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The pharmacokinetics of voriconazole

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Voriconazole (Vfend®; Pfizer Global Research and Development, Sandwich, Kent, UK) is a broad-spectrum antifungal triazole that is structurally related to fluconazole. As with all triazole antifungal agents, voriconazole works principally by inhibition of cytochrome P450 14-α-demethylase (P450 14DM) [1, 2]. This enzyme is in the sterol biosynthesis pathway that leads from lanosterol to ergosterol. This causes a build up of 14-α-methyl sterols and is thought to impair the function of membrane-bound enzyme systems by disrupting the close packing of the acyl chains of phospholipids. This results in reduced fungal growth. Compared with fluconazole, voriconazole inhibits P450 14DM to a greater extent [3–5].

Absorption of voriconazole is essentially complete but the elimination of voriconazole is characterized by non-linear pharmacokinetics [6]. Consequently, pharmacokinetic parameters are dependent upon dose. *In vivo* and *in vitro* studies have demonstrated that voriconazole is extensively metabolized, with the major circulating metabolite resulting from N-oxidation [7]. Voriconazole is a substrate for CYP2C9, CYP2C19, and CYP3A4. Therefore, CYP2C19 genotype and/or coadministration of drugs that modulate CYP2C19 or CYP3A4 activities could affect voriconazole plasma concentrations [7]. The purpose of this Supplement is to present the oral and intravenous pharmacokinetics of voriconazole in humans; to demonstrate the effect of food on the pharmacokinetics of the drug during multiple dosing; to show that there are no clinically significant effects of a histamine H_2 receptor antagonist (cimetidine), macrolide antibiotics (erythromycin and azithromycin), a CYP2C19 substrate (omeprazole) and a protease inhibitor (indinavir) on voriconazole pharmacokinetics; to confirm that voriconazole does not alter the steady-state disposition of digoxin; to recommend dose adjustments of voriconazole when given with phenytoin; to warn of the potential for prolonged bleeding times when the drug is given with warfarin.

The papers presented in this Supplement gather together what is known about the pharmacokinetics of voriconazole in man. By documenting the clinically unimportant and important drug–drug interactions of voriconazole in one place the Supplement will assist physicians in the safe and effective use of this drug.

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