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

Ana-Elena CHIRALI,[1] Iulia Maria CIOCOTIȘAN,[1] Ana-Maria VLASE,[2] Dana Maria MUNTEAN[*],[1] and Laurian VLASE[1]

[1]*Department of Pharmaceutical Technology and Biopharmacy, Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8th Victor Babeș Street, 400347 Cluj-Napoca, Romania*
[2]*Department of Pharmaceutical Botany, Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8th Victor Babeș Street, 400347 Cluj-Napoca, Romania*

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.

1. Introduction

Olanzapine, a second-generation antipsychotic, is widely prescribed for the management of schizophrenia and bipolar disorder [1-5]. Metabolized primarily via the CYP1A2 enzyme pathway, olanzapine produces two major metabolites: N-desmethyl olanzapine, which is pharmacologically active, and 7-hydroxy olanzapine, considered an inactive metabolite [6,7]. The active nature of N-desmethyl olanzapine raises the possibility of pharmacokinetic interactions at metabolic level when olanzapine is co-administered with other drugs that influence the CYP1A2 activity [8-10].

Ciprofloxacin and norfloxacin are fluoroquinolone antibiotics known to inhibit the activity of the cytochrome P450 enzyme CYP1A2, which is critical for the metabolism of several drugs, including olanzapine [11-13]. Inhibition of CYP1A2 can result in increased plasma concentrations of olanzapine, potentially prolonging its therapeutic effects and raising the risk of adverse reactions [14]. Understanding the kinetic interactions between olanzapine and these antibiotics is crucial for optimizing therapeutic strategies and avoiding potential complications in clinical settings.

Pharmacokinetics, through the quantitative study of drug absorption, distribution, metabolism, and elimination (ADME) over time, offers valuable insights into the relationship between the administered dose and its pharmacological effects. By understanding these processes, pharmacokinetics helps to predict drug behavior in the body and optimize therapeutic outcomes [15].

The compartmental modelling approach in pharmacokinetics represents the body as a system of interconnected compartments, each with distinct properties and specific affinities for the drug or its metabolites [16]. After administration, the drug is absorbed from its site of administration into the central compartment, from which it can be distributed to peripheral compartment(s) in a bidirectional manner. Ultimately, the drug is irreversibly eliminated from the body through metabolism and/or excretion [17]. Each of these ADME processes is characterized by transfer rate constants. In cases of linear (first order) kinetics, these constants are proportional to the amount of drug available for transfer [18].

Pharmacokinetic analysis typically employs two methods: non-compartmental and compartmental approaches. The non-compartmental approach is useful for assessing drug exposure without explicitly modelling the underlying kinetic mechanisms that govern drug disposition in the body [19]. This method is commonly applied in clinical scenarios where dosage adjustments are required due to individual physiological or pathological factors. On the other hand, the compartmental approach offers a more detailed understanding of a drug's disposition, describing the kinetics of the parent compound and its metabolite(s) based on the ADME processes [20, 21]. This modelling

[*] Corresponding author. *E-mail address:* dana.muntean@umfcluj.ro (Dana Maria Muntean)

technique provides crucial insights into how kinetic parameters may be altered, especially in the presence of drug-drug interactions, offering a more precise characterization of drug behavior within the body [19, 20].

The aim of this study was to create and to use a pharmacokinetic model that can accurately describe the kinetic processes involved in ADME processes of olanzapine (OLZ) and its main metabolite, N-desmethyl olanzapine (OLZ-M), after oral administration of a single dose of OLZ with ciprofloxacin and norfloxacin, after repeated doses administration of these two enzymatic inhibitors, by comparing predicted values with actual experimental data obtained in a preclinical study performed on adult male Wistar rats.

2. Experimental

2.1. Chemical and reagents

Olanzapine intended for animal administration was purchased from Actavis/Teva (Parsippany-Troy Hills, NJ, USA), while the olanzapine and N-desmethyl olanzapine analytical standards for LC-MS analysis were obtained from Sigma-Aldrich/Merck Group (Darmstadt, Germany). Ciprofloxacin (Ciprinol®) and norfloxacin (Nolicin®) were provided by KRKA (Novo Mesto, Slovenia). For animal anesthesia, ketamine (Vetased®) was bought from Farmavet (Romania), xylazine (XylazinBio®) from Bioveta (Czech Republic), and diazepam from Terapia (Cluj-Napoca, Romania). Heparin sodium 5000 IU/mL was purchased from Belmedpreparaty (Minsk, Belarus). Both formic acid and methanol (analytical grade) were acquired from Merck (Darmstadt, Germany), and carboxymethyl cellulose from Sigma-Aldrich (Taufkirchen, Germany).

2.2. Study design

This study was approved by the local ethics committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, as well as the National Sanitary Veterinary and Food Safety Authority, in accordance with Law 43/2014 on the protection of animals used for scientific purposes, as published in Romania's "Monitorul Oficial." This law implements Directive 2010/63/EU of the European Parliament and the Council, dated 22 September 2010, on the protection of animals used for scientific purposes, as published in the Official Journal of the European Union. The ethics committee approval reference is No. 313, dated 20 May 2022. The study was conducted at the Centre for Experimental Medicine and Practical Skills in Cluj-Napoca, Romania, and followed an open-label, three-period sequential design.

The study consisted of three periods: one reference period and two test periods, each involving 14 rats weighing between 235-410 g. During the reference period, the rats were given a single oral dose of 12 mg/kg body weight (b.w.) of olanzapine. In the first test period, the rats received an oral pretreatment of 15 mg ciprofloxacin for 5 days, followed by a combination of ciprofloxacin and olanzapine (12 mg/kg b.w.) on the 6th day. The second test period followed the same procedure, except ciprofloxacin was replaced by 30 mg of norfloxacin. Both olanzapine and norfloxacin were suspended in 1% carboxymethylcellulose and vortexed for 5 minutes before each administration, with oral doses given via gavage.

2.3. Sample preparation

To collect venous blood samples for plasma analysis of olanzapine (OLZ) and its metabolite (OLZ-M), each rat underwent surgery on the left femoral vein. Prior to surgery, rats were anesthetized with a combination of ketamine, xylazine, and diazepam (1:1:1) administered via intramuscular injection. The cannulation of the left femoral vein was performed to connect the rats to the BASi Culex ABC® automated blood collection system (BASi Research Products, West Lafayette, IN, USA), allowing direct, consistent blood sampling without the need for human intervention, thus minimizing variability. The cannulation procedure was performed one day before olanzapine administration.

Blood samples (200 µL) were collected at several time points: 5, 10, 15, 30, and 45 minutes, and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours post-olanzapine administration, and stored at -20°C for further analysis. For sample preparation, 180 µL of methanol was added to 60 µL of blood, vortexed for 10 seconds, and centrifuged at 10,000 rpm for 8 minutes. The supernatant was transferred to autosampler vials and injected into the HPLC-MS system for quantification.

2.4. HPLC-MS analysis

Olanzapine and its active metabolite concentrations in rat plasma samples were simultaneously quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS) method. The HPLC system consisted of an Agilent 1100 series (equipped with a binary pump, autosampler, and thermostat, all from Agilent Technologies, Santa Clara, CA, USA), coupled to an Agilent Ion Trap 1100 SL mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Chromatographic separation was performed using a Zorbax SB-C18 column (100 x 3.0 mm, 3.5 µm) (Agilent Technologies, Santa Clara, CA, USA). The mobile phase was a mixture of 0.3% formic acid in water (v/v) and methanol at an 89:11 ratio, with isocratic elution for 3.2 minutes. The injection volume was 4 µL, with a flow rate of 1 mL/min, and the column temperature was maintained at 45 °C. Mass spectrometric detection was carried out in multiple reaction monitoring (MRM) mode with an electrospray ionization source in positive ion mode. The mass transitions monitored were *m/z* 256 from *m/z* 313 for olanzapine, and *m/z* (230, 239) from m/z *299* for its metabolite. Calibration curves for both olanzapine and its metabolite were linear over a concentration range of 6 to 900 ng/mL, with a correlation coefficient greater than 0.992. At quantification limit, the precision and accuracy were 9.28% and -6.8% for intra-day analysis (n = 5), and 12.8% and 11.8% for inter-day analysis, respectively.

Kinetic and statistical analysis of data

A three-tiered modelling approach was implemented to manage the large number of variables, which would

otherwise lead to an overwhelming number of possible model combinations, making computation impractical.

In the first step, the primary focus was on establishing an optimal model for the parent compound, excluding both the metabolite and any potential kinetic interactions. This initial model was designed to isolate and characterize the kinetic properties of olanzapine, laying the groundwork for incorporating more complex variables in the subsequent steps. The characteristics of the models evaluated for the kinetics of OLZ are summarized in Table 1.

Table 1. Kinetic models of olanzapine used in compartmental analysis

Kinetic model	Absorption kinetics	Lag time	Number of compartments
M1	1st order	No	1
M2	1st order	Yes	1
M3	1st order	No	2
M4	1st order	Yes	2

Additionally, the three-tier modelling scheme used to further investigate the kinetics of OLZ's primary metabolite (N-desmethyl olanzapine – OLZ-M), as well as the combined kinetics of OLZ and OLZ-M in the presence of drug-drug interactions with ciprofloxacin and norfloxacin, is illustrated in Figure 1.

The Akaike Information Criterion (AIC) was selected as the model discrimination method and selection criterion for identifying the kinetic model that best fitted the experimental data [22]. The AIC value considers the number of data observations, the goodness of fit, the complexity of the model, and is calculated using the following formula: AIC = m * ln (WSSR) + 2 * p, where *m* represents the number of observations, WSSR is the weighted sum of squares of residuals, and *p* is the number of structural parameters in the model [15-18, 23]. The quality of the fit is reflected by the WSSR value, considering that the smaller its value, the better the fit of the data with the model, and the lower the AIC value [23]. The models with a higher number of parameters (*p* value) are disadvantaged, as the AIC increases proportionally with this term. Therefore, when comparing two models with the same quality of fit (i.e., identical WSSR), the model with fewer parameters will have a lower AIC value and be selected as the better model. Overall, a lower AIC indicates a better fit, considering the same data and error assumptions are used across models [15-18].

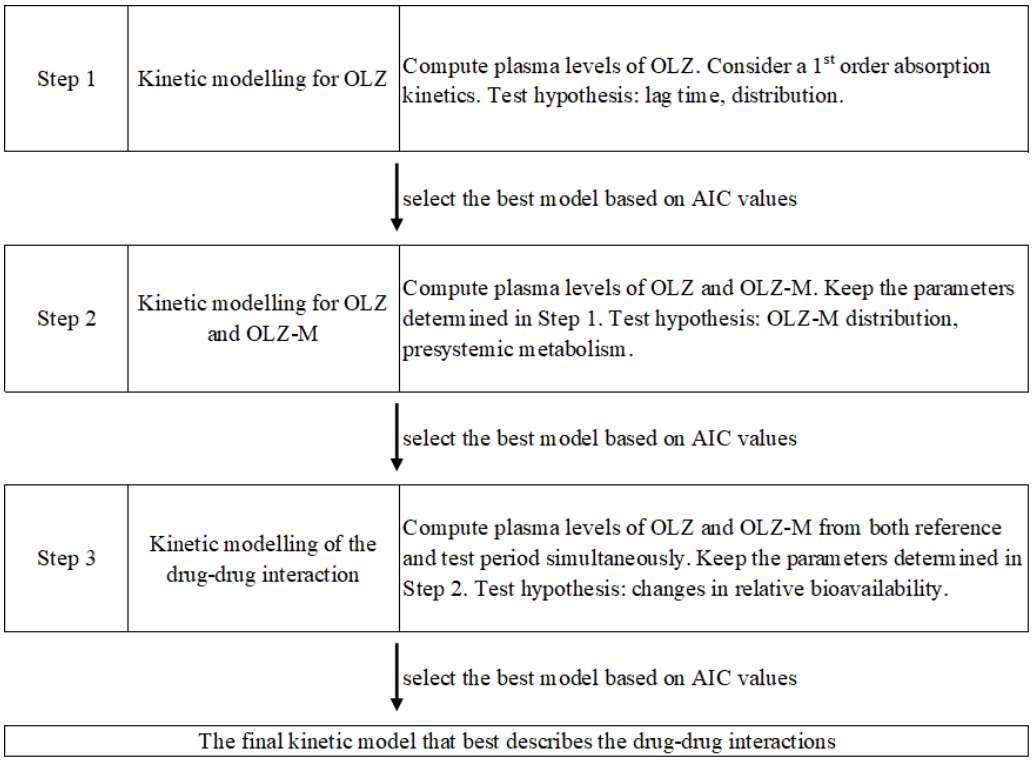

Figure 1. The three-tier scheme employed for kinetic modelling of olanzapine (OLZ), its main metabolite (N-desmethyl olanzapine – OLZ-M), and the drug-drug interactions between olanzapine and fluoroquinolone antibiotics (ciprofloxacin and norfloxacin)

3. Results and discussion

Figure 2 illustrates the mean plasma concentration profiles of OLZ and its main metabolite OLZ-M over time. These graphics offer a clear depiction of the extent of drug exposure following the co-administration of OLZ with the fluoroquinolone antibiotics, providing valuable insights into the pharmacokinetic interactions.

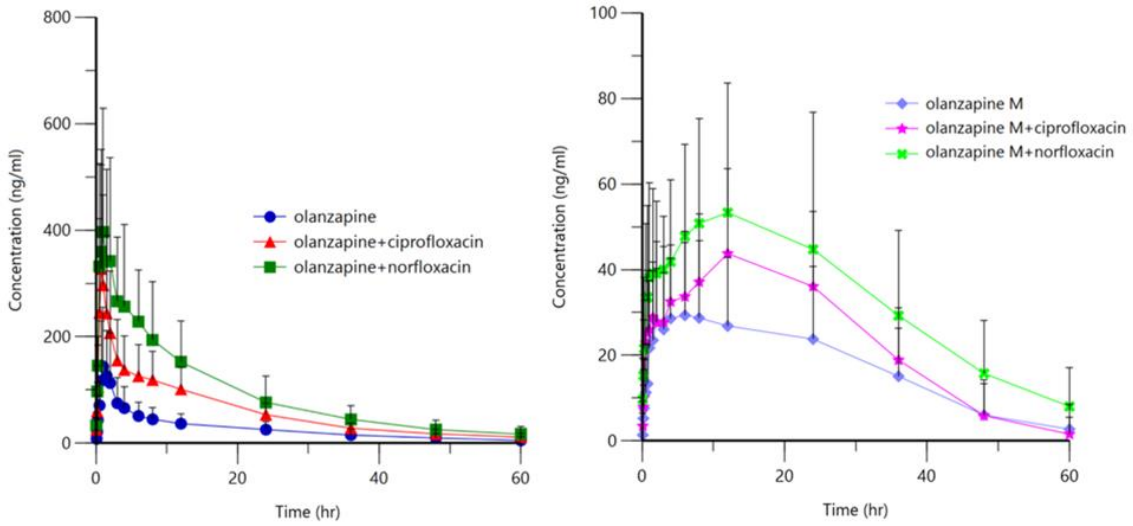

Figure 2. Mean plasma concentrations versus time profile of **olanzapine** administered as a single dose (12 mg/kg b.w., *p.o.*) as monotherapy (○), after previous 6-day treatment with ciprofloxacin (15 mg) (Δ) and after previous 6-day treatment with norfloxacin (30 mg (□) (data are presented as mean values + standard deviation) (left); Mean plasma concentrations versus time profile of **N-desmethyl olanzapine** corresponding to the previously mentioned administrations (right).

Following the first step of fitting the data with different models and evaluating the AIC values, model 4 (M4) was identified as the optimal choice for further analysis. Consequently, M4 was selected as the starting point for subsequent modelling steps. This model assumes 1st order absorption kinetics with lag time and bi-compartmental distribution of the parent drug (OLZ). The AIC results that support this selection are provided in Figure 3.

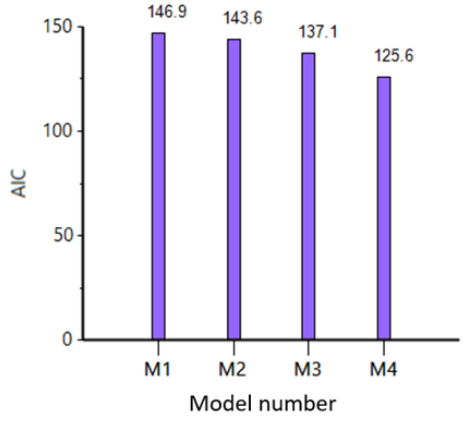

Figure 3. AIC values of M1-4 kinetic models describing the ADME processes of olanzapine following oral administration

In the second step of the analysis, five additional models were developed based on the previously selected M4, with their specific variations detailed in Table 2. Model M44b was derived from M44, based on the observation that elimination from the central compartment was negligible, with a rate constant below 0.0001 hr^{-1}. After evaluation using the AIC values (illustrated in Figure 4), M44b was identified as the most representative model.

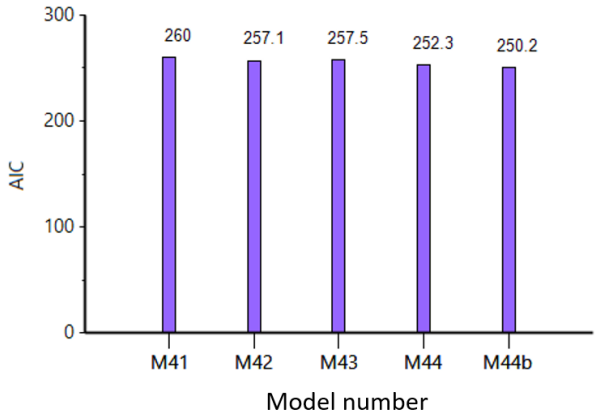

Figure 4. AIC results for five models describing the kinetics of N-desmethyl olanzapine after oral administration of olanzapine

Table 2. Kinetic models of olanzapine (OLZ) and N-desmethyl olanzapine (OLZ-M) used in compartmental analysis

Kinetic model	Absorption kinetics	Lag Time	Number of compartments for OLZ-M	Presystemic metabolism	Systemic metabolism	Other elimination routes from central compartment for OLZ
M41	1st order	Yes	1	No	Yes	Yes
M42	1st order	Yes	1	Yes	Yes	Yes
M43	1st order	Yes	2	No	Yes	Yes
M44	1st order	Yes	2	Yes	Yes	Yes
M44b	1st order	Yes	2	Yes	Yes	No

The selected model, M44b, describes 1st order absorption kinetics with a lag time and bi-compartmental distribution for OLZ, consistent with the model M4 chosen in the first data modelling step. Additionally, it indicates that OLZ is eliminated exclusively via the metabolic pathway, with no alternative routes. The model also indicates the kinetics of N-desmethyl olanzapine (OLZ-M), which results

from both systemic metabolism (during the first hepatic pass) and presystemic metabolism (during intestinal absorption, following oral administration). Similar to the parent compound, OLZ-M is characterized by bi-compartmental distribution.

In the third step of the analysis, to explore the kinetic interactions of olanzapine (OLZ) with ciprofloxacin and norfloxacin, and their effects on the disposition of OLZ and its metabolite OLZ-M, two parallel analyses were conducted using modified models: M44b1 and M44b2.

Table 3. Kinetic models of olanzapine (OLZ) and N-desmethyl olanzapine (OLZ-M) used in compartmental analysis of the interactions with both fluoroquinolone antibiotics

Kinetic model	Number of compartments for OLZ and OLZ-M	Presystemic metabolism	Other elimination routes for OLZ	Relative bioavailability
M44b1	2	Yes	No	Same
M44b2	2	Yes	No	Different

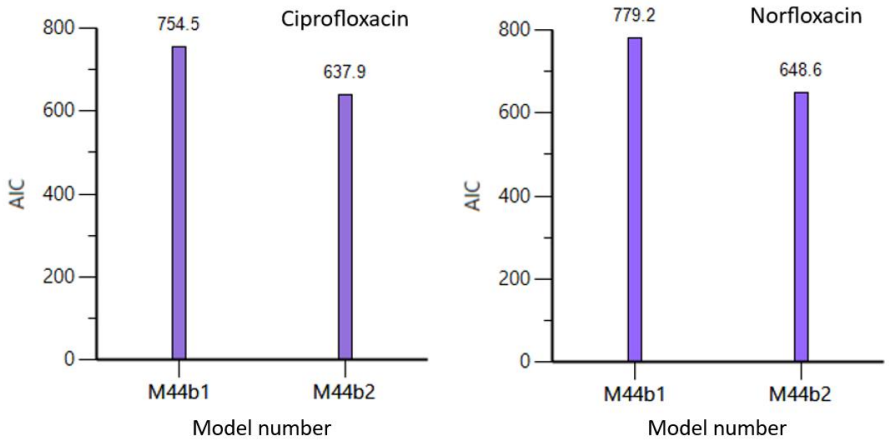

Figure 5. AIC results for the compartmental kinetic modelling of drug-drug interactions between olanzapine and ciprofloxacin and norfloxacin

Based on the AIC values (shown in Figure 5), M44b2 provided the best fit for the experimental data concerning both evaluated drug interactions. This model incorporates the following assumptions: 1st order absorption kinetics with a lag time for OLZ, bi-compartmental distribution for both OLZ and OLZ-M, elimination of OLZ exclusively via metabolism to OLZ-M, and presystemic and systemic metabolism as pathways for OLZ-M formation. Additionally, the model considers the change in the amount of OLZ reaching the systemic circulation between study periods (reference vs. test periods), indicating a drug-drug interaction with relative bioavailability different from 100% (the amount of OLZ in the systemic circulation is altered).

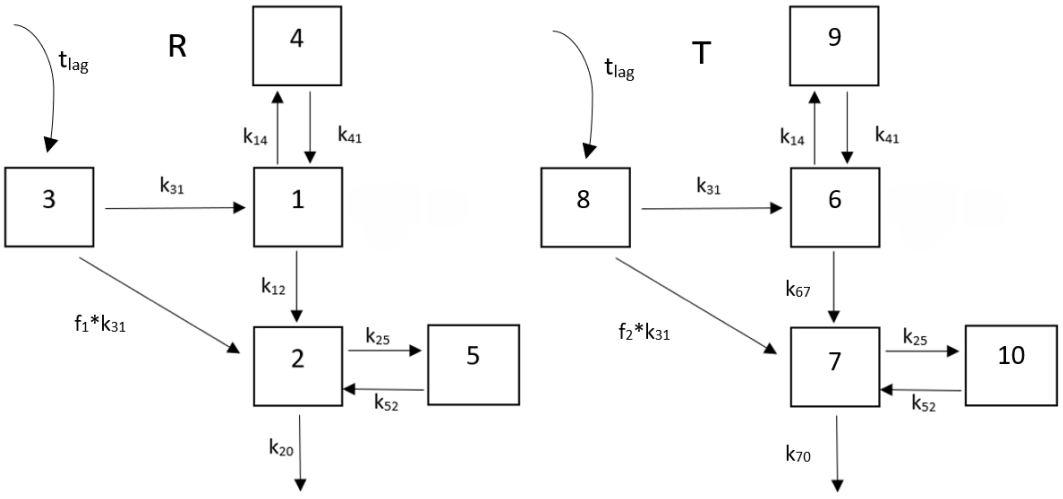

Figure 6. Schematic representation of kinetic processes from model M44b2. *Left*: 3 is the extravascular absorption site; 1, 2 are the central compartments of olanzapine and N-desmethyl olanzapine; 4, 5 are their corresponding peripheral distribution compartments. *Right*: 8 is the extravascular absorption site; 6, 7 are the central compartments of olanzapine and N-desmethyl olanzapine for the reference period; 9, 10 are their corresponding peripheral distribution compartments for the test periods; t_{lag} is the latency time for absorption; k_{31} is the absorption rate constant of olanzapine; f_1 and f_2 are the fraction of olanzapine converted into metabolite during absorption (presystemic metabolism) for reference and test periods, respectively; k_{14}, k_{41}, are the distribution rate constants for the reference period and k_{25}, k_{52} the distribution rate constants for the test periods; k_{12} is the systemic metabolisation rate constant of olanzapine to metabolite; k_{20} and k_{70} are the elimination rate constants for olanzapine (non-metabolic) and N-desmethyl olanzapine, for the reference period and the test periods, respectively.

Figure 6 illustrates the kinetic processes described by the M44b2 model, detailing the flow of OLZ and OLZ-M between compartments and the kinetic processes that link these compartments, along with their corresponding rate constants.

In this kinetic modeling, compartmental models were employed to describe the movement of OLZ and OLZ-M through various compartments (central and peripheral) over time [15, 16]. The partial derivative equations for each compartment represent the rate of change in drug concentration or amount, governed by key kinetic processes such as absorption, distribution, metabolism, and excretion (ADME). These equations are derived from the law of mass balance, which states that the rate of change in a compartment is the net result of drug entering and leaving that compartment [17, 18].

The use of rate constants in these equations forms the mathematical framework for understanding the time-dependent kinetics of OLZ and OLZ-M across different compartments. Specifically, the equations for the kinetic model M44b2, which describe OLZ and OLZ-M kinetics during both the reference (without inhibitors) and test periods (with ciprofloxacin or norfloxacin as CYP1A2 inhibitors), were written based on the general mass balance equation:

$$\frac{\partial Ai}{\partial t} = (Rate\ of\ drug\ entering\ the\ compartment) - (Rate\ of\ drug\ leaving\ the\ compartment)$$

where *Ai* represents the amount of drug in compartment *i*, and *t* is time. These equations are provided in Figure 7.

$$M44b2 \begin{cases} \frac{\partial QO_{c1}}{\partial t} = k_{31} * QO_{abs3} * (1 - f_1) - k_{12} * QO_{c1} - k_{14} * QO_{c1} + k_{41} * QC_{p4} \\ \frac{\partial QN_{c2}}{\partial t} = k_{12} * QO_{c1} * 0.995 - k_{20} * QN_{c2} - k_{25} * QO_{c2} + k_{52} * QO_{p5} + k_{31} * f_1 * QO_{abs3} * 0.995 \\ \frac{\partial QO_{abs3}}{\partial t} = -k_{31} * QO_{abs3} \\ \frac{\partial QO_{p4}}{\partial t} = k_{14} * QO_{c1} - k_{41} * QO_{p4} \\ \frac{\partial QN_{p5}}{\partial t} = k_{25} * QN_{c2} - k_{52} * QN_{p5} \\ \frac{\partial QO_{c6}}{\partial t} = k_{31} * QO_{abs8} * (1 - f_2) - k_{67} * QO_{c6} - k_{14} * QO_{c6} + k_{41} * QO_{p9} \\ \frac{\partial QN_{c7}}{\partial t} = k_{67} * QO_{c6} * 0.995 - k_{70} * QN_{c7} - k_{25} * QN_{c7} + k_{52} * QN_{p10} + k_{31} * f_2 * QO_{abs8} * 0.995 \\ \frac{\partial QO_{abs8}}{\partial t} = -k_{31} * QO_{abs8} \\ \frac{\partial QO_{p9}}{\partial t} = k_{14} * QO_{c6} - k_{41} * QO_{p9} \\ \frac{\partial QN_{p10}}{\partial t} = k_{25} * QN_{c7} - k_{52} * QN_{p10} \end{cases}$$

Figure 7. The mathematical equations of the kinetic model M44b2, where $QO_{c1/6}$ and $QO_{p4/9}$ are the amount of olanzapine in the central and peripheral compartment, respectively; $QN_{c2/7}$ and $QN_{p5/10}$ are the amount of metabolite in its central and peripheral compartments; the molar ratio between olanzapine and N-desmethyl olanzapine was determined to be 0.995 and was used as a conversion factor from molar to mass units in metabolic processes; all the other parameters were previously presented in Figure's 6 legend.

Table 4. The kinetic parameters of olanzapine and N-desmethyl olanzapine determined with model M44b2

Parameter	Unit	M44b2 – T1	Standard error	M44b2 – T2	Standard error
f_1	-	0.0537	0.009	0.0451	0.0104
f_2	-	<0.0001	<0.0001	0.0344	0.0051
f_{rel}	-	2.2369	0.5711	3.2750	0.6422
k_{12}	hr^{-1}	0.0889	0.0272	0.0889	0.0237
k_{14}	hr^{-1}	0.4423	0.0361	0.2032	0.0457
k_{20}	hr^{-1}	0.3255	0.0468	0.3066	0.0744
k_{25}	hr^{-1}	0.0002	0.0001	0.0027	0.0013
k_{31}	hr^{-1}	2.7861	0.2275	2.6430	0.1621
k_{41}	hr^{-1}	0.2893	0.0244	0.3113	0.0346
k_{52}	hr^{-1}	0.0155	0.0067	0.0007	0.0003
k_{67}	hr^{-1}	0.0721	0.0179	0.0655	0.0123
k_{70}	hr^{-1}	0.1533	0.0218	0.1348	0.0327
t_{lag}	hr	0.1257	0.0962	0.0699	0.0135
V_F	L	62.5320	13.3014	78.3888	10.4912

The model M44b2 – T1 refers to the kinetic modelling of interaction between OLZ and ciprofloxacin. During the reference period, approximately 5.37% of OLZ is metabolized to OLZ-M during absorption from the small intestine following oral administration (f_1 = 0.0537). However, when co-administered with ciprofloxacin, the inhibition of the CYP1A2 enzyme, predominantly expressed in the liver

[8], completely blocks the presystemic metabolism of OLZ, eliminating this pathway ($f_2 < 0.0001$). This inhibition alters hepatic drug metabolism, leading to a significant increase in the amount of OLZ reaching systemic circulation, which is 2.2 times higher in the test period than during the reference period ($f_{rel} = 2.2369$). Additionally, the metabolization constant (k_{67}) for OLZ decreases by about 20% during the test period, reflecting the inhibited metabolic pathway due to ciprofloxacin co-administration. Furthermore, the parameter associated with the elimination of OLZ-M (k_{70}) decreases by approximately 53% in the test period, indicating that the elimination of the main metabolite is also inhibited. This could explain the increased concentration of OLZ-M observed during the test period.

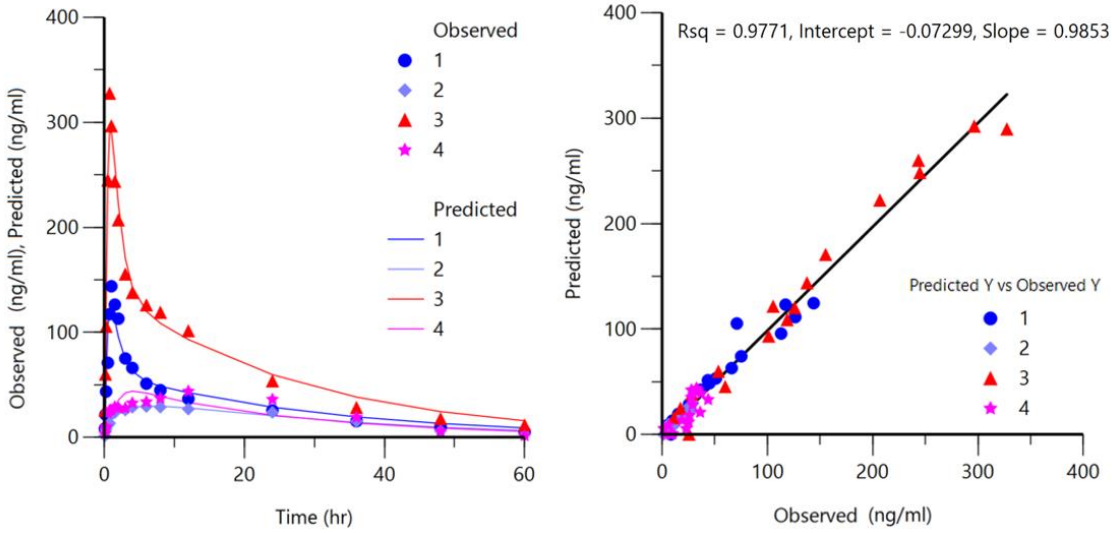

Figure 8. The kinetic fitting of M442b during the first test period (left) and the correlation between the experimental and fitted values (right); 1 is olanzapine in the central compartment during the reference period, 2 is N-desmethyl olanzapine in the central compartment during the reference period, 3 is olanzapine in the central compartment during the first period (with ciprofloxacin), and 4 is N-desmethyl olanzapine in the central compartment during the first test period

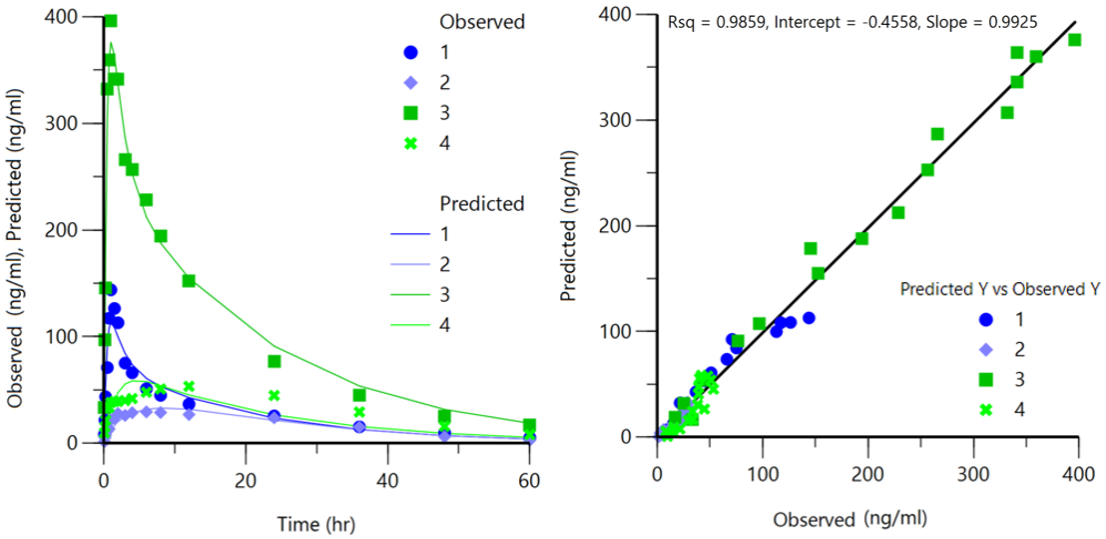

Figure 9. The kinetic fitting of M442b during the second test period (left) and the correlation between the experimental and fitted values (right); 1 is olanzapine in the central compartment during the reference period, 2 is N-desmethyl olanzapine in the central compartment during the reference period, 3 is olanzapine in the central compartment during the second period (with norfloxacin), and 4 is N-desmethyl olanzapine in the central compartment during the second test period

The model M44b2 – T2 refers to the kinetic modelling of interaction between OLZ and norfloxacin. In the reference period, approximately 4.51% of OLZ ($f_1 = 0.0451$) is metabolized to OLZ-M during absorption in the small intestine after oral administration. Upon co-administration with norfloxacin, due to CYP1A2 inhibition, the presystemic metabolism of OLZ is reduced, but unlike the interaction with ciprofloxacin, this pathway is not eliminated ($f_2 = 0.0344$). The drug-drug interaction with norfloxacin, however, results in significantly greater drug exposure to OLZ compared to its interaction with ciprofloxacin. This can be visually observed in Figure 2, where the area under the curve (AUC), a measure of drug exposure, is noticeably higher for the olanzapine-norfloxacin co-administration. This increase is caused by a change in relative bioavailability, which is about 3.2 times higher during the interaction with norfloxacin compared to the reference period ($f_{rel} = 3.275$). Additionally, the metabolization rate constant (k_{67}) for OLZ decreases by approximately 26% due to the enzyme inhibition from norfloxacin, similar to the effect observed with ciprofloxacin. The elimination

constant (k_{70}) for OLZ-M also decreases by about 56%, suggesting that, as with the ciprofloxacin interaction, the elimination of the main metabolite is inhibited, leading to higher OLZ-M concentrations during the test period.

The fitting of the M442b model on plasma data are shown in Figures 8 and 9.

The experimental data and model predictions show strong concordance, as evidenced by the correlation coefficient (R^2). For the OLZ alone and OLZ-ciprofloxacin dataset, the R^2 value is 0.9771 (Figure 8), while for the OLZ alone and OLZ-norfloxacin dataset, the R^2 value is 0.9589 (Figure 9), indicating a high degree of correlation between the experimental data and values predicted by the model.

4. Conclusions

Given the complexity of kinetic analysis and the multitude of variables involved, a large number of model variants could result. To address this issue, a systematic three-step compartmental kinetic modelling approach was employed. In the first step, compartmental modelling focused exclusively on the parent compound, olanzapine, because its kinetics influence the kinetics of its metabolite, and not vice versa. In the second step, the metabolite was introduced into the model, allowing simultaneous fitting of two datasets - the parent compound and the metabolite - while incorporating additional parameters such as metabolite distribution and the effects of presystemic and systemic metabolism. The third step involved the simultaneous fitting of four datasets, taking into account the kinetic interactions between olanzapine and ciprofloxacin or norfloxacin. This step considered changes in presystemic and systemic metabolism due to enzymatic inhibiton, together with variations in the relative bioavailability of olanzapine between the reference and test periods.

This rational, staged approach provides a detailed mechanistic understanding of the interactions between olanzapine and the two fluoroquinolone antibiotics, providing valuable information for optimizing dosing strategies in clinical settings where simultaneous administration is required.

Conflict of interest

The authors declare that there is no conflict of interest concerning the publication of this research article.

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