Arwa Hassan

‘‘Dr. SC.hum.‘‘

Evaluation and interpretation of very low voriconazole concentrations in routine therapeutic drug monitoring

Promotionsfach: Klinische Pharmakologie
Doktorvater: Prof.Dr. med. Walter Emil Haefeli

Very low voriconazole concentrations are commonly observed during therapeutic drug monitoring (TDM). Possible mechanisms include inappropriate dose selection, rapid metabolism (due to genetic polymorphisms or enzyme induction), and also nonadherence.

The aim of this study was to (1) develop and apply a method to distinguish between rapid metabolism and probable nonadherence based on quantification of voriconazole metabolites in single blood samples from routine TDM, (2) to assess the effect of CYP2C19 genotype and co-medication on trough concentrations of voriconazole and voriconazole-N-oxide in healthy volunteers receiving controlled dosage of voriconazole, and (3) to assess the relevance of common CYP2C19 polymorphisms in patients/volunteers with very low voriconazole plasma concentrations**.**

In a retrospective study, samples with voriconazole concentrations ≤0.2µg/mL in routine TDM (as quantified by HPLC) were evaluated. Voriconazole and its N-oxide metabolite were quantified in residual blood using a highly sensitive LC/MS/MS method (LOQ=0.03µg/mL). Genetic polymorphisms of CYP2C19 were determined by real-time PCR using the hybridization probe format and the PCR-RFLP format.

A total of 747 routine TDM plasma/blood samples of 335 patients treated with systemic voriconazole were analyzed and in 18.7% of all samples voriconazole concentrations ≤0.2µg/mL were found. In 32 samples (30 patients) with adequate dosage and timing of blood withdrawal, nonadherence was evaluated and was strongly suspected in seven patients because voriconazole-N-oxide concentrations

were below 0.03µg/mL, which was not observed in a reference group of 51 healthy volunteers with controlled drug intake.

In 10 TDM patients, of whom EDTA blood was available, the ultrarapid genotype UM (*CYP2C19*1*17*, *CYP2C19*17*17*) was found in 80% and its prevalence was significantly higher as compared to a reference group (P=0.02).

In conclusion, quantification of the metabolite voriconazole-N-oxide allowed for detection of suspected nonadherence in 25.9% of patients with very low voriconazole concentrations after oral administration. In addition, rapid metabolism due to the *CYP2C19*17* polymorphism appears to play a significant role. Thus, even after administration of standard doses voriconazole concentrations may be below effective values in almost one in three patients and likely reasons are the presence of the UM genotype of CYP2C19 and probably nonadherence. It might therefore be essential to document effective antifungal concentrations at least once in every patient receiving voriconazole therapeutically.