REVIEW

A SHORT REVIEW OF SOME PHARMACOLOGICAL, THERAPEUTIC AND TOXICOLOGICAL PROPERTIES OF PRAZIQUANTEL IN MAN AND ANIMALS

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ABSTRACT

Praziquantel is the current drug of choice against many trematodes and cestodes in both man and animals. This article summarizes the main pharmacological, therapeutic and toxicological properties of the drug, especially that have been reported during the last 10 years. In most cases, the effectiveness and safety of the drug have been confirmed, although there are currently concerns about the resistance/ decreased effectiveness of the drug to certain Schistosome isolates, and also about the mutagenicity of the drug.

Keywords*:* Praziquantel, toxicity, pharmacology, therapy, resistance.

INTORDUCTION

Praziquatel is an acylated quinoline-pyrazine (fig. 1) that has been originally developed for veterinary applications, and is now one of the most important drugs that has been added to the armamentarium of anti-parasitic drugs for human and veterinary use since the 1970s.

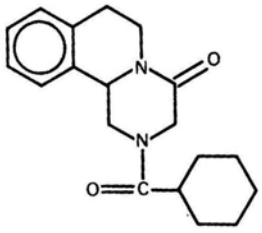

Fig.1: Praziquantel

Chemistry

Chemically piperazine is 2-cyclohexylcarbonyl-1,2,3,6,7, 11b-hydropypyrazino {2,1-a} isoquinolin-4-one. Only the enantiomor is active. It is present as a white to practically white, hygroscopic, bitter tasting, crystalline powder, either odorless or having a faint odor. It is very slightly soluble in water and freely soluble in alcohol.

Mechanism of action

Praziquantel has activity against a wide spectrum of trematodes and cestodes, but is generally ineffective against other organisms such as nematodes. The exact mechanism of action of praziquantel against cestodes has not been fully determined. At low concentrations *in vitro*, the drug appears to impair the function of the worms' suckers and stimulates their. At higher concentrations *in vitro*, praziquantel increases the contraction (irreversibly at very high concentrations) of the worm's strobilla (chain of proglottids) (Cioli and Pica-Mattoccia, 2003). Also, praziquantel causes irreversible focal vacuolization with subsequent cestodal disintegration at specific sites of the cestodal integument (Martin, 1997). In schistosomes and other trematodes, praziquantel directly kills the parasite, possibly by increasing calcium ion (Ca^{++}) flux into the worm (Greenberg, 2005 a, b). There is experimental evidence that praziquantel increases the permeability of the membranes of parasite cells for Ca^{++} The drug thereby induces contraction of the parasites resulting in paralysis in the contracted state (Martin, 1997; Greenberg, 2005 a, b; Jeziorski and Greenberg, 2006).The dying parasites are dislodged from their site of action in the host organism and may enter systemic circulation or may be destroyed by host immune reaction (phagocytosis). Additional mechanisms - focal disintegrations and disturbances of ovipositor (laying of eggs) - are seen in other types of sensitive parasites (Dollery, 1999). Focal vacuolization of the integument follows and the parasite is phagocytized. Praziquantel may adversely affect the parasite's glutathione and intracellular calcium concentrations, with secondary effects on the metabolism and antigenicity (Ribeiro *et al.*, 1998; Dollery, 1999).

Methods of determination in tissues

There are several high performance liquid chromatographic (HPLC) methods for the determination of praziquatel in serum, urine or tissue homogenates. These include, for example, the methods of Xiao *et al.* (1983), Liu and Stewart (1997) and Dollery (1999). Newer HPLC/mass spectrometry methods measure praziquatel and its metabolites (e.g. Meier and Blaschke, 2000; Meier and Blaschke, 2001). These methods can detect praziquantel itself and its different phase I metabolites, in addition to their glucuronidated and sulfated conjugates

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Pharmacokinetics

Pharmacokinetics of praziquantel is characterized by great variability (Dayan, 2003; Mandour *et al*, 1990; Castro *et al.*, 2003). The influence of the dosage and brand on the efficacy bioavailability and tolerance of praziquantel was studied in Sudan (Homeida *et al.*, 1989) and Egypt (Metwally *et al*, 1995). The former authors (Homeida *et al.*, 1989) found that tolerance to a Korean brand was found to be better than the German brand Biltricide^{R}. Metwally *et al.* (1995) found no significant differences in the kinetics or efficacy between a German brand (Biltricide^{R}) and an Egyptian one (Distocide^{R}).

Absorption: Praziquantel is rapidly and nearly completely absorbed after oral administration, but there is a significant first-pass effect after oral administration. Absorption has recently been shown to be by passive diffusion (Gonzalez-Esquivel *et al.*, 2005). Peak serum levels are achieved after 30-120 minutes in dogs and 3 to 4 h in humans (Dayan, 2003). About 75 to 100% of the orally-administered praziquantel dose is absorbed in rats, dogs, monkeys and man. The half life ($t_{1/2}$) of praziquantel in normal humans was reported to be 1.5 h (Dollery, 1999) and between 1 – 3 h (Sotelo and Jung, 1998). The latter authors have found that peak concentration in serum is reached after 1 to 2 hours and that praziquantel permeates the blood-brain barrier, thus explaining its effectiveness on parenchymal brain cysticercosis. The $t_{1/2}$ of praziquantel increases to about 3 – 8 h in patients with schistosomiasis associated with liver cirrhosis and splenomegaly according to Child's classification of hepatocellular function (El Guiniady *et al.*, 1994).

There are unexplained and considerable variations and inter-individual variations in the rate of absorption and clearance of the drug. It has been shown that a carbohydrate – rich meal enhances absorption in man, probably by increasing the dissolution of the drug (Mandour *et al.*, 1990; Castro *et al.*, 2002), and that schistosomiasis decrease the $t_{1/2}$ of the drug, as it was 11.9 ± 5.4 h in patients with schistosomiasis and 2.3 ± 0.4 h in the controls (Mandour *et al.*, 1990). It was suggested by these authors that the lower plasma levels and longer duration of action of praziquatel may be advantageous in reducing side effects and prolonging exposure of the schistosomes to the drug.

It has been reported that co-administration of chloroquine and pre-administration of carabamezipine and phenoytoin (antiepileptic drugs that can induce the activities of drug metabolizing enzymes) may reduce the bioavailability of praziquatel (Bittencourt *et al.*, 1992; Masimirembwa and Hasler, 1994). It is possible that carbamazepine and phenoytoin displace praziquantel from protein binding sites (Bittencourt *et al*., 1992; Sotelo and Jung, 1998).

Distribution: Praziquantel is distributed throughout the body and crosses the blood-brain barrier into the CNS and across the intestinal wall. The volume of distribution for praziquantel has not been determined, and about 80% of the drug is bound to plasma proteins in man and animals (Mandour *et al.*, 1990).

Metabolism: Praziquantel is stereoselectively metabolized in the liver, yielding preferentially monohydroxylated metabolites (Meier and Blaschke, 2001). A few of the metabolites possess some but weaker antiparasite activity. The main metabolites are *cis*-and *trans*-4-hydroxyl-praziquantel. Different enantimoers of praziquatel are metabolized to qualitatively and quantatively different degrees in isolated rat hepatocytes. In addition to the *cis*-and *trans*-4- hydroxypraziquantel, several metabolites have been identified and isolated, but their structure is still unknown (Meier and Blaschke, 2001; Godawska-Matysik *et al.*, 2004).

It has been shown that, in Egyptian schistosomiasis patients, the kinetics of praziquatel is significantly modified by hepatic dysfunction. Several kinetic parameters such as the half-life of elimination, the half-life of absorption, the maximum concentration, the time to maximum concentration, and the area under the concentration-time curve increased proportional to the degree of hepatic insufficiency (El Guiniady *et al*., 1994).

Grapefruit juice, which is known to inhibit the first-pass metabolism of many drugs mainly by suppression of the cytochrome P450 enzyme (CYP3A4) in the small intestine (Arayne *et al*., 2005) has been shown to significantly later several kinetic parameters of praziquantel in healthy men (Castro *et al*., 2002) and beagle dogs (Giorgi *et al*., 2003). After a single oral dose of praziquantel with 250 ml of grapefruit juice to men, the area under the concentration-time curve and the maximum concentration in plasma of praziquantel (C_{max}) were significantly increased (C_{max} for water treatment, 637.71 ± 128.5 ng/ml; and C_{max} for grapefruit juice treatment, 1,037.65 ± 305.7 ng/ml, $P < 0.05$). No statistically significant differences were found in the time to maximum concentration of drug in plasma or elimination half-life. Furthermore, Giorgi *et al* (2003) found that both freeze-dried grapefruit juice and commercial liquid grapefruit juice significantly increase plasma concentrations and $t_{1/2}$ of praziquantel in dogs.

Excretion: Praziquantel and its metabolites are excreted primarily in the urine and the metabolites in the urine account for about 38, 66 and 80% of an oral dose in rats, dogs and humans, respectively. The elimination half-life is approximately 1-2 h in most species and 3 hours in the dog (Dayan, 2003). In man, the metabolites are completely cleared by four days after an oral dose.

Praziquatel and its major metabolites are excreted in human milk, at a quarter of their levels in plasma (Putter and Held, 1979).

Some pharmacological properties

In normal rabbits it has been shown that no significant changes were obtained after praziquantel administration at dose levels of 40 and 800 mg/kg body weight. Higher doses of 1600 mg/kg and 2000 mg/kg resulted in a significant decrease in the activities of the three drug-metabolizing hepatic enzymes (aminopyrine N-demethylase, aniline 4-hydroxylase and UDP-glucuronyltransferase) in the livers of treated rabbits (Kheir *et al*., 1995).

Previous studies have shown decreased activities of some of the microsomal drug-metabolizing enzymes in the livers of *S. mansoni*-infected mice. It has been shown that praziquatel treatment (in a total dose of 1000 mg/kg given on two consecutive days each of 500 mg/kg body weight) in mice with or without previous *S. mansoni* infection significantly inhibited the activities of some liver microsomal drug-metabolizing enzymes that include aminopyrine-N-demethylase and aniline hydroxylase (Ezzat *et al*., 2001).

Indications and therapeutic properties

Praziquantel is used against many helminthic and protozoan infections. In humans (Adach *et al*., 2005; Kjetland *et al*., 2006; Liu and Weller, 1996; Markoski et al., 2005; Ming-Gang, 2005), domestic animals (Bushara *et al*., 1983; Jenkins, 2005) and pet rodents and reptiles (Mehlorn *et al*., 2005), the drug is generally used in the treatment of several varieties of trematodal infections such as schistosomiasis and fascioliasis, and cestodal infections. Common human cestodes treatable by praziquantel include *Taenia solium* and *Diphyllobothrium latum* and common human trematodes, or flukes, are *Clonorchis sinensis* and *Opisthorchis viverrini*. Although praziquantel can treat human neurocysticercosis, albendazole has been shown to be show more effectiveness in this disease (Palomares *et al*., 2006).

Recently, a case report indicated the success of praziquatel (at a single oral dose of 600 mg) in completely treating the intestinal cestodes *Diphyllobotrium latum* in Brazil (Santos and de Faro, 2005). This cestode is mostly reported in temperate zones, and only few reports have come out from South America. The treatment was complete and not accompanied by any adverse effects.

Surveys of long-term effect of single-dose praziquantel on morbidity and mortality from *Schistosoma mansoni* was investigated in Central Sudan (Kheir *et al.*, 2000) and in children under six years of age living in an endemic area for *Schistosoma haematobium* in Zimbabwe (Mduluza *et al*., 2001). In Sudan, it has been shown that praziquantel treatment was effective in reducing the prevalence of infection from 53% to 34%, and the intensity of infection from 31% to 18% (Kheir et al., 2000). In Zimbabwe, praziquantel therapy reduced infection prevalence and mean intensity from 51.8% and 110 eggs per 10 ml urine, respectively, before starting re-treatment programme to very low levels thereafter. Praziquantel was not accumulated after periodic administration (once every eight weeks for two years) in children (Mduluza *et al*., 2001).

Praziquantel has recently shown to be ineffective in treating *Mansonella perstans*, a filariasis widely present in Africa and equatorial America (Bergani *et al*., 2006). A major weakness of praziquantel is its relative inefficacy against recent infections, a factor that may occasionally result in low cure rates in hyperendemic areas (Cioli and Pica-Mattoccia, 2003).

Resistance to praziquantel

With the ever increasing use of praziquantel there is a possibility of the development of resistance by schistosomes (and other susceptible parasites) to the drug, hence the necessity to explore the activities of other compounds (Bennett *et al*., 1997; Southgate *et al*., 2005).

The first alarming reports of possible praziquantel resistance came from an intensive focus in northern Senegal, where the drug had produced very low cure rate (Ciolo and Pica-Mattoccia, 2003). A decade ago in Egypt, it has been shown that a number of schiztosome isolates werer established in the laboratory from the eggs excreted by patients who had been treated unsuccessfully (3 times) with praziquantel (Ismail *et al*., 1999). The same group of workers in Egypt suggested that there is no rapid emergence of resisitance to praziquantel, as there has not been an increase in the drug failure, despite more than a decade of therapueutic pressure in those villages where there had been resisiatnt infections and worms with decreased response to praziquantel (Botros *et al*., 2005). However, investigators continue to find, for variosu ill-defined reasons, field isolates showing decreased responsiveness to paraziquantel.

Adverse effects

The adverse effects of praziquantel in humans at the therapeutic dose ranges are not very serious. A pre- and post-treatment symptom questionnaire to Ugandans patients given single and repeated (6 weeks apart) praziquantel treatment (40 mg/kg) in a *Schistosoma mansoni*-endemic focus revealed a broad range of side effects, including abdominal pain and diarrhoea. However, no serious or long-lasting complications affecting compliance were observed (Kabatereine *et al*., 2003).

When used orally, praziquantel can cause anorexia, vomiting, lethargy or diarrhea in dogs, but the incidence of these effects is less than 5%. In cats, adverse effects were quite rare (<2%) in field trials using oral praziquantel with salivation and diarrhea being reported.

An increased incidence of adverse effects has been reported after using the injectable product. In dogs, pain at the

injection site, vomiting, drowsiness and/or a staggering gait were reported from field trials with the drug. Some cats (9.4%) showed symptoms of diarrhea, weakness, vomiting, salivation, sleepiness, transient anorexia and/or pain at the injection site (Zajac, 1993).

Overdosage/acute toxicity

Praziquantel has a wide margin of safety. In rats and mice the oral LD_{50} is at least 2 g/kg. An oral LD_{50} could not be determined in dogs, as at doses greater than 200 mg/kg, the drug induced vomiting. Parenteral doses of 50 - 100 mg/kg in cats caused transient ataxia and depression. Injected doses at 200 mg/kg were lethal in cats.

No particular toxic effects were noted in rats treated with praziquatel up to 1000 mg/kg/day for 4 weeks, and in dogs with up to 180 mg/kg/day for 13 weeks (Frohberg, 1984; Frohberg 1989). The no-observed-effect levels (NOELS) for those experiments were 33 mg/kg/day and dog 60 mg/kg/day. Rabbits given praziquantel at a dose rate of 2000 mg/kg died 10-20 hours following the treatment (Kheir *et al*., 1995). Recently, Omar *et al* (2005) reported that praziquantel (1500 mg/kg, weekly for 6 weeks) induced a significant increase in the mean values of some liver function tests (AST, ALT and bilirubin) with areas of hyaline degeneration, fatty changes, dysplasia and necrosis in the liver sections. The drug also induced a significant increase in the incidence of chromosomal aberrations as polyploidy, fragment, deletion and ring chromosome as compared with control group. It was concluded that at the dose and duration used, praziquantel has hepatotoxic, genotoxic and carcinogenic effects in albino rats. The genotoxicity of praziquantel has been adequately reviewed by Montero and Ostrosky (1997). Although initial reports on genotoxicity of praziquantel gave mostly negative results in tests in bacteria, yeasts, mammalian (mice) reproductive cells and Drosophila, more recent reports in humans and pigs have suggested that praziquantel induces a greater frequency of hyperploid lymphocytes as well as structural chromosomal aberrations, but not in all the individuals treated. *In vitro* studies have demonstrated that praziquantel can induce micronuclei in Syrian hamster embryonic (SHE) cells and in lymphocytes of some individuals. The same was found about structural chromosomal aberrations.

Fetal death and fetal resorption were found when praziquantel was administered in high doses to pregnant rats between the 6th and 10th day of gestation (Frohberg, 1989). The high volume of distribution of praziquantel and its metabolites suggests that it can enter the placenta. However, clinically it has reported that the drug is safe to use during pregnancy (Adam *et al*., 2004; Adam *et al*., 2005).The safety of a single dose of praziquatel (40 mg/kg) orally-administered during different stages of pregnancy was confirmed in 25 Sudanese women afflicted with schistosomiasis mansoni (Adam *et al*., 2005). Neither the treated mothers, nor their babies (who were followed for up to one year of age) were adversely affected by the treatment. This confirms earlier work which concluded that praziquantel is safe in pregnant and lactating mothers (for a review see: Olds, 2003). The drug is also approved for use in pregnant sheep, cats and dogs (Zajac, 1993; Dayan, 2003).

It has been confirmed that praziquatel was without any carcinogenic or teratogenic effects. Recently, however, concerns over its genotoxicity have mounted. Due to its extensive use in multiple reinfections, and in infected and non-infected and non-diagnosed individuals, there are fears that the dug may not only be mutagenic per se, but also contribute to the development of neoplasm (Montero and Ostrosky, 1997).

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