Impact of infection status and cyclosporine on voriconazole pharmacokinetics in an experimental model of cerebral scedosporiosis

Titre	Impact of infection status and cyclosporine on voriconazole pharmacokinetics in an experimental model of cerebral scedosporiosis
Type de publication	Article de revue
Auteur	Lelièvre, Bénédicte [1], Briet, Marie [2], Godon, Charlotte [3], Legras, Pierre [4], Riou, Jérémie [5], Vandeputte, Patrick [6], Diquet, Bertrand [7], Bouchara, Jean-Philippe [8]
Editeur	American Society for Pharmacology and Experimental Therapeutics
Type	Article scientifique dans une revue à comité de lecture
Année	2018
Langue	Anglais
Date	Mai 2018
Numéro	2
Pagination	408-412
Volume	365
Titre de la revue	Journal of Pharmacology and Experimental Therapeutics
ISSN	0022-3565
Mots-clés	antifungal drugs [9], Blood-Brain Barrier [10], cerebrospinal fluidinfection [11], Pharmacokinetics [12]
Résumé en anglais	Cerebral Scedosporium infections usually occur in lung transplant recipients as well as in immunocompetent patients in the context of near-drowning. Voriconazole is the first-line treatment. The diffusion of voriconazole through the blood-brain barriers in the context of cerebral infection and cyclosporine administration is crucial and remains a matter of debate. To address this issue, the pharmacokinetics of voriconazole were assessed in the plasma, cerebrospinal fluid (CSF), and brain, in an experimental model of cerebral scedosporiosis in rats receiving or not cyclosporine. A single dose of voriconazole (30 mg/kg, i.v.) was administrated to six groups of rats randomized according to the infection status and the cyclosporine dosing regimen (no cyclosporine, a single dose or three doses 15 mg/kg each). Voriconazole concentrations in plasma, CSF, and brain samples were quantified using UPLC-MS/MS and HPLC-UV methods and documented up to 48 hours after administration. Pharmacokinetic parameters were estimated using a non-compartmental approach. Voriconazole pharmacokinetic profiles were similar for plasma, CSF, and the brain in all groups studied. Voriconazole Cmax and AUC0=>48h were significantly higher in the plasma than in the CSF (CSF/plasma ratio, median [range] = 0.5 [0.39-0.55] for AUC0=>48h and 0.47 [0.35 and 0.75] for Cmax). Cyclosporine administration was significantly associated with an increase in voriconazole exposure in the plasma, CSF, and brain. In the plasma but not in the brain, an interaction between the infection and cyclosporine administration reduced the positive impact of cyclosporine on voriconazole exposure. Together these results emphasize the impact of cyclosporine on the brain voriconazole exposure.

URL de la notice	http://okina.univ-angers.fr/publications/ua16874 [13]
DOI	10.1124/jpet.117.245449 [14]
Lien vers le document	http://jpet.aspetjournals.org/content/early/2018/02/28/jpet.117.245449 [15]
Titre abrégé	J Pharmacol Exp Ther

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