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Pharmacokinetic Interactions between Udenafil and Ketoconazole

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Background/Aims: Udenafil (DA-8159), a phosphodiesterase type 5 inhibitor, is effective therapy for erectile dysfunction. The primary aim of this study was to investigate the effect of the potent CYP3A4 inhibitor ketoconazole on the pharmacokinetics (PK) of DA-8159 and its major metabolite DA-8164.

Methods: An open-label, 1-sequence, 2-period, 2-treatment study was conducted. In period 1, 12 healthy male volunteers received a single dose of 100 mg DA-8159 orally. In period 2, they received 400 mg ketoconazole once daily for 3 days and a single dose of 100 mg DA-8159 coadministered on the 3rd day of ketoconazole therapy. Serial blood samples were collected at defined intervals for 72 h in each period. Plasma concentrations of DA-8159 and DA-8164 were determined by LC-MS/MS. PK parameters were estimated by a non-compartmental analysis.

Results: Following ketoconazole coadministration, Cmax and AUC of DA-8159 increased from 313 ug/L to 574 ug/L (1.9-fold, $P<0.001$) and from 2,143 ug*h/L to 6,682 ug*h/L (3.1-fold, $P<0.001$), respectively. On the contrary, Cmax and AUC of DA-8164 decreased from 187 ug/L to 19 ug/L (0.1-fold, $P<0.001$) and from 2744 ug*h/L to 934 ug*h/L (0.34-fold, $P<0.001$) during ketoconazole coadministration, respectively. Metabolic ratio of the AUC of DA-8164 to that of DA-8159 after DA-8159 administration alone was 1.33 and decreased to 0.15 after ketoconazole coadministration.

Conclusion: The effect of ketoconazole on DA-8159 is consistent with inhibition of the CYP3A4-mediated metabolism. Ketoconazole coadministration increases exposure to DA-8159 up to 3.1-fold.