Use of triazole antifungal drugs in setting up an animal model of cerebral scedosporiosis

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Auteur	Lelièvre, Bénédicte [1], Legras, Pierre [2], Abbara, Chadi [3], Bouchara, Jean-Philippe [4], Diquet, Bertrand [5]
Mots-clés	cerebral diffusion [6], posaconazole [7], Scedosporiosis [8], voriconazole [9]
Résumé en anglais	*Scedosporium apiospermum* is a soil fungus which may cause severe and often fatal cerebral mycosis in immunocompetent patients in the case of near drowning and in immunosuppressed patients such as lung transplant recipients. Due to the low susceptibility of the fungus to antifungal drugs and to the low permeability of the blood-brain barrier, it might be difficult to reach a therapeutic tissue concentration. Indeed, the diffusion of the drug in the brain depends on several parameters such as integrity of the blood-brain barrier. To evaluate the drug diffusion, two experimental models were developed in immunocompetent and immunosuppressed rats. Inocula of *S.apiospermum* (strain IHEM 3817): 106 spores in immunocompetent and 105 spores in immunosuppressed rats were administered in the penile vein and a scale (graded from 0 to 9) was established based on weight, clinical and neurological signs evaluated by the tail suspension test. Cerebral involvement was confirmed among others by magnetic resonance imaging of brain, which highlighted differences in localisation of fungal abscesses in brain depending on the immune status. As voriconazole or posaconazole exhibit an in vitro activity against the tested strain (E-test), they were given to the rats at doses ranging from 10 to 50 mg/kg/d by i.v. or oral route, respectively (6 rats per dose and controls). The efficacy criteria was defined as time doubling the survival time and absence of neurological sequelae. Whatever the immune status, the effective doses were 30 mg/kg/d for voriconazole and 50 mg/kg/d for posaconazole. The chosen doses of voriconazole and posaconazole were higher than the doses calculated on the basis of data published for mice, rabbits and guinea pigs.This might be explained by the chosen animal species and criteria of efficacy. So, this infectious model appears to be a valuable tool to evaluate the cerebral diffusion of two antifungal drugs in rats. The data enable to perform pharmacokinetic (PK) and pharmacodynamic (PD) studies for PK-PD modelling.
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