SBFTE

58 Anos

1966 - 2024

56th Brazilian Congress of Pharmacology and Experimental Therapeutics

II National Pain Symposium

Abstracts

October 07-10, 2024

Balneário Camboriú/SC

11.017 **Development of a PBPK Model to Predict Drug-Drug Interactions (DDI) Following Oral Administration of Ayahuasca and Synthetic Medications.** Ribeiro GSG, Martins FS, Marcourakis T USP

Introduction: Ayahuasca is a psychedelic beverage traditionally used in rituals and therapies by indigenous groups in the Amazon. It consists of N,N-dimethyltryptamine (DMT) and B-carbolines such as harmine (HRM), which has the ability to reversibly inhibit monoamine oxidase A (MAO-A), allowing DMT to be absorbed and distributed to the central nervous system (Riba, J. *Drug Test. Anal*., v.7, p.401, 2015. Medications like fluoxetine (FL), prescribed for the treatment of depression, are biotransformed into their active metabolite norfluoxetine (NFL) predominantly by the CYP2D6 and CYP2C9 enzymes (Mandrioli, R. *Curr. Drug Metab*., v.7, p.127, 2006). Theoretically, the concomitant use of FL with ayahuasca could lead to serotonin syndrome, as FL is a strong inhibitor of CYP2D6, an enzyme also involved in the metabolism of HRM and DMT. This study aimed to develop a PBPK model to predict the interaction between HRM and DMT, as well as interactions between HRM, DMT, and FL. **Methods:** The models were constructed using PK-Sim V11 software. Information based on *in vitro* parameters and clinical data observed in volunteers after oral administration of ayahuasca and FL was used. The distribution volumes of DMT and HRM were predicted using the Rodgers and Rowland method, and FL using the Schmitt method. The models incorporated enzyme kinetic data for the enzymes involved in the metabolism of HRM (CYP2D6, CYP2C9, CYP2C19, CYP1A1, and CYP1A2), DMT (MAO-A, CYP2D6, and CYP2C19), which are presumed to be the main contributors to the metabolism of FL into NFL. The PBPK models were validated with PK data observed in 2 clinical studies on ayahuasca (Callaway, J. *J. Ethnopharmacol*., v.65, p.243, 1999; Yritia, M. *J. Chromatogr*. *B*, v.779, p.271, 2002) and 17 on FL, with doses of 20, and 40 mg (Al-Tamimi, D. *Iraqi J. Pharm. Sci*., v.31, p.153, 2022; Green, R. *Chromatogr*, v.55, p.133, 2002), by visually inspecting plasma concentration versus time graphs and comparing observed and predicted PK parameters. **Results:** The mean fold error (MFE) is considered satisfactory when the predicted parameters are within twice the corresponding observed value (Guo, H. *J. Pharm. Sci.*, v.102, p.2819, 2013). Thus, the model validation was satisfactory. The area under the plasma concentration versus time curve (AUC) for DMT ranged from 0.89 to 1 and the maximum blood concentration (Cmax) ranged from 0.85 to 1.33 when dividing predicted data by captured data. The predicted/observed MFE results for FL and NFL were considered satisfactory, i.e., between 0.5 and 2. Fluoxetine-HRM interaction scenarios are being simulated to analyze the extent of the drug interaction between HRM and DMT after simultaneous administration with FL and thus determine the risk of serotonin syndrome. **Conclusions**: The PBPK models accurately predicted the kinetic disposition of DMT, HRM, FL, and NFL, with AUC and Cmax results within acceptable mean fold error (MFE) limits. Validation confirmed that the models will be able to effectively simulate interactions between DMT, HRM, and FL. These findings suggest that the use of FL with ayahuasca will be able to increase the risk of serotonin syndrome due to CYP2D6 inhibition. Thus, the PBPK models are valuable for predicting drug interactions and understanding the ADME processes of these compounds, with important implications for the safety and efficacy of treatments involving ayahuasca and FL. This study is funded by the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Finance Code 001.