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Evaluation of a Potential Metabolism-Mediated Drug-Drug Interaction between Carvedilol and Fluvoxamine in Rats

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Abstract : Background information: The objective of this study was to investigate the effect of multiple-dose fluvoxamine on the pharmacokinetic profile of single-dose carvedilol in rats, in order to evaluate this possible drug-drug pharmacokinetic interaction. Methods: A preclinical study, in 28 white male Wistar rats, was conducted. Each rat was cannulated on the femoral vein, prior to being connected to BASi Culex ABC®. Carvedilol was orally administrated in rats (3.57 mg/kg body mass (b.m.)) in the absence of fluvoxamine or after a pre-treatment with multiple oral doses of fluvoxamine (14.28 mg/kg b.m.). The plasma concentrations of carvedilol were estimated by high performance liquid chromatography-tandem mass spectrometry. The pharmacokinetic parameters of carvedilol were analyzed by non-compartmental method. Results: After carvediol co-administration with fluvoxamine, an approximately 2-fold increase in the exposure of carvedilol was observed, considering the significantly elevated value of the total area under the concentration versus time curve ($AUC_{0-\infty}$). Moreover, an increase by approximately 145% of the peak plasma concentration was found, as well as an augmentation by approximately 230% of the half life time of carvedilol was observed. Conclusion: Fluvoxamine co-administration led to a significant alteration of carvedilol's pharmacokinetic profile in rats, these effects could be explained by the existence of a drug-drug interaction mediated by CYP2D6 inhibition. Acknowledgement: This work was supported by CNCS Romania – project PNII-RU-TE-2014-4-0242.

Keywords : carvedilol, fluvoxamine, drug-drug pharmacokinetic interaction, rats
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