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Preclinical pharmacokinetics of new thiazolidinedione LYSO-7

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Thiazolidinediones (TZDs) are PPAR-γ (Peroxisome Proliferator Activated Receptors) activating drugs currently used to treat diabetes mellitus and are among the marketed representatives of which only pioglitazone remains available. Besides glycemic control, the activation of PPAR-γ regulates anti-inflammatory responses which led the Researchers of the Laboratory of Drug Synthesis and Planning from the Federal University of Pernambuco to synthesize the LYSO-7, a thiazolidine-2,4-dione planned to act not only on PPAR-γ but also as a COX-2 inhibitor and showed promising anti-inflammatory activity. Drug candidates often fail to progress through clinical phases due to pharmacokinetic incompatibilities. In this work, we aimed to assess the intravenous and oral pharmacokinetics of LYSO-7 and also determine a key physicochemical property, i.e., logP in order to improve pharmacokinetic interpretation. Pharmacokinetic experiment was carried out in Wistar rats which received 3.6 mg/kg and 18 mg/kg of LYSO-7 intravenously or orally (n=5 each group), respectively. LogP was assessed by chromatographic method. All quantification analyses were performed by previously validated UPLC-UV methods. The LYSO-7 showed logP around 6.5. Pharmacokinetic parameters determined after IV administration were: elimination half-life (t1/2) of 2.31 (±0.63) hours, clearance (Cl) 33.18 (±13.25) mL/min/kg and volume of distribution (Vd) of 6648.71 (±2027.15) mL/kg. The LYSO-7 could not be detected in plasma of animals after oral administration (LOQ=78.125 ng/mL). The limited oral bioavailability may be explained by LYSO-7's high logP. This work provides punctual information about the IV pharmacokinetic parameters of this molecule as well as its flaws which can be further addressed in order to improve its oral bioavailability.

Biography

Padilha E C is has a master's degree in Toxicology from Sao Paulo State University. He is currently a PhD student in Pharmacology with emphasis in Pharmacokinetics. He is a researcher in preclinical pharmacokinetics and toxicology of new molecules and formulations and has published 6 papers in reputed journal of pharmacokinetics, toxicology, drug discovery, biopharmaceutics and chromatography.

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