Evaluation of maternal drug exposure following the administration of antenatal corticosteroids during late pregnancy using PBPK Modeling

Alice Ban Ke[1], Mark A. Milad [2]

[1] Certara, Princeton, NJ

[2] Milad Pharmaceutical Consulting LLC, Plymouth, MI

Abstract

Betamethasone and dexamethasone are the most widely studied antenatal corticosteroids (ACS) administered to pregnant women, just prior to the birth of a pre-term neonate, to accelerate fetal lung maturation. Although betamethasone, predominantly used in developed countries, has been shown to be an effective and safe intervention for reducing neonatal mortality, the choice of ACS and optimal dosing in low middle income countries (LMICs) remains unclear. This is primarily because the exposure-response relationships have not been established for ACS despite the long history of use. As the first step towards the optimal use of ACS in LMICs, we developed physiologically based pharmacokinetic (PBPK) models to describe the kinetics of ACS following intravenous, oral or intramuscular dosing. *In vitro* data describing the CYP3A4 enzyme contribution were incorporated and this was refined using clinical data. The models can be applied prospectively to predict kinetics of ACS in pregnant women receiving various dosing regimens.

Background

- ACS are administered to pregnant women between 24- and 34-weeks' gestation who are at imminent (within 48 hours) risk for preterm delivery. The common treatment in ACS consists of either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone administered intramuscularly every 12 hours.
- The two corticosteroids differ in their pharmacokinetic characteristics: betamethasone has a longer half-life (5.6 hours for betamethasone *versus* 2.4 hours for dexamethasone) because of its lower clearance and larger volume of distribution.

Methods

- The Simcyp Simulator V17 R1 was used for all simulations.
- A full PBPK distribution model was used for both ACS. A first-order absorption model with F_a and K_a estimated from clinical data was developed to describe the kinetics of ACS following intravenous, oral or intramuscular dosing.
- A single modification was made to the Sim-pregnancy file: an updated CYP3A4 function (Eq. (1)) informed by a midazolam PK study was used.

$$\text{Fraction of CYP3A4 activity} = 1-0.0016*GW+0.0019*GW^2- 0.00003*GW^3 \quad \text{Eq. (1)}$$

Results

- The workflow of model development and verification is presented in Figs. 1 (dexamethasone) and 2 (betamethasone).

Fig. 1. The workflow of dexamethasone model development

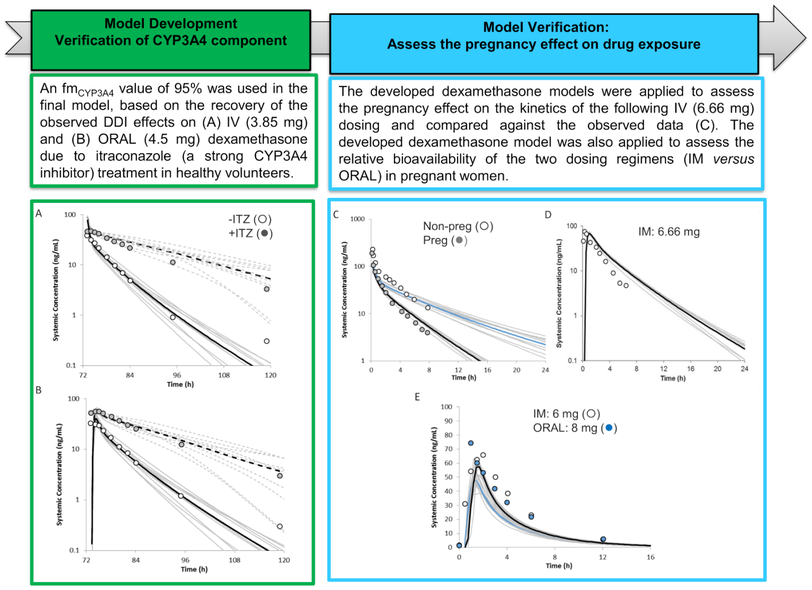


Fig. 2. The workflow of betamethasone model development

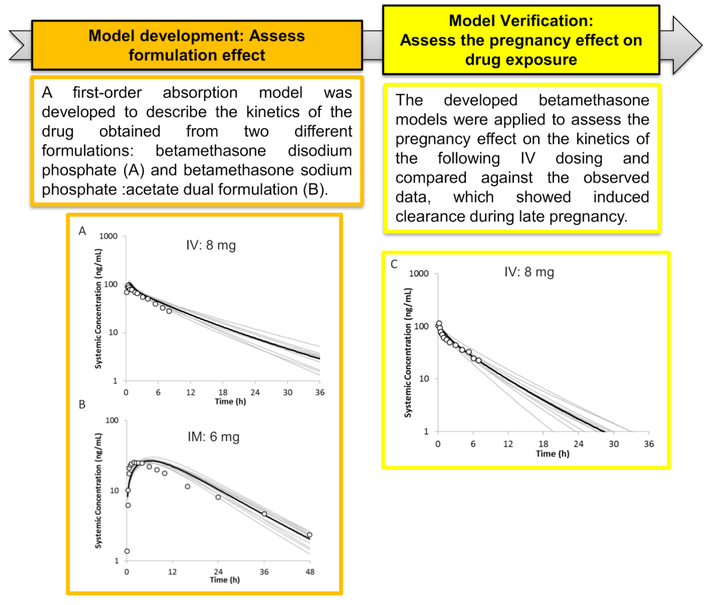
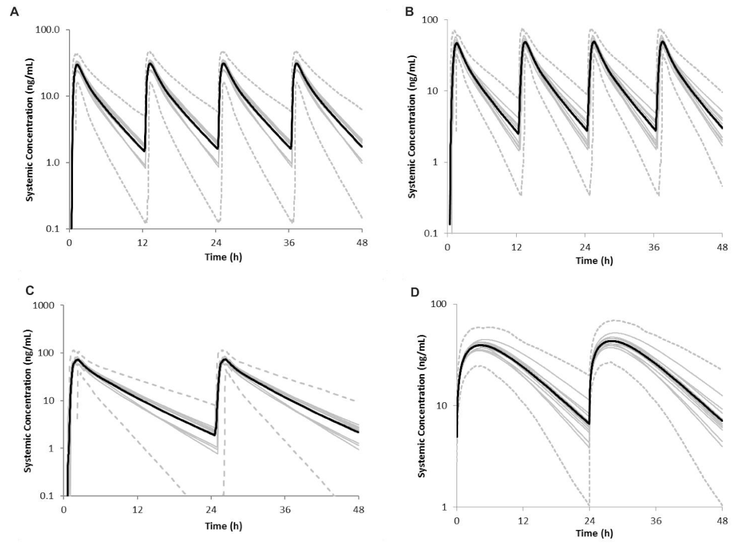


Fig. 3. Model application to predict the kinetics of ACS in pregnant women(mean gestational age: 30 weeks) receiving four oral (A) doses of 6 mg dexamethasone, four intramuscular (B) doses of 6 mg dexamethasone, two oral (C) doses of 12 mg betamethasone phosphate and two intramuscular (D) doses of 12 mg betamethasone phosphate: acetate.



Conclusions

- The developed models for ACS can be applied prospectively to predict the maternal kinetics of the two corticosteroids in pregnant women receiving various dosing regimens.
- Ongoing efforts are underway to link the developed maternal models for these two corticosteroids to a fully mechanistic fetal model to simulate the drug PK in fetal and neonates, following the administration of the drugs to pregnant women.

References

- Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst. Rev.*, CD004454 (2006)
- Petersen et al., Pharmacokinetics of betamethasone in healthy adults after intravenous administration. *Eur. J. Clin. Pharmacol.* **25**, 643-650 (1983)
- Tsuei SE et al.,. Disporition of synthetic glucocorticoids. II. Dexamethasone in parturient women. *Clin. Pharmacol. Ther.* **28**, 88-98 (1980)

ACKNOWLEDGEMENTS: We thank the Bill & Melinda Gates Foundation for providing the funding for this research.

ASCPT 2019, Washington D.C.

PIII-067