Experimental models of disseminated scedosporiosis with cerebral involvement

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Résumé en anglais	Scedosporium apiospermum is a soil fungus which can cause severe and often fatal cerebral infections in both immunocompetent patients in the event of near drowning and immunosuppressed patients such as lung transplant recipients. Because of the low susceptibility of this fungus to antifungal drugs, and the low permeability of the blood-brain barrier (BBB), therapeutic drug monitoring is necessary to reach an effective tissue concentration with limited side effects. Indeed, diffusion of the drug in the brain is dependent on several parameters, such as the integrity of the BBB and the activity of efflux pumps. To evaluate drug diffusion, two experimental models were developed in immunocompetent and immunosuppressed rats. Inocula were administered via the penile vein and a clinical scale (0-9) was established, based on weight and clinical and neurologic signs evaluated by the tail suspension test. Cerebral involvement was confirmed by magnetic resonance imaging and histologic examination of brain sections after hematoxylin-eosin-safran or silver staining. Voriconazole or posaconazole was given to the rats at doses ranging from 10 to 75 mg/kg/day via i.v. or oral routes, respectively. Whatever the immune status, the effective doses (defined by a doubling of the survival time and the absence of neurologic sequelae) were 30 mg/kg/day for voriconazole and 50 mg/kg/day for posaconazole. Overall, the results demonstrated that these models may constitute valuable tools for the performance of pharmacokinetic and pharmacodynamic studies for pharmacokinetic-pharmacodynamic modeling.
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