FTOX019

Pharmacokinetic of a new chemical delivery system candidate designed for tuberculous meningitis treatment in rats

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Introduction: Tuberculous meningitis (TBM) is the most severe form of *Mycobacterium tuberculosis* infection in humans. The therapeutic scheme used for TBM is ethambutol (ETB) always associated with other antituberculous drugs. Despite being useful for its mechanism of action, ETB does not cross the blood-brain barrier satisfactorily, which certainly reduces its effectiveness in the treatment, leading to side effects and bacterial resistance. That is why it was prepared an ethambutol prodrug (DEREMB) by a chemical delivery system (CDS) aiming at improving its kinetic disposition, leading to an increase in the drug availability in the central nervous system (CNS), minimizing side effects with increased efficacy. The DEREMB pharmacokinetics is indispensable to determine its clinical potential for the treatment of TBM. **Objective:** to study the DEREMB kinetic disposition and ETB release in the systemic blood stream of wistar male rats treated with a single intravenous (iv) dose. **Methods:** it was administered in 20 wistar male rats (weigh~200g), in fastened state of 12 hours a single 25 mg/kg iv dose of DEREMB. After the administration it was collected by the tail and decapitation serial samples of 500 µL of blood at the intervals 5, 10, 15, 20, 30, 45, 60, 90 e 120 minutes to plot the plasmatic concentration curve *versus* time. The blood samples were centrifuged and the levels of the prodrug and of released ETB in plasma were determined by high-performance liquid chromatography analysis. The phamacokinetic parameters were calculated based on plasmatic concentration curves *versus* time and the maximum drug concentration (C_{max}) and time (Tmax) were obtained directly from individual concentration time. A Kruskal-Wallis test was used to determine the statistical significance of the differences unit, with a significance level set at 5% ($P<0.05$) for the comparison between the five replicate the plasmatic concentration curves *versus* time, using the GraphPad Instat®. The results were shown by means values and confidence interval of 95%. **Results:** the DEREMB pharmacokinetic parameters were: C_{max} (ug/mL)= 10,4 (6,7–14,2); AUC^{0-t}(ug/mL.min)= 252,7 (200,8–292,9); $AUC^{0-\infty}$(ug/mL.min)= 294,3 (256,7–331,9); Vd (L/kg)= 4,3 (3,1–4,9); CI_T (mL/min/kg)= 86,4 (72,3-99,9); t ½ (min) =34,1 (28,5–39,6); β (min^{-1})= 0,021 (0,0180–0,025). ETB detectable levels from DEREMB were only possible to be determined in the initial 30 minutes with average values of 0,75 ug/mL; 1,22 ug/mL and 1,5 ug/mL in the intervals 5, 15 and 30 minutes after the administration respectively. **Conclusion:** the results suggest that iv DEREMB can be a promising candidate for the treatment of TBM once it does not release significantly ETB in the systemic circulation and has a lipophilic pharmacokinetic profile which makes it possible to penetrate the CNS.

Keywords: tuberculosis, central nervous system, latentiation, pharmacokinetics.

Financial support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).