sciendo

DOI: 10.2478/auoc-2024-0018

Ovidius University Annals of Chemistry Volume 35, Number 2, pp. 137 - 145, 2024

Kinetic modelling of olanzapine interactions with ciprofloxacin and norfloxacin in adult male Wistar rats: unraveling the mechanism of drug-drug interaction

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Abstract. This study aimed to investigate the kinetic modelling of drug-drug interactions between olanzapine and the antibiotics fluoroquinolone, ciprofloxacin and norfloxacin, using a three-step compartmental modelling approach. Olanzapine is metabolized mainly by CYP1A2, which is inhibited by both antibiotics, affecting its disposition in the body. The proposed models evaluated the absorption, distribution, metabolism, and excretion of olanzapine and its main metabolite, N-desmethyl olanzapine, given alone and during co-administration with antibiotics. Ciprofloxacin completely inhibited presystemic metabolism, resulting in a 2.2-fold increase in olanzapine exposure, whereas norfloxacin reduced but did not eliminate this metabolic pathway, resulting in a 3.2-fold increase in olanzapine exposure. Both antibiotics also reduced the clearance of N-desmethyl olanzapine, leading to increased concentrations of the metabolite. These results provide insight into the kinetic interactions between olanzapine and fluoroquinolones, helping to optimize dosing strategies when co-administration is nedeed.

***Keywords*:** kinetic modelling; drug-drug interaction; preclinical study; olanzapine; fluoroquinolone antibiotics.

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