Quetiapine dose optimisation during gestation: a pharmacokinetic modelling study

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ABSTRACT

Objectives: The second generation antipsychotic quetiapine has been demonstrated to undergo gestation related changes in pharmacokinetics. This study applied pharmacokinetic modelling principles to investigate the mechanism of these changes and to propose new dosing strategies to counteract these changes

Methods: A pharmacokinetic modelling approach was implemented using virtual population groups. Changes in quetiapine trough plasma concentration during gestation were quantified across all trimesters and dose adjustment strategies were applied to counteract these changes by targeting a therapeutic range of 50-500 ng/mL throughout gestation

Findings: The application of the model during gestation predicted a decrease in trough concentration. A maximum decrease of 58 % was predicted during trimester 2, and being associated with a statistically significant decrease in oral clearance at gestation week 25, 204 L/h ± 100.8 L/h compared to non-pregnant subjects, 121.9 L/h ± 51.8 L/h. A dosing optimisation strategy identified that dose increases to 500-700 mg twice daily would result in 32-55 % of subjects possessing trough concentration in excess of 50 ng/mL.

Conclusions: Quetiapine doses in pregnancy should be increased to 500-700 mg twice daily to counteract a concomitant increase in metabolic clearance, increase in volume of distribution and decrease in plasma protein binding.

KEYWORDS

Quetiapine; pregnancy; pharmacokinetics; PBPK; dose optimisation.

1. INTRODUCTION

Quetiapine is a second generation antipsychotic that was first approved by the US Food and Drug Administration (FDA) in 1997 for the management of schizophrenia in both adults and adolescents in addition to a range of other psychiatric disorders [1, 2].

Several reports have highlighted that quetiapine is the most commonly prescribed atypical antipsychotic in women of childbearing age [3-5]. A key advantage of quetiapine over other atypical antipsychotics is that it is unlikely to be associated with extrapyramidal symptoms and is prolactin (PRL)-sparing but is associated with weight gain [6].

However, the use of pharmacological interventions for psychiatric disorders during pregnancy is particularly challenging, given the need to balance stabilisation of maternal mental state with the potential teratogenic effects of the prescribed drug. Often, this results in the cessation of treatment during the gestational period, particularly in trimester 1 [7].

In the wider context of pregnancy, approximately 15 % of women have some form of psychiatric illness with up to 13 % of women taking prescribed psychotropic pharmacological interventions [8, 9]. Clinicians are likely to be faced with the possibility of treatment (or not) within the perinatal setting. However, clinical studies have demonstrated that pregnancy should be considered as a 'high-risk' period for relapse in the context of a discontinuation of any maintenance treatment options [10-14]. This is particularly important given that recent reports in the UK have suggested that 1 in 25 women (aged 20-35 years) who die by suicide, do so during the perinatal periods (conception-pregnancy and post-natal) [15]. And further, that poor mental health during gestation is highly correlated with poor mental health postnatally [14].

Mounting evidence supports the notion that cessation of therapy during pregnancy may be detrimental to the mother for some antipsychotics, a choice which requires consideration of the risks and benefits of pharmacological interventions during gestation [7, 16, 17]. Although the risks of antipsychotic use during pregnancy may be outweighed by the clinical benefits, gestation brings about significant changes in the physiology of the mother which can have drastic changes on the pharmacokinetics of drugs administered during pregnancy. Quetiapine is primarily metabolised by the phase-1 Cytochrome P450 enzyme CYP 3A4 [18], and gestation can result in a significant increase in the expression of CYP3A4 [19-21] by between 25-40 % [22], which would enhance quetiapine metabolic clearance and hence results in a net reduction in quetiapine plasma concentrations. An obvious change occurs in body composition with a 40-50 % increase in plasma volume [23, 24] throughout gestation along with a

concomitant increase in body fat, approximately 4 kg, resulting in alterations of the volume of distribution of hydrophilic and lipophilic drugs during gestation which would generally reduce plasma drug concentration In addition, decreases in the plasma-proteins albumin and alpha-1-acidic glycoprotein will in turn increase the free drug fraction and directly influence the volume of distribution [25-27].

In a recent retrospective study, the plasma levels of a range of antipsychotics were analysed during gestation and it was identified that significant decreases in serum levels were evident, particularly for quetiapine, which decreased by up to 70 % in trimester 3 [28].

At present, there are no well-controlled or reliable studies of quetiapine use during pregnancy, and because of this reason the FDA have classified quetiapine as a category C drug, suggesting it should be used during pregnancy only if the benefits to the mother outweigh any risks to the patient. However, the US Office of Paediatric Therapeutics conducted a review of 220 adverse reports associated with quetiapine, which were submitted to the FDA adverse event reporting systems and identified that there doesn't seem to be a risk of congenital anomalies but acknowledge the limited nature of the data reported [29]. Further, the clinical toxicology database TOXBASE® (https://www.toxbase.org) from the National Poisons Information Service Unit [30], has provided guidance for the use of quetiapine during gestation and does not advocate its cessation necessarily, rather places emphasis on the consideration of the risk of relapse on cessation compared to the benefits to the mother and child during gestation.

We have, for the first time, applied the principles of mechanistic pharmacokinetic modelling and virtual clinical trials to better elucidate the causative effects of this decrease in plasma quetiapine levels during gestation, to provide a clinically relevant dosing adjustment strategy that could be implemented to maintain plasma quetiapine levels during gestation.

The objectives of this study were to: (i) develop a robust and validated pharmacokinetic model for quetiapine; (ii) identify a suitable therapeutic window for quetiapine and (iii) explore the impact of gestation on quetiapine plasma levels and address any alterations with clinically appropriate dose adjustments.

2. METHODS

Simulations were performed using the virtual clinical trial simulator Simcyp (Simcyp® Ltd, a Certara company, Sheffield, UK, Version 16). The 'Healthy Volunteer' population group was used for 'non-pregnant' females and the 'Pregnancy' population group utilised for all 'pregnancy' studies. The latter population group included necessary gestational dependant changes in physiology, such as blood volume and organ/tissue perfusion and enzyme/protein expression, which are thought to play a role in altering the pharmacokinetics of drugs [31-34]. A 4-stage modelling approach was implemented. A previously validated model of quetiapine [35] was utilised with adaptations through the inclusion of CYP3A5 metabolic clearance pathway [36, 37].

2.1 Step 1: Validation of quetiapine

In order to implement a pregnancy model within Simcyp the previously validated quetiapine model [35] required modification as the model primarily implemented a minimal-PBPK model, which does not allow consideration of a distinct foetal/placental tissue compartment and physiological alterations in other maternal tissues during gestation. For simulations in pregnant subjects, a full-PBPK distribution model was required and therefore tissue-partition coefficient (Kp) estimates were calculated using the Rogers and Rowland approach [38, 39]. These were then parameter estimated (using a Weighted Least Square (WLS) method and the Nelder-Mead minimisation approach) through the optimisation of a tissue partition coefficient scalar, Kp_{scalar}, using a total of 3 single dose studies and 1 multi-dose study: (i) 12 men (24-42 years old) dosed a single oral dose of 25 mg [40]; (ii) 15 men and 3 women (29-63 years old) dosed at 25 mg twice daily on day 1, 50 mg twice daily on day 2, 100 mg twice daily on day 3, 200 mg twice daily on day 4 and 300 mg twice daily on day 5 until day 10 [40]; (iii) 10 men (35-55 years old) dosed at 25 mg three times daily (TID) (6 am, 2 pm and 10 pm) on day 1 and dose escalated to 50 mg TID on day 2, 75 mg TID on day 3, 100 mg TID on day 4 and by 50 mg increments daily until 250 mg TID on days 7 and 8 [41]; (iv) 11 men and 2 women (19-58 years) dosed at 25 mg twice daily (BD) on day 1 and dose escalated to 50 mg BD on day 2, 75 mg BD on day 3, 100 mg BD on day 4 and by 50 mg increments daily until 300 mg BD on 8 until day 21 [42].

Model simulations were run to match the reported age range and patient number reported by each study. However, in the absence of this information, a default trial size of 100 subjects (10x10 design) aged 20-40 years old was used.

Quetiapine model parameters can be found in Supplementary Materials: Section 1.

2.2 Step 2: Validation of CYP3A5 metabolic clearance modification

To further validate the appropriateness of modifications made to the CYP3A5 intrinsic clearance [37], three retrospective clinical drug-drug interactions studies were used to further validate the model and consisted of: (i) ketoconazole dosed alone for days 1 to 3 and in conjunction with quetiapine on day 4 [40]; (ii) quetiapine dose escalated to 300 mg twice daily by day 5 and maintained for 34 days. Thereafter carbamazepine initiated with a 200-mg dose on the evening of day 9, followed by 200 mg twice daily on days 10- 12, and increased to 200 mg three times daily from days 13-33 with a final dose on the morning of day 34 [40] and (iii) quetiapine dose escalated from 25 to 250 mg three times daily by day 10 and maintained until day 23 with phenytoin administered at 100 mg three times daily on days 13-33 in conjunction with quetiapine [41].

Where possible, trial design and sampling duration was replicated from the original studies.

2.3 Step 3: Validation during gestation

A recent report by Westin *et al* [28] retrospectively collated serum level of antipsychotics before, during and after pregnancy. Data for quetiapine consisted of 66 measurements during pregnancy, 11 during the first 12 weeks following pregnancy and 144 at baseline, from 33 women. Subjects were stabilised on 400 mg/daily. This data was extracted, pooled and utilised as 'observed' data for validation purposes.

In simulating quetiapine pharmacokinetics during gestation, a 38-week trial design was utilised, with simulations conducted using a 10x10 trial design with dosing adjusted on a daily basis by 50 mg/day to 200 mg twice daily for all subjects.

For all dosing approaches in pregnancy, unless otherwise stated, the pre-dose (trough) plasma concentration was ascertained 10 hours following each dose. For assessment of plasma concentration, all concentrations were dose adjusted to the defined daily dose (DDD), whereby the simulated plasma concentration was divided by the daily dose and subsequently multiplied by the DDD (the average maintenance dose per day for its main indication in adults)[43].

For comparison, the trial design was also replicated for Healthy Volunteer population of non-pregnant females dosed under the same dosing strategy.

2.4 Step 4: Dose adjustment during gestation

Limited data currently exists purporting to show a relationship between plasma quetiapine levels and clinical responses and these have recently been summarised in a review by Mauri et al (2018) [44]. Further, a suggested therapeutic window of between 100-500 ng/mL has been proposed by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) [45] and this was adopted as the potential therapeutic window. However, the region of 50-100 ng/mL was also considered as a 'borderline' range, given that doses in the range of 150-800 mg daily can yield mean trough concentrations in the range of 27-387 ng/mL [46-50]. Although the FDA advocated maximum recommended dose is 800 mg daily [51], a number of studies have assessed the safety of higher doses in non-pregnant subjects to a maximum of 1400 mg daily [52-54] with no significant safety concerns.

In a recent case report the need for dose adjustment to be made during pregnancy for women with bipolar disorder was highlighted [55], with dose escalation by up to an additional 350 mg/daily in some cases to maintain symptom control during gestation. Further, previous reports of foetal exposure of quetiapine have occurred at dose ranges of 300-600 mg/day during gestation with no harmful effects on the new-born [56-59]. Interestingly a dose of 1200 mg/day was also used at mid-pregnancy (21 weeks gestation) as identified in a case report by Çabuk [60], which resulted in a normal birth. Although mainly case reports, these serve as useful guidance for potential dose escalation strategies required.

In order to assess the requirement for dose optimisation, simulations were conducted with 100 subjects (10x10 design) aged 20-30 years. Simulations were commenced on day 1 of gestation and terminated on day 1 of week 39. Dose escalation studies included 'baseline' simulations of 200 mg twice daily and subsequently by 50 mg increments every 3 days to a maximum of 700 mg twice daily. Data was sampled on the final 24 hour period of every 5^{th} week up to and including week 38.

2.5 Predictive Performance

For all simulations in steps 1-3, a prediction of a pharmacokinetic metric to within two-fold (0.5-2.0 fold) of published clinical data was generally accepted as part of the 'optimal' predictive performance [61-63].

2.7 Visual Predictive Checks

Model predictions in step 1-3 were compared to clinical studies using a visual predictive checking (VPC) strategy [64]. In this approach, the predicted mean/median and 5th and 95th percentiles of the concentration–time profiles (generated from Simcyp®) were compared against the observed data for any validation data sets. The prediction was assumed to be valid when the predicted data points overlapped with the observed data sets.

2.8 Data and statistical analysis

All observed data obtained from clinical studies were extracted using WebPlotDigitizer v.3.10 (http://arohatgi.info/WebPlotDigitizer/). Statistical analysis was conducted using a non-parametric Kruskal-Wallis with a Dunn's multiple comparison post-hoc test. Statistical significance was confirmed where a $P < 0.05$ was computed.

3. RESULTS

3.1 Step 1: Validation of quetiapine

A previously published quetiapine model was adapted with the incorporation of a full-PBPK model in order to predict tissue partition coefficient and enable a full mechanistic model to be utilised, in addition to the incorporation of a CYP3A5 metabolic pathway. The adapted file was validated against a range of published clinical studies using the Simcyp Healthy Volunteer population group (See section 2.1). For all single and multi-dose studies (Supplementary Materials: Section 2 Figure S1) along with drug-drug interactions simulations (Supplementary Materials: Section 2 Figure S2), the simulated plasma concentration-time profiles were successfully predicted to within the observed range for each study and model-predicted t_{max}, C_{max}, and AUC were predicted to within 2-fold of the reported parameters for each study, confirming successful validation (Table 1).

When compared to non-pregnant females (baseline), the median steady-state trough plasma concentrations of quetiapine decrease during gestation (Figure 1) with a statistically significant difference between baseline and the mid-point of trimesters 1-3 (final day of weeks 6, 20 and 32 respectively) ($P < 0.001$, Dunn's post-hoc comparison) (Table 2). During gestation the predicted median plasma concentration decreased by between 52-58 %.

The reduced plasma concentration during gestation was associated with a concomitant increase in oral clearance (CL/F) which was significantly different from baseline from gestational week 10 onwards ($P < 0.05$, Dunn's post-hoc comparison) and reached a maximum at GW 25, 204 L/h ± 100.8 L/h compared to baseline, 121.9 L/h ± 51.8 L/h (Figure 2A). Further, changes in volume of distribution are significant from week 25 onwards, rising from a baseline of 329.2 L ± 71 L to 368.4 L ± 71.3 L at GW 38 (Figure 2B). A statistically significant increase in unbound fraction was also noted from GW 10 onwards and with fu_{plasma} being 21-26 % greater from weeks 30 onwards (fu_{plasma} = 0.0218-0.0225) (Figure 2C).

Understanding the importance of maternal physiological changes during gestation on quetiapine pharmacokinetics is clearly multifaceted. Therefore we conducted a sensitivity analysis using a non-pregnant and pregnant (GW: 10, 20 and 30) female population group where we directly examined the impact of variation in the CYP 3A4 hepatic abundance (137 pmol/mg protein to 180 pmol/mg protein, representing a 30 % increase from baseline levels) and Kp scalar (1 to 3, representing a Vss range of 3.8 L/kg to 11 L/kg; implemented using Simcyp estimated Kp's) (Figure 3). When considering non-pregnant subjects, the trough serum concentrations are largely sensitive to changes in both Vss (Kp scalar) and CYP 3A4 abundance, although the former has a greater influence. Conceptually, an increase in Vss would result in a net reduction in peak (C_{max}) plasma concentrations with a concomitant shift in the distribution and elimination phases of the drug. However, this shift in the latter phases of the plasma concentration-time profile would result in a net increase in the trough plasma concentration (C_{min}) (Figure 3A). At a fixed hepatic abundance, for example the default hepatic abundance in healthy (non-pregnant) subjects of 137 pmol/mg protein, any increase in Kp scalar (and hence increased in Vss) would increase the C_{min} (Figure 3B). However, during gestation the increase in CYP 3A4 hepatic abundance would negate the impact of an increase in Vss on the C_{min}, and result in a net reduction in trough plasma concentration (Figure 3).

3.4 Step 4: Dose adjustment during gestation

In order to address the reduced plasma concentration during gestation, a dose escalation strategy was explored, whereby doses were increased by 50 mg increments every 3 days to a maximum of 500 mg twice daily, from a baseline dose of 200 mg twice daily.

As expected, the dose increase during gestation resulted in an increase in median plasma concentration (Figure 4). A dose increase of 300 mg (i.e. 500 mg twice daily) was required to

yield > 70 % of subjects with a trough plasma concentration in excess of 50 ng/mL throughout gestation (Table 3). However, a dose increase of 500 mg (i.e. 700 mg twice daily) was required to ensure >60 % of subjects possessed a trough plasma concentration in excess of 100 ng/mL throughout gestation (Table 3).

4. DISCUSSION

The decision to use any pharmacological intervention during pregnancy is challenging for the mother in addition to the prescriber and requires clear knowledge of potential harmful effects on the developing foetus and risks such as the development of gestational diabetes. However, the choice to continue treatment or not, can be overshadowed by the clinical need for therapy during gestation, and the potential consequences of withdrawing treatment [13, 14].

Gestation brings about clear physiological changes which are known to alter the pharmacokinetic profile of drugs. However, the consequences of such changes are often difficult to ascertain clinically in a controlled trial for obvious ethical reasons. However, in an attempt to assess the potential impact of pregnancy on antipsychotic therapy, the use of robust mechanistic pharmacokinetic models allows for a prospective assessment of the potential impact and changes in plasma concentrations.

A recent report by Westin *et al* [28] examined the plasma concentrations of antipsychotics during gestation from retrospective analysis of therapeutic drug monitoring (TDM) clinical data from Norway. They identified that quetiapine and apriprazole exhibited a significant decrease in plasma concentrations during gestation, by between 50-80 % by trimester 3. Further decrease were noted for perphenazine and haloperidol, but this was limited by the number of TDM measurements available. Nevertheless, the potential for gestation-related decrease in antipsychotic plasma concentrations was noted.

Given the lack of more detailed clinical studies examining these phenomena, this study applied the principle of pharmacokinetic modelling to prospectively assess the use of quetiapine in pregnancy population groups and attempted to relate changes in plasma concentrations during gestation to a potential therapeutic window region. The Simcyp Pregnancy PBPK model has been utilised by our group [65] and others [32, 33] for prediction of the impact of changes in

plasma concentrations associated with gestation, however this is the first time it has been utilised in the context of quetiapine.

The model developed incorporated adaptations to two existing quetiapine PBPK models [35, 37] and was validated against single and multiple dose studies (Supplementary Materials: Section 2 Figure S2). The resulting predictions were within 2-fold of those reported along with appropriate VPC confirming population level variability in plasma concentrations were appropriately predicted in relation to the clinically reports variability. Further, the inclusion of the revisions to the CYP 3A5 component [37] were able to recapitulate the impact of appropriate DDIs on plasma concentrations (Supplementary Materials: Section 2 Figure S3).

To our knowledge, Westin *et al* [28] is the only publication (to date) containing quetiapine plasma concentrations throughout gestation and this was used as the basis for validating the quetiapine pregnancy PBPK model. Simulations were run for the entire gestation period (38 weeks) with sampling of the first day on each week for every 5 weeks reported (Figure 1). For non-pregnant subjects (baseline), model predicted plasma concentrations (54.59 ng/mL ± 26.98 ng/mL) were within 2-fold of those reported by Westin *et al* [28] (75.6 ng/mL) (Table 2), whilst also spanning across a similar range. Westin *et al* [28] reported a 22 %, 57 % and 76 % decrease in mean plasma concentration at for trimesters 1, 2 and 3 respectively. Using the PBPK model we demonstrated a similar decrease of 52-58 % across gestation, although the predicted decrease for trimester 1 was greater than that reported [28]. Nonetheless, the trend throughout gestation for a decrease in plasma concentration was similar, and represents an important phenomenon, which is likely to result in sub-therapeutic plasma concentrations if we assume a lower limit of the therapeutic window to be 100 ng/mL.

In order to identify the cause of this change in plasma concentrations during gestation, we first examined the impact of changes in CYP 3A4 expression on oral clearance. Previous reports have identified significant alterations in CYP 3A4 expression with gestation, and given the major contribution of CYP 3A4 to overall CYP-mediated metabolic clearance, > 90 % [18, 40], this is a key component for the overall pharmacokinetics of quetiapine. The impact of gestation on the metabolic clearance of CYP 3A4 substrates has been previously reported as leading to an approximate 25-40 % increase in the clearance [22, 66]

An increase in oral clearance was observed at week 5 for pregnant subjects, (149.5 L/h ± 75.17 L/h) compared to baseline (non-pregnant) subjects at the same time point (121.9 L/h ± 51.53 L/h) (Figure 2A), however this was not statistically significant. From week 10 to 38, the oral

clearance increased, compared to baseline subjects, with week 20 demonstrating the greatest difference (184.1 L/h ± 100.5 L/h) ($P < 0.001$) (Figure 2A). Further, an increase in total body water and plasma volume that occur throughout gestation did not have a significant impact on the Vss until week 25, where Vss reached 357.2 L ± 71.9 L, compared to 329.2 L ± 71 L for non-pregnant subjects (Figure 2B). Previous reports have demonstrated Vss can range from 400-800 L for non-pregnant subjects, for both single and multidose studies [67-69]. The approximate 10 % increase in Vss during gestation, although significant, may only contribute a minor role to the change in trough concentration. A net increase in the unbound fraction plasma (fu_{plasma}) (21-26 % greater from weeks 30 onwards) was also simulated when comparing baseline (Figure 2C). This net increase would result in an increase in circulating unbound drug, resulting in an increase in the volume of distribution whilst also partly contributing to potentially enhanced exposure of drug to the liver. However, the conceptualisation of this effect on trough levels is multifaceted. The gestation-mediated increase in CYP 3A4 hepatic abundance negates the impact of an increase in the volume of distribution and results in a net reduction in trough plasma concentration (Figure 3).

To address the reduction in quetiapine plasma concentrations during gestation, we assessed the impact of dose escalation which was required to recapitulate trough plasma concentrations to within the therapeutic window. Because of the uncertainty surrounding the precise range of the therapeutic window, a lower limit was set at either 50 ng/mL or 100 ng/mL (see section 2.4). In non-pregnant subjects, a 200 mg twice daily dose yielded a median steady-state trough concentration of 59.47 ng/mL ± 26.98 ng/mL, which significantly decreased during gestation to a minimum of 30.55 ng/mL at GW 20 ($P < 0.001$, Dunn's post-hoc comparison) (Figure 4) (Supplementary Materials: Section 3 Table S2). Further, this resulted in a significant number of subjects failing to attain the lower therapeutic window, < 35 % of subjects for 50 ng/mL (Table 4) and < 15 % of subjects for 100 ng/mL (Table 3). This trend broadly concurs with those reported by Westin *et al* [28], where the majority of reported plasma concentrations during gestation fell below the 50 ng/mL lower limit (Figure 1), highlighting the need to consider dose escalation during gestation.

Although a dose increase to 500 mg twice daily would be sufficient to ensure 30-50 % of subjects attained the upper therapeutic window of 100 ng/mL (Table 3), a dose increase to 700 mg twice daily was identified as satisfying the requirement to attain both the 50 ng/mL and 100 ng/mL lower windows (Figure 4), with attainment of > 95 % and > 62 % of subjects respectively. Whilst trials have suggested an upper dose of 800 mg/day [2, 70, 71], higher

doses of between 800-2000 mg/day [72-76] have been reported to be tolerated in acute and maintenance therapy. Further, sparse case reports are available of significantly higher overdoses of least 20-24 g being ingested with little acute effects [77, 78].

The increase in dose may warrant closer monitoring with possible monthly clinical evaluations during gestation. This would allow for assessment for any worsening of mood disorder symptoms during administration of higher doses of quetiapine. This can consist of trained clinician administered structured interviews (e.g. SIGH-ADS[79] or MRS[80]). Furthermore, recommendations from the Royal College of Psychiatrists Consensus Statement [81] advocated the use of scales such as the Brief Psychiatric Rating Scale (BPRS)[82] and Health of the Nation Outcome Scales (HoNOS)[83] in addition to assessing adverse effects through the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)[84], for high dose antipsychotic use.

Given that the metabolic clearance of quetiapine is mediated largely by CYP3A4 [18], and gestation can result in a significant increase in the expression of CYP3A4 [19-21], an increase in dose would be necessary during gestation to ensure trough plasma concentrations are in excess of the lower therapeutic window.

Although limited studies have examined the need for a dose increase during pregnancy, those that have reported this have shown that a 2-to-3 fold increase in dose is required in many cases [60, 85, 86], dose increase were required in 80 % of the patients studied during pregnancy.

5. CONCLUSIONS

The primary outcome of our work is that quetiapine doses as high as 1400 mg/day may be required during gestation, which is supported by case reports and clinical studies demonstrating few adverse clinical effects when using at doses of in excess of 800 mg/day.

For the first time, through the implementation of virtual clinical trials analysis, we have demonstrated that the reduction in quetiapine plasma concentrations are driven by both alterations in tissue physiology and the impact this has on the overall Vss, in addition to variation in CYP 3A4 abundance changes during gestation. However, for other antipsychotics, this phenomenon would largely depend upon the gestational changes in specific CYP isozymes. For example, clozapine metabolic clearance is primarily mediated by CYP 1A2, which itself can undergo significant decreases in pregnancy.

Further studies are required to assess both the extent of this gestational change on plasma concentrations but also to also better identify a potential therapeutic range to better optimise any necessary dose adjustments. However, we believe this study will provide a pragmatic basis with which to consider dose adjustment throughout gestation.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Table 1: Summary pharmacokinetics parameters for validation studies in non-pregnant subjects

Study	Sampling day		C_{max} (ng/mL)	t_{max} (h)	AUC (ng/mL.h) [a]
Grimm[40]	**Day 1**	Predicted	42.53 (25.32)	1 (0.23)	144.29 (97.29)
		Observed	45	1.25	181
	Day 6 +Ketoconazole	Predicted	123.02 (27.76)	1.28 (0.29)	1002.99 (409.18)
		Observed	150	1.25	1123
	Day 9	Predicted	663.42 (405.11)	1 (0.23)	2784.12 (2317)
		Observed	1042	1.5	4650
	Day 34 +Carbamazepine	Predicted	320.61 (131.19)	0.93 (0.22)	1137 (650.54)
		Observed	205	1.3	621
Wong[41]	**Day 8**	Predicted	765.48 (339.7)	1 (0.22)	3168.82 (1673.07)
		Observed	1048 (363)	1.4 (0.5)	3642 91375)
	Day 8 +Phenytoin	Predicted	439.01 (267.12)	0.94 (0.21)	1414.03 (1167.38)
		Observed	359 (328)	1.13 (0.36)	728 (445)
Potkin [42]	**Day 21**	Predicted	1032.71(50)	0.98 (0.65-1.40)	4223.86 (61)
		Observed	1124.6 (31.9)	1.23 (0.5-3)	4508.9 (39.8)

Data represents mean (Standard deviation). [a] Calculated for current dosing period.

Table 2: Trough plasma quetiapine concentration during pregnancy

	Baseline [a]	T1	T2	T3
	(ng/mL)			
Median	59.47	28.07	24.94	26.43
Mean	54.59	39.12	34.66	36.74
SD	26.98	29.09	25.26	26.41
SEM	4.61	6.20	5.38	5.63
CI high	47.71	46.82	41.39	44.18
CI low	31.09	22.16	19.96	21.23
Change (%) [b]		52.81	58.06	55.53

T1-T3 refers to each trimester; Data calculated from mid-point of each trimester; CI: confidence interval; SD: Standard deviation; SEM: standard error of the mean. [a] Baseline represents non-pregnant females; [b] Change refers to % changes from baseline.

Table 3: Percentage of subjects with quetiapine trough concentrations greater than 50 and 100 ng/mL

	Dose Adjustment (mg)							
	50 ng/mL lower limit				100 ng/mL lower limit			
Week	**Baseline**	**100**	**300**	**500**	**Baseline**	**100**	**300**	**500**
5	34	66	86	98	14	24	55	81
10	28	58	82	97	9	21	43	73
15	25	48	75	96	6	19	34	69
20	24	45	72	95	4	18	33	65
25	24	44	72	95	4	16	32	63
30	24	45	74	95	4	18	33	62
35	28	54	81	96	9	20	38	68
38	31	60	83	96	12	22	44	69

Data calculated from day 1 of each week; Baseline represents non-pregnant females.

LIST OF FIGURES

Figure 1: Simulated quetiapine plasma concentrations during gestation

Simulated quetiapine plasma concentrations were generated during gestation using the Simcyp Pregnancy population group, with the population group (n=33) redefined on a daily basis to update study group physiology during gestation. Simulated concentrations represent post-dose (trough concentrations) sampled 10 hours after dosing. Subjects were administered a 200 mg twice daily dose (dose escalated from 25 mg twice daily over 1 week). 'Baseline' refers to non-pregnant females. Simulated concentrations represent post-dose (trough concentrations) sampled 10 hours after dosing and collated at 5-week intervals over the gestation period. Red open circles represent observed (pooled) plasma concentrations obtained from a total of 33 subjects. Black open circles present simulated plasma concentrations.

Figure 2: Impact of physiological alterations during pregnancy on quetiapine pharmacokinetics

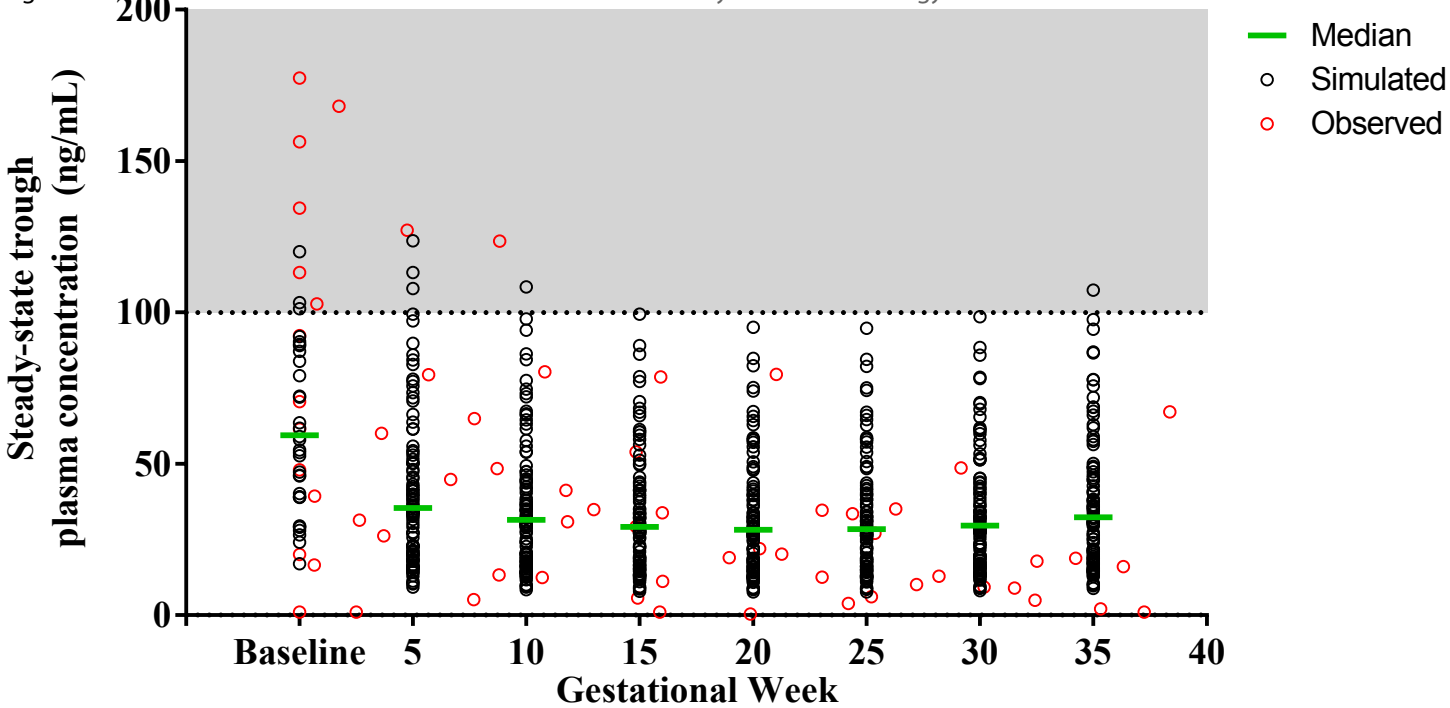
Changes in quetiapine (A) clearance, (B) volume of distribution and (C) unbound fraction in plasma at baseline (non-pregnant females) and during gestation. Gestational week is indicated by GW. Box-plots ideates range (upper and lower bars) with calculation of median and $25^{th}/75^{th}$ percentiles. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

Figure 3: Impact of alterations in Kp and CYP 3A4 abundance during pregnancy on quetiapine plasma concentrations

(A) The impact of changes in Kp scalar and CYP 3A4 hepatic abundance on quetiapine plasma concentrations following multiple 200 mg oral doses (12-hourly). Solid lines represent fixed CYP 3A4 abundance but increasing Kp scalar, with dashed lines representing changes in Kp scalar but fixed CYP 3A4 abundance. (B) A sensitivity analysis comparing the impact of variation in Kp scalar (1 to 3) and CYP 3A4 abundance (137 to 180 pmol/mg protein) on final dose trough plasma concentrations in non-pregnant (red) and GW10 to 30.

Figure 4: Dose optimisation of quetiapine during gestation

The impact of dose escalation on median quetiapine plasma concentrations during gestation. Box-plots indicate range (upper and lower bars) with calculation of median and 25^{th}/75^{th} percentiles. Baseline dose was 200 mg twice daily with escalation indicated as the additive increase in dose from baseline. Dark shaded region indicates the proposed therapeutic window (100-500 ng/mL) with the lighter shaded region (50-100 ng/mL) indicating the proposed 'extended' range of the therapeutic window.


Steady-state trough plasma concentration (ng/mL)
200
150
100
50
0
Baseline
5
10
15
20
25
30
35
40
Gestational Week
Median
Simulated
Observed

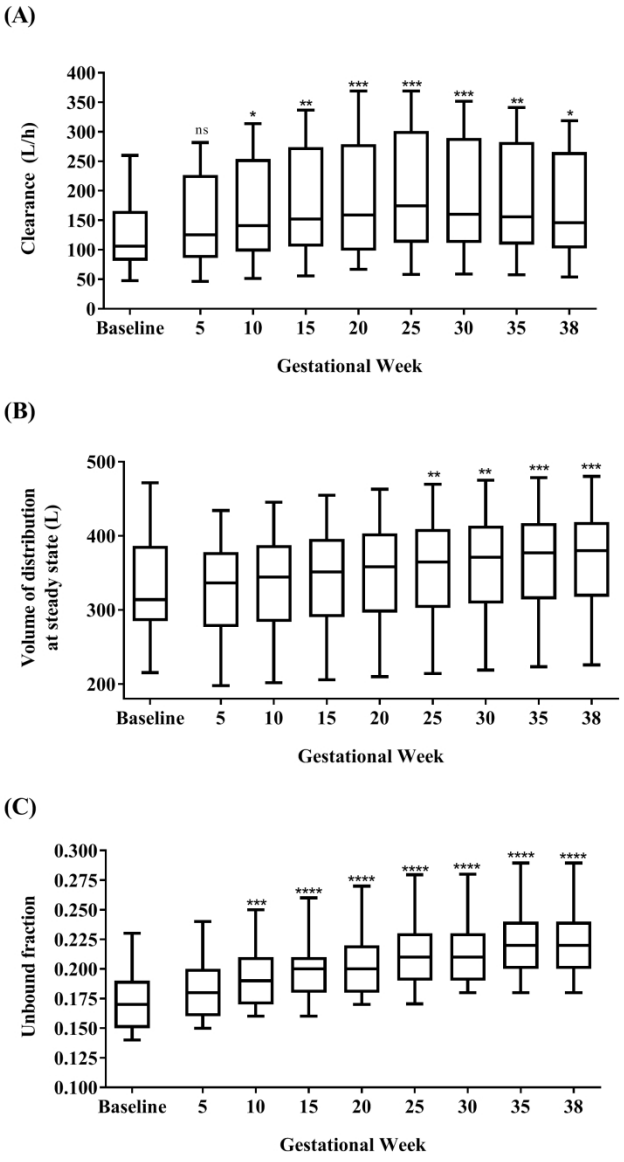


Figure 2

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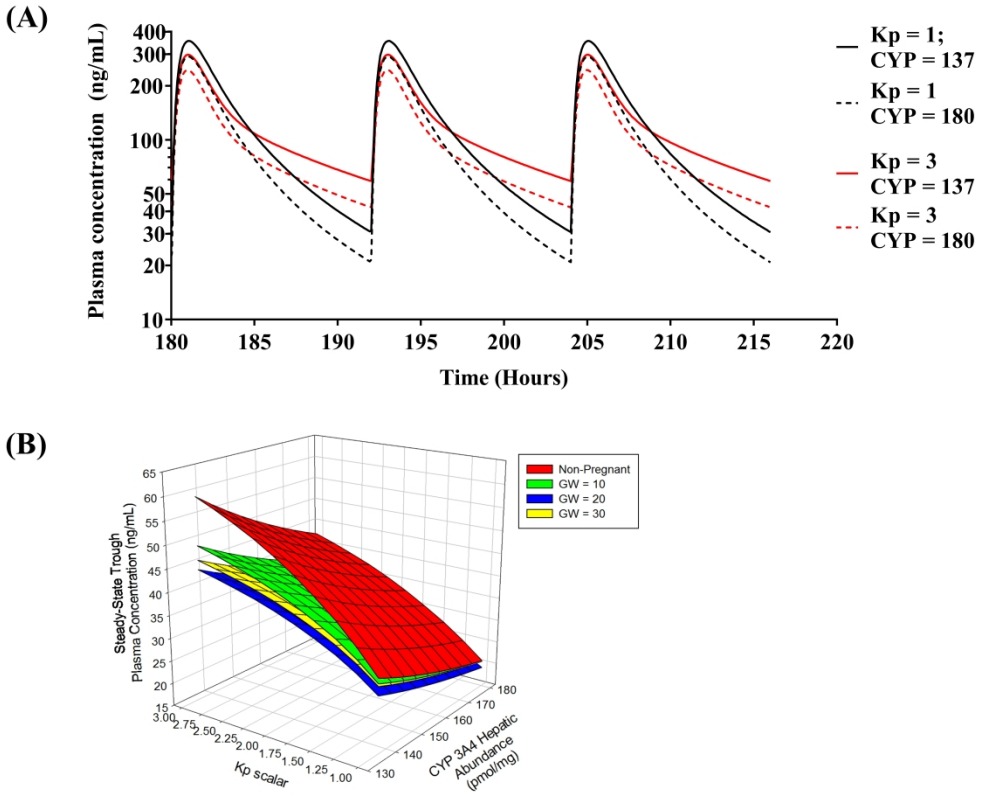

Figure 3

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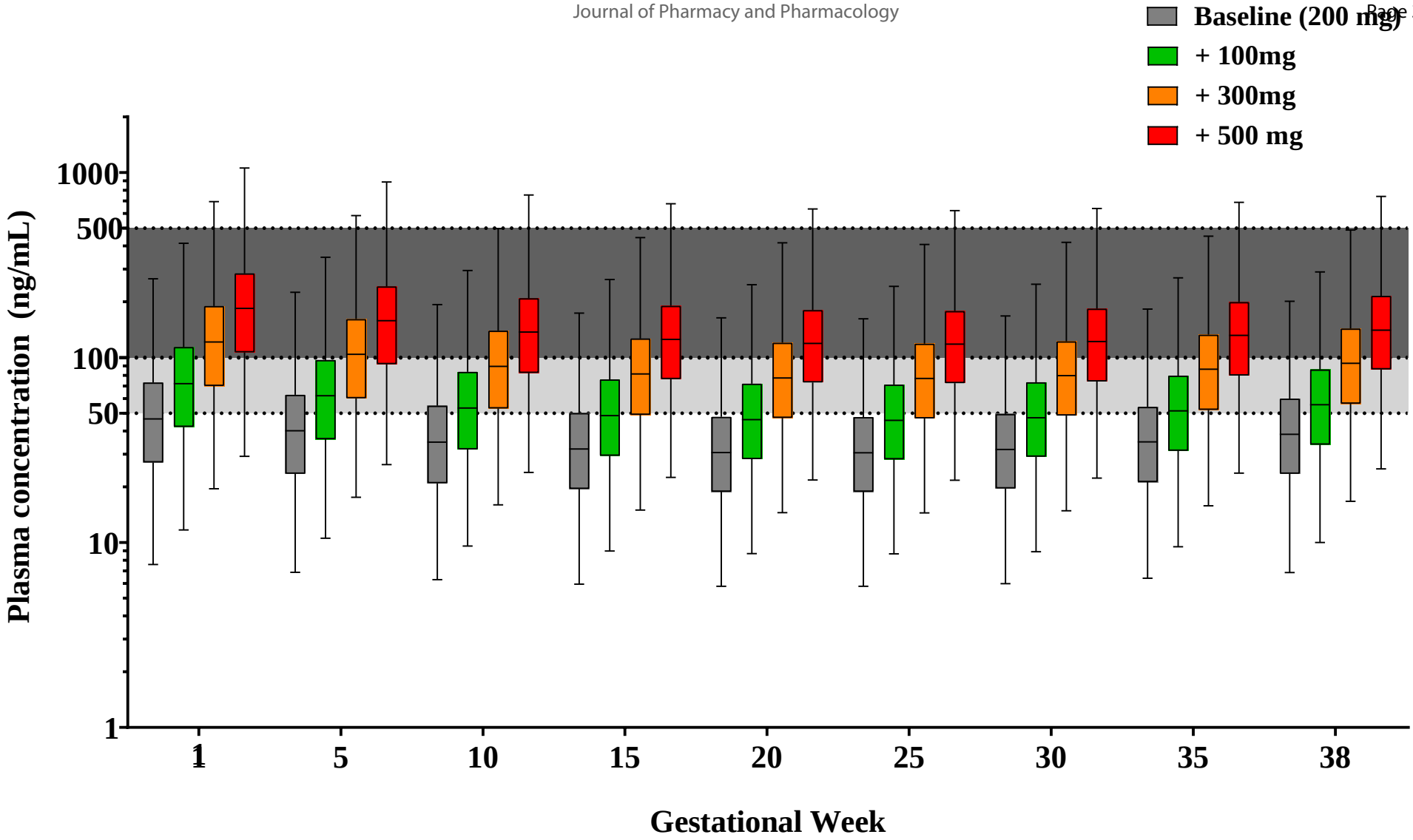
Baseline (200 mg)
+ 100mg
+ 300mg
+ 500 mg
Plasma concentration (ng/mL)
1000
500
100
50
10
1
1
5
10
15
20
25
30
35
38
Gestational Week