Clinical Pharmacokinetics

Physiologically based pharmacokinetic modeling to characterize acetaminophen pharmacokinetics and NAPQI formation in non-pregnant and pregnant women

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ESM_1

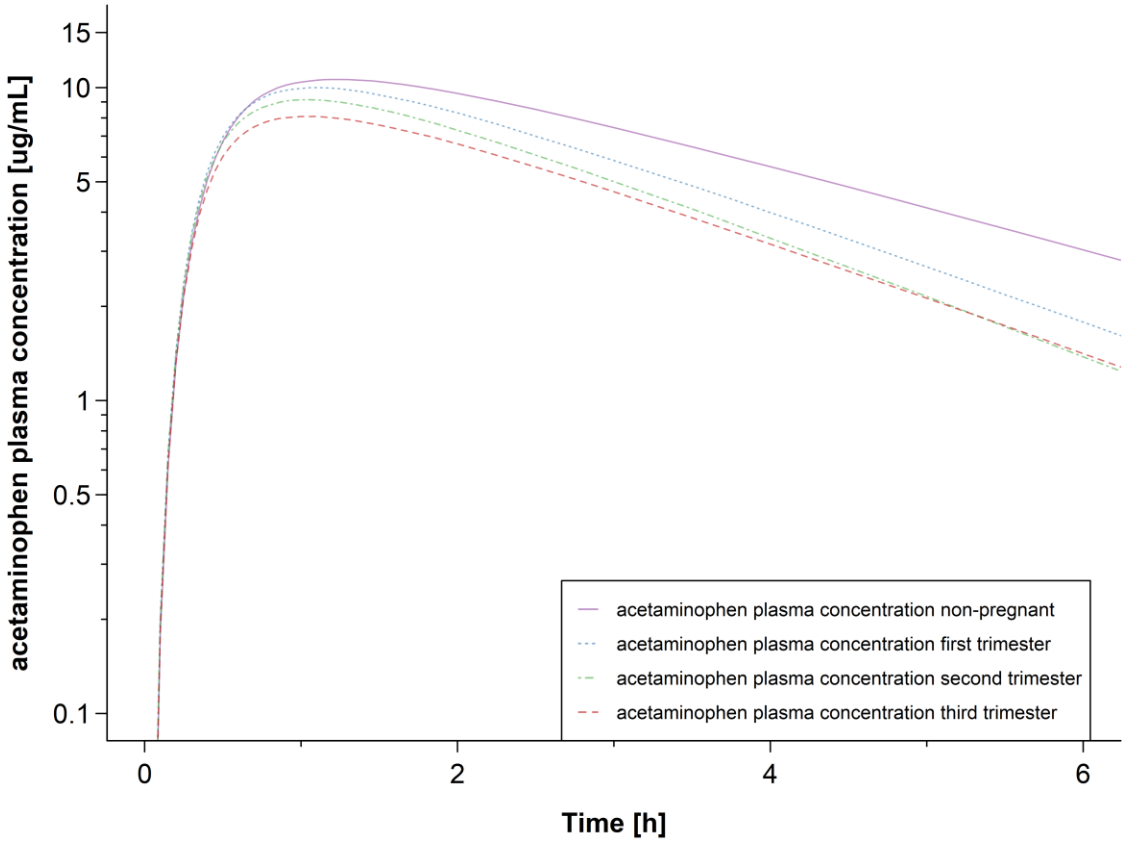
Methods: Development of PBPK models for acetaminophen

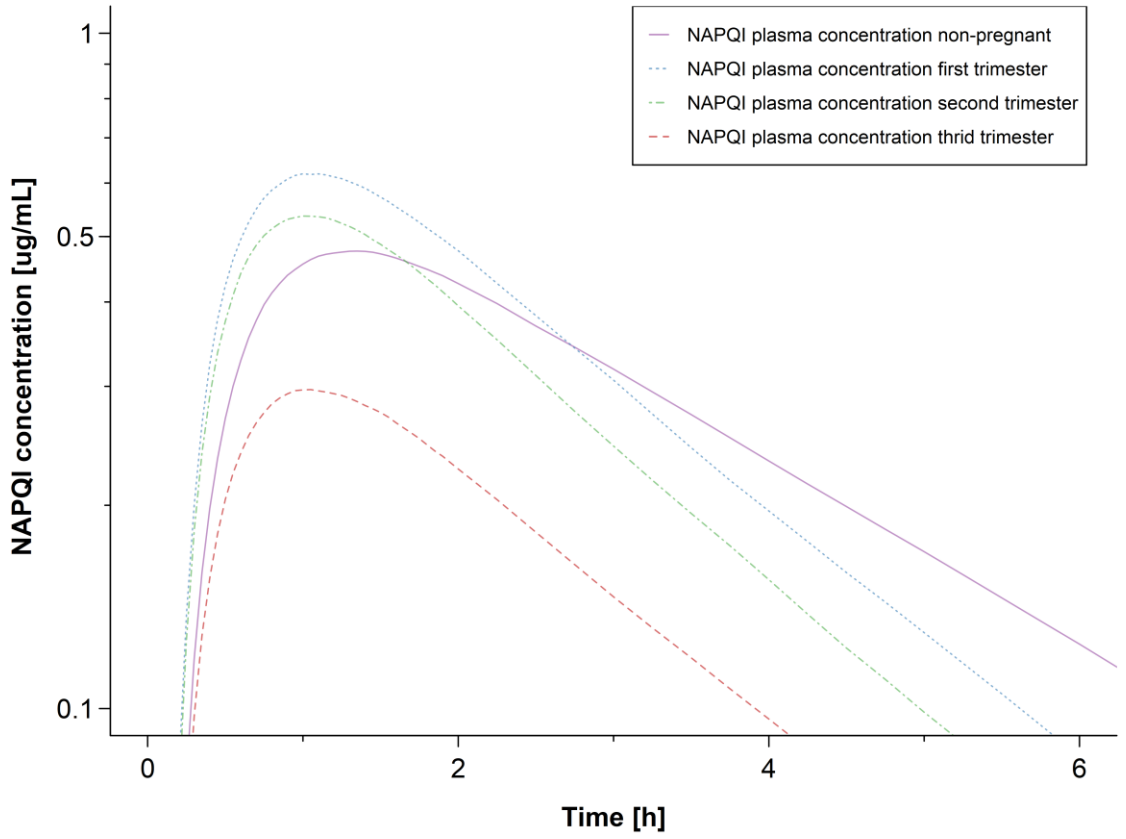
Based on in vivo observations [32, 35-37], it was assumed in the constructed PBPK model for non-pregnant women that the average dose fraction metabolized via UGT is 0.58, via SULT 0.3 and oxidized to NAPQI 0.08, while the remainder was assumed to represent the dose fraction excreted unchanged in urine (Table 1). For IV administration, simulated acetaminophen PK in non-pregnant subjects was compared with in vivo data from 8 healthy non-pregnant women (who did not take oral contraceptives) receiving 2000 mg IV acetaminophen [31]. Characteristics of the comparison studies are described in Table 2. In the PBPK model, biotransformation via UGT1A1 and SULT1A1 was modelled via first-order and Michaelis-Menten kinetics respectively, while biotransformation of NAPQI was modelled as specific intrinsic clearance via CYP2E1. Renal elimination processes for the UGT1A1- and SULT1A1-metabolite was implemented as tubular secretion via first-order and Michaelis-Menten kinetics, respectively; while NAPQI clearance was modelled as both tubular secretion via first order kinetics and glomerular filtration. Renal excretion of unchanged acetaminophen was implemented as glomerular filtration. Drug-specific parameters were loaded from a drug template incorporated per default in PK-Sim®[14]. In this PK-Sim® template, UGT1A1 and SULT1A1 are the dominant isoforms for acetaminophen glucuronidation and sulfation, respectively, and therefore only these enzymes were used here [13]. Furthermore, multiple CYP enzymes (CYP2E1, CYP2D6, CYP2C9, CYP2C19, CYP1A2) are implemented in this template for the conversion of acetaminophen to NAPQI. As acetaminophen is primarily metabolized to NAPQI by CYP2E1[10], only this enzyme was used here. Due to missing literature information, detoxification kinetics of NAPQI could not be parameterized and it was therefore assumed that the concentration of cysteine and mercapturate is equivalent to that of NAPQI [14].

In the non-pregnant PBPK model, lipophilicity and the clearance parameters of each elimination pathway (specified in PK-Sim® as reference concentration of UGT1A1, SULT1A1 and CYP2E1 and the glomerular filtration rate (GFR) fraction) were simultaneously fitted to the observed plasma concentration-time profile and metabolite-urine concentration-time profile and to the overall mass balance of each elimination pathway (Table 1). Predicted PK profiles in pregnant women were evaluated using in-vivo data from Allegaert *et al.* [31] who investigated the PK after IV administration of a loading dose 2000 mg of acetaminophen followed by 3 multiple doses of 1000 mg each administered every 6 hours in 47 women during caesarian with an average gestational age (GA) of 35 weeks. For oral administration, simulated acetaminophen in non-pregnant subjects was compared with in vivo data obtained from literature from 7 and 10 non-pregnant women (who did not take oral contraceptives) receiving 1500 and 650 mg acetaminophen, respectively (Table 2) [33, 34]. Thereafter, the intestinal permeability and the 50% dissolution time of the Weibull tablet dissolution function were simultaneously fitted to the in vivo PK profiles given in the comparison studies [33, 34].

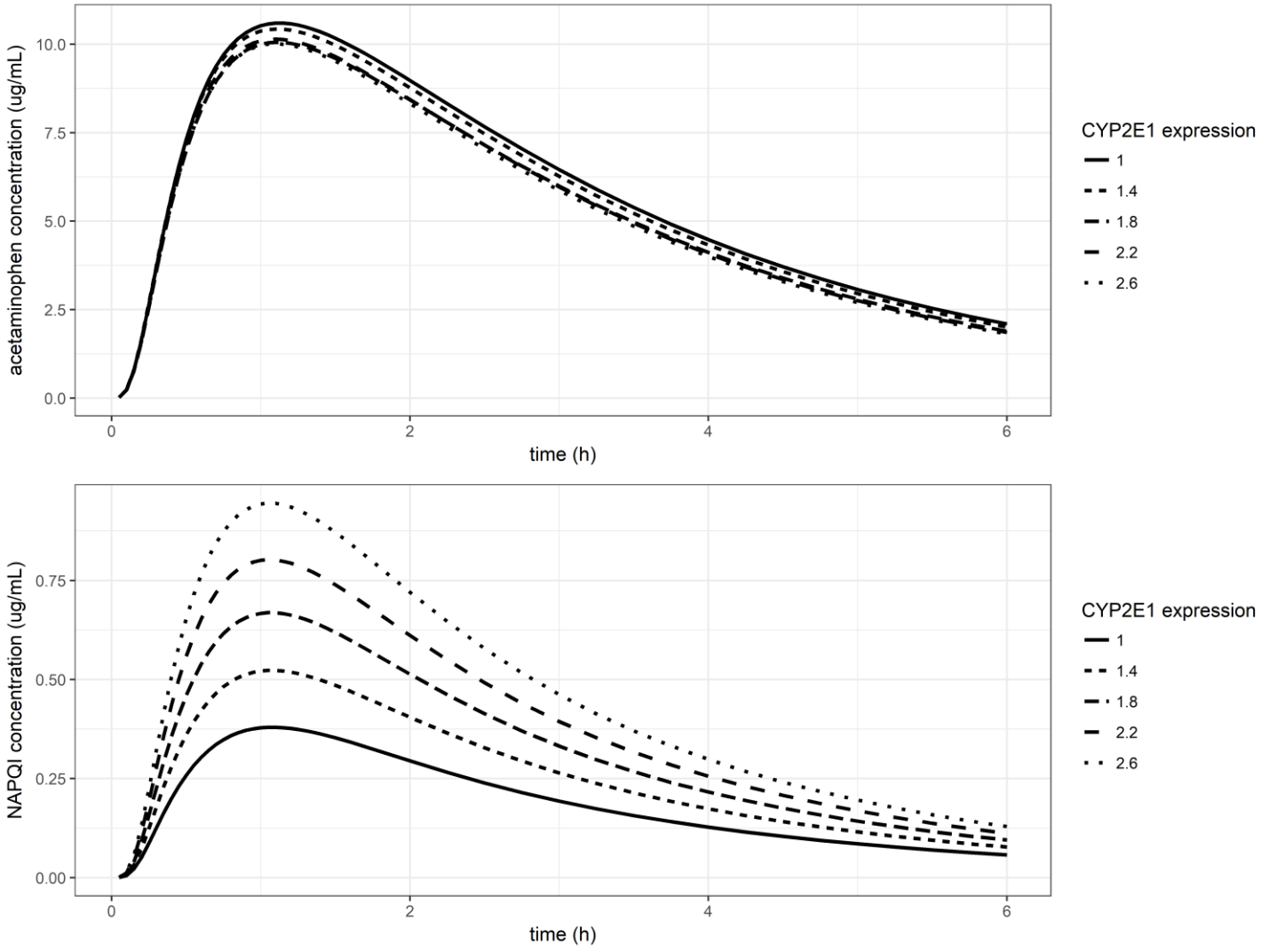
To evaluate the pregnancy-PBPK models for earlier stage (first trimester) of pregnancy, the study from Beaulac-Baillargeon.*et al.* was used (Table 2), that investigated 650 mg acetaminophen PK after oral administration in 8 women at 11 weeks of GA [33, 38].

ESM_2: Simulated plasma concentration-time profile of acetaminophen (A) and NAPQI (B) after 1000 mg oral acetaminophen administration in non-pregnant women and first, second, third trimester pregnant women.





ESM_3: Sensitivity analysis of CYP2E1 expression, ranging from 0-160% induction [in graph indicated as 1-2.6 respectively], with respect to maternal plasma acetaminophen and NAPQI concentration-time profiles after 1000 mg oral acetaminophen.



CYP2E1 Cytochrome-p-450 2E1, *NAPQI N*-acetyl-*p*-benzoquinone imine