Prediction of Midazolam Pharmacokinetics in Pregnant Women with Coeliac Disease using Simcyp Pregnancy PBPK Model

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Introduction

Pregnant women with coeliac disease have a higher rate of spontaneous abortion and premature delivery of low birth weight babies than non-coeliac pregnant women [1]. Coeliac patients have an average abundance of 2 pmol CYP3A4 per mg intestinal microsomal protein [2]. This is compared with 12 pmol CYP3A4 per mg intestinal microsomal protein in healthy subjects.

Pregnancy is associated with many physiological and biochemical changes that vary with gestational age, including CYP3A4 activity [2].Physiologically based pharmacokinetic (PBPK) models can integrate both the drug characteristics and the underlying physiology, along with its variability within a population to predict drugs kinetics. Once the model performance is verified for a particular drug in a specific population, it can be assessed with increased confidence in another population with different characteristics.

Objectives

The objective of this study is to use PBPK approach to illustrate the potential impact of coeliac disease during pregnancy on midazolam pharmacokinetics taking into account the influence of temporal physiological changes in the system parameters using Simcyp Pregnancy population.

Materials and Methods

The Sim-pregnancy population, which accounts for physiological changes during pregnancy, including CYP3A4 activity [3], was selected from the population library in Simcyp Simulator V15R1. The compound Sim-Midazolam was selected from the compound library within the simulator. Absorption profile was predicted using first order absorption model based on predicted permeability of 6.045 $x10^{-4}$ cm/s using default Caco-2 information in the compound file, together with lag time of 0.2 hr. The full PBPK distribution and default enzyme kinetics were used to describe the disposition kinetics of midazolam.

Simulations were first performed to predict midazolam pharmacokinetics in healthy non-pregnant and pregnant populations. Simulated Profiles were compared to published clinical observations, where 2 mg midazolam was given orally to 13 healthy women during pregnancy, 28-32 gestational weeks, and repeated at 6–10 weeks postpartum [4]. Secondly, the library value of the content of CYP3A4 in the gut was reduced from 66.2 to 11.03 nmol/total gut to account for the relative loss of enzyme in coeliac patients. Additional scenario was simulated where the abundance of CYP3A5 was reduced by the same factor from 24.6 to 4.1 nmol/total gut, assuming that changes in CYP3A4 are reflective of overall CYP3A changes. A total of 10 virtual trials of 13 female individuals aged between 22 – 40 years were simulated from the pregnant population and the gestational age was set to 30 weeks, while it was zero for non-pregnant women.

Results and Discussion

Simulated profiles were in agreement with the reported concentration time profiles (Figure 1). Predicted/observed ratio for AUCinf, Cmax, CLpo and Tmax were 1.7, 1.1, 0.81 and 0.77 for non-pregnant and 2.0, 0.95, 0.74, and 0.75 for pregnant women. Plasma concentration in healthy pregnant women is lower than that in non-pregnant women due to the increase in CYP3A4 activity and reduction in the albumin plasma concentration during pregnancy. The reduction in CYP3A4 abundance in coeliac pregnant women resulted in a reduction in the midazolam first-pass clearance and an increased AUC compared with healthy pregnant women (Figure 2). This increase in the drug exposure in coeliac patients led to a comparable level to those predicted in healthy non-pregnant women (Table 1). These finding may be further investigated to inform dosing regimen in coeliac pregnant women and illustrate the utility of PBPK models in complex patients.

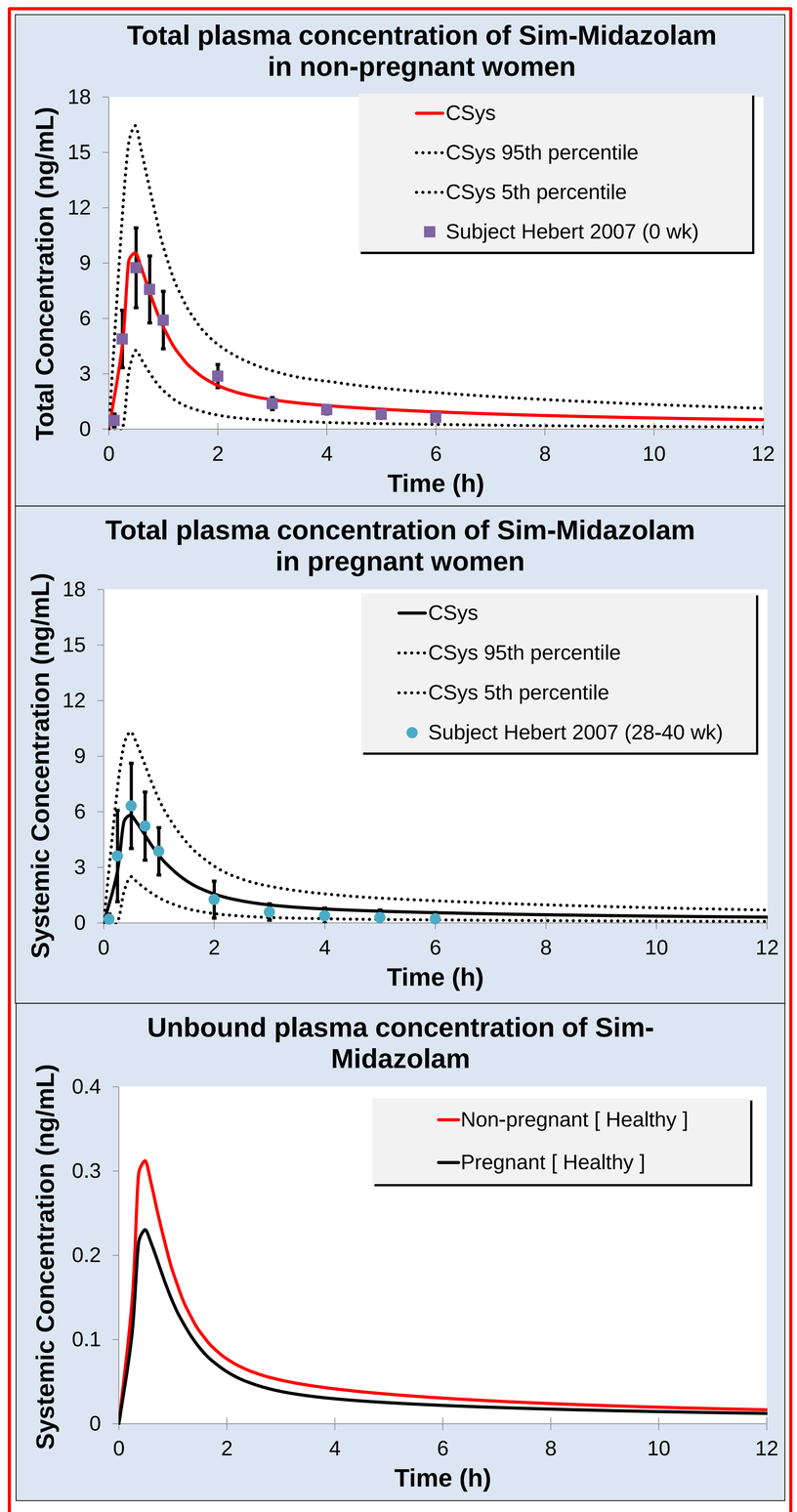

Figure 1. Predicted midazolam plasma concentration (lines) and observed mean[4] in pregnant and non-pregnant women.

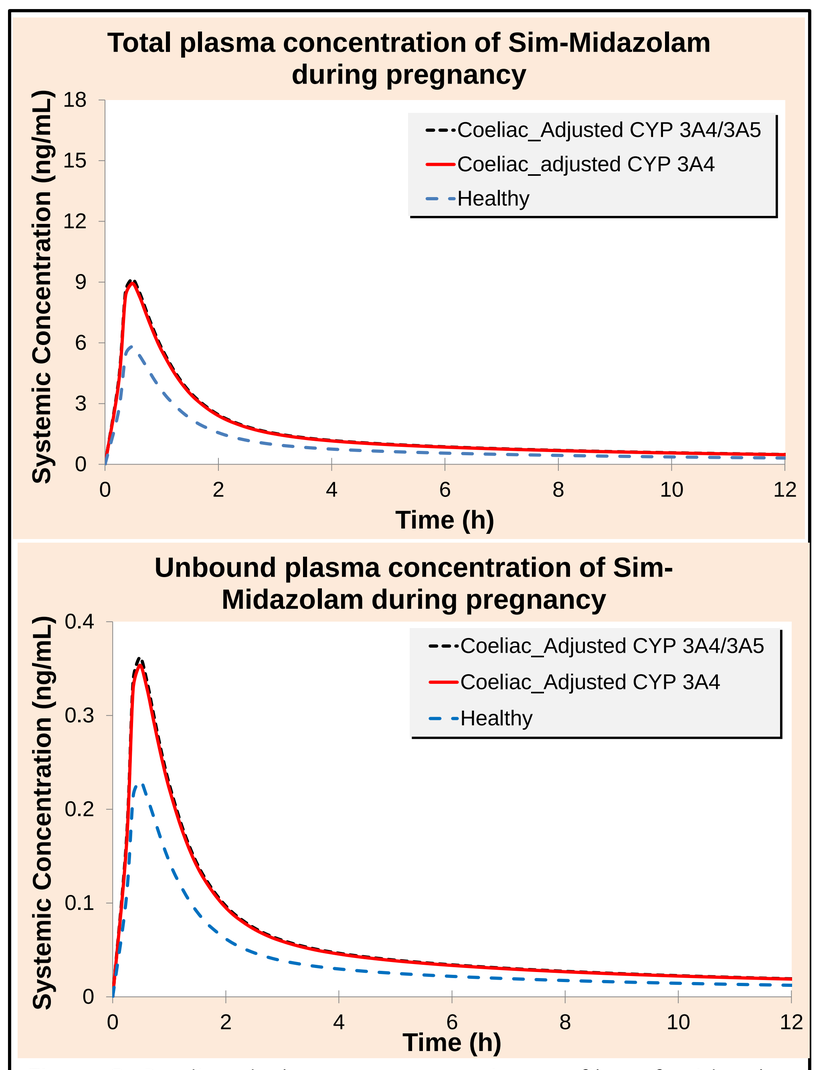

Figure 2. Predicted plasma concentration profiles of midazolam in pregnant women(30 gestational weeks) with and without coeliac disease.

	Total drug in plasma			Free drug in plasma		
	TMax (h)	CMax (ng/mL)	AUC,0-24h (ng/mL.h)	TMax (h)	CuMax (ng/mL)	AUCu,0-24h (ng/mL.h)
Healthy non-pregnant	0.41	10.1	23.6	0.41	0.33	0.77
Coeliac non-pregnant	0.41	15.0	34.9	0.41	0.49	1.14
Healthy pregnant	0.42	6.08	14.7	0.42	0.24	0.58
Coeliac pregnant (adjusted 3A4)	0.42	9.34	22.6	0.42	0.37	0.89
Coeliac pregnant (adjusted 3A4/3A5)	0.42	9.57	23.0	0.42	0.38	0.91

Table 1. Predicted pharmacokinetic parameters of Midazolam in non-pregnant and pregnant women with and without coeliac disease

References

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