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The Influence of Gender on Itraconazole Pharmacokinetic Parameters in Healthy Adults

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Abstract : Itraconazole (ITZ) is a weak base and extremely lipophilic compound, with water solubility as a rate-limiting step in its absorption from the gastrointestinal tract. Its absolute bioavailability, about 55%, is maximal when its oral formulation, capsules, are taken immediately after a full meal. Peak plasma concentrations (Cmax) are reached within 2 to 5 hrs after their administration. ITZ undergoes extensive hepatic metabolism by human CYP3A4 isoenzyme and more than 30 different metabolites have been identified. One of the main ones is hydroxyitraconazole (HITZ), in which plasma concentrations are almost twice higher than those of ITZ. Gender differences in drug PK (Pharmacokinetics) have already been recognized, but variations in metabolism are believed to be their major cause. The aim of the study was to investigate the influence of gender on ITZ PK parameters after administration of oral capsule formulation, following 100 mg single dosing in healthy adult volunteers under fed conditions. The single-center, open-label PK study was performed. PK analyses included PK parameters obtained after a single 100 mg dose administration of itraconazole capsules to 48 females and 66 males. Blood samples were collected at pre-dose and up to 72.0 h after administration (1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 9.0, 12.0, 24.0, 36.0 and 72.0 hrs). The calculated pharmacokinetic parameters, based on the plasma concentrations of itraconazole and hydroxyitraconazole, were Cmax, AUClast, and AUCtot. Plasma concentrations of ITZ and HITZ were determined using a validated liquid chromatographic method with mass spectrometric detection, while pharmacokinetic parameters were estimated using non-compartmental methods. The pharmacokinetic analyses were performed using Kinetica software version 5.0. The mean value of ITZ Cmaxmen was 74.79 ng/ml, and Cmaxwomen was 51.291 ng/ml (independent samples test; $p = 0.005$). Hydroxyitraconazole had a mean value of Cmaxmen 106.37 ng/ml, and the mean value Cmaxwomen was 70.05 ng/ml. Women had, on average, lower AUClast and Cmax than men. AUClastmen for ITZ was 736.02 ng/mL*h and AUClastwomen was 566.62 ng/mL*h, while AUClastmen for HITZ was 1154.80 was ng/mL*h and AUClastwomen for HITZ was 708.12 ng/mL*h (independent samples test; $p = 0.033$). The mean values of ITZ AUCtotmen were 884.73 ng/mL*h and AUCtotwomen was 685.10 ng/mL*h. AUCtotmen for HITZ was 1290.41 ng/mL*h, while AUCtotwomen for HIZT was 788.60 ng/mL*h ($p < 0.001$). The results could point out to lower oral bioavailability of ITZ in women, since values of Cmax, AUClast, and AUCtot of both ITZ and HITZ were significantly lower in women than in men, respectively. The reason may be higher expression and activity of CYP3A4 in women than in men, but there also may be differences in other PK parameters. High variability of both ITZ and HITZ concentrations in both genders confirmed that ITZ is a highly variable drug. Further examinations of its PK are needed to justify strategies for therapeutic drug monitoring in patients treated by this antifungal agent.

Keywords : itraconazole, gender, hydroxyitraconazole, pharmacokinetics
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