CHAPTER 4

RESULTS

1. Method validation tests

1.1 Linearity of the standard calibration curve

The standard calibration curve for praziquantel at concentration of 100, 200, 400, 800, 1600, and 2,000 ng/ml was linear with the correlation coefficient (r) of 0.999 (Figure 6) The equation of linear regression line was y = 8.0487E-04 + 7.2484E-04x with slope and intercept values of 0.0007 and 0.0008, respectively.

1.2 Precision

The intra-day assay coefficients of variation (CV) for praziquantel in mobile phase were 1.91% at 100 ng/ml, 4.18% at 200 ng/ml, 1.02% at 400 ng/ml, 6.15% at 800 ng/ml, 1.29% at 1600 ng/ml and 1.92% at 2000 ng/ml, whereas the inter-day assay was assessed on 10 individual days; the CV were 7.05% at 100 ng/ml, 7.61% at 200 ng/ml, 8.08% at 400 ng/ml, 5.52% at 800 ng/ml, 6.87% at 1600 ng/ml and 6.35% at 2000 ng/ml. All results are shown in Table 2 and 3, respectively.

The intra-day assay coefficients of variation (CV) for praziquantel in human plasma were 3.81% at 100 ng/ml, 6.12% at 200 ng/ml, 2.18% at 400 ng/ml, 2.04% at 800 ng/ml, 1.51% at 1600 ng/ml and 2.59% at 2000 ng/ml, whereas the inter-day assay was assessed on 10 individual days; the CV were 4.87% at 100 ng/ml, 8.07% at 200 ng/ml, 5.38% at 400 ng/ml, 4.04% at

800 ng/ml and 8.82% at 1600 ng/ml and 6.82% at 2000 ng/ml. All results are shown in Table 4 and 5, respectively.

1.3 Accuracy

The mean absolute recovery values of the present HPLC method throughout the linear range are presented in Table 6. The results in Table 6 reflect that the method is obviously accurate and this ensures reliable results.

1.4 Limit of detection

The lower limit of detection (LOD) of praziquantel in plasma was approximately 12.25 ng/ml by considering a signal-to-noise of 3 :1.

2. Chromatograms

The chromatograms showed that a peak of praziquantel was well separated from the other peaks in plasma (Figures 7-9). There was no interference from the peak of rifampicin in this analytical method. The retention time for praziquantel and diazepam (internal standard) were approximately 14 and 17 min, respectively.

3. The plasma concentration-time data of praziquantel

According to the wide interindividual variations of the subject and the different drug administration schedule (single and multiple dose regimen), the noncompartment model was used to determine the pharmacokinetics data of praziquantel in this study. The summary of pharmacokinetic data of praziquantel in the present study was compared to other published data in human volunteers (Table 15). The pharmacokinetic parameters (C_{max}, T_{max} and Cl/f) of praziquantel in subjects receiving praziquantel alone were similar to

the previous reports but AUC and Vd/f of praziquantel were different to the previous reports may be because of wide interindividual variations in metabolism of praziquantel.

4. Adverse Effects

Ten adult healthy Thai male volunteers were enrolled and completed in this study. No serious side effects were observed after taking 600 mg of rifampicin. For a multiple oral doses of praziquantel, one subject reported rash at left arm, which could be treated by a 4 mg chlorpheniramine (CPM) tablet. One subject reported dizziness, lassitude and nausea, and one subject reported nausea and vomiting. The symptoms occurred for one day and transient, and were not required any specific treatment. However, all subjects were well tolerated to all drugs throughout the study. No marked laboratory abnormalities occurred in any subjects, and physical examinations revealed no abnormal finding at the end of the study.

5. Pharmacokinetics

5.1 Pharmacokinetics of praziquantel alone in the single and multiple doses

After a single oral dose of 40 mg/kg praziquantel alone in ten subjects, the C_{max} value of 1024.0 ± 417.5 ng/ml was reached at 2.3 ± 0.8 hours. The values for AUC_{0-12}, $AUC_{0-\infty}$, $t_{1/2,Z}$, Cl/f, V_Z/f and MRT were 4538.9 ± 1321.3 ng/ml.hr, 5021.6 ± 1488.3 ng/ml.hr, 3.4 ± 0.9 hours, 8.5 ± 2.1 l/kg/hr, 42.4 ± 16.7 l/kg and 4.5 ± 0.5 hours, respectively.

After a multiple oral dose of 25 mg/kg praziquantel alone, the C_{max} value of 763.5 ± 378.4 ng/ml was reached at 1.9 ± 0.9 hours. The values for

AUC_{0-12}, $AUC_{0-\infty}$, $t_{1/2,Z}$, Cl/f, V_Z/f and MRT were 2836.6 ± 1059.9 ng/ml.hr, 3135.2 ± 1097.1 ng/ml.hr, 3.1 ± 0.8 hours, 8.9 ± 3.2 l/kg/hr, 39.7 ± 15.8 l/kg and 4.0 ± 0.4 hours, respectively. The results showed that C_{max}, AUC_{0-12}, $AUC_{0-\infty}$ and MRT were significantly different between parameters of a single oral dose phase and a multiple oral dose phase, while there were no significant difference in λ_Z, $t_{1/2,Z}$, T_{max}, Cl/f and V_Z/f (Table 7).

5.2 Pharmacokinetics of praziquantel in subjects whose praziquantel plasma concentrations could be measured in the single and multiple doses after pretreatment with rifampicin compared with praziquantel alone.

In the single doses of praziquantel, the mean plasma concentration-time profile of praziquantel was shown in Figure 10. Praziquantel concentrations after rifampicin pretreatment could only be detected in 3 (number 8-10) out of 10 subjects, the other 7 subjects (number 1-7) are undetectable. The values of C_{max}, AUC_{0-12}, $AUC_{0-\infty}$, T_{max}, $t_{1/2,Z}$, Cl/f, V_Z/f and MRT in 3 subjects receiving praziquantel alone were 740.0 ± 209.5 ng/ml, 4240.4 ± 435.2 ng/ml.hr, 4664.2 ± 355.9 ng/ml.hr, 2.7 ± 1.5 hr, 2.9 ± 0.5 hr, 8.7 ± 0.7 l/kg/hr, 37.3 ± 7.4 l/kg and 5.0 ± 0.2 hr, respectively, whereas the values of C_{max}, AUC_{0-12}, $AUC_{0-\infty}$, T_{max}, $t_{1/2,Z}$, Cl/f, V_Z/f and MRT in 3 subjects with measurable concentrations when praziquantel was administered with rifampicin were 143.3 ± 50.3 ng/ml, 629.6 ± 347.8 ng/ml.hr, 771.9 ± 471.2 ng/ml.hr, 2.3 ± 0.6 hr, 1.6 ± 0.8 hr, 67.9 ± 41.2 l/kg/hr, 130.0 ± 16.2 l/kg and 3.0 ± 1.1 hr, respectively. The results indicated that C_{max}, AUC_{0-12}, $AUC_{0-\infty}$ and V_Z/f of praziquantel in 3 subjects with measurable concentrations after pretreatment with rifampicin were significantly different compared with those values when praziquantel was

administered alone. There were no significant differences in λ_z, $t_{1/2,Z}$, T_{max}, Cl/f and MRT (Table 8).

In the multiple doses of praziquantel, the mean plasma concentration-time profile of praziquantel was shown in Figure 11. Praziquantel concentrations after rifampicin pretreatment, could only be detected in 5 (number 1, 2, 7, 9 and 10) out of 10 subjects, the other 5 subjects (number 3-6 and 8) are undetectable. The values of C_{max}, AUC_{0-12}, $AUC_{0-\infty}$, T_{max}, $t_{1/2,Z}$, Cl/f, V_Z/f and MRT in subject number 1, 2, 7, 9 and 10 receiving praziquantel alone were 734 ± 377.1 ng/ml, 3018.0 ± 1066.8 ng/ml.hr, 3342.0 ± 1096.1 ng/ml.hr, 1.8 ± 1.2 hr, 3.2 ± 0.8 hr, 8.1 ± 2.3 l/kg/hr, 38.0 ± 14.8 l/kg and 4.1 ± 0.3 hr, respectively, whereas, the values of C_{max}, AUC_{0-12}, $AUC_{0-\infty}$, T_{max}, $t_{1/2,Z}$, Cl/f, V_Z/f and MRT in 5 subjects whose praziquantel plasma concentrations could be measured when praziquantel was administered with rifampicin were 194.0 ± 42.8 ng/ml, 601.7 ± 251.3 ng/ml.hr, 737.4 ± 270.8 ng/ml.hr, 2.1 ± 1.4 hr, 1.8 ± 0.3 hr, 38.3 ± 15.8 l/kg/hr, 103.6 ± 47.8 l/kg and 3.3 ± 1.0 hr, respectively. The results indicated that C_{max}, AUC_{0-12}, $AUC_{0-\infty}$, λ_z, $t_{1/2,Z}$, Cl/f and V_Z/f of praziquantel in 5 subjects with measurable concentrations after pretreatment with rifampicin were significantly different when compared with those values when praziquantel was administered alone. There were no significant differences in T_{max} and MRT (Table 8).

5.3 The C_{max} and AUC_{0-24} of praziquantel in subjects whose praziquantel plasma concentrations could not be measured in the single and multiple doses after pretreatment with rifampicin compared with praziquantel alone.

In a single oral dose of 40 mg/kg praziquantel, plasma praziquantel

concentrations after rifampicin pretreatment could only be detected in 3 out of 10, the other 7 subjects (number 1-7) are undetectable. The C_{max} and AUC_{0-12} of praziquantel in subject No. 1-7 were determined on the basis of the praziquantel detection limit (12.25 ng/ml). The values of C_{max}, AUC_{0-12} in 7 subjects after single oral dose of praziquantel alone were 1145.7 ± 435.0 ng/ml and 4666.9 ± 1578.5 ng/ml.hr, respectively, whereas, the values of C_{max} and AUC_{0-12} in subjects whose praziquantel plasma concentrations could not be measured when praziquantel was administered with rifampicin were 12.25 ± 0.0 ng/ml and 147.0 ± 0.0 ng/ml.hr, respectively. The results showed that C_{max} and AUC_{0-12} of praziquantel were significantly different between those groups receiving praziquantel alone and praziquantel after rifampicin treatment (Table 9).

In a multiple oral dose of 25 mg/kg praziquantel, plasma praziquantel concentrations after rifampicin pretreatment could only be detected in 5 out of 10, the other 5 subjects (number 3-6 and 8) are undetectable. The C_{max} and AUC_{0-12} of praziquantel in subject No. 3-6 and 8 were determined on the basis of the praziquantel detection limit (12.25 ng/ml). The values of C_{max}, AUC_{0-12} in 5 subjects after single oral dose of praziquantel alone were 793.0 ± 421.8 ng/ml and 2655.2 ± 1143.5 ng/ml.hr, respectively, whereas, the value of C_{max}, AUC_{0-12} in subjects whose praziquantel plasma concentrations could not be measured when praziquantel was administered with rifampicin were 12.25 ± 0.0 ng/ml, 147.0 ± 0.0 ng/ml.hr, respectively. The results showed that C_{max} and AUC_{0-12} of praziquantel were significantly different between those groups receiving praziquantel alone and praziquantel after rifampicin treatment (Table 9).

5.4 The C_{max} and AUC_{0-24} of praziquantel in ten subjects in the single and multiple doses alone and after pretreatment with rifampicin.

In a single oral dose of 40 mg/kg praziquantel, plasma praziquantel concentrations after rifampicin pretreatment could only be detected in 3 out of 10, the other 7 subjects (number 1-7) are undetectable. The C_{max} and AUC_{0-12} of praziquantel in subject No. 1-7 were determined on the basis of the praziquantel detection limit (12.25 ng/ml). The values of C_{max}, AUC_{0-12} in 10 subjects after single oral dose of praziquantel alone were 1024.0 ± 417.5 ng/ml and 4538.9 ± 1321.3 ng/ml.hr, respectively, whereas, the values of C_{max} and AUC_{0-12} in ten subjects when praziquantel was administered with rifampicin were 51.6 ± 67.6 ng/ml and 291.8 ± 285.0 ng/ml.hr, respectively. The results showed that C_{max} and AUC_{0-12} of praziquantel were significantly different between those groups receiving praziquantel alone and praziquantel after rifampicin treatment (Table 10).

In a multiple oral dose of 25 mg/kg praziquantel, plasma praziquantel concentrations after rifampicin pretreatment could only be detected in 5 out of 10, the other 5 subjects (number 3-6 and 8) are undetectable. The C_{max} and AUC_{0-12} of praziquantel in subject No. 3-6 and 8 were determined on the basis of the praziquantel detection limit (12.25 ng/ml). The values of C_{max}, AUC_{0-12} in 10 subjects after single oral dose of praziquantel alone were 763.5 ± 378.4 ng/ml and 2836.6 ± 1060.0 ng/ml.hr, respectively, whereas, the values of C_{max} and AUC_{0-12} in ten subjects when praziquantel was administered with rifampicin were 103.1 ± 99.9 ng/ml and 374.4 ± 292.4 ng/ml.hr, respectively. The results showed that C_{max} and AUC_{0-12} of praziquantel were significantly different between those groups receiving praziquantel alone and praziquantel after rifampicin treatment (Table 10).

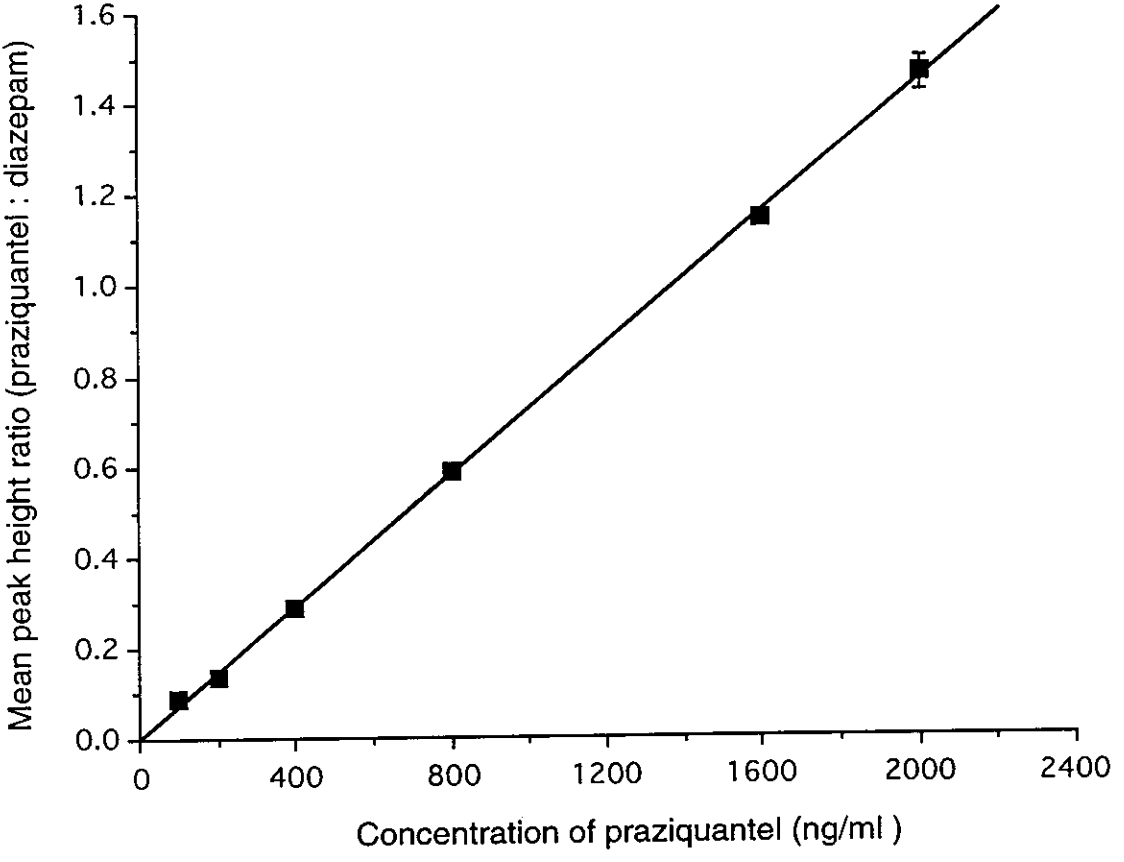

Figure 6. Correlation between peak height ratio of praziquantel to diazepam (internal standard) in plasma. The correlation coefficient (r) of regression line for praziquantel is 0.999. Each point represents mean ± SD

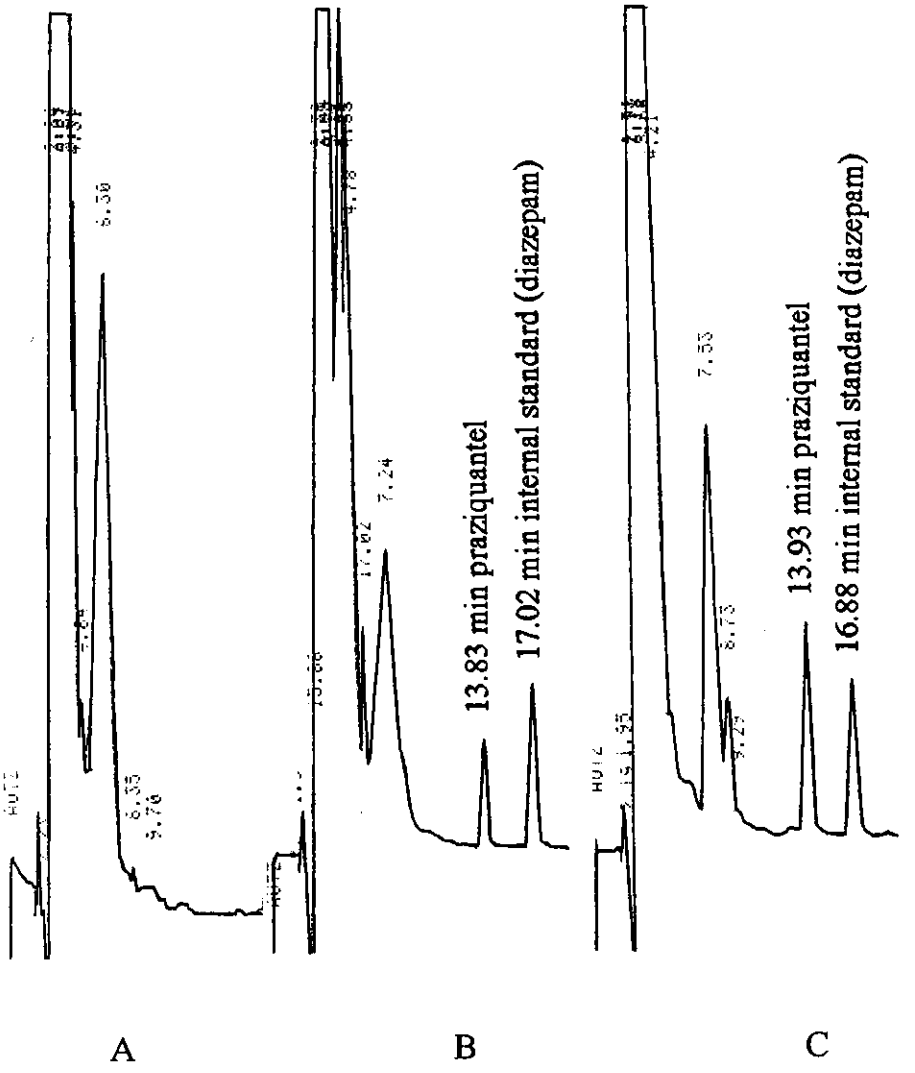

Figure 7 Representative chromatograms of 100 µl human plasma samples. Key : (A) blank human plasma ; (B) and (C) spiked with standard praziquantel 800 and 1,600 ng/ml, respectively. The mobile phase consisted of deionized water-acetonitrile-methanol (54 : 36 : 10 vol/vol/vol) at flow rate of 1.5 ml/min. Chart speed and attenuation were 3 mm/min and 16 mVF.S., respectively.

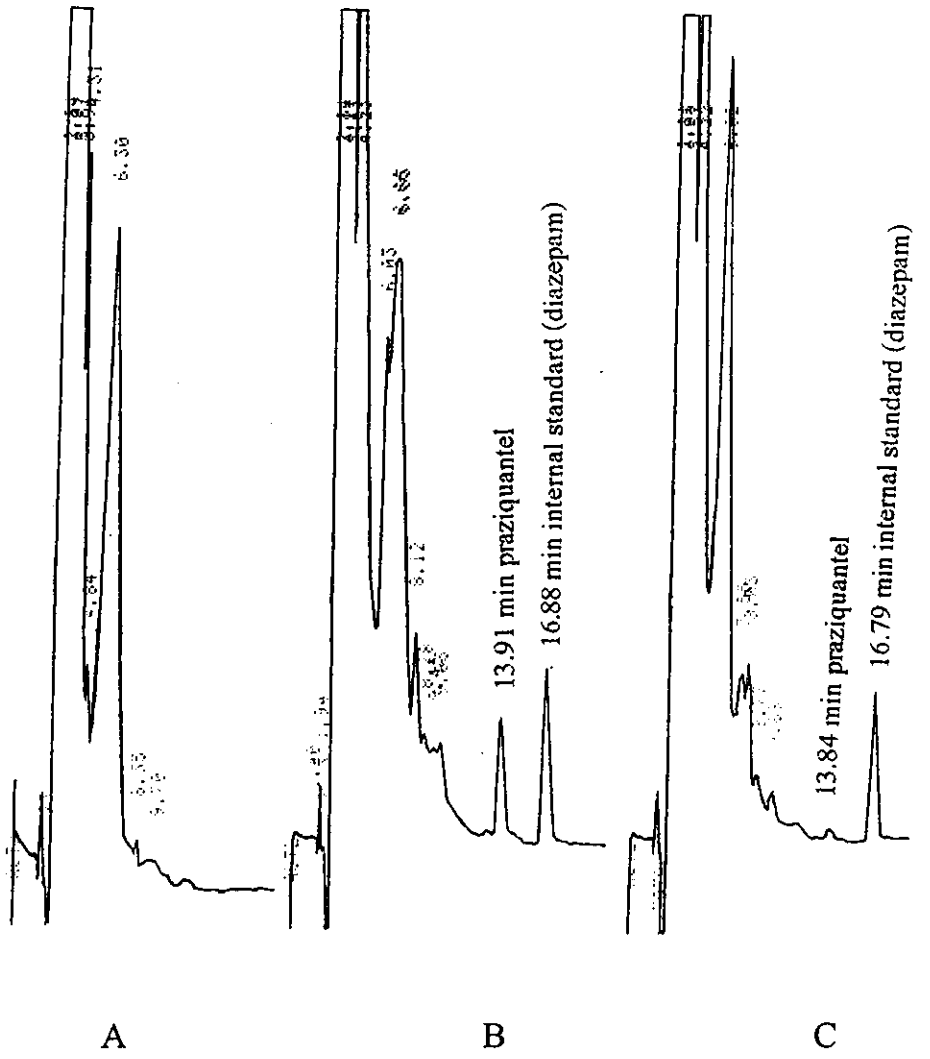

Figure 8 Representative chromatograms of 100 µl human plasma samples. Key : (A) blank human plasma ; (B) plasma obtained from a subject receiving 40 mg/kg PZQ alone at 4 hours ; (C) plasma obtained from a subject receiving 40 mg/kg PZQ at 4 hours after pretreatment with rifampicin The mobile phase consisted of deionized water-acetonitrile-methanol (54 : 36 : 10 vol/vol/vol) at flow rate of 1.5 ml/min. Chart speed and attenuation were 3 mm/min and 16 mVF.S., respectively.

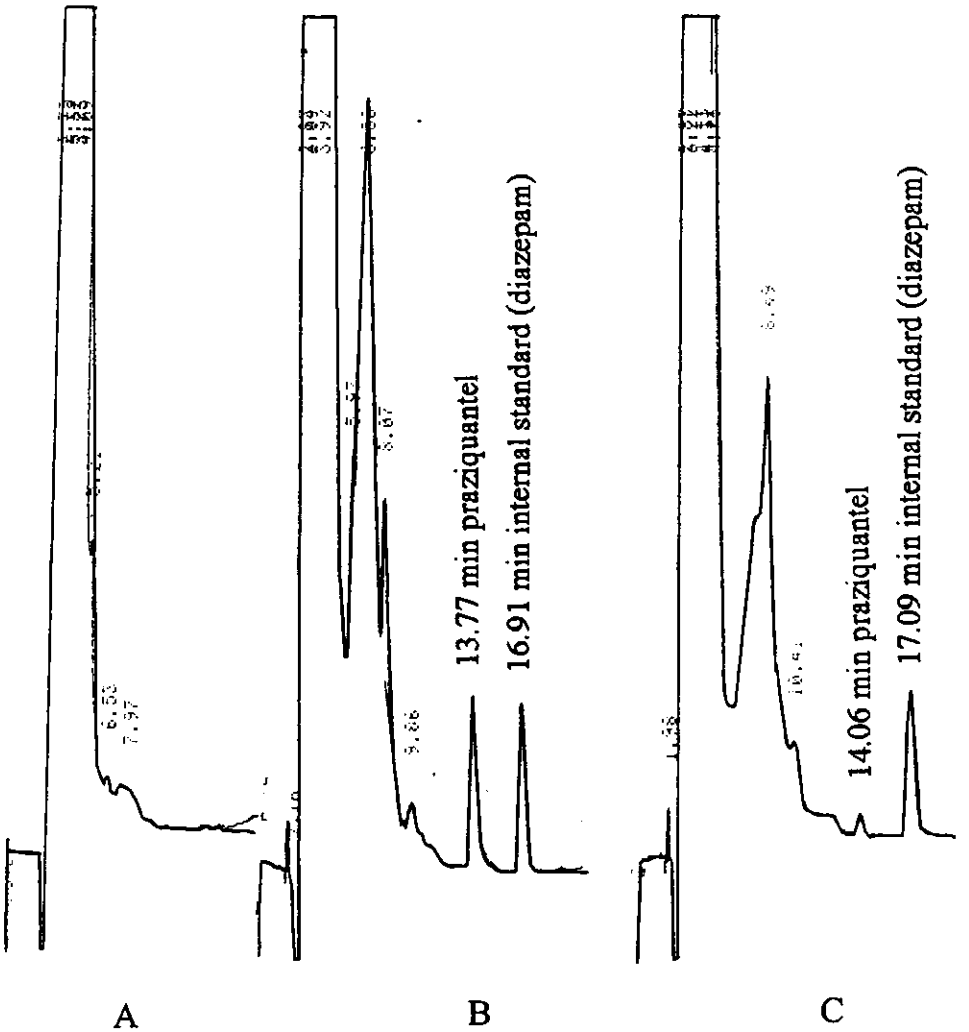

Figure 9 Representative chromatograms of 100 µl human plasma samples. Key : (A) blank human plasma ; (B) plasma obtained from a subject receiving 25 mg/kg (3 times) PZQ alone at 2 hours ; (C) plasma obtained from a subject receiving 25 mg/kg (3 times) PZQ at 2 hours after pretreatment with rifampicin The mobile phase consisted of deionized water-acetonitrile-methanol (54 : 36 : 10 vol/vol/vol) at flow rate of 1.5 ml/min. Chart speed and attenuation were 3 mm/min and 16 mVF.S., respectively.

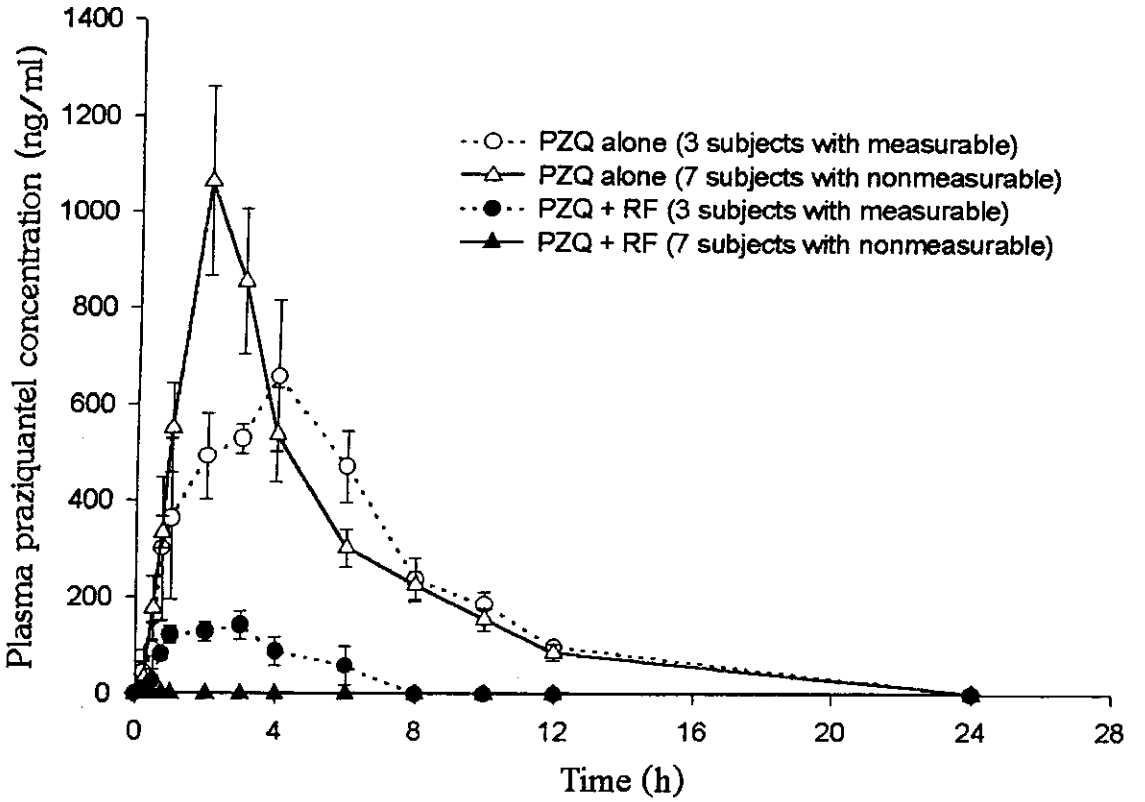

Figure 10 Mean plasma praziquantel concentrations after a single oral dose of 40 mg/kg praziquantel administration alone (○——○ : in 3 subjects; Δ——Δ: in 7 subjects) and after rifampicin pretreatment (●——●: in 3 subjects with measurable; ▲——▲: in 7 subjects with nonmeasurable).

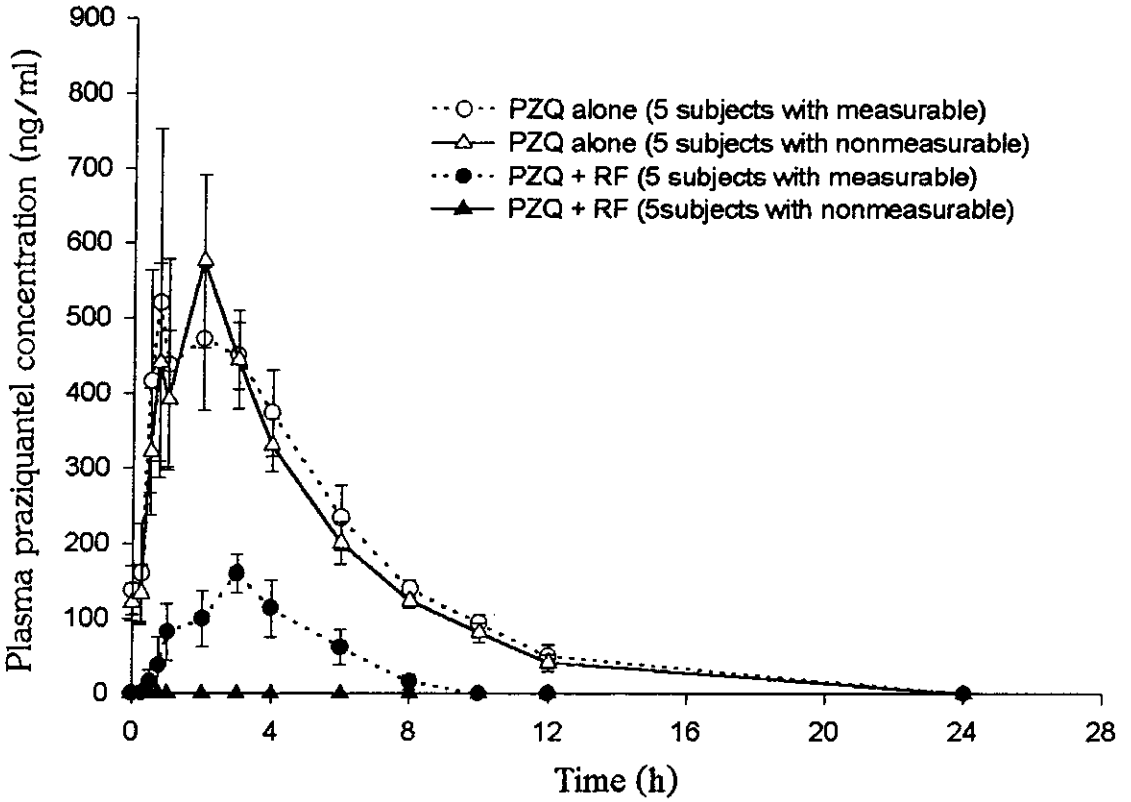

Figure 11 Mean plasma praziquantel concentrations after a multiple oral dose of 25 mg/kg praziquantel administration alone (○—○: in 5 subjects; Δ——Δ: in 5 subjects) and after rifampicin pretreatment (●——●: in 5 subjects with measurable; ▲——▲: in 5 subjects with nonmeasurable).

Table 7 Pharmacokinetic parameters (mean ± SD) of praziquantel in ten subjects after receiving a single oral dose of 40 mg/kg or a multiple oral dose of 25 mg/kg praziquantel alone.

Parameters	Praziquantel alone		*P*-value *t*-test
	Single dose phase (n=10)	Multiple dose phase (n=10)	
C_{max} (ng/ml)	1024.00 ± 417.48	763.50 ± 378.44	$P < 0.05$
$AUC_{(0-12)}$ (ng/ml.hr)	4538.94 ± 1321.26	2836.62 ± 1059.96	$P < 0.001$
$AUC_{(0-\infty)}$ (ng/ml.hr)	5021.59 ± 1488.33	3135.16 ± 1097.07	$P < 0.001$
λ_z (hr^{-1})	0.21 ± 0.05	0.24 ± 0.07	NS
$t_{1/2,Z}$ (hr)	3.45 ± 0.92	3.13 ± 0.79	NS
T_{max} (hr)	2.30 ± 0.82	1.90 ± 0.96	NS
Cl/f (l/kg/hr)	8.51 ± 2.11	8.91 ± 3.17	NS
V_Z/f (l/kg)	42.43 ± 16.75	39.74 ± 15.81	NS
MRT (hr)	4.48 ± 0.46	4.00 ± 0.40	$P < 0.001$

NS; no significant difference from control of a single dose phase

Table 8 Pharmacokinetic parameters (mean ± SD) of praziquantel in subjects whose praziquantel plasma concentrations could be measured after receiving a single oral dose of 40 mg/kg or a multiple oral dose of 25 mg/kg praziquantel alone, and after pretreatment with 600 mg rifampicin orally for 5 days.

Parameters	Single dose phase		*P*-value *t*-test	Multiple dose phase		*P*-value *t*-test
	PZQ alone (n=3)	PZQ[a] plus rifampicin (n=3)		PZQ alone (n=5)	PZQ[a] plus rifampicin (n=5)	
C_{max} (ng/ml)	740.00 ± 209.52	143.33 ± 50.33	$P < 0.05$	734.00 ± 377.07	194.00 ± 42.79	$P < 0.05$
$AUC_{(0-12)}$ (ng/ml.hr)	4240.42 ± 435.22	629.58 ± 347.77	$P < 0.01$	3018.00 ± 1066.81	601.75 ± 251.30	$P < 0.01$
$AUC_{(0-\infty)}$ (ng/ml.hr)	4664.16 ± 355.91	771.94 ± 471.17	$P < 0.01$	3342.01 ± 1096.09	737.41 ± 270.82	$P < 0.01$
λ_z (hr^{-1})	0.24 ± 0.04	0.51 ± 0.27	NS	0.23 ± 0.06	0.38 ± 0.06	$P < 0.02$
$t_{1/2,z}$ (hr)	2.96 ± 0.46	1.64 ± 0.82	NS	3.24 ± 0.80	1.85 ± 0.30	$P < 0.05$
T_{max} (hr)	2.67 ± 1.53	2.33 ± 0.58	NS	1.85 ± 1.19	2.15 ± 1.36	NS
Cl/f (l/kg/hr)	8.66 ± 0.75	67.92 ± 41.22	NS	8.06 ± 2.32	38.29 ± 15.82	$P < 0.02$
V_z/f (l/kg)	37.30 ± 7.43	129.99 ± 16.17	$P < 0.01$	37.98 ± 14.82	103.60 ± 47.78	$P < 0.05$
MRT (hr)	5.01 ± 0.19	2.97 ± 1.08	NS	4.15 ± 0.28	3.29 ± 0.98	NS

NS; no significant difference from control

[a]After rifampicin pretreatment, plasma concentrations of praziquantel could be measured in 3 and 5 out of the 10 subjects of the single and multiple does phase, respectively.

Table 9 Pharmacokinetic parameters (mean ± SD) of praziquantel in subjects whose praziquantel plasma concentrations could not be measured after receiving a single oral dose of 40 mg/kg or a multiple oral dose of 25 mg/kg praziquantel alone, and after pretreatment with 600 mg rifampicin orally for 5 days.

Parameters	Single dose phase		*P*-value *t*-test	Multiple dose phase		*P*-value *t*-test
	PZQ alone (n=7)	PZQ[a] plus rifampicin (n=7)		PZQ alone (n=5)	PZQ[a] plus rifampicin (n=5)	
C_{max} (ng/ml)[b]	1145.71 ± 434.96	12.25 ± 0.00	$P < 0.001$	793.00 ± 421.76	12.25 ± 0.00	$P < 0.02$
$AUC_{(0-12)}$ (ng/ml.hr)[b]	4666.87 ± 1578.54	147.00 ± 0.00	$P < 0.001$	2655.25 ± 1143.51	147.00 ± 0.00	$P < 0.01$

[a]After rifampicin pretreatment, plasma concentrations of praziquantel could not be measured in 7 and 5 out of the 10 subjects of the single and multiple does phase, respecttively.

[b]The AUC and C_{max} of subjects whose PZQ plasma concentrations could not be measured were calculated on the basic of PZQ detection limit (12.25 ng/mL).

Table 10 Pharmacokinetic parameters of praziquantel in each of ten subjects receiving a single oral dose of 40 mg/kg praziquantel alone.

Parameters	*Subject number* (S1-S10)											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
Age (yrs)	28	36	37	29	28	36	21	22	20	32	28.9	6.38
Weight (kgs)	54	68	62	60	60	60	55	59	55	60	59.3	4.08
C_{max} (ng/ml)	580.00	1230.00	1650.00	940.00	1780.00	860.00	980.00	560.00	970.00	690.00	1024.00	417.48
$AUC_{(0\text{-}12)}$ (ng/ml.hr)	3148.75	5162.50	6392.50	3953.75	7053.75	3035.62	3921.25	3770.00	4322.50	4628.75	4538.94	1321.26
$AUC_{(0\text{-}\infty)}$ (ng/ml.hr)	3774.19	5293.59	7174.64	4106.36	8083.23	3516.59	4274.85	4288.40	4707.91	4996.18	5021.59	1488.33
λ_z (hr^{-1})	0.14	0.30	0.18	0.26	0.14	0.17	0.23	0.21	0.28	0.22	0.21	0.05
$t_{1/2,Z}$ (hr)	4.82	2.27	3.87	2.64	4.76	4.17	3.06	3.27	2.43	3.18	3.45	0.92
T_{max} (hr)	2.00	2.00	2.00	2.00	2.00	2.00	3.00	3.00	4.00	1.00	2.30	0.82
Cl/f (l/kg/hr)	10.79	7.50	5.39	9.74	4.95	11.37	9.36	9.48	8.50	8.01	8.51	2.11
V_z/f (l/kg)	77.07	25.00	29.94	37.46	35.36	66.88	40.69	45.14	30.36	36.41	42.43	16.75
MRT (hr)	4.58	3.99	4.54	3.81	4.03	4.21	4.62	5.07	5.17	4.80	4.48	0.46

Table 11 Pharmacokinetic parameters of praziquantel in each of ten subjects receiving a single oral dose of 40 mg/kg praziquantel after pretreatment with 600 mg rifampicin orally for 5 days.

Parameters	*Subject number* (S1-S10)											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
Age (yrs)	28	36	37	29	28	36	21	22	20	32	28.9	6.38
Weight (kgs)	54	68	62	60	60	60	55	59	55	60	59.3	4.08
C_{max} (ng/ml)	-	-	-	-	-	-	-	150.00	190.00	90.00	143.33	50.33
$AUC_{(0-12)}$ (ng/ml.hr)	-	-	-	-	-	-	-	585.00	997.50	306.25	629.58	347.77
$AUC_{(0-\infty)}$ (ng/ml.hr)	-	-	-	-	-	-	-	676.83	1283.41	355.57	771.94	471.17
λ_z (hr^{-1})	-	-	-	-	-	-	-	0.43	0.28	0.81	0.51	0.27
$t_{1/2,z}$ (hr)	-	-	-	-	-	-	-	1.59	2.48	0.85	1.64	0.82
T_{max} (hr)	-	-	-	-	-	-	-	2.00	3.00	2.00	2.33	0.58
Cl/f (l/kg/hr)	-	-	-	-	-	-	-	60.10	31.17	112.49	67.92	41.22
V_z/f (l/kg)	-	-	-	-	-	-	-	139.77	111.32	138.88	129.99	16.17
MRT (hr)	-	-	-	-	-	-	-	2.79	4.13	2.00	2.97	1.08

Table 12 Pharmacokinetic parameters of praziquantel in each of ten subjects receiving a multiple oral dose of 25 mg/kg praziquantel alone.

Parameters	*Subject number* (S1-S10)											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
Age (yrs)	28	36	37	29	28	36	21	22	20	32	28.9	6.38
Weight (kgs)	54	68	62	60	60	60	55	59	57.50	60	59.55	3.86
C_{max} (ng/ml)	520.00	1380.00	1380.00	385.00	970.00	845.00	720.00	385.00	430.00	620.00	763.50	378.44
$AUC_{(0-12)}$ (ng/ml.hr)	2248.75	4716.25	3718.75	1363.75	3951.25	2422.50	2538.75	1820.00	2182.50	3403.75	2836.62	1059.96
$AUC_{(0-\infty)}$ (ng/ml.hr)	2425.55	5145.77	4246.70	1758.36	4102.88	2610.95	3037.95	1922.69	2576.23	3524.55	3135.16	1097.07
λ_z (hr^{-1})	0.23	0.21	0.17	0.20	0.26	0.21	0.16	0.39	0.20	0.33	0.24	0.07
$t_{1/2,Z}$ (hr)	3.06	3.31	4.07	3.42	2.63	3.26	4.32	1.78	3.41	2.09	3.13	0.79
T_{max} (hr)	3.00	0.75	2.00	2.00	2.00	0.75	0.50	3.00	3.00	2.00	1.90	0.96
Cl/f (l/kg/hr)	10.31	4.71	5.70	14.22	6.09	9.57	8.08	13.22	10.13	7.09	8.91	3.17
V_Z/f (l/kg)	44.83	22.43	33.53	71.10	23.42	45.57	50.50	33.90	50.65	21.48	39.74	15.81
MRT (hr)	4.51	3.74	4.18	3.65	3.45	3.44	4.06	4.51	4.21	4.23	4.00	0.40

Table 13 Pharmacokinetic parameters of praziquantel in each of ten subjects receiving a multiple oral dose of 25 mg/kg praziquantel after pretreatment with 600 mg rifampicin orally for 5 days.

Parameters	*Subject number* (S1-S10)											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
Age (yrs)	28	36	37	29	28	36	21	22	20	32	28.9	6.38
Weight (kgs)	54	68	62	60	60	60	55	59	57.5	60	59.55	3.86
C_{max} (ng/ml)	140.00	190.00	-	-	-	-	190.00	-	260.00	190.00	194.00	42.79
$AUC_{(0-12)}$ (ng/ml.hr)	287.50	731.25	-	-	-	-	555.00	-	950.00	485.00	601.75	251.30
$AUC_{(0-\infty)}$ (ng/ml.hr)	393.93	990.93	-	-	-	-	651.19	-	1035.48	615.54	737.41	270.82
λ_z (hr^{-1})	0.37	0.35	-	-	-	-	0.41	-	0.47	0.31	0.38	0.06
$t_{1/2,z}$ (hr)	1.84	2.00	-	-	-	-	1.67	-	1.48	2.26	1.85	0.30
T_{max} (hr)	1.00	0.75	-	-	-	-	2.00	-	4.00	3.00	2.15	1.36
Cl/f (l/kg/hr)	63.46	24.49	-	-	-	-	37.69	-	25.19	40.61	38.29	15.82
V_z/f (l/kg)	171.51	69.97	-	-	-	-	91.93	-	53.59	131.00	103.60	47.78
MRT (hr)	2.15	2.77	-	-	-	-	2.94	-	4.50	4.10	3.29	0.98

Table 14 Praziquantel pharmacokinetic data were compared to other published data

Data	Sources				
	Castro 2000	Mandour 1990	Masimirembwa 1994	Homeida 1994	Present study*
Subjects	9 men	8 men	8 men	9 men	10 men
Age (yr)	33.44 (26-47)	28.0 ± 0.4	27.0 ± 4.0	25.7 ± 1.0	28.9 ± 6.38
Dose (mg)	1800	40 mg/kg	40 mg/kg	40 mg/kg	40 mg/kg
Route	oral	oral	oral	oral	oral
AUC (ng/ml.hr)	882.33 ± 416.79	4089 ± 1594	11750 ± 8100	2979 ± 825	4538.94 ± 1321.26
C_{max} (ng/ml)	318.81 ± 227.19	978 ± 220	2130 ± 1740	1018 ± 321	1024 ± 417.48
T_{max} (hr)	1.39 ± 0.98	2.6 ± 0.3	1.89 ± 0.38	1.89 ± 0.23	2.30 ± 0.82
$T_{1/2}$ (hr)	2.03 ± 0.24	3.3 ± 0.3	1.93 ± 0.54	2.10 ± 0.29	3.45 ± 0.92
Cl/f (l/kg/hr)	-	16.4 ± 4.5	6.95 ± 7.09	-	8.51 ± 2.11
Vd/f (l)	-	4646 ± 1173	-	-	2485.57 ± 894.01

*Data obtained from subjects receiving a single oral dose of praziquantel alone