Effect of Ketoconazole on the Pharmacokinetics of a Single Oral Dose of Mefloquine in Healthy Volunteers

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ABSTRACT

The objective of this study is to examine the effect of co-administration of ketoconazole and mefloquine on the pharmacokinetics of mefloquine in healthy volunteers. The pharmacokinetic parameters mefloquine were determined in 8 male volunteers after receiving mefloquine 500 mg as a oral single dose with ketoconazole 400 mg given orally once daily for 5 days prior to mefloquine administration and continued ketoconazole 400 mg orally once daily for 5 day after 500 mg mefloquine administration. The plasma mefloquine and mefloquine carboxylic metabolite concentrations during 56 days were measured using High Performance Liquid (HPLC). Statistical analysis using one way ANOVA indicated that when mefloquine and ketoconazole were co-administration, ketoconazole increased the mean of mefloquine $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, and C_{max} when compared to mefloquine alone (phase 1) by 1.8 fold (159.66 ± 33.28 vs 286.05 ± 64.25 mg/l/hr; $P<$ 0.001), 1.8 fold 205.22 ± 32.58 vs 360.49 ± 81.98 mg/l/hr; $P<$ 0.001), 1.4 fold (322.68 ± 99.95 vs 448.41±103.88 hr; $P<$ 0.05) and 1.7 fold (345.10 ± 43.22 vs 567.65 ± 88.69 ng/ml; $P<$ 0.001), respectively, whereas Ke, V_d/f and Cl/f were significantly decreased by 1.4 fold (0.0022 ± 0.0006 vs 0.0016 ± 0.0003 hr^{-1} ;$P<$ 0.05), 1.4 fold (1.40 ± 0.20 vs 1.00 ± 0.21 l/kg; $P<$ 0.05) and 2.1 fold

(0.0031 ± 0.0007 vs 0.0015 ± 0.0003 l/hr/kg; $P< 0.001$), respectively. In addition, the $AUC_{0\text{-last}}$, and C_{max} of mefloquine metabolite were decreased by 1.4 fold (492.43 ± 141.66 vs 352.29 ± 47.08 mg/l/hr; $P<0.05$) and 1.4 fold (606.11 ± 184.00 vs 419.65 ± 45.02 ng/ml; $P<0.05$), respectively, whereas V_d/f was significantly increased by 1.4 fold (0.77 ± 0.40 vs 1.09 ± 0.16 l/kg; $P<0.05$) when compared to mefloquine alone. The Cl/f was not significantly increased when compared to mefloquine alone. In conclusion, oral pre-treatment and co-administration of ketoconazole with mefloquine for 10 days did not affect the absorption of orally co-administered mefloquine, while distribution and elimination of mefloquine were significantly affected. These findings suggested that hepatic metaolism of mefloquine was decreased. One of the possibility of alteration in hepatic mefloquine metabolism may be due to the inhibition of CYP3A4 isozyme by ketoconazole. Therefore, if mefloquine is co-administered with ketoconazole, the dose of mefloquine should be adjusted to maximize the therapeutic efficacy and to reduce the cost of therapy.