Effects of Ketoconazole and Itraconazole on the Pharmacokinetics of a Single Oral Dose of Praziquantel in Healthy Volunteers

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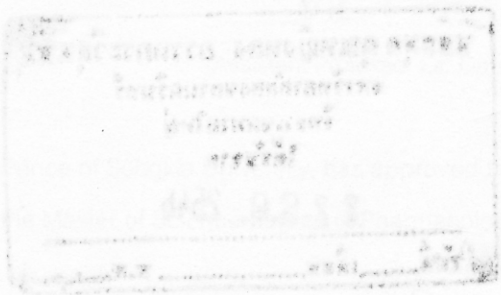

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ABSTRACT

Praziquantel, a pyrazinoisoquinoline derivative, is a broadspectrum anthelminthics against trematodes (flukes) and cestodes (tapeworms). Praziquantel undergoes extensive metabolism by cytochrome P450 (CYP), especially of CYP3A. These enzymes play a major role in hydroxylation of praziquantel. Ketoconazole and itraconazole, azole antimycotics, are potent inhibitors of CYP 3A4 activity that can increase plasma concentrations of various drugs when concomitantly administered during treatment. Therefore, ketoconazole and itraconazole may alter the pharmacokinetics of praziquantel when these drugs are coadministered. The objective of this study is to examine the effect of ketoconazole or itraconazole on the pharmacokinetics of a single oral dose of praziquantel in healthy volunteers.

In the present study, ten Thai male volunteers were divided into 3 groups. The study was performed using an open randomized three phase crossover design. The washout period between each study phase was 2 weeks. In phase I, each volunteer received a single oral dose of 20 mg/kg praziquantel alone while in phase II and III, each volunteer received an oral dose of 400 mg ketoconazole and 200 mg itraconazole, respectively once daily after breakfast (at 7.00 AM.) for 5 days prior to praziquantel administration. In day 6 of phase II and phase III (after pretreatment with ketoconazole and itraconazole for 5 days), after an overnight fast, each volunteer took a 20 mg/kg praziquantel. Blood samples (5 ml) were collected at the specific time points (0, 0.5,

0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours) and plasma praziquantel concentrations were determined by HPLC method for pharmacokinetic analysis.

In phase I (praziquantel alone), mean C_{max}, AUC_{0-12}, $AUC_{0-\infty}$, *K*a, λ_z, $T_{1/2}$, T_{max}, Cl/f, V_Z/f and MRT values of praziquantel were183.38 ± 138.82 ng/ml, 793 ± 895 ng/ml.hr, 956 ± 973 ng/ml.hr, 0.48 ± 0.40 hr^{-1}, 0.29 ± 0.22 hr^{-1}, 3.80 ± 3.03 hr, 2.05 ± 1.14 hr, 2.65 ± 2.03 l/kg/hr, 10.75 ± 6.55 l/kg and 6.35 ± 3.20 hr, respectively. In phase II, ketoconazole significantly increased the mean C_{max}, *K*a, AUC_{0-12} and $AUC_{0-\infty}$ of praziquantel when compared with phase I by 102.48% (371.31 ± 141.10 ng/ml vs 183.38 ± 138.82 ng/ml; $P<0.01$), 119.96% (1.06 ± 0.41 hr^{-1} vs 0.48 ± 0.40 hr^{-1}; $P<$ 0.01), 97.09% (1563 ± 756 ng/ml.hr vs 793 ± 895 ng/ml.hr; $P<0.01$) and 92.78% (1843 ± 1064 ng/ml.hr vs 956 ± 973 ng/ml.hr; $P<0.01$), respectively, whereas it significantly decreased mean Cl/f and V_Z/f by 58.11% (1.11 ± 1.09 l/kg/hr vs 2.65 ± 2.03 l/kg/hr; $P<$ 0.01), and 58.88% (4.42 ± 2.06 l/kg vs 10.75 ± 6.55 l/kg; $P<0.01$), respectively. In phase III, itraconazole significantly increased the mean C_{max} and *K*a by 70.58% (312.81 ± 204.98 ng/ml vs 183.38 ± 138.82 ng/ml; $P<0.05$) and 83.38% (0.88 ± 0.45 hr^{-1} vs 0.48 ± 0.40 hr^{-1}; $P<0.01$) respectively. Thus, ketoconazole increased C_{max}, *K*a and AUC of praziquantel whereas itraconazole increased C_{max} and *K*a of praziquantel. If ketoconazole or itraconazole is coadministered with praziquantel, the dose of praziquantel should be adjusted to maximize the therapeutic efficacy and to reduce the cost of therapy.