REVIEW ARTICLE

PRAZIQUANTEL

Auratai Aramphongphan

Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand.

SUMMARY

Since the introduction of the first antischistosomicide, tartar emetic, many compounds have been tested with the aim to develop the ideal antischistosomicidal drug with the following qualities :

1) Absence of side effects and toxicity in man, 2) High activity against the three major species of schistosomes parasitic in man, 3) Effective after a single or a one day-treatment preferably after oral administration, 4) Active against all stages of schistosomes in man. These lead to a new heterocyclic pyrazino isoquinoline with high anti-parasitic efficacy, praziquantel.

Praziquantel is a newly developed anthelminthic drug with excellent activity against all schistosome species parasitic in man. A further progress is the fact that the efficacy of this drug is not significantly influenced by inter-strain variation of schistosomes in contrast e.g. to hycanthone and oxamniquine, and it is effective against all stages of the immature infection. It has also been effective against Clonorchis sinensis (Chinese liver fluke), Metagonimus yokogawai (intestinal fluke), and adult larval stages of important human tapeworms, including Hymenolepis nana and cysticercosis.

Praziquantel acts by increasing the permeability of the worm's cell membrane to calcium ions, causing massive contraction and paralysis of its musculature, followed by disintegration of its tegumental layer. A rapid absorption, distribution and elimination after oral application in man were observed. No major toxic reactions have yet been found with praziquantel. Transient abdominal pain can occur, especially when the drug is given as a single oral dose. Praziquantel has not been found to be mutagenic in a variety of assays. Chronic toxicity tests in small animals so far offered no indication of carcinogenic potential.

Schistosomiasis - Schistosomes are by far the best known of all blood flukes because of the serious and major disease that they cause in man. Schistosoma japonicum is found in Southeast Asia, Japan, China and the Phillipines, S.mansoni occurs in Africa, the Middle East and South America; S.haematobium is found in Africa and the Middle East. Heavy chronic infection can cause inflammation, obstruction and fibrosis, particularly of

Thai J. Pharmacol.
Vol.6 No.1 Jan.-Mar. 1984

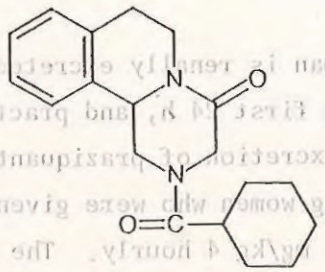
the liver and lower urinary tract. S.japonicum and S.mansoni, which migrate to the mesenteric vein before laying their eggs, can cause portal hypertension and esophageal varices. S.haematobium migrates mainly to the pelvic veins and excretes its eggs into the bladder, where it can cause hematuria, dysuria, and obstructive uropathy, Patients heavily infested with S.haematobium have an increased incidence of bladder cancer. Chronic, severe schistosomiasis can also cause bloody diarrhea, cor pulmonale, glomerulonephritis, and various signs and symptoms due to involvement of the central nervous system (1).

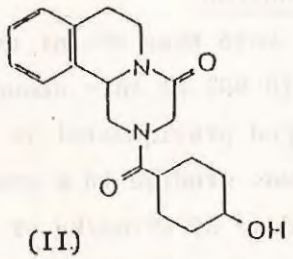
Until very recently, the available alternatives for chemotherapy were the antimonials (severely limited by their toxicity and inconvenient mode of administration), niridazole (limited by CNS toxicity and lack of efficacy against S.mansoni in children and S.japonicum), and hycanthone (which has shown mutagenic liability, limited oral efficacy and lack of activity against S.japonicum). Other two are oxamniquine (the best available agent against S.mansoni, although apparently not equally effective against all geographical strains), and metrifonate which is effective only for S.haematobium infection).

Praziquantel has a very broad spectrum of activity against parasitic trematodes and cestodes. Owing to its high efficacy, its excellent tolerability and its simple scheme of administration, it is equally well suited for indicidual and for large scale treatment (2). Pharmacological data on this drug will be summarized and its therapeutic advance will be illustrated by detailing the scope of its therapeutic activity.

Chemistry

Praziquantel is 2-cyclohexyl-carbonyl-1, 2, 3, 6, 7, 11 b-hexahydro-4H-pyrazino-(2,1-a) isoquinoline-4-one, a derivative of a novel heterocyclic system. It is a colourless crystalline powder of bitter taste. The compound is stable under normal conditions and melts at 136-140°C with decomposition. The active substance is hygroscopic. Praziquantel is easily soluble in chloroform and dimethylsulfoxide, soluble in ethanol and very slightly soluble in water. The empirical formula is $C_{19}H_{24}N_2O_2$, molecular weight of 312.4 and the structural formula is shown below (I).


(I)


(II)

Pharmacokinetics

The pharmacokinetics of praziquantel have been extensively studied in rodents, dogs, sheep, and man (2-9) using several techniques for the quantitative determination of praziquantel in biological material. The sum of unchanged ^{14}C-labelled praziquantel and labeled metabolites can be determined by radiometric techniques. Further, praziquantel and its metabolites can be separated using thin-layer chromatography(5). A biological assay determining all biologically active compounds and parent drug by gas liquid chromatography(10) and by fluorometry(11) have also been used. The assays by gas liquid chromatography and by fluorometry are both specific for the parent drug and yield comparable results(7).

A. Absorption

In man praziquantel is rapidly absorbed after oral intake.Maximum serum concentrations are reached 1-4 h after application. The active substance is rapidly and completely metabolized. The serum elimination half-life of unchanged praziquantel is about 1-1.5 h. (7,8).

B. Metabolism

Praziquantel reaching the liver via the portal vein is then extensively metabolized at high rate to final products (glucuronides and/or sulfate conjugate). The major metabolites of intermediary polarity in man are hydroxylation products of praziquantel(12). The major metabolite in serum of man and all animal studied so far was identified as 2-(4-hydoxycyclohexylcarbonyl)-1,2,3,6,11 b-hexahydro-4H-pyrazino (2,1-a)isoquinolin-4-one (structure II) which is an active metabolite.

Thai J. Pharmacol.
Vol.6 No.1 Jan.-Mar. 1984

C. Elimination

More than 80% of the dose given in man is renally excreted within 4 days with 90% of this amount appears in the first 24 h, and practically no unchanged praziquantel is excreted (7-8). Excretion of praziquantel into the milk was studied in a group of 10 lactating women who were given either a single dose of 50 mg/kg or three doses of 20 mg/kg 4 hourly. The concentrations of unmetabolized praziquantel in the milk parallel those in the plasma. On average, concentrations in milk were only 22% of those in the plasma, and only 0.0008% of the dose was excreted in the milk. This indicates that the drug is not secreted into the milk, but passively equilibrates between serum and milk(9).

D. Distribution

Rapid distribution of ^{14}C-praziquantel throughout the body was shown in rats, mice, beagle dogs, rhesus monkeys and sheep (3-5). The time-dependent concentrations in various organs as well as the quantitative data suggest that none of the 27 organs or tissues examined showed a specific accumulation(4).

Toxicology

Since praziquantel represents a novel chemical class of anthelmintics it has been very throughly studied not only in acute and subacute toxicity tests, but also in embryotoxicity, teratogenicity, mutagenicity, and carcinogenicity. The results of these shedies have been summarized by the manufacturers of praziquantel(13).

The degree of acute toxicity of praziquantel tested in rat, mice, rabbits and dogs was very low. Rats and dogs telerated repeated oral administration of up to 1000 mg/kg for 4 weeks, and up to 180 mg/kg for 13 weeks, respectively without any organ damage. Praziquantel did not disturb the reproductive process (up to F_2-generation) in rats, and no teratogenic effect was observed in mice, rats or rabbits(13). In extensive mutagenicity trials, various effects, including induction of point mutations, gene conversion, damage to DNA-repair mechanisms, sister chromatid exchanges, and x-linked recessive lethals were never detected(14-16). In addition, Salmonela

tests with urines of praziquantel-treated mice, rats, healthy and schistosome-infected persons gave no indication of a mutagenic effect(15). One study indicates that the drug can act as a weak comutagen by increasing the mutagenicity of some chemicals in animal cells(17). The results of carcinogenicity studies with oral doses of 100-250 mg-praziquantel/kg given once weekly to syrian hamster for 80 weeks and to rats for 104 weeks, respectively, show that there is no indication of carcinogenic potential of praziquantel in small rodents. Also in mice infested with Schistosoma mansoni the acute toxicity of praziquantel was within the same range as in healthy animals(18).

Tolerability

Clinical studies have shown that a one-day treatment with oral doses between 1 x 20 and 3 x 25 mg praziquantel/kg was well tolerated(8). Clinicians who investigated the tolerability and efficacy of different dosage schedules in double-blind studies in schistosomiasis patients(19-22) and in liver fluke patients(23-27) have concluded that praziquantel is well tolerated. No major side effects have been observed, transient abdominal pain with or without nausea, dizziness and fever can occur, especially when the drug is given as a single oral dose(26). Patients with sickle cell triat and glucose-6-phosphate dehydrogenase (G-6PD) deficiency tolerated praziquantel without difficulty.

Mode of action

Two phenomena were observed in both trematodes and cestodes exposed to praziquantel; an almost instantaneous tetanic contraction of the parasite's musculature(28) and a rapid vacuolization of the syncytial tegument(29-33). The secondary effects are depolization of the schistosome tegument, inhibition of glucose uptake and decrease of glycogen content of Hymenolepis diminuta, S.mansoni and S.japonicum. The rapid contraction induced by praziquantel has been explained on the basis of a change in divalent cation fluxes, especially calcium.It has been shown that uptake by male schistosomes of calcium was increased by praziquantel.And this stimulating effect is eliminated in the presence of verapamil.These suggest that praziquantel increases

Thai J. Pharmacol.
Vol.6 No.1 Jan.-Mar. 1984

the permeability of the liver fluke tegument to Ca^{+2}, probably by interfering with the mechanism that regulates Ca^{+2} binding or transport across the tegumental membrane(33). The vacuolization appears to be a calcium-dependent process, it is a rapid phenomenon (30 seconds). Death of the parasites occurred as soon as vacuolization and tegumental damage became severe enough, so that neutrophilic granulocytes attached to the parasite and entered the schistosome tissues through the tegumental lesions. The morbid worms became fixed to the walls of blood vessels by fibroblasts and had completely disintegrated 14 to 18 days later(34).

Therapeutic efficacy

Schistosomes

Praziquantel was subsequently shown to be equally effective against S.mansoni, S.haematobium, S.japonicum, S.intercalatum, and S.mattheii in comparative study in hamsters(35). The investigation of the efficacy of praziquantel in human schistosomiasis was begun as a multicenter study in Japan and the Phillippines for S.japonicum, in Brazil for S.mansoni, and in Zambia for S.haematobium(19-23). In all, more than 25,000 schistosomiasis patients have now been treated and from these very intensive clinical studies it has been concluded that, with respect to population based chemotherapy, the following dosages are recommended(36) for the treatment of individual patients infested by schistosomes (Table 1).

Table 1 Recommended dosages for the treatment of schistosomiasis

Species of parasite	Daily dose (mg/kg)	Day of treatment
S.haematobium	1 x 40	1
S.mansoni	1 x 40 or 2 x 20	1
S.intercalatum	1 x 40 or 2 x 20	1
S.japonicum	2 x 30	1

Based on the results of parasitological follow-up examinations for 6 and 12 months after therapy, cure rates of infections with S.haematobium, S.mansoni, and S.japonicum were 97%, 89% and 66%, respectively (Table 2).

Table 2 Assessment of efficacy of praziquantel

Species of parasite	Number of patients treated	Follow-up results* at 6 months	12 months
S.haematobium	80	72/73 93.6%	64/66 97%
S.mansoni	89	63/69 91.3%	64/72 88.9%
S.japonicum	86	61/79 77.2%	39/59 66.1%

* Cured/examined patients in effective numbers and in %

A distinct advantage of parziquantel as compared to metrifonate or oxamniquine is its ability to kill both S.mansoni and S.haematobium. Praziquantel is highly effective against all schistosome species parasitic in man(36,37). A further progress is the finding that the efficacy of this drug is not significantly influenced by inter-strain variation of schistosomes in contrast e.g. to hycanthone and oxamiquine. And the efficacy is not affected by sex, age, and strain of the host(36,37). A very interesting property of praziquantel is its efficacy against all stages of the immature infection(35,37). As the drug is equally effective against S.intercalatum infestations and the naturally occurring hybrids between S.intercalatum and S.haematobium(38) it is now possible to treat all African forms of schistosomiasis with the same dosing schedule of 1x40 mg/kg. Since it is effective against all schistosome species and is well tolerated, patient acceptability is good and it is easily administered as a single oral dose or as a 1-day course of treatment. Therefore the drug is ideally suitable for large scale treatment directed at controlling schistosomiasis.

Thai J. Pharmacol.
Vol.6 No.1 Jan.-Mar. 1984

Other trematodes

The data of the therapeutic use of praziquantel against nonschistosome trematodes are shown in Table 3. The therapeutic means that were available before the introduction of praziquantel have been very limited and the drugs that had to be used, hexachloro-para-xylene, dehydroemetine, bithionol, and niclofolan all have short-comings in terms of tolerability, efficacy, and also availability(39,40). Praziquantel is now offering for the first time the possibility of a reliable and well torelated therapy of human lung and liver flukes infestations, which are especially found in Southeast Asia. Liver flukes have been considered as an etiological agent in the development of bile-duct carcinoma in man(41). Similar association between cancer and parasitic infections has also been described for S.japanicum and colorectal carcinoma, and for S.haematobium and bladder cancer(42,43).

Liver flukes

The efficacy of praziquantel in man has been investigated for Clonorchis sinensis(23-25) and Opisthorchis viverrini(23, 26, 27). A clinical trial of praziquantel was carried out in Thailand in fifty-eight patients infected with Opisthorchis viverrini. Based on faecal egg counts, cure rates of 90.9-100% were obtained (followed up for 180 days)(26,27). For both Clonorchis sinensis and Opisthorchis viverrini infections, a 1-day course of treatment with 3x25 mg/kg or a single dose of 40 mg/kg was found to give excellent parasitological cure rates with low incidence of untoward side effect(25-27). It appears that praziquantel is the first drug found to be effective in the treatment of human opisthorchiasis(26,27).

Lung flukes

Paragonimus westermani has been rather refractory to praziquantel *in vitro* as it responded less markedly with tegumental alterations than schistosomes or liver flukes. This may be due to the dense texture of the thick tegument(44). The recommended dosing schedule is a 2-day of treatment with 3x25mg/kg/day(45). Administration of praziquantel is more convenient than bithionol since the latter drug must be given in a repeated dose on alternate days(30-50 mg/kg) with frequent photosensitivity skin reactions.

Intestinal flukes

The human intestinal flukes Metagonimus yokogawai and Heterophyes sp. have been successfully eliminated with praziquantel, and similar result can be expected for Fasciolopsis buski and other intestinal flukes(46). The recommended dosing is a 2-day treatment of 2x20 mg/kg/day(40,47). The advantage of praziquantel over tetrachloroethylene is that food and alcoholic beverage is not contraindicated before or 12 h after therapy.

Adult Cestode

In clinical trials, single oral doses of 15 to 25 mg/kg resulted in parasitological cures of more than 90% of patients infected with Hymenolepis nana(48). Patients haboring very young infections with H.nana, in which the cysticercoids are not fully developed are not always cured by a single treatment with 25 mg/kg. In such instances, a second treatment given 4 days later can completly eradicate the infection(49). The infections with Taenia saginata and Taenia solium were also treated successfully with a single oral dose of 5 to 10 mg/kg while a dose of 25 mg/kg was required for the removal of Diphyllobothrium latum, 15 mg/kg for hymenolepsis nana, and 10 mg/kg for D.pacificum(50-54).

Table 3 Recommended dosages for the treatment of trematodes other than schistosomes infection.

Parasite	Daily dose(mg/kg)	Day of Treatment
C.sinensis	3x25	1
O.viverrini	3x25	1
P.westermani	3x25	2
P.heterotremus	3x25	2
M.yokogawai	2x20	1
F.hepatica	1x20	3

Thai J. Pharmacol.
Vol.6 No.1 Jan.-Mar. 1984

Cysticercosis

In the treatment of human infections with cysticercus cellulosae, a difference in susceptibility between muscle and cerebral cysticerci is likely to be due to the pharmacokinetic behavior of praziquantel. In the case of the cerebrally located metacestode, the drug has to pass two diffusional barriers before it reaches the parasite, the blood-brain barrier and the cyst wall, while there is only the cyst wall in the case of the muscle larva. A short treatment with high doses should be more effective than a lengthy treatment with low daily doses. In patients with symptom of cerebral involvement, disappearance of cutaneous cyst was observed at 1 month after a 3-to 4-day course of treatment (3x25 mg/kg/day) and to continue for another 5 months(55,56). For neurocysticercosis, clinical trials have been done in Mexico, Columbia, Chili, Brazil and Korea, and dosing schedules of 50 mg/kg divided into 3 doses daily for 10-14 days is recommended. And it is still strongly recommended to give additional corticosteroid treatment in order to prevent the development of endocranial hypertension resulted from the disintegration of cerebral cyst(57). Praziquantel is as effective as niclosamide against adult cestode. The advantage of praziquantel is that it is the first drug which appears to be useful in the treatment of cysticercosis.

Table 4 Recommended dosages for the treatment of cestode infection.

Parasite	Daily dose (mg/kg)	Day of treatment
Adult cestode		
T. saginata	5-10	1
T. solium	5-10	1
H. nana	1x15	1
D. latum	1x25	1
Cysticercoses		
cutaneous cyst	3x25	3-4
neurocysticercosis	1x50	10-14

In conclusion, praziquantel is a new and apparently safe anthelmintic drug, effective against all types of schistosomiasis in a single oral dose or in several doses taken on the same day. The drug is also active against infections caused by other flukes and some tapeworms, including cysticercosis. As a general rule, praziquantel should not be taken during the first three months of pregnancy, although animal experiments do not suggest any harmful effects on either pregnant woman or the fetus. Finally, to reach the goal of anthelmintic therapy, sanitary improvement and health education are also important.

ACKNOWLEDGEMENTS

The auther is grateful to Ms. Supa Sangoubol and Mrs. Tasnee Jareanwatana for their help in the preparation of this manuscript.

REFERENCES

1. Goldsmith, R.S. Infectious Disease: Helminthic. In Current Medical Diagnosis & Treatment . ed. by M.A.Krupp and M.J. Chatton pp.916-942. Maruzen Asia Edition, 1984.
2. Werbel, L.M., Elslager, E.F. and Worth, D.F. Recent advances in the experimental chemotherapy of Schistosomiasis. In: Advances in Pharmacology and Therapeutics, vol 10. Chemotherapy, ed by M. Adolphe. pp 3-8, Pergamon Press, 1978.
3. Steiner, K., Garbe A., Diekmann, H.W. and Nowak, H. The fate of praziquantel in the organism. I. Pharmacokinetics in animals. Eur. J. Drug Metab Pharmacoknet. 1:85-95, 1976.
4. Steiner, K. and Gasbe A. The fate of praziquantel in the organism II. Distributions in rats. Eur. J. Drug Metab. Pharmacokinet. 1:97-106, 1976.
5. Diekmann, H.W. and Buhring, K.U. The fate of praziquantel in the organism III. Metabolism in rat, beagle dog and Rhesus monkey. Eur J. Drug Metab. Pharmacoknet.1:107-112, 1976.
6. Andrew, P. Pharmacokinetic studies with praziquantel in animals using a biological assays. Vet. Med. Nachr., 154-165, 1976. (English ed.)

7. Patzschke, K., Putter, J., Wegner, L.A., Horster, F.A., and Diekmann, H.W. Serum concentrations and renal excretion in humans after oral administration methods. Eur. J. Drug Metab. Pharmacokinet. 3:149-156, 1979.
8. Leopold, G., Ungethum, W., Groll, E., et al. Clinical Pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes. Eur. J. Drug Metab. Pharmacokinet. 14:281-291, 1978.
9. Putterm J. and Held, F. Quantitative studies on the occurrence of praziquantel in milk and plasma of lactating women. Eur. J. Drug Metab. Pharmacokinet. 4:193-198, 1979.
10. Diekmann, H.W. Quantitative determination of praziquantel in body fluids by gas liquid chromatography. Eur. J. Drug Metab. Pharmacokinet. 4:139-141, 1979.
11. Putter, J. Fluorometric method for the determination of praziquantel in blood-plasma and urine. Eur. J. Drug Metab. Pharmacokinet. 4:143-148, 1979.
12. Buhring, K.U., Diekmann, H.W., Muller, H., et al. Metabolism of praziquantel in man. Eur. J. Drug Metab. Pharmacokinet. 3:179-190 1978.
13. Frohberg, H., and Schulze-Schencking, M. Toxicological profile of praziquantel, a new drug against cestode and schistosome infections as compared to some other schistosomicides. Arzneim. Forsch. (Drug Res) 31: 555-565, 1981.
14. Bartsch, H., Kuroki, T., Malaveille C., et al. Absence of mutagenicity of praziquantel, a new, effective, anti-schistosomal drug in bacteria yeast, insects and mammalian cells. Mutation Res. 58:133-142, 1978.
15. Obermeier, J. and Frohberg H. Mutagenicity studies with praziquantel, a new anthelmintic drug: tissue-host-and urine-mediated mutagenicity assays. Arch. Toxicol. 38:149-161, 1977.
16. Machemer, L., and Lorke, D. Mutagenicity studies with praziquantel, a new anthelmintic drug in mammalian systems. Arch. Toxicol. 39:187-197, 1978.
17. Billings, P.C., and Heidelberger, C. Effects of praziquantel, a new antischistosomal drug on the mutation and transformation of mammalian cells. Cancer Res. 42:2692-2696, 1982.

18. Andrew, P., Dyeka, J., and Frank, G., Effect of praziquantel on clinical chemical parameters in healthy and schistosome-infected mice. Ann. Trop. Med. Parasitol. 74:167-177, 1980.

19. Ishizaki, T., Kamo, E. and Boehme, K. Double-blind studies of tolerance to praziquantel in Japanese patients with Schistosome japonicum. Bull. W.H.O. 57:787-791, 1979.

20. Davis., A. Biles, J.E. and Ulrich, A.M. Initial experiences with praqiquantel in the treatment of human infections due to Schistosome haematobium. Bull. W.H.O. 57:773-779, 1979.

21. Katz, N., Rocha, R.S.and Chaves, A. Preliminary trial praziquantel in human infection due to Schistosome mansoni. Bull. W.H.O.57:781-785,1979.

22. Santos, A.T., Blas, B.L., Nosenas, J.S. et al. Preliminary clinical trials with praziquantel in Schistosome japonicum infection in the Phillipines. Bull W.H.O. 57:793-799, 1979.

23. Ambroise-Thomas, P. Goullier, A. and Wegner, D.G.H. Praziquantel in the treatment of Far-eastern liver-fluke infection due to Clonorchis sinesis or Opisthorchis viverrini. Bull. Soc. Path. Exot., 74:426-433, 1981.

24. Rim, H.J. and Kwang, S.Y., Chemotherapeutic effect of praziquantel (EMBAY 8440) in the treatment of Clonorchis sinensis. Univ. Med. J. (Korea). 16:459-470, 1979.

25. Rim. H.J., Lyu, K.S., Lee, J.S. and Joo, K.H. Clinical evaluation of the therapeutic efficacy of praziquantel (EMBAY 8440) against Clonorchis sinensis infection in man. Ann.Trop. Med. Parasitolol. 75:27-33, 1981.

26. Bunnag, D. and Harinasuta T. Studies on the chemotherapy of human Opisthorchiasis in Thailand: I. Clinical trial of praziquantel. Southeast Asia J. Trop. Med. Pub. Hlth. 11: 528-531, 1980.

27. Bunnag, D.and Harinasuta T. Studies on the chemotherapy of human Opisthorchiasis III. Minimum effective dose of praziquantel. Southeast Asia J. Trop. Med. Pub. Hlth, 12: 413-417, 1981.

28. Xiao, S.H., Shao, B.R. and Xu, Y.Q. The in vitro effect of "Pyquiton" on Schistosome japonicum. Acta Pharm. Sin. 15:105-108,1980.

29. Becker, B., Mehlhorn, H., Andrew, P., et al. Light and electron microsocopic studies on the effect of praziquantel on Schistosome mansoni,

Dicrocoelium dendriticum and Fasciola hepatica (Trematode) in vitro. Z. Parasitenkd. 63: 113-128, 1980.

30. Becker, B., Mehlhorn, H., Andrew. P., and Thomas, H. Scanning and transmission electron microscope studies on the efficacy of praziquantel on Hymenolepsis nana. (Cestoda) in vitro. Z. Parasitenkd. 61:121-133, 1980.

31. Becker, B., Mehlhorn, H., Andrew. P., and Thomas, H. Ultrastructural investigations on the effect of praziquantel on the tegument of five species of cestode. Z. Parasitenkd. 64:257-269, 1980.

32. Conder, G.A., Marchiondo, A.A. and Anderson, F.L. Effect of praziquantel on adult Echinococcus granulosus in vitro: scanning electron microscopy. Z. Parasitenkd. 66:191-199, 1980.

33. Ruenqongsa, P., Hatadilok, N. and Yuthavong, Y. Stimulation of Ca^{+2} uptake in the human liver fluke Opisthorchis viverrini by praziquantel. Life Sci. 32:2529-2534, 1983.

34. Mehlhorn, H., Becker, B., Thomas, H., and Andrew, P. The mode of action of biltricide in schistosomiasis as demonstrated by electron microscopy. Arzneim. Forsch. (Drug Res.) 31:544-554, 1981.

35. Webbe, G., and James, C. Acomparison of the susceptibility to praziquantel of Schistosoma haematobium, S.japonicum, S.mansoni, S. intercalatum and S. mattheei in hamster. Z. Parasitenkd. 52:169-177, 1977.

36. Biltricide^{R}, prospectus, Bayer AG (1980)

37. Gonnert, R. and Andrew, P.Praziquantel a new broad-spectrum antischistosomal agent. Z. Parasitenkd, 52:129-150, 1977.

38. Omer, A.H.S., Praziquantel in the treatment of mixed S-haematobium and S. mansoni infection in Sudan. Arzneim. Forsch.(Drug Res) 31:605-608, 1981

39. Chung. H.L., Hsu, G.P., TsAO, W.C., et al. Hexachloro-paraxylol in treatment of Clonorchiasis sinesis in animal and man. Chinese Med. J. 83:232-247, 1975.

40. Rim, H.J., Chu, D.S., Lee., et al. Anthelmintic effects of various drugs against metagonimiasis. Korean J. Parasitolol. 16:117-122. 1978.

41. Flavell, D.J. Liver fluke infection as an aetiological factor in bile

duct carcinoma of man. Trans. R. Soc. Trop.Med. Hyg. 75:814-824, 1981.

42. El-Bolkaing, M.N., Chu, E.W., Chonein, M.A. and Ibrahim, A.S. Cytologic detection of bladder cancer in a rural Egyptian population infection with Schistosomiasis. Acta. Cytol. 26:303-310, 1982.

43. Attah, E.b. and Nkposong, E.Q. Schistosomiasis and carcinoma of the bladder: a critical appraisal of causal relationship. Trop. Geogr. Med. 28:268-272, 1976.

44. Mehlhorn, H., Kojima, S., Rim, H.J., et al. Ultrastructural investigations on the effects of praziquantel on human trematodes from Asia: C. sinensis, M. Yokogawai, O.viverrini, P.westermani and S. japonicum. Arzneim. Forsch. 33:91-98, 1983.

45. Rim, H.J., Chang, Y.S., Lee, J.S., et al. Clinical evaluation of praziquantel (EMBAY 8440 Biltricide) in the treatment of Paragonimus westermani. Korean J. Parasitol. 19:27-37. 1981.

46. Bunnag, D. and Harinasuta, T. Chemotherapy of intestinal parasites in Southeast Asia. Southeast Asia J. Trop. Med. Pub. Hlth. 12:422-430, 1981.

47. The Medical Letter: Drugs for parasitic infections. 24:5-12, 1982.

48. Rim, H.J., Park, C.Y., Lee, J.S., Joo, K.H. and Lyu, K.S. Therapeutic effects of praziquantel (EMBAY 8440) against Hymenolepis nana infection. Korean J. Parasitol. 16:82-87, 1978.

49. Thomas, H. and Gonnert, R. The efficacy of praziquantel against experimental cysticercosis and hydatidosis. Z.Parasitenkd. 55:165-179, 1978.

50. Schenone, H. Caldames, M. and Schenone, D., Treatment of Taenia saginata infection in adults with a single dose of praziquantel. Bol. Chil. Parasitol. 33:41-44, 1978.

51. Rim, H.J., Park, S.B., Lee, J.S. and Joo, K.H., Therapeutic effects of praziquantel (EMBAY 8440) against Taenia solium infection. Korean J. Parasitol. 17:67-72, 1979.

52. Paz, G. Treatment of taeniasis saginata with praziquantel (EMBAY 8440). Bol. Chil. Parasitol. 32:14-16, 1977.

53. Groll, E., Praziquantel for cestode infections in man. Act Trop. 37:293-296, 1980.

54. Banranski, M.C. Treatment of human taeniasis and hymenolepis nana with praziquantel (EMBAY 8440) Bol. Chil. Parasitol. 32:37-39, 1977.

55. Rim, H.J., Won, C.R. and Chu, J.W. Studies on human cysticercosis and its therapeutic trial with praziquantel (EMBAY 8440). Korean Univ. Med. J. 17:459-473, 1980.

56. Rim, H.J. Won, C.Y. and Chu, J.W. Therapeutic effect of praziquantel (EMBAY 8440) on human cysticercosis, Korean. J. Parasitol. 18:115, 1980.

57. Groll, E. Human cysticercosis and praziquantel: a survey of first clinical experiences. Bol. Chil. Parasitol. 36:29-37, 1980.