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PHARMACOKINETIC INTERACTIONS BETWEEN VORICONAZOLE AND ST JOHN´S WORT AND ITS MODULATION BY GENETIC POLYMORPHISM OF CYP2C19

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Voriconazole (VRC) is a new triazole broad spectrum second generation antifungal drug approved for systemic treatment of severe fungal infections. It is metabolised mainly via the isoenzyme CYP2C19, which is characterised by a genetic polymorphism. According to their ability to express CYP2C19 and consequently according to the actual isoenzyme activity, individuals can be characterised as extensive metabolisers (homozygous and heterozygous EMs) and poor metabolisers (PMs).

The herbal medicine St John's wort (SJW) is used for treatment of mild to moderate depression and mood and anxiety disorders and has become subject to extensive self-medication. The activity of the enzyme system responsible for the biotransformation of a large number of drugs, the cytochrome P450 (CYP450) system, is susceptible to adverse effects of SJW: Constituents of SJW preparations, which may vary in composition for several reasons, *in vivo* can induce the cytochrome isoenzymes CYP3A4, 2C9, and 2C19, but *in vitro* were shown also to inhibit them.

A genetic polymorphism of an isoenzyme, for instance of CYP2C19, can result in a high inter-individual variability in the pharmacokinetics of drugs. It is possible that the extent of induction or inhibition of CYP2C19 resulting from co-medication, for instance with SJW, also varies with the genetic polymorphism. Therefore the present study investigated the effects of acute and prolonged intake of SJW on the kinetics of VRC depending on the CYP2C19 genotype.

Methods: In a controlled, open-label study 16 healthy men were stratified according to their CYP2C19 genotype into homozygous EMs (CYP2C19*1*1), heterozygous EMs (CYP2C19*1*2) and PMs (CYP2C19*2*2). All received a single oral dose of 400 mg VRC on study day 1 for determination of VRC baseline kinetics, on study day 3 for assessment of the acute interaction of VRC with 3 x 300 mg SJW, and on study day 17 after 15 days of SJW intake for quantification of the effects of prolonged intake of SJW on VRC kinetics. Venous blood samples were drawn on study days 1, 3 and 17 for measurement of VRC concentrations in plasma and urine. After solid-phase-extraction VRC was determined by high-performance liquid chromatography with mass-spectrometric detection (LC/MS).

Results: The baseline kinetics of VRC (study day 1) showed the lowest absolute plasma concentrations of VRC in the group of homozygous EMs; heterozygous EMs were higher, but did not completely reach values of PMs. Drug exposure as assessed by $AUC_{0\text{-}10h}$ and $AUC_{0\text{-}inf}$ was lower in homozygous EMs than in heterozygous EMs and PMs ($AUC_{0\text{-}10h}$: 10.2 ± 2.19/ 14.3 ± 4.49/ 18.1; $AUC_{0\text{-}inf}$: 14.3 ± 3.48/ 31.2 ± 20.7/ 37.1 h*μg/ml respectively). As an acute effect of SJW (day 3) an initial increase of drug exposure as represented by $AUC_{0\text{-}10h}$ was found in all three genotypes (absolute values: 11.6 ± 2.85/ 17.7 ± 7.87/ 24.8 h*μg/ml, corresponding to an increase of 14/ 24/ 37 % respectively). There was no significant acute influence of SJW on $AUC_{0\text{-}inf}$ (absolute values: 15.4 ± 4.12/ 32.4 ± 20.5/ 42.8 h*μg/ml respectively).
Prolonged SJW intake (day 17) resulted in a significant decrease of $AUC_{0\text{-}10h}$ (absolute values: 5.08 ± 0.65/ 8.84 ± 4.21/ 11.2 h*μg/ml; relative reduction compared to baseline: -48/ -39/ -38 % respectively) and $AUC_{0\text{-}inf}$ (5.84 ± 0.84/ 12.5 ± 7.61/ 16.2 h*μg/ml; relative reduction:-60/ -60/ -56 % respectively). These results to a large extent also were reflected by C_{max} values and significant differences of the oral VRC clearance.

Discussion and conclusions: In this study, the first co-administered dose of SJW resulted in an acute small increase in VRC exposure compatible with an enhancement of VRC absorption either due to inhibition of intestinal transport proteins or intestinal metabolism. This was followed by an extensive reduction of VRC exposure after prolonged administration of SJW indicating greatly enhanced VRC metabolism due to enzyme induction. The relative reduction of VRC $AUC_{0\text{-}inf}$

and the relative increase in CL/F were similar between the three genetic groups. Therefore, the relative extent of the interaction between SJW and VRC appears to be independent of the CYP2C19 genotype. However, for treatment effectiveness the absolute drug concentrations may be more important. Although a clear correlation between plasma concentrations and efficacy of VRC has not yet been described, halving of VRC exposure is likely to be of clinical relevance because VRC exposure could fall below the levels needed for antifungal activity. As a consequence CYP2C19 wild type individuals may be at the highest risk for potential VRC treatment failure due to SJW. The recent finding of about 7 % prevalence of undeclared exposure to SJW in hospitalised patients underlines the importance of considering this interaction in the clinical setting.