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Safety of Voriconazole in a Patient with *CYP2C9*2*/*CYP2C9*2* Genotype

Voriconazole, a broad-spectrum triazole antifungal agent, is well absorbed, with a high oral bioavailability of 96% (6). Maximal plasma concentrations are observed 1 to 2 h after drug administration. The volume of distribution is estimated to be 4.6 liters/kg, and the plasma protein binding is 58%. A terminal elimination half-life ($t_{1/2}$) of 8 h in CYP2C19 extensive metabolizers (EMs) and a $t_{1/2}$ of 15 h in CYP2C19 poor metabolizers (PMs) were reported (4). Due to a possible saturation of metabolism, voriconazole exhibits nonlinear pharmacokinetics (6). The main metabolite is voriconazole N oxide, which is formed by CYP2C19, CYP3A4, and to a lesser extent CYP2C9 (2).

CYP2C19 is a polymorphically expressed enzyme, with 2.2% of the Caucasian population being PMs (9) with a genetically determined absence of active enzyme. It is known that voriconazole pharmacokinetics are substantially influenced by the CYP2C19 genotype (4, 7). A reduction of voriconazole metabolic clearance in PMs of CYP2C19 is expected; data published so far indicate approximately threefold higher voriconazole area-under-the-concentration-time-curve or maximum-concentration-of-drug-in-serum values in CYP2C19 PMs than in homozygous EMs (4, 7).

Two common allelic variants of CYP2C9 have a markedly reduced catalytic activity (about 20% for CYP2C9*2 and less than 10% for CYP2C9*3) compared with that of the wild-type enzyme (CYP2C9*1) (3). Accordingly, PMs have an impaired metabolism of phenytoin, tolbutamide, glipizide, and warfarin, although PMs are very uncommon (0.2 to 1.0% of Caucasians but essentially 0% of Southeast Asians) (10). So far no in vivo data are available on the influence of CYP2C9 genetic polymorphism on voriconazole pharmacokinetics.

An ongoing study on the pharmacokinetics of voriconazole patients included those who had received their oral loading dose of voriconazole (400 mg) as a regular therapeutic drug treatment during hospitalization and a 12-h (dosing interval) pharmacokinetic profile after the first dose was obtained. We identified one Caucasian patient as a homozygous carrier of the CYP2C9*2 allele, using an established genotyping method using real-time fluorescence PCR on a LightCycler (Roche, Mannheim, Germany) (1). Additionally, the CYP2C19 genotype was also determined, which was homozygous for the wild-type allele (*CYP2C19*1*/*CYP2C19*1*). Plasma voriconazole concentrations were determined in the reference laboratory at Heidelberg University using a fully validated high-pressure liquid chromatography (HPLC) assay as described elsewhere (5, 8). Noncompartmental pharmacokinetic parameters were calculated using WinNonlin 4.1 (Pharsight, Mountain View, CA).

We compared the obtained pharmacokinetic parameters with those from an earlier study with volunteers whose CYP2C9 and CYP2C19 genotypes were characterized (4). In our patient, the apparent oral clearance (Cl/F), area under the concentration-time curve from zero hours to infinity ($AUC_{0-\infty}$), volume of distribution (*Vz*), and $t_{1/2}$ values for voriconazole were not different from those of CYP2C9 EMs who were also CYP2C19 EMs after a single oral dose of 400 mg voriconazole (4) (shown in Table 1).

A conclusion could be that a reduced-metabolizer status of CYP2C9, and therefore low catalytic activity of the enzyme, does not alter the pharmacokinetics of voriconazole. From our data it can be supported that CYP2C9 plays only a minor role in the elimination (metabolism) of voriconazole.

TABLE 1. Pharmacokinetic parameters after administration of 400 mg voriconazole as a single oral dose in a *CYP2C9*2*/*CYP2C9*2* patient (CYP2C19 homozygous EM) compared to results for eight CYP2C9 EM healthy volunteers (CYP2C19 homozygous EM)

Patient or group	$AUC_{0-\infty}$ (μg · h/ml)	*Vz* (liters/kg)	Cl/F (ml/min)	Cl/F (ml/min/kg)	$t_{1/2}$ (h)
*CYP2C9*2*2* subject	16.61	3.51	401	6.68	6.05
CYP2C9 EM subjects[a]	16.52 ± 7.21	4.38 ± 1.73	463 ± 168	6.34 ± 2.47	8.11 ± 1.35

[a] Results for the CYP2C9 EM group are expressed as means ± standard deviations.

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