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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Original Research Article

Physiologically-based pharmacokinetic modeling predicts altered maternal pharmacokinetics of amitriptyline during pregnancy

Short running title: Amitriptyline PBPK model during pregnancy

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Amitriptyline, peripartal depression, pharmacokinetics, PBPK-modeling

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Bullet point summary:

1) What is already known about the subject:
   - Pharmacotherapy of maternal peripartum depression is challenging due to inadequate adherence during pregnancy.
   - Amitriptyline is often used during pregnancy, but knowledge on pharmacokinetics in pregnancy is lacking.
   - We aimed to add new information in amitriptyline pharmacokinetics for an effective and safe pharmacotherapy in pregnant women.

2) What the study adds
   - Using PBPK-modeling valuable information on pharmacokinetics of amitriptyline during pregnancy were added (increased AMI concentration, decreased NOR concentration).
   - Active moiety serum concentration may be comparable to before pregnancy, however, tolerability may be affected due to increased serum concentrations of amitriptyline alone, and as consequence increased anticholinergic effects.

Abstract

Aim: Pharmacotherapy of maternal peripartum depression is an increasing challenge. Amitriptyline (AMI) is the most often used tricyclic antidepressant during pregnancy, but knowledge on pharmacokinetics in this special phase is lacking. Physiologically based pharmacokinetic modeling (PBPK) is a powerful tool to better understand pregnancy-induced pharmacokinetic changes of medication. We aimed to improve the knowledge about AMI pharmacokinetics during pregnancy using PBPK modeling. Consequently, we aimed to add new information for an effective and safe pharmacotherapy in pregnant women.

Methods: A PBPK model, including AMI, but also its active metabolite nortriptyline (NOR), was developed to investigate pregnancy-induced pharmacokinetic changes after AMI administration. The predicted drug exposure was compared to observed concentrations in pregnant patients in clinical routine. The PBPK model was set up using PK-Sim® Version 11.

Results: Serum concentration profiles were described successfully. During pregnancy, active moiety serum concentration of AMI (AMI+NOR) did not change, however AMI concentration increased, whereas NOR concentration decreased.

Conclusion: With this model, we added valuable information on AMI pharmacokinetics during pregnancy (increased AMI concentration, decreased NOR concentration). For clinical practice the treating physician should be aware that despite active moiety serum concentration comparable to before pregnancy, tolerability may be affected due to increased AMI serum concentrations and as consequence increased anticholinergic effects. To keep the risk of therapy discontinuation during pregnancy low, we suggest to perform TDM, especially to check the AMI serum concentration.

1. Introduction

Maternal depression in the peripartum period, and its pharmacotherapy is an increasing challenge, as the prevalence of maternal peripartum mood and anxiety disorders increased (from 18.4 to 40.4 per 1000 deliveries between 2006 and 2015) [1], but women are more reluctant to use medication during pregnancy, due to possible teratogenic risks [2]. Nevertheless, antidepressants rank among the most prescribed medications during pregnancy [3,4]. Especially in peripartum depression, low rates of adherence to pharmacotherapy (45.0% and 48.8%) were reported; also, severity of psychiatric symptoms were associated with an increased likelihood of low medication adherence [2,5,6]. Mental disorders during pregnancy do not only affect the woman´s well-being, but can also affect the infant´s cognitive and emotional development [1]. Consequently, it is important, not only for the woman, but also for the infant, that an effective and safe treatment is continued or initiated. In the evidence-based clinical practice guidelines for prevention, screening and treatment of peripartum depression (available at: https://riseupppd18138.com/clinical-practice-guidelines-html/; date accessed: 29th January 2025), the use of antidepressants is strongly recommended after careful consideration of the individual benefit-risk ratio; moreover, therapy discontinuation during pregnancy is not recommended due to the risk of relapse [7].

Tricyclic antidepressants are considered safe for the infants based on clinical observations and data, and no increased risk of birth defects has been reported in infants exposed to these substances during pregnancy [1]. Among the tricyclic antidepressants, amitriptyline (AMI) is the most commonly prescribed medication in pregnancy [8]. The TDM task force of the working group on neuropsychopharmacology (Arbeitsgemeinschaft fuer Neuropsychopharmakologie und Pharmakopsychiatrie, AGNP) defined in their best practice guidelines for TDM atherapeutic reference range for the active moiety of AMI (AM(AMI); cumulative serum concentration of AMI and nortriptyline (NOR)) in trough concentration with 80-200 ng/ml [9]. The authors suggested that this reference range defines a range of the drug´s serum concentration with the highest probability for response and the lowest probability for adverse drug effects [9]. Especially for amitriptyline data are available that reported associations

between serum concentrations and adverse drug effects [10-12]. In vivo, amitriptyline is metabolized mainly by the cytochrome P450 enzyme (CYP) 2D6 and CYP2C19 [13,14]. In-vivo, CYP2C19 is the major enzyme for formation of nortriptyline (desmethylation), whereas CYP2D6 is responsible for hydroxylation to less active metabolites [13]. Hydroxy-nortriptyline is the most abundant metabolite, formed by hydroxylation of nortriptyline via CYP2D6 [13]. Other enzymes are involved in the metabolism of amitriptyline and nortriptyline also, for example CYP1a2, CYP2C9, or CYP3A4, however with less share [13]. Nevertheless, there is little knowledge about pharmacokinetics of AMI and its metabolites during pregnancy. In previously published exploratory findings, we described that serum concentration of AM(AMI) decreased from the 1st to the 2nd trimester, but did not change to the 3rd trimester [15]. However, the number of included serum concentrations were low (1st trimester: N=2, 2nd: N=4, 3rd: N=3 [15]), and no “before-pregnancy” serum concentrations were available to compare non-pregnancy with pregnancy concentrations. Knowledge on alterations in serum concentration from before pregnancy to pregnancy would be advantageous in order to be prepared for pregnancy-associated alterations and, therefore, to preventive adapt the pharmacotherapy accordingly to ensure an effective and safe therapy during pregnancy. To best of our knowledge, no more information about serum concentrations of AMI during pregnancy are currently available.

Physiologically based pharmacokinetic modeling (PBPK) becomes increasingly important for pharmacokinetic, but also pharmacodynamic considerations and is a powerful tool to better understand pregnancy-induced pharmacokinetic changes of medication [16]. In general, PBPK models to simulate drug concentrations of antidepressants are scarce [16]. Models are available e.g. for venlafaxine [17,18], esketamine [19], or amitriptyline [20,21] outside pregnancy. During pregnancy, only one PBPK model is currently available (sertraline) [22], despite the call for more PBPK modeling to improve pharmacokinetic knowledge during pregnancy [16].

We therefore aimed to improve the knowledge about AMI pharmacokinetics during pregnancy using PBPK modeling to provide new information on safety and efficacy.

2. Methods

2.1. Amitriptyline serum concentrations in pregnancy

For this investigation, we analysed amitriptyline serum concentrations that were part of a previously published naturalistic retrospective study on clinical routine data [15]; a detailed description can be found elsewhere [15]. Just briefly, this was a naturalistic clinical sample with broad inclusion criteria (age ≥18 years, current or previous treatment for a peripartal mental illness, German language skills). Patients were included only with written informed consent. The study adhered to the Declaration of Helsinki, 17th revision, 2013, and was approved by the ethic committees of the University Hospital of Frankfurt and Würzburg (Approval No. 136/17 and 18/20-sc). The authors confirm that the PI for this paper is Sarah Kittel-Schneider and that she had direct clinical responsibility for patients.

Data from three patients (one patient in the second, as well as third trimester, one patient in the second, and one patient in the third trimester) with a defined time interval between taking the medication and blood withdrawal were included for pregnancy model evaluation. Patients were 27, 33, and 33 years old, two patients were treated with amitriptyline due to recurrent depressive disorder (ICD-10: F33.2), one patient due to mixed anxiety and depressive disorder (ICD-10: F42.2). AM(AMI) serum concentration was reported, although they were referred to as amitriptyline concentration in Leutritz et al. [15].

2.2. Software

PK-Sim® Version 11, and MoBi® Version 11, two freely available softwares, which are part of the Open System Pharmacology Suite were used for model building, optimization and sensitivity analysis of amitriptyline and nortriptyline [23]. PK-Sim® was used for model building of non-pregnant individuals, MoBi® was used for model building of pregnant individuals and transferred to PK-Sim® for population simulations. For parameter optimization the integrated

Monte Carlo algorithm was used. Data from clinical studies from published literature used for model development and evaluation were extracted with the semi-automated tool WebPlotDigitizer (Version 4.3, Ankit Rohatgi, Pacifica, CA, USA). Plots were generated using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) [24]. Model performance was calculated using Microsoft Excel 2016 Version 16.0 (Microsoft Corporation, Redmond, WA, USA).

2.3. General workflow

The PBPK model for AMI and NOR was first built and evaluated in non-pregnant individuals. As the psychiatric disease itself does not cause any change in pharmacokinetics of a drug, model validation in solely healthy volunteers would have no added values compared to non-pregnant individuals. Therefore, we did include pharmacokinetic data of healthy volunteers in the datasets of non-pregnant individuals. Then, the model was updated for pregnant women including nine additional compartments (breast, myometrium, endometrium, maternal and fetal placenta, fetus, arterial and venous blood pools of the umbilical cord, amniotic fluid) [25]. Finally, the pregnancy model was compared to serum concentrations observed in pregnant patients.

2.4. Amitriptyline PBPK Model Building

Initially, an extensive literature research was conducted to obtain physicochemical properties of AMI and NOR (e.g., molecular weight, lipophilicity, solubility), as well as other drug specific parameters (e.g., partition coefficients, intestinal permeability, clearance).

An intravenous (iv) model was built based on a published PBPK model of AMI, describing its concentration in the heart after iv administration [20], as well as from the Summary of Product Characteristics [26]. In the initial AMI model total hepatic clearance [26] was used, not considering specific CYP-enzymes to precisely optimize drug parameters affecting permeability and distribution without considering elimination pathways. In consequence, NOR was not included in this initial model. Data from a safety assessment study of Fridrich et al. (iv administration AMI; doses: 25mg, 50mg, 75mg) [27] were used as training dataset for

parameter optimization. Lipophiliciy (logP), as well as logP(veg.oil/water) (necessary for partition coefficient calculation according to Rodgers and Rowland [28,29]), and cellular permeability methods were optimized in a stepwise process.

For the initial NOR model, data from a PBPK model simulating its concentration in the heart after AMI administration [20] were extracted. Again, total hepatic clearance was considered [30], not specific enzymes. Data from one study (intramuscular (im) administration NOR; dose: 42mg) [31] was used as training dataset for parameter optimization. Lipophiliciy (logP), as well as logP(veg.oil/water), and cellular permeability methods were optimized in a stepwise process. The model was tested with data from four studies administering oral NOR [31-34] to prove the elimination of NOR. Secondly, total hepatic clearance was replaced by specific CYP enzymes (CYP2D6 hydroxylation, CYP1A2 demethylation, CYP2C19 demethylation, CYP2D6 demethylation) according to Tylutki et al. [20]. Again, data from Alvan et al. [31] were used as training dataset for optimization of CYP2D6 hydroxylation kcat (katalytic rate constant), as main metabolizing enzyme of NOR [14]. The same four studies as before were used to test the model [31-34].

In a next step, the AMI model and the NOR model were joined and specific enzymes for the metabolism of AMI were included (Demethylation: CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4; Hydroxylation: CYP2B6, CYP2D6, CYP3A4) according to Tylutki et al. [20]. Data from a safety assessment study of Fridrich et al. (iv administration AMI; doses: 25mg, 50mg, 75mg) [27] and another study from Schulz et al. [35] were used to test the model.

Further, the model was transferred to per oral (po) administration. Data from three studies, two single dose (SD) studies [36,37] and one multiple dose (MD) study [38] were used as training data. Optimized parameters were specific intestinal permeability, dissolution time, lag time (initial value according to [21]), and dissolution shape, improved by manual adjustment. Due to inaccuracy of the model, elimination/metabolism of AMI was restricted to the main path, demethylation via CYP2C19 [14,39]. Parameters (CYP2C19 demethylation AMI kcat,

logP(veg.oil/water) AMI, CYP2D6 hydroxylation NOR kcat) have been further specified and improved by manual adjustment using the po administration training datasets [36-38].

The parameters were tested using SD and MD from clinical studies [40-46], and routine clinical data collected at the university hospital of Würzburg from 2023 to 2024 (MD; doses: 50mg, 75mg, 100mg, 125mg, 150mg, 200mg).

A schematic workflow of the AMI and NOR model development and evaluation including optimized parameters is shown in Figure 1. A summary of the studies and their assignment as training or test dataset is documented in Supplemental Table 1 (Table S1).

2.5. Amitriptyline PBPK Model Evaluation

The final AMI PBPK model was evaluated using different methods according to the available guidelines by the EMA [47] and the FDA [48].

The trajectories of the predicted serum concentration of AMI and NOR were compared to the observed profiles for a first visual interpretation of model performance. A goodness-of-fit plot in which the predicted serum concentration was plotted against the observed serum concentration was generated.

To evaluate model accuracy and precision, prediction error (PE), mean prediction error (MPE), and mean absolute prediction error (MAPE) were calculated (Equation (1)-(3)).

$$PE[\%] = \frac{c_{predicted,i} - c_{observed,i}}{c_{observed,i}} \times 100\% \quad (1)$$

$$MPE[\%] = \frac{1}{n} \times \sum_{i=1}^{n} PEi \quad (2)$$

$$MAPE[\%] = \frac{1}{n} \times \sum_{i=1}^{n} |PEi| \quad (3)$$

Model performance was calculated using mean relative deviation (MRD, Equation (4)), which is defined as the average distance of the observed serum concentration values from the predicted value on a logarithmic scale [49]. Adequate model performance was characterized as MRD values ≤ 2.

$$MRD = 10^{x}; x = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(\log_{10} c_{predicted,i} - \log_{10} c_{observed,i})^2} \quad (4)$$

$c_{predicted,i}$ predicted serum concentration; $c_{observed,i}$ corresponding observed serum concentration; n number of observed values.

Local sensitivity analysis, measured as relative changes in trough concentrations (c_{trough}) of parameters that had been optimized, was conducted with a variation range of 10.0 and a maximum number of 9 steps.

2.6. Amitriptyline pregnancy model

The final AMI PBPK model was then translated to pregnancy following a previously described workflow [50]. In short, the general model was transferred to MoBi®, the standard model structure was replaced by the pregnancy model structure, in detail described by Dallman et al. [25]. After export to PK-Sim® pregnancy-related enzyme activity changes [51] (Table S2) were applied to the model. The model was used to predict the pharmacokinetics of amitriptyline in the 2nd, and 3rd trimester as enzyme specific data for the 1st trimester were lacking [51]. The fertilization age, and in consequence the trimester, was defined via the age range of the population. The age of 30 years corresponded to the onset of pregnancy, the maximum fertilization age of 38 weeks corresponds to an age of 30.75 years [50].

In the pregnancy model CYP2D6 hydroxylation of amitriptyline was included, as its importance increased during pregnancy due to CYP2D6 induction caused by hormonal changes [51,52].

Pharmacokinetics were predicted in a virtual population of 100 individuals for each trimester. Population was built based on the pregnant individual according to Dallmann et al, 2017 [25]. Mean weight was 60 kg, mean height was 163 cm; mean age was 30 years and corresponded to the onset of pregnancy.

Serum concentrations of AMI and NOR in pregnant women were available from one retrospective analysis [15] (for details, see above).

Here again, the trajectories of the predicted serum concentration of AMI and NOR in pregnancy were compared to the observed profiles for a first visual interpretation of model performance. A goodness-of-fit plot in which the predicted serum concentration was plotted against the observed serum concentration was generated for the second and third trimester.

To evaluate model accuracy and precision, PE, MPE, and MAPE were calculated (Equation (1)-(3)). Model performance was calculated using MRD (Equation (4)).

Local sensitivity analysis, measured as relative changes in c_{trough} of parameters that had been optimized, as well as the 9 pregnant specific compartments and the new included CYP2D6 hydroxylation of AMI, was conducted for the 2nd, as well as the 3rd trimester with a variation range of 10.0 and a maximum number of 9 steps.

2.7. Comparison of PK in non-pregnant and pregnant individuals

Predicted trough serum concentrations of AMI, NOR and the active moiety (AMI+NOR; AM(AMI)) in pregnant women in the 2nd and 3rd trimester were visually compared to predicted serum concentrations in non-pregnant patients, to consider differences in pregnant vs. non-pregnant pharmacokinetics of AMI and NOR.

Key ligand in this article (amitriptyline) is hyperlinked to corresponding entries in http://www.guidetopharmacology.org.

3. Results

3.1. Amitriptyline PBPK Model Building and Evaluation

The final input parameters for the model are given in Table 1.

The final AMI PBPK model was successfully used to describe the observed AMI and NOR serum concentrations after oral single, and multiple dose administration.

The trajectories of the predicted serum concentration of AMI and NOR were in close agreement with the observed profiles (Figure 2). 85.86% of the simulated serum concentrations of AMI,

and 93.94% of the serum concentrations of NOR were within 2-fold of the corresponding observed serum concentrations (Figure S1).

For amitriptyline oral administration MPE for AMI in all simulations was 12.78% (-33.55% - 86.07%), MAPE ranged from 11.90% to 101.72% (mean: 39.12%), and MRD of all predicted serum concentrations was ≤2 (range: 0.57 – 1.46). MPE of NOR for all simulations was 6.18% (range: -21.97% - 41.42%), MAPE ranged from 6.61% to 66.67% (mean: 28.85%) and MRD of all predicted serum concentrations was ≤2 (range: 1.00 – 1.39) (Table S3).

The local sensitivity analysis showed that for AMI, variation in its lipophilicity had the greatest impact on serum concentration prediction. For NOR variation in its lipohilicity, followed by variation in AMI lipophilicity had the greatest impact on serum concentration prediction (Figure S2).

3.2. Amitriptyline pregnancy model

The verified healthy non-pregnancy model was updated for 2nd and 3rd trimester of pregnancy. The model was evaluated by simulating steady-state trough concentrations of AMI and NOR after oral administration.

The trajectories of the predicted serum concentration of AMI and NOR in pregnancy were in agreement with the observed profiles (Figure 3). 100% (4 of 4) of the simulated serum concentrations of AMI, and 75% (3 of 4) of the serum concentrations of NOR during pregnancy were within 2-fold of the corresponding observed serum concentrations (Figure S3).

For amitriptyline oral administration MPE for AMI in all simulations (N=4) was 128.11% (47.81% - 307.81%), MAPE ranged from 47.81% - 307.81% (mean: 128.11%), and MRD of all predicted serum concentrations was ≤2 (1.36). MPE of NOR in all simulations (N=4) was 35.78% (-19.91% - 94.37%), MAPE ranged from 3.85% to 94.37% (mean: 47.66%), and MRD of all predicted serum concentrations was ≤2 (1.09).

The local sensitivity analysis showed that in the 2nd, as well as in the 3rd trimester of pregnancy for AMI variation in its lipophilicity, for NOR variation in lipophilicity of amitriptyline followed by

variation in NOR lipophilicity, and kcat of CYP2D6 hydroxylation of nortriptyline had the greatest impact on serum concentration prediction during pregnancy (Figure S4).

3.3. Comparison of PK in non-pregnant and pregnant individuals

Simulated serum concentrations of AMI, NOR and AM(AMI) in non-pregnant, as well as pregnant women are shown in Figure 4.

c_{trough} (time after first administration to ensure steady-state conditions: 143.75 h) in non-pregnant patients in steady-state (amitriptyline: median (IQR) [ng/ml] 21.29 (3.78 – 77.72); nortriptyline: 41.86 (9.53 – 154.19); AM(AMI): 63.15 (13.31 – 231.91)), in pregnant women in 2nd trimester (amitriptyline: 55.83 (11.05 – 178.56); nortriptyline: 21.85 (3.36 – 97.13); AM(AMI): 77.67 (14.41 – 275.69)), and in 3rd trimester (amitriptyline: 48.07 (11.83 – 144.08); nortriptyline: 21.27 (4.41 – 103.88); AM(AMI): 69.34 (16.24 – 247.96)) are shown in Figure S5. Interquartile ranges of AMI, NOR and AM(AMI) overlap; however, for AMI median serum concentration was lower in non-pregnancy, whereas for NOR median serum concentration was lower in pregnancy. In summary, median AM(AMI) serum concentrations may not differ between pregnant and non-pregnant women (Figure S5).

4. Discussion

This is the first reported PBPK model of AMI predicting the serum concentration of AMI including also its active metabolite NOR in pregnancy. For amitriptyline there were two PBPK models published [20,21,55]. Howell et al. developed a model to predict the efficacy of drug overdose treatment of amitriptyline with liposomes [55] and Tylutki et al. developed a model to predict the cardiac concentration of AMI and NOR [20,21]. They also predicted serum concentration, however, mean NOR concentration was within two-fold of the respective clinically observed concentration only in 8 out of 15 studies (53.3%) [21]. In our model, in non-pregnant patients predicted serum concentrations for AMI, but also for NOR was within two-fold of the respective clinically observed concentration in 85.86%, and 93.94% of the simulated serum concentrations of AMI and NOR, respectively. Considering the individual serum

concentrations of only our own clinical population (clinical routine data, University Hospital of Würzburg) in non-pregnant individuals, 98.87% of the AMI concentrations, and 92.79% of the NOR concentrations were within the prediction interval. Thus, model performance in non-pregnant patients was better than in the previously published model. Nevertheless, as AMI is a drug with narrow therapeutic index classified by drug bank (https://go.drugbank.com/categories/DBCAT003972; accessed: 17.03.2025), a more stringent model performance criteria than the common 2-fold criteria may be advantageous [56]; however, there are no explicit recommendations for a quality criterion in these drugs [56].

Model development for AMI was challenging, as the model included also pharmacokinetic modeling of its active metabolite NOR. Optimized model parameters for AMI and NOR included lipophilicity (logP(octanol/water)) that links membrane permeability and drug absorption and distribution with the clearance. As the logP (octanol/water) is an estimate with variable values available in the literature, optimization for model performance is essential to obtain good agreement with experimental data [57]. In addition, as data for the logP(veg.oil/water), necessary for cell-plasma partition calculation, were lacking in literature, these values, in combination with the partition calculation methods were optimized. Individual catalytic rate constants for the metabolizing enzymes, also, are not available in literature; therefore, parameter optimization to fit the experimental data was mandatory. To exclude inaccuracies due to interaction between AMI and NOR pharmacokinetics, parameters of NOR were optimized in a model including only NOR administration, before including NOR in the AMI model. For establishing the model for po administration it is recommended to modify parameters that influence absorption, for example specific intestinal permeability of AMI [57]. Due to sparse data on formulation-specific properties, additionally, optimization of dissolution time, lag time, and dissolution shape was done. Parameter optimization was helpful to fit concentration-time data appropriately so that the observed concentration-time profiles were within the prediction intervals. Parameters that describe the pharmacokinetics after absorption were successfully described based on iv data. In consequence, inaccuracies and bias from absorption processes were eliminated.

In pregnant patients, 100% (4 of 4) of the predicted serum concentrations of AMI, and 75% (3 of 4) of the predicted concentrations of NOR were within 2-fold of the corresponding observed serum concentrations (Figure 4). With exception of one analysis published prior by our group [15], there was no study available reporting serum concentrations of AMI and/or NOR in pregnant patients; therefore, only limited data were available to test model performance.

In pregnancy, observed AMI and NOR serum concentrations of patients were lower than the predicted ones, even if they met the acceptance criteria for model performance. This could possibly be due to the following reason: As we used clinical routine data, adherence to the medication was not controlled. Especially in pregnancy, adherence to medication often is inadequate, due to increased anxiety among pregnant women about medication in pregnancy [2]. Two studies, investigating adherence in maternal depression specifically, reported low rates of adherence (45.0% and 48.8%) [2,5,6]. Moreover, deviations between predicted and observed AMI and NOR concentrations in pregnant patients in the clinical routine may be caused by the retrospective sampling of the data, because time of last dose intake and time of sampling were estimated, as data were not documented. In addition, data on alterations of enzyme activity in/during pregnancy are scarce [51,52], and, therefore, susceptible to bias. Nevertheless, this is the first PBPK model that successfully predicts AMI and NOR serum concentrations following AMI administration in pregnant patients.

PBPK-model predicted AM(AMI) trough serum concentrations during pregnancy did not differ from non-pregnant values (Figure 4; 23.0%, and 9.8% increase from non-pregnancy to 2nd, and 3rd trimester). In contrast, in our previously published naturalistic retrospective study we descriptively found a decrease in AM(AMI) serum concentration [15], however, due to the limited number of patients (1st trimester N=2, 2nd trimester N=4, 3rd trimester N=3) no statistics were calculated. Moreover, as discussed above, we cannot assume full adherence to medication in our sample. Beside this explorative results no study investigated pharmacokinetics of amitriptyline during pregnancy [4]. Despite constant AM(AMI) trough serum concentrations during pregnancy, c_{trough} of AMI increased by 162.2%, and 125.8% from

non-pregnancy to 2nd, and 3rd trimester, respectively. In contrast, c_{trough} of NOR decreased by 47.8%, and 49.2% from non-pregnancy to 2nd, and 3rd trimester, respectively. This decrease of NOR is in line with two prior studies, reporting a decrease in NOR concentration in the 3rd trimester when administering NOR [4]. Consequently, during pregnancy, the ratio between AMI and NOR changes. Due to the specific pharmacodynamic profile of AMI and NOR, this may affect the therapeutic effect, but also adverse drug reactions. For example, the risk for cardiotoxic effects due to high NOR concentrations is lower during pregnancy [10]. Moreover, NOR administration seems better tolerated than AMI administration [58], possibly due to less anticholinergic and less sedative properties compared to AMI [59]. In addition, it was shown that NOR leads to less weight gain than AMI [60]. In consequence, during pregnancy, tolerability of AMI administration may be reduced due to the shift in the AMI/NOR ratio, and therefore, due to increased AMI concentration. Consequently, for clinical routine, treating physicians should be aware that even if the serum concentrations of AM(AMI) in pregnant women did not change compared to before pregnancy concentrations, tolerability may be decreased and adverse effects may occur due to high AMI concentrations. Therefore, in pregnancy, we suggest to perform therapeutic drug monitoring especially to check the AMI concentration, even if there is no therapeutic reference range for AMI alone [9], so that the risk of therapy discontinuation due to adverse effects remains as low as possible. This is supported by previous results, as a shift in the metabolite-to-parent ratio to higher AMI concentrations is comparable to a poor metabolizer status in CYP2C19 which may affect side effects; TDM is recommended in this case also [14].

4.1. Strengths and limitations

This is the first PBPK model successfully describing serum concentrations of AMI and NOR in non-pregnant patients, but also in pregnancy. With our model, we can add valuable information on AMI pharmacokinetics during pregnancy, as for the first time, we showed increasing AMI serum concentration and decreased NOR serum concentration during pregnancy that may explain decreased tolerability of amitriptyline administration during pregnancy. For model evaluation in non-pregnant patients we used previously reported studies, but also own clinical

data obtained in daily clinical practice; thus, model performance has been tested in daily clinical routine. For model evaluation in pregnancy, there were only a limited number of patients with available serum concentrations. No data were available in literature. Thus, this warrants further observational studies of AMI treatment in pregnant women to gain additional understandings of the pharmacokinetics and pharmacodynamics during pregnancy. However, model performance including the available data was acceptable. Thus, this is the first model describing serum concentrations of AMI and NOR in pregnancy. PBPK modelling for 1st trimester of pregnancy is lacking, as it is not described how enzyme function changes during the 1st trimester [51,52]. There are some main reasons for imprecision in predicting serum concentrations, especially in pregnancy. As this were clinical routine data, it was not controlled for adherence. Moreover, as data on CYP2D6, and/or CYP2C19 genetic variants were not available, we did not control for these genetic variants, even if they can affect serum concentrations of AMI and NOR [62]. Moreover, data on alterations of enzyme activity in/during pregnancy are scarce and, therefore, susceptible to bias. In consequence, to improve the predictive performance of the pregnancy-model, studies are necessary where patient adherence is controlled, as well as the time range between drug intake and blood withdrawal. Moreover, data on genetic variants may also be advantageous for improving precision. Even if there is one available study reporting that amitriptyline, as well as nortriptyline cross the human placenta [61] and, therefore, may be available in the fetus, we did not include fetal serum concentration in our model. Before including modelling of fetal concentration, the predictive performance of the pregnancy-model has to be improved to gain precise modelling results in the fetus. Data on fetal concentrations are lacking, therefore, no model evaluation would be possible. Further research is necessary to address this question. Clinical data on therapy outcome or adverse drug effects were not recorded.

4.2. Conclusion

The developed PBPK model successfully predicted serum concentrations for AMI and NOR after AMI administration in non-pregnant patients, but also in pregnant women (2nd and 3rd trimester). With this model, we added valuable information on AMI pharmacokinetics during

pregnancy. Although AM(AMI) serum concentration in pregnant women did not significantly differ in comparison with non-pregnant women, the ratio AMI/NOR differed with more as twice as high serum concentrations of AMI in 2nd and 3rd trimester, and about half as high concentrations of NOR. During pregnancy, as it is important not only for the woman, but also for the infant, that an effective and safe treatment is continued or initiated [1], AMI is a well-known effective and safe treatment option. Nevertheless, the treating physician should be aware that despite AM(AMI) serum concentration comparable to before pregnancy, tolerability may be affected due to increased AMI serum concentrations. To keep the risk of therapy discontinuation during pregnancy low, we suggest performing TDM, especially to check the AMI serum concentration.

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Conflicts of interest: M Scherf-Clavel received advisor honorarium from Rovi. S. Kittel-Schneider has received speaker's honoraria from Janssen, Takeda and Medice Arzneimittel Pütter GmbH & Co KG in the past 3 years. S. Walther received honoraria from Lundbeck, Mepha and Neurolite. S. Unterecker received honoraria from Rovi and Janssen. AL Leutritz and A. Gehrmann have no conflicts of interest.

Availability of data and material: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval: All procedures performed in the analysis involving human participants were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study in which our own data were collected was approved by the ethic committees of the University Hospital of Frankfurt and Würzburg (Approval No. 136/17 and 18/20-sc).

Author contributions:

Project administration: M. Scherf-Clavel, S. Kittel-Schneider

Data collection: M. Scherf-Clavel, A.L. Leutritz

Analysis and interpretation of the data: M. Scherf-Clavel

Writing—original draft preparation: M. Scherf-Clavel

Writing—review and editing: All authors have approved of the contents of this manuscript and provided consent for publication.

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Tables

Table 1 Summary of the drug dependent, as well as formulation parameters used in the final amitriptyline PBPK model.

Parameter	Unit	Value used in PBPK model	Literature value	Reference	Description
			AMITRIPTYLINE		
MW	g/mol	277.4	277.4	[20]	Molecular weight
***p*Ka**		9.41	9.41	[20]	Acid dissociation constant
fu_P		0.05	0.05	[20]	Fraction unbound in plasma
logP		4.03*	4.62	[20]	Lipophilicity
Solubility (pH 7)	mg/l	9.71	9.71	[53]	Solubility
Partition coefficients		Rodgers and Rowland	Rodgers and Rowland	[20]	Calculation method cell to plasma coefficients
logP (veg.oil/water)		0.44*	3.23	PK-Sim Calculation	Lipophilicity used for partition calculation method
Cellular permeabilities		PK-Sim Standard*	PK-Sim Standard		Calculation method permeation across cell membranes
Specific renal clearance	1/min	0.07	0.07	PK-Sim Calculation; [20]	
CYP2C19 Demethylation#					
Km	µM	8.52	8.52	[20]	Michaelis-Menten constant
kcat	1/min	17.37*	4.22		Katalytic rate constant
Specific intestinal permeability	cm/min	$1.23*10^{-5}$*	$1.23*10^{-5}$	[20]	Permeability in AMPA test
			NOTRIPTYLINE		
MW	g/mol	263.38	263.38		Molecular weight
***p*Ka**		10.10	10.10	[20]	Acid dissociation constant
fu_p		0.08	0.08	[20]	Fraction unbound in plasma
logP		3.96*	4.39	[20]	Lipophilicity
Solubility (pH 7)	mg/l	0.87	0.87	[54]	Solubility
Partition coefficients		Rodgers and Rowland	Rodgers and Rowland	[20]	Calculation method cell to plasma coefficients
logP (veg.oil/water)		0.44*	3.23	PK-Sim Calculation	Lipophilicity used for partition calculation method
Cellular permeabilities		PK-Sim Standard*	PK-Sim Standard		Calculation method permeation across cell membranes
Specific renal clearance	1/min	0.19	0.19	PK-Sim Calculation; [20]	
CYP1A2 Demethylation					
Km	µM	54.20	54.20	[20]	Michaelis-Menten constant
kcat	1/min	0.11	0.11		Katalytic rate constant
CYP2C19 Demethylation					
Km	µM	118.0	118.0	[20]	Michaelis-Menten constant
kcat	1/min	1.55	1.55		Katalytic rate constant
CYP2D6 Demethylation					
Km	µM	0.48	0.48	[20]	Michaelis-Menten constant
kcat	1/min	0.32	0.32		Katalytic rate constant
CYP2D6 Hydroxylation					
Km	µM	0.74	0.74	[20]	Michaelis-Menten constant
kcat	1/min	4.7*	2.17		Katalytic rate constant
			FORMULATION		
Dissolution shape		0.925*	0.92	PK-Sim Calculation	Dissolution profile shape
Dissolution time (min)		15*	240	PK-Sim Calculation	Dissolution time (50% dissolved)
Lag time		1.33*	1.33 h	[20]	

* Parameters that were optimized during model evaluation; # The elimination/metabolism of AMI was restricted to the main path, demethylation via CYP2C19, to make a more accurate prediction

Legends of the tables

Table 1 Summary of the drug dependent, as well as formulation parameters used in the final amitriptyline PBPK model.

Legends of the Figures

Fig. 1 Schematic workflow showing the development and evaluation of the AMI and NOR PBPK model. Initial model development started with basic input parameters from the literature. Parameters optimized during model building and evaluation are shown. Final input parameters are given in Table 1. The entire process was supported by using clinical study data (training or test dataset; see Table S1 for allocation)

Fig. 2 Linear serum concentration-time profiles after oral administration of amitriptyline outside pregnancy. AMI is shown in black, NOR is shown in red. Population simulations (n=100) median (lines) and the predicted interquartile ranges (95%) (shaded areas) were shown. Observed data were shown as circles, and triangles

Fig. 3 Linear serum concentration-time profiles after oral administration of amitriptyline in pregnancy. AMI is shown in black, NOR is shown in red. Population simulations (n=100) median (lines) and the predicted interquartile ranges (95%) (shaded areas) were shown. Observed data from patients were shown as circles

Fig. 4 Serum concentrations of amitriptyline, nortriptyline and the active moiety in non-pregnant and pregnant women

Electronic Supplemental Material

Supplemental Figures

Figure S1 Goodness-of-fit plots for AMI (left) and NOR (right) comparing the predicted serum concentrations with the observed serum concentrations. Line of identity (black solid line), 1.25-fold deviation (black dotted lines), and 2-fold deviation (black dashed lines) are shown.

Figure S2 Sensitivity for parameters that were estimated during model building was measured as relative changes in c_{trough} of multiple dose administration (75mg) of AMI. Variation range was range was 10.0 with maximum number of steps = 9.

Figure S3 Goodness-of-fit plots for AMI (left) and NOR (right) comparing the predicted serum concentrations with the observed serum concentrations in pregnancy. Line of identity (black solid line), 1.25-fold deviation (black dotted lines), and 2-fold deviation (black dashed lines) are shown.

Figure S4 Sensitivity for parameters that were estimated during model building, as well as the 9 pregnant specific compartments and the new included CYP2D6 hydroxylation of amitriptyline was measured as relative changes in c_{troug}h of multiple dose administration (75mg) of AMI during pregnancy. Variation range was range was 10.0 with maximum number of steps = 9.

Figure S5 Comparison of median and IQR of trough serum concentrations for amitriptyline, nortriptyline and the active moiety in non-pregnant, as well as pregnant women.

Supplemental Tables

Table S1 All clinical studies used for amitriptyline model building and evaluation.

Table S2 Pregnancy-related enzyme activity changes. ND, no data

Table S3 Bias (mean prediction error), precision (mean absolute precision error) and mean relative deviation (MRD) of the AMI PBPK model