



The Effect of Rifampicin on the Pharmacokinetics of Single and Multiple Oral Doses of Praziquantel in Healthy Volunteers

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ABSTRACT

Praziquantel, a pyrazinoisoquinoline derivative, is a broadspectrum anthelmintic against trematode and cestode infections. Praziquantel is highly metabolized in the liver by cytochrome P450 isozymes, especially of CYP3A. There were evidences, which support that CYP3A enzymes are involved in the hydroxylation of praziquantel. In addition, praziquantel is also metabolized by conjugation processes. Rifampicin, an antituberculosis drug which is a potent inducer of CYP3A4. It has been known to markedly decrease plasma concentrations of various drugs which are concomitantly administered during treatment. Therefore, rifampicin may alter the pharmacokinetics of praziquantel when these two drugs are coadministered. The objective of this study is to examine the effect of rifampicin on the pharmacokinetics of single and multiple oral doses of praziquantel in healthy volunteers.

In the present study, the pharmacokinetic parameters of praziquantel were determined in 10 healthy male volunteers. An open, randomised two-phase crossover design was used in each study of single or multiple doses.

In single dose study, each subject ingested single dose of 40 mg/kg praziquantel alone (phase 1) or received the same dose after pretreatment with 600 mg of oral rifampicin once daily for 5 days (phase 2). In multiple doses study, all participants received multiple doses of 3 x 25 mg/kg praziquantel alone (phase 1) or received the same dose after a 5-days pretreatment with 600 mg of oral rifampicin once daily (phase 2). Plasma concentrations of praziquantel at the specific times (0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hr.) were determined by the HPLC method for pharmacokinetic analysis.

The results in single dose study showed that plasma concentrations of praziquantel could only be detected in 3 out of 10 subjects after pretreatment with rifampicin. In 3 subjects with measurable concentrations, rifampicin increased the Cl of praziquantel by 684% (8.66 ± 0.75 vs 67.92 ± 41.22 l/kg/hr; $P > 0.05$), and the $t_{1/2}$ was shorter by 45% (2.96 ± 0.46 vs 1.64 ± 0.82 hr; $P > 0.05$), the C_{max} and AUC_{0-12} significantly decreased by 81% (740.00 ± 209.52 vs 143.33 ± 50.33 ng/ml; $P < 0.05$) and 85% (4240.42 ± 435.22 vs 629.58 ± 347.77 ng/ml; $P < 0.01$), respectively, when compared with the administration of praziquantel alone group. The C_{max} and AUC_{0-12} of praziquantel in 7 subjects with undetectable concentrations after rifampicin pretreatment compared to those values after praziquantel alone reduced by 99% (1145.71 ± 434.96 vs 12.25 ± 0.00 ng/ml; $P < 0.001$) and 94% (4666.87 ± 1578.54 vs 147.00 ± 0.00 ng/ml.hr; $P < 0.001$), respectively.

In multiple dose study, the results showed that plasma concentrations of praziquantel could only be detected in 5 out of 10 subjects after pretreatment with rifampicin. In the 5 subjects with measurable concentrations, rifampicin increased the Cl of praziquantel by 375% ($8.06 \pm$

2.32 vs 38.29 ± 15.82 l/kg/hr; $P < 0.02$), and the $t_{1/2}$ was shorter by 43% (3.24 ± 0.80 vs 1.85 ± 0.30 hr; $P < 0.05$), the C_{\max} and AUC_{0-12} significantly decreased by 74% (734.00 ± 377.07 vs 194.00 ± 42.79 ng/ml; $P < 0.05$) and 80% (3018.00 ± 1066.81 vs 601.75 ± 251.30 ng/ml; $P < 0.01$), respectively, when compared with the administration of praziquantel alone group. The C_{\max} and AUC_{0-12} of praziquantel in the 5 subjects with undetectable concentrations after rifampicin pretreatment compared to those values after praziquantel alone were reduced by 98% (793.00 ± 421.76 vs 12.25 ± 0.00 ng/ml; $P < 0.02$) and 89% (2655.25 ± 1143.51 vs 147.00 ± 0.00 ng/ml.hr; $P < 0.01$), respectively.

The alteration in praziquantel pharmacokinetic parameters may be due to the induction of CYP450, mainly CYP3A isozyme, and other possible mechanisms. For example, induction of UDP-glucuronyl-transferase enzyme by rifampicin. Therefore, clinicians should consider increasing the dose of praziquantel in the patient who is taking rifampicin especially if the patient does not respond to an initial treatment with praziquantel or if it is possible, rifampicin should not be coadministered with praziquantel in order to maximise the therapeutic efficacy of praziquantel.

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