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EVALUATION OF NANOENCAPSULATED VORICONAZOLE PHARMACOKINETICS AND BRAIN PENETRATION BY MICRODIALYSIS

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Introduction: The past two decades were marked by a dramatic growth in the frequency of fungal infections caused by species of *Candida*[1], mainly due to spread of AIDS and neoplasic diseases. Among the fungi that can compromise the central nervous system (CNS) after systemic infection, *Candida* species are the most prevalent[2] and the infection manifests in the form of meningitis[3]. Aiming to improve the treatment of systemic candidiasis, new antifungal agents have been developed, such as voriconazole (VRC), which has an overall effect on inhibition of fungal cell replication. VRC has a non-linear and variable pharmacokinetics (PK) and a moderate CNS penetration (CSF/plasma ratio of 0.46)[4]. The use of nanotechnology could increase VRC central penetration as well as reduce the drug PK variability. It has been reported that nanocapsules coated with polyethylene glycol render the particle stealth to the reticuloendothelial system, and that nanoparticles prepared with polysorbate derivatives have the ability to bind to the apoprotein E and to the low-density lipoprotein (LDL) receptors present at the blood-brain-barrier, increasing drugs brain penetration[5]. CNS drug penetration can be assessed by microdialysis, a sampling technique that allows continuous determination of free drug levels in awaked animals[6]. In this context, the development of stealth nanoparticles target to CNS penetration could improve VRC pharmacokinetics to treat fungal meningitis.
Objectives: To prepare, characterize and evaluate the CNS penetration of VRC loaded nanocapsules viewing to increase the drug efficacy to treat fungal meningitis.
Materials and Methods: VRC nanocapsules will be prepared by interfacial deposition of preformed polymer[7] and will be characterized according to pH, particle size, zeta potential, drug content and entrapment. Nanocapsules composition will be investigated viewing to increase CNS delivery of the antifungal. The stability of the formulation will be investigated up to 30 days with sampling every 7 days. Plasma PK will be investigated after 5 mg/kg i.v. dosing of free and nanoencapsulated drug. CNS penetration will be assessed by microdialysis in awake *Wistar* rats after same dose and via of dosing (n = 6/group). The microdialysis probe recovery and the conditions of the microdialysis experiments (sampling time and perfusion flow rate) will be determined *in vitro* and *in vivo* using dialysis and retrodialysis techniques, previous to the animal experiments. The plasma and CNS PK parameters obtained after VRC free and nanoencapsulated administration will be compared by Student "t" test ($\alpha = 0.05$). The project will be submitted to the Ethics in Animal Use Committee of the University for approval.
Conclusions: As a result of this investigation one expects to obtain a VRC nanoparticle formulation which promotes the drug CNS penetration and reduces its PK variability.

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