and 0.7 those of Distocide®) but the sample size was small.[22] Different products appear to have varying dissolution profiles and bioavailabilities. Kaojarern *et al.*[28] showed that two products that revealed lower AUC values were characterized by a longer disintegration time and lower dissolution.

Although only four studies have been conducted in patients, disease status appears to increase exposure.[22,23,25,26] In a study comparing praziquantel disposition in HNVs and patients after the administration of 40 mg/kg, C_{max} and AUC were 1.7- and 4.2-fold higher in patients, the T_{max} was shorter (0.6 times) and the $t_{1/2}$ was 5.2 times longer.[22] Data in HNVs are relevant as a proportion of individuals receiving praziquantel preventative chemotherapy are not infected. The lower exposure in these subjects accounts for the drug's good tolerability.

In very young children, compared with older children, one might expect slower rates of absorption, especially for drugs with limited water solubility (such as praziquantel), that are related to developmental changes in gastrointestinal motility, resulting in a longer time required to achieve the maximal plasma concentration.[36]

Distribution

In non-clinical studies, praziquantel was found to distribute throughout the body and concentrate especially in the liver and kidneys. Concentrations higher than those in plasma were found in the lung, pancreas, adrenal glands, pituitary and salivary gland.[15] The volume of distribution is not known. Praziquantel crosses the blood–brain barrier, explaining its effectiveness in neurocysticercosis.[37] Concentrations in breast milk are approximately one-fourth of the plasma concentration.[38]

Praziquantel is highly protein-bound (~80%, nearly exclusive to albumin),[39,40] which makes the levels of free drug subject to factors such as nutrition and inflammation[41] (and further explains the differences seen between healthy volunteers and patients). It is also possible that the fraction of free drug will be higher in very young children (<1 year old), who have a lower amount of total plasma proteins, including albumin.[36]

Metabolism

Praziquantel undergoes an extensive first-pass metabolism in the liver by the CYP system (CYP1A2, CYP3A4, CYP2B1, CYP3A5 and CYP2C19).[15,39] This makes its pharmacokinetics susceptible to variability due to: (i) interindividual pharmacogenetic differences; (ii) interactions with drugs or substances taken concomitantly that induce or inhibit specific isoenzymes of the CYP system (e.g. increased exposure with cimetidine or grapefruit juice[42] and decreased exposure with the anti-epileptic CYP inducers carbamazepine and phenytoin[43] or rifampicin[44]); and (iii) the condition of the liver function (exposure increases with the severity of hepatic impairment[22]).

The metabolism of praziquantel is stereo-selective. Several studies have analysed the metabolites of praziquantel *in vivo* (mouse, rat and man) and *in vitro* (rat and human liver microsomes). Identified metabolites vary depending on the species and analytical methods but are in general hydroxylation products containing one,

two, or three hydroxyl groups. The precise structure of many of these metabolites and the position of the hydroxyl group is still unknown. Studies in rat hepatocytes have shown that the main metabolites are *cis*- and *trans*-4′-hydroxypraziquantel, the first being most abundant in the rat. The main metabolite in man is *trans*-4-hydroxypraziquantel. *S*-PZQ also produces additional monohydroxypraziquantel metabolites.[45] A recent study[46] identified up to nine metabolites of praziquantel, two dehydrogenated and seven monohydroxylated metabolites, using human liver microsomes; no dihydroxylated metabolites were found. Two studies have examined the enantioselective kinetic disposition of praziquantel in HNVs and reported $AUC_{R/S}$ ratios of 1.67[47] and 1.79–2.6[48] for 4′-hydroxypraziquantel. Differences may be due to an enantioselective first-pass metabolism.

The *R-trans*-4′-hydroxypraziquantel was found to have a similar activity to *R*-PZQ on adult *S. mansoni in vitro*.[49] On the other hand, *S. japonicum* were less affected by *trans*-4′-hydroxypraziquantel than praziquantel: spasmodic contractions were observed only at a high concentration of 30 μg/mL. Since these levels are not achieved *in vivo,* the authors concluded that *trans*-4′-hydroxypraziquantel is not therapeutically relevant.[50]

The maturation of drug-metabolizing enzymes is delayed and almost all liver metabolic processes are slower in infants than in the older child and adult. The maturation of different Phase 1 and Phase 2 reactions (e.g. conjugation) may vary extensively. Hence, a prolonged $t_{1/2}$ of praziquantel might be expected in young children, although further studies are warranted.[36,51]

Elimination

Elimination of praziquantel is essentially renal (80% within 4 days, of which 90% occurs within 24 h);[15] as the product is extensively metabolized, <0.01% is found in the urine as the parent compound. No studies are available in patients with renal impairment. Generally, it takes 6–12 months for the various renal functions of an infant to reach adult values;[51] the elimination of praziquantel should therefore be similar in preschool-aged children and adults.

Pharmacodynamics

In vitro and in vivo activity of praziquantel

A concentration of 1 μg/mL praziquantel is effective against all intramammalian stages of *S. mansoni* (7–48 days old; derived from lungs, liver and mesentery).[52] Praziquantel disrupts Ca^{2+} homeostasis in adult worms, which induces a spasmodic muscular contraction and immobilization of the worm's body.[53] Worms treated with 1 μg/mL praziquantel stop moving immediately, as demonstrated by microcalorimetric studies.[54] Adult worms are slightly more susceptible to praziquantel (LC_{50} 0.03 μg/mL at 72 h) than schistosomula (0.68 μg/mL at 72 h).[55]

High doses of praziquantel are needed to achieve a high reduction in worm burden in *Schistosoma*-infected rodents. For example, in the *S. mansoni* mouse model, praziquantel given at 172 mg/kg and 592 mg/kg is estimated to achieve reductions in worm burden of 50% and 95%, respectively.[56] A similar ED_{95} of 479 mg/kg was determined when the drug was administered over 5 days.[52] However, the therapeutic potency of praziquantel can be increased by applying multiple oral doses at short intervals on a single treatment day (ED_{95} 200 mg/kg).[52] The tegument of the worm suffers severe damage following praziquantel treatment, which results in exposure of the worm's antigens. The host humoral immune response therefore plays an important role in the activity of praziquantel, which is significantly less active in B cell-depleted mice.[57]

Enantioselective in vitro and in vivo activity

A handful of studies have evaluated the anti-schistosomal activity of *R*-PZQ and *S*-PZQ *in vitro* and *in vivo*. Xiao and Catto[58] demonstrated that spasmodic contractions and vacuolization of the tegument of *S. mansoni* occurred at concentrations of 0.1 μM praziquantel and 0.05 μM *R*-PZQ *in vitro*. *In vivo* studies were done in *S. japonicum*-infected rabbits and mice and *S. mansoni*-infected mice.[58–61] *R*-PZQ was superior to *S*-PZQ against *S. japonicum in vivo*.[59,61] Findings reported on the activity of *R*-PZQ in *S. mansoni*-infected mice are contradictory. While Xiao and Catto[58] have documented a reduction in worm burden of 72% following the administration of *R*-PZQ to *S. mansoni*-infected mice, a low worm burden reduction of 32% (compared with 51% for *S*-PZQ) was observed in another study.[59] Similarly, *S. mansoni* recovered from infected mice treated with *R*-PZQ showed no significant damage of the reproductive organs and tegument, in contrast to worms exposed to *S*-PZQ.[60]

Clinical findings on praziquantel and R-PZQ

The recommended treatment schedule for praziquantel is 20 mg/kg three times a day at 4 hourly intervals on a single day (Biltricide® monograph; http://www.bayer.ca/files/BILTRICIDE-PM-ENG-30NOV2007-116425-2.pdf). For practical reasons, the WHO recommends 40 mg/kg in a single administration for all forms of schistosomiasis in preventive chemotherapy programmes.[62] Cochrane systematic reviews show a dose-effect for *S. mansoni* in the range 20–40 mg/kg and no further efficacy increase beyond 40 mg/kg[63], while the dose–response curve in that dose range appeared to be flat for *S. haematobium*.[64] Although these data cannot be strictly compared, in the *S. mansoni* trials included in the Cochrane systematic review, the average failure rate decreased with increasing doses (51%, 35%, 23% and 17% with 20, 30, 40 and 60 mg/kg).

A systematic review and meta-analysis identified 56 comparative and non-comparative trials of praziquantel, of which 36 enrolled ~7000 preschool- and school-aged children and adolescents treated with 40 mg/kg praziquantel (P. Olliaro and J. Zwang, unpublished data). A multivariate mixed-effect model with random effect on the study site showed a significant relationship between age and cure rate [but not egg reduction rate (ERR)] for *S. mansoni* and *S. japonicum*, and no age effect for *S. haematobium* (although preschool-aged children were not present in this group).

To date, three studies have evaluated the clinical activity of *R*-PZQ, of which only one has used the common Kato–Katz method in intestinal schistosomiasis and comparable *R*-PZQ and praziquantel dosages.[65] In this trial, 278 patients with *S. japonicum* were treated with 20 mg/kg *R*-PZQ or 40 mg/kg praziquantel. Four months post-treatment, cure rates of 94.8% and 97.1% were observed for *R*-PZQ and praziquantel, respectively. Importantly, significantly fewer adverse events were observed in patients treated with *R*-PZQ.[65,66]

Pharmacokinetic/pharmacodynamic correlations

It is challenging to derive pharmacokinetic/pharmacodynamic estimates for anthelminthic drugs. The above-mentioned non-clinical *in vivo* data indicate that the anti-schistosomal activity of praziquantel is not related to the absolute C_{max} but rather to the duration of exposure. The peak/MIC ratio in mice was high (>100), with the C_{max} in the mouse plasma ranging from 10.7 to 33 μg/mL after receiving a 500 mg/kg dose,[67] and much higher levels in the mesenteric and portal veins, where the adult worms reside (Figure 2). This means that adult worms will encounter praziquantel before it is metabolized in the liver through first-pass. For example, in *S. japonicum*-infected rabbits the concentration of praziquantel in the portal venous plasma was 10-fold greater than in the femoral venous plasma.[68] Note that the location in the lungs most likely explains the lower susceptibility of juvenile worms to praziquantel. On the other hand, the time during which the serum level exceeds the MIC is short (the $t_{1/2}$ in mice is ∼1 h),[67] and the therapeutic potency of praziquantel increases by applying multiple oral doses at short intervals on a single treatment day,[52] which increases the duration of exposure.

Obviously, it is even more difficult to examine the pharmacokinetic/pharmacodynamic relationship in patients. The effects are customarily measured by counting eggs (in the faeces or urine)—a proxy for the viability of adult worms—and expressed as either (i) the cure rate (the proportion of patients who are negative post-treatment) or (ii) the ERR (the proportional reduction in the mean egg counts of the patient population treated from pre- to post-treatment); furthermore, ERR could be based on either arithmetic or geometric mean egg counts.[69] This approach has clear limitations: the limited sensitivity of the methods in use (the Kato–Katz being the most widely used technique) and the fact that it does not detect direct effects on adult (or juvenile) worms. Newer, more contemporary methods are being tested, such as the circulating anodic antigen[70] and the circulating cathodic antigen levels,[71] which should provide a more reliable and standardized way of measuring efficacy and relating it to drug exposure.

Practical aspects of the development and deployment of praziquantel

In the absence of robust data (which are, among others, to be generated by a consortium on paediatric praziquantel development),[8] it is not possible at present to quantify the potential advantages of an enantiomerically pure product over the racemic mixture.

A paediatric formulation (of either product) can indeed improve the dosing accuracy and acceptability when used programmatically; practical dosing indications are also needed. The customary method used by many control programmes is the dosing pole (dosing based on height, rather than weight)—originally for children >110 cm[72] and recently extended to children >60 cm.[73] Where scales are available, adequate dosing (within the 40–60 mg/kg range) is achieved with formulations containing 150 mg of the racemate using practical weight categories from 5 kg body weight.[74]

Conclusions

Scant information is available on the pharmacokinetic properties and pharmacokinetic/pharmacodynamic relationship of praziquantel, especially in children, the population chiefly affected by schistosomiasis, and hence those who are more intensely treated.

The need for this information is particularly acute now that paediatric formulations are being developed and that younger children too are considered for targeted treatment.

In the few available studies, praziquantel disposition appears to vary widely; factors such as the product and the subject (whether healthy or infected, and fasting or fed) seem to influence the disposition, but direct comparisons are difficult to make.

Regarding the dose, unless the pharmacokinetic/pharmacodynamic characteristics of praziquantel are studied more systematically, it will not be possible to understand whether dose adjustments are required for subjects of different ages, particularly small children, and to have a pharmacologically guided dose selection for new products.

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Transparency declarations

P. D.-R. is an employee of PharmaLex GmbH and a consultant for Merck-Serono GmbH (Darmstadt, Germany). Both other authors: none to declare.

Disclaimer

The opinions expressed in this paper are those of the authors and may not reflect those of their employing organizations. P. O. is a staff member of the WHO; the authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the WHO.

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