# PLASMA CONCENTRATIONS OF PRAZIQUANTEL DURING THE THERAPY OF NEUROCYSTICERCOSIS WITH PRAZIQUANTEL, IN THE PRESENCE OF ANTIEPILEPTICS AND DEXAMETHASONE

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**Abstract.** Plasma praziquantel concentrations were measured in 11 Thai patients with active neurocysticercosis (8 males and 3 females). Praziquantel (Biltricide® 600 mg per tablet) was given at a daily dose of 45 mg/kg given in 3 divided doses for 15 consecutive days. All partients had significant improvement with resolution of symptoms and signs, and reduction of active lesions of cysticercosis shown by the brain computed tomographic scanning. After oral administration, the drug was rapidly absorbed from the gastrointestinal tract. There was substantial inter-individual variability in plasma concentrations of praziquantel. After the first dose, maximum plasma concentrations in the range of 42-540 ng/ml was attained at 30 minutes to 5 hours. In all cases, the drug almost totally disappeared from plasma within 8 hours; drug levels measured prior to the first doses on the following days showed undetectable levels. The area under the plasma concentration-time curves of praziquantel following the first dose were between 125 and 990 ng hour/ml. The results suggested that the unusual low plasma availability of the drug observed in this group of patients could be a consequence of pharmacokinetic drug interactions of the concomitant therapy with antiepileptic drugs and dexamethasone. Active metabolite(s), rather than praziquantel itself, may play a significant part in the therapy of neurocysticercosis.

## INTRODUCTION

Neurocysticercosis is one of the most important parasitic infections of the central nervous system affecting several developing countries in Latin America, Asia and Africa, where sanitation and socioeconomic conditions are suboptimal (Botero and Castano, 1982; Garsolia and Wiederholt, 1982; Takayanagui, 1990). The disease is caused by the cystic larval stage of the pork tapeworm, *Taenia solium,* and leads to a broad range or neurological disturbances (Escobar and Nieto, 1972; Mc-Cormick *et al,* 1982).

Praziquantel, a pyrazinoisoquinoline, is a wide spectrum anthelmintic which has been found to be an effective drug for the treatment of neurocysticercosis (Zhu *et al,* 1981; Botero and Castano, 1982; Spina-Franca *et al,* 1982; Sotelo *et al,* 1984). The recommended regimen of this drug in the treatment of the disease is a daily dose of 50 mg/kg given in 3 divided doses for 15 to 30 consecutive days, with prolonged remission being achieved in approximately 60 to 80% of the patients (Botero and Castano, 1982; Spina-Franca *et al,* 1982; Ciferri, 1984; Sotelo *et al,* 1984; Leblanc *et al,* 1986; Robles *et al,* 1987; Vasconcelos *et al,* 1987). One of the major problems in the chemotherapy of this parasitic infection with this drug is its variable plasma/CSF availability due to its substantial first-pass metabolism. This is especially profound when concomitant therapy with drugs which are potent inducers of hepatic drug metabolizing enzymes (antiepileptics, and the anti-inflammatory steroid, dexamethasone) are being prescribed. We therefore investigated plasma levels of praziquantel attained after a daily dosage of 45 mg/kg for 15 days in Thai patients with active neurocysticercosis who were also under treatment with these drugs. Details of tolerability and efficacy of this therapeutic regimen have been reported elsewhere (Vanijanonta *et al,* 1991).

## MATERIALS AND METHODS

Eleven Thai patients (8 males and 3 females) presenting with symptoms and signs of active neurocysticercosis supported by characteristic lesions on computed tomographic scanning, were included into the study. They were aged between 24-62 years, weight ranged from 51-67 kg. The patients were

hospitalized into the Bangkok Hospital for Tropical Diseases during the treatment period for 1 month, and returned for follow-up 1 year later. Written informed consent to participate in the study was obtained from all patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

The patients were treated with praziquantel (Biltricide®, 600 mg per tablet) at a daily oral dose of 45 mg/kg given in 3 divided doses during each day (15 mg/kg at hours 0, 8 and 16) for 15 consecutive days. The tablets were administered with a glass of water under supervision. All patients were taking antiepileptic drugs and were permitted to continue these medications as necessary.

Prior to and after the first dose of praziquantel administration, 3 ml of blood samples were collected, into lithium-heparinized plastic tubes at 15, 30 minutes and 1, 1.5, 2, 3, 4, 5, 6 and 8 hours. The following blood samples were taken prior to the first dose of each day. Plasma was separated from blood samples and stored at -70°C until analysis. Concentrations of praziquantel in plasma were analyzed by using high-performance liquid chromatography, according to the method of Xiao *et al* (1983). This method has a lower limit of sensitivity of 2.5 ng/ml, and a relative standard deviation of 2.6% at concentrations of 5 ng/ml.

## RESULTS

Praziquantel given at a daily dose of 45 mg/kg given as 3 divided doses during the day for consecutive 15 days was effective; all patients showed marked clinical improvement with resolution of symptoms and signs and reduction of active lesions of cysticercosis shown by brain computed tomographic scanning. Convulsive seizure was the most common presentation in all patients. Others included mild and transient side effects, *eg* headache, nausea, abdominal pain and myalgia. During the course of treatment, one patient had increased intracrannial pressure presented by severe headache, nausea and vomiting. This patient was given intravenous dexamethasone (5 mg), followed by 0.5 mg tablet thrice daily for 3 days. All patients received anticonvulsants, either phenytoin or phenobarbitone (4 and 8 cases, respectively), in order to suppress seizures. Other drugs occasionally prescribed included paracetamol (3 cases), chlorpheniramine (1 case), vitamin $B_{1\text{-}6\text{-}12}$ (5 cases), dimenhydrinate (1 case), pentoxifylline (1 case).

Plasma concentration of praziquantel in the patients are shown in Fig 1. After oral administration of the first dose, the drug was rapidly absorbed from the gastrointestinal tract. There was marked inter-individual variability in the plasma concentrations of praziquantel in each individual. Maximum plasma concentrations in the range of 42-540 ng/ml were attained at 30 minutes to 5 hours. In all cses, the drug almost totally disappeared from plasma within 8 hours; drug levels measured prior to the first dose of the following days showed undetectable levels. The area under the plasma concentration-time curves of praziquantel following the first dose were between 125 and 990 ng hour/ml.

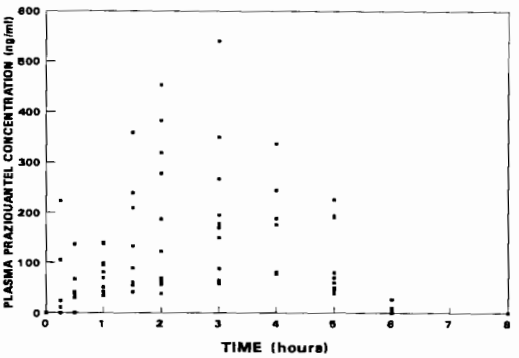


Fig 1–Plasma concentrations of praziquantel in each individual patient with neurocysticercosis following the first dose of praziquantel.

## DISCUSSION

The concentration-time profiles of praziquantel in plasma after the present regimen of praziquantel in this group of patients were in broad agreement with other previously published pharmacokinetic characteristics of the drug, showing low systemic availability with large inter-individual variation, and rapid drug clearance (Leopold *et al,* 1978; Patzschke *et al,* 1979; Steiner *et al,* 1976; Na-Bangchang *et al,* 1993). Comparing with the results reported by Jung *et al* (1990) and Bittencourt *et al* (1990), plasma levels of drug observed in our study were much lower. Furthermore, in contrast to that reported by Vasquez (1987) where the steady state level of approximately 3,000 ng/ml was attained on repeated

dosage of the same regimen, no accumulation of drug levels was observed in our study. This is probably due to the fact that blood samples were taken prior to the first dose of the day which was 8 hours after the previous dosing.

Therapy with praziquantel in neurocysticercosis is frequently complicated by the aggravation of symptoms which follow the inflammation produced by the acute destruction of cycticerci. Dexamethasone is a common drug used for the purpose of treatment of these adverse inflammatory reactions in neurocysticercosis (Sotelo *et al,* 1984). In addition, anticonvulsant therapy with phenobarbital, phenytoin, or carbamazepine is usually prescribed to these patients during the course of praziquantel treatment as a high percentage of them have seizures. These concomitant drugs have been well established as potent hepatic drug metabolizing enzyme inducing agents. Pretreatment with phenobarbital, phenytoin, and carbamazepine resulted in lowered maximum serum levels and reduced bioavailability of praziquantel (Bittencourt *et al,* 1992; Masimirembwa *et al,* 1994). Simultaneous administration of dexamethazone with praziquantel was shown to reduce plasma levels of praziquantel to approximately 50% as compared with levels when praziquantel was administered alone (Vazquez *et al,* 1987). In our study, all of the patients received anticonvulsants either phenytoin or phenobarbital, and one received dexamethazone. These drugs would be expected to significantly increase clearance secondary to induction of extensive first-pass metabolism of praziquantel, and relatively low plasma/CSF availability of the drug consequently resulted.

Despite this very low concentration attained during the therapy, high effective treatment outcome was achieved in this group of patients. The minimum effective plasma/serum concentration of praziquantel which reflects adequate CSF concentrations was reported to be at least 250 ng/ml (Bittencourt *et al,* 1990). Praziquantel is 80% bound to plasma protein and the remaining portion of only 15% is in equilibrium with CSF concentrations (Spina-Franca *et al,* 1985). However, it has been shown that there is a good correlation between CSF and plasma/or serum praziquantel concentrations, and plasma/serum concentrations can therefore provide a guide for the CSF concentrations (Leopold *et al,* 1978; Bittecourt *et al,* 1990). Maximum drug concentrations attained in this group of patients were approximately fifty percent lower than the reported effective concentrations. This probably indicates the significant role of active metabolite(s), rather than praziquantel itself in the therapy of neurocysticercosis since the drug undergoes rapid and extensive first-pass metabolism to a numbers of compounds (Ali *et al,* 1990).

## ACKNOWLEDGEMENTS

The study was supported by The Faculty of Tropical Medicine Research Grant. We thank medical and laboratory staff of the Bangkok Hospital for Tropical Diseases, and Mr Vick Banmairuroi, Clinical Pharmacology Unit, Faculty of Tropical Medicine, for their assistance.

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