CHAPTER I

INTRODUCTION

I. Background and Rationale

Praziquantel (EMBAY 8840) is a new developed anthelmintic agent. It was synthesized by Seubert and Pohlke in laboratories of E. Merck (1) and first evaluated for antiparasitic activity by Bayer A.G. in 1972 (2). Recently, numerous clinical studies with praziquantel have been carried out in the endemic area of the developing countries. Results reveal that praziquantel is an available agent for the treatment of schistosomiasis, paragonimiasis, clonorchiasis, opisthorchiasis and other trematode and cestode infections(3,4).

In Thailand , Opisthorchiasis (Appendix A) is a serious public problem (5). It has been estimated that about 7 millions of the population were infected with this liver fluke. Although the mortal rate is not high, the morbidity causes increasing loss of man power and economic problems to the people.

Recently, a successful treatment of opisthorchiasis with praziquantel has been reported by several investigators (6,7,8,9,10,11,12). It was reported to be effective even when the drug was given as a single oral dose , 40 mg/kg. Since then the ministry of public health has estabished a nation-wide programme using praziquantel (Biltricide^{R}) for controlling of human trematode infection in endemic area in the Northeast of Thailand.

At present, at least 6 different generic brands of 600-mg praziquantel tablets are available in the market. One is a well known foreign manufactured brand, with high retail price*. The others are various local manufactured brands. Although praziquantel has been used clinically since 1980, there appears to be little information on its bioavailabity and pharmacokinetic characteristics (13,14,15,16). Meanwhile it is well-documented that the method of manufacture and the final formulation of the drug can markedly affect the bioavailability of the drug (17). Hence, an extensive study was designed to compare the relative bioavailability of different commercial praziquantel tablets and to investigate the pharmacokinetics of praziquantel after admistration of tablets orally to healthy volunteers.

Objectives :

1. To compare the bioavailability of commercial praziquantel tablets marketed in Thailand.

2. To investigate the pharmacokinetics of praziquantel after single oral administration of praziquantel tablets in Thai healthy volunteers.

3. To evaluate whether the local manufactured brands of praziquantel tablets are equivalent regarding to the quality and performance as the innovator's product.

4. To correlate relative *in vivo* bioavailability of different tablets with their *in vitro* disintegration time and dissolution rate.

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* The retail cost for one bottle of six 600-mg tablets (one patient course) is about 500-600 bahts.

Significance of the study :

1. This study will provide significantly an information about the bioavailability of praziquantel tablets.

2. From the pharmacokinetic parameters describing the serum concentration-time curves obtained for different brands, we would be able to justify whether the local manufactured brand of praziquantel tablets are equivalent to that of the original product. It also enables to evaluate and select the economical products which produce equivalently therapeutic effect.

3. This study should provide several meaningful information about the pharmacokinetic of a new drug, praziquantel, in Thai healthy adult volunteers. The result will be compared with previously reported studies which were conducted in other countries. The effects of races and tribes on the pharmacokinetics of this drug could thus be notified.

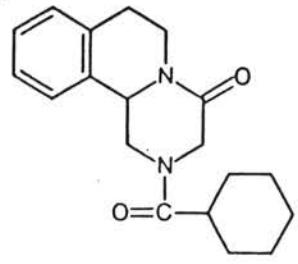
II. Review of Praziquantel

Praziquantel (EMBAY 8440, Biltricide^{R}, Cesol^{R}, Droncit^{R}) is an effective anthelmintic agent against trematodes and cestodes. It was synthesizied by Seubert and Pohlke (1) in the laboratories of E.Merck, Damstadt and first evaluated for anthelmintic activity by Bayer A.G., Leuverkusen (2).

Physicochemical Properties (18).

Chemically, Praziquantel is a 2-cyclohexylcarbonyl - 1,2,3,6, 7,11, b-hexahydro- 4H - pyrazinol [2,1-a] isoquinolin-4-one compound.

Structural formula:



Empirical formula: $C_{19}H_{24}N_2O_2$

Molecular weight: 312.4

Figure 1 Structural formula of praziquantel

Description : It is a colourless, almost odorless, crystalline powder of bitter taste.

Solubility : Soluble in chloroform (56.79 g/100 ml) and dimethyl sulfoxide, sparingly soluble in ethanol (9.7 g/ 100 ml) and very slightly soluble in water (0.043 g/100 ml at 25°C)

Stability : It is well stable in normal temparature and in neutral or weak acid or weak alkaline medium. Degradation normally proceeds oxidation-reduction reaction.

Melting point : 136° - 139°C (with decomposition)

Mode of Action

Primary effect ; Two striking phenomena were observed in both trematodes and cestodes exposed to praziquantel : an almost instantaneous tetanic contraction of the parasite musculature (19) and a rapid vacuolization of the syncytical tegument (20,21). Andrew (22) demonstrated that the concentration of praziquantel in the serum of animals and man that had received therapeutically effective doses were above the threshold of about 0.3 µg/ml. This would almost instantaneous contraction and paralysis of the parasites. The mechanism of this contraction has been elucidated by Ruenwongsa *et al.* (23). They found that praziquantel increases permeability of the muscle

cell membrane of susceptible worm to calcium. Andrew (22) also reported the reduction in endogenous glycogen, a decrease in alanine and an increase in lactate release of the metabolic integrity of the schistosome by praziquantel might be secondary effects.

Toxicology

The extensive toxicity studies of praziquantel were concluded by Froberg and Schencking (24). Praziquantel did not reveal any undesired pharmacodynamic effects. Its acute toxicity tested in rats, mice, rabbits and dogs was very low as compared with other schistosomicidal drugs. After repeated oral administration in rats with tolerated daily doses up to 1000 mg/kg for four weeks, and in dogs with the dose up to 180 mg/kg for thirteen weeks. There were no organ damage has been observed. Praziquantel had neither disturbed the whole reproductive process in rats, nor revealed teratogenic effects in mice, rats and rabbits. There were no indication of any mutagenic effects and/or carcinogenic potentials of praziquantel in other animals studies.

Tolerability

Clinicians who investigated the tole bility and efficacy of different dosage schedules in double-blind studies with normal healthy volunteers and liver fluke infected patients have concluded that praziquantel was safe and well tolerable (6,9,12). Adverse reactions such as ; abdominal discomfort,central effect like headache,dizziness and skin manifestion were both mild and transient.

Pharmacokinetic Studies

1. Animal Studies

The pharmakinetics of praziquantel were studied first in animals ; rodents, dogs, monkeys and sheep using radiometric techniques (25). Intravenously administered ^{14}C-praziquantel was distributed quickly in all tissues of the studied animals. The sum of unchanged praziquantel and its metabolites were rapidly eliminated out of the intravascular space with half-life of 3 hours (phase I) and 8 hours(phase II). The elimination for praziquantel itself however was considerably shorter, i.e. about 1 hour. Praziquantel was almost completely absorbed from the gastro-intestinal tract after oral administration. Maximum serum concentration was reached within 30 minutes to 1 hour. Unmetabolized praziquantel showed due to an intense first-pass effect in the liver only lowering maximum serum concentrations. Its serum protein binding was about 80 percent. The distributive behaviour of ^{14}C-praziquantel was also investigated by Steiner and Garbe (26). Results showed that ^{14}C-praziquantel was localised mainly in the liver and kidneys. Higher concentrations than in plasma were also found in the lung, pancreas, adrenals, pituitary gland and gastrointestinal mandibularis. In contrast, the concentration of praziquantel in brain appeared low. Diekmann and Buhring (27) also showed that praziquantel was excreted exclusively via its metabolites, as conjugated form with glucurohic and/or sulfuric acid. An unmetabolized praziquantel was not found in the excretory products of all studied animals.

2. Absorption, Metabolism and Elimination in Man.

The pharmacokinetics of praziquantel after oral administration in healthy volunteers were reported by several investigations(13,15,16). Leopold *et al.* (13) showed that praziquantel was rapidly absorbed and metabolized with hepatic first-pass effect. The peak concentration in

serum was reached within 1-2 hours, and the elimination half-life of unchanged praziquantel from serum was 1-1.5 hours. Similar results were found by Patzschke *et al.* (15) who summarized three methods for analysis of unmetabolized drug and metabolites after oral administration of 14 and 46 mg/kg ^{14}C-praziquantel. They also noted that, approximately 80 to 85 percent of the administered ^{14}C-radioactivity doses were found in urine within 4 days. As in animal, no unmetabolized praziquantel is excreted by man, except for a minute trace of 0.0001 to 0.001 percent of the dose (15,27).

Buhring *et al.* (14) also showed that praziquantel was rapidly and completely metabolized within 4 hours after oral administration. The major metabolites were mono-and polyhydroxylated products.

Excretion of praziquantel into the milk was studied by Putter and Held (16) in a group of 10 lactating women who received either a single dose of 50 mg/kg or three doses of 20 mg/kg every 4 hours. The concentrations of unmetabolized praziquantel in the milk increased and decreased in paralleled with the concentrations in the plasma. On average, the milk concentrations were only 22 percent of the plasma concentrations. The mean excretion with the milk of the 10 women was 0.0008 percent of the dose given.

3. Bioavailability Studies.

Bioavailability studies of praziquantel were rarely reported. Shao *et al.* (28) reported that the bioavailability of praziquantel in rats was higher after intramuscular administration than that after oral admintration ,and the rates of absorption and excretion of the drug were slower in mice infected with *Schistosoma japanicum* than

in healthy mice. Steiner *et al.* (25) also showed that the extent of absorption of ^{14}C-praziquantel,calculated by comparing area under the blood level-time curve after oral administration in rats, dogs, monkeys and sheep were 77,90,75 and 100 percent, respectively.

Therapeutic Efficacy

A. Clinical Efficacy in Trematode Infections.

1. Schistosomes

The investigation of the efficacy of praziquantel in human schistosomes was begun as a multicenter study in Japan and Philippines for *Schistosoma japanicum* (29,30), in Brazil for *Schistosoma mansoni* (31) and in Zambia for *Schistosoma haematobium* (32). Results of many clinical Studies have been summarized and concluded that, with respect to population based chemotherapy, a single oral dose of 1×40 mg/kg was the most suitable dose for *S. haematobium* and *S.mansoni* infections where as a 1-day with 2×30 mg/kg of praziquantel was recommended for *S.japanicum* infection. The parasitological cure rates resulted from treatment with these recommended dosing schedules were about 95, 90 and 70 percent, respectively.

2. Liver Flukes

The efficacy of praziquantel in man has been investigated for *Clonorchis sinensis* in Korea (33,34) and *Opisthorchis viverini* in Thailand (6,7,8,9,10,11,12,). Results showed that a 1-day course of treatment with 3 x 25 mg/kg gave excellently parasitological cure rate in both species infections.

3. Other Trematode Infections

Rim (35) reported the efficacy of praziquantel against *Paragonimus westermani* in Korea using 1-2 days of dose 3×25 mg/kg

B. Clinical Efficacy in Cestode Infection

1. *Taenia saginata*

Groll (36) showed that infections with *T.saginata* were cured by 10 mg/kg in 376 of 387 patients. Successful treatment was checked by investigating the stool.

2. *Hymenolepis nana*

Schemone (37) reported that a single dose of 2.5 mg/kg for children who were most often affected by this infection gave highly cure rate.

3. Larval Cestodes Infection in Man.

The results of first clinical studies in cysticercosis patients with praziquantel have been published by many investigators (36). Disappearance of cutancous cysts were observed to begin 1 month after a 3 to 4 days course of treatment (3 x25 mg/kg , 21 day) and to continue for another 5 months.