Transplacental Passage of Acetaminophen in Term Pregnancy

Joshua F. Nitsche, MD, PhD1 Avinash S. Patil, MD2 Loralie J. Langman, PhD3 Hannah J. Penn4 Douglas Derleth, MD4 William J. Watson, MD5 Brian C. Brost, MD5

1 Department of Maternal–Fetal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina
2 Department of Maternal–Fetal Medicine and Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana
3 Department of Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota
4 Department of Neonatology, Mayo Clinic College of Medicine, Rochester, Minnesota
5 Department of Maternal–Fetal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota


Abstract

Objective The objective of this study was to determine the maternal and fetal pharmacokinetic (PK) profiles of acetaminophen after administration of a therapeutic oral dose.

Study Design After obtaining Institutional Review Board approval and their written informed consent, pregnant women were given a single oral dose (1,000 mg) of acetaminophen upon admission for scheduled cesarean delivery. Maternal venous blood and fetal cord blood were obtained at the time of delivery and acetaminophen levels were measured using gas chromatography-mass spectroscopy. PK parameters were calculated by noncompartmental analysis. Nonparametric correlation of maternal/fetal acetaminophen levels and PK curves were calculated.

Results In this study, 34 subjects were enrolled (median, 32 years; range, 25–39 years). The median maternal weight was 82 kg (range, 62–100 kg). All but two subjects were delivered beyond 39 weeks’ gestation. The median newborn birth weight was 3,590 g (interquartile range, 3,403–3,848 g). Noncompartmental analysis described similar PK parameters in the maternal (T1/2, 84 minutes; apparent clearance [Cl/F], 28.8 L/h; apparent volume of distribution [Vd/F], 57.5 L) and fetal compartments (T1/2, 82 minutes; Cl/F, 31.2 L/h; Vd/F, 61.2 L). Paired maternal/fetal acetaminophen levels were highly correlated (p < 0.0001).

Conclusion Fetal acetaminophen PKs in the fetus parallels that in the mother suggesting that placental transfer is flow limited. Maternal acetaminophen levels can be used as a surrogate for fetal exposure.

Keywords ► fetalf drug exposure ► acetaminophen ► pregnancy ► pharmacokinetics

Acetaminophen is taken by nearly two-thirds of pregnant women, making it the most commonly utilized over-the-counter medication in pregnancy.1 Despite the perception of safety, maternal acetaminophen use has been associated with increased risks to the newborn of attention deficit hyperactivity disorder (ADHD),2 drug-induced liver injury (DILI),3 and asthma in childhood.4 The extent of fetal exposure from a standard acetaminophen dose is not well understood. Acetaminophen has been demonstrated to cross the placenta after maternal overdose5 as well as after therapeutic doses.6 Two
In this study, 34 subjects were enrolled at a median age of 32 years (range, 25–39 years). Subjects were primarily Caucasian (31/34 or 91%), with the remainder Asian (2/34 or 6%) or Hispanic (1/34 or 3%). The median maternal weight was 82 kg (range, 62–100 kg). Two women delivered at 38 weeks’, 30 delivered at 39 weeks’, and 2 women delivered at 40 weeks’ gestation. The median newborn birth weight was 3,590 g (interquartile range, 3,403–3,848 g). Noncompartmental PK analysis described acetaminophen disposition in the maternal compartment with a half-life of 84 minutes and Cl/F of 28.8 L/h. In the fetal compartment, acetaminophen half-life was 82 minutes with a Cl/F of 31.2 L/h. Peak concentrations of acetaminophen (maternal 12.3 μg/mL; fetal 11.2 μg/mL) and Vd/F (maternal 57.5 L; fetal 61.2 L) were similar. Linear regression analysis revealed that maternal acetaminophen level was a significant predictor of fetal level (p > 0.0001) and that maternal and fetal levels were very highly correlated (r = 0.91). PK parameters and curves are provided in → Fig. 1.

![Acetaminophen PKs in maternal and fetal compartments. Maternal and fetal PK curves are juxtaposed with key parameters listed later. Points on the graph are individual acetaminophen levels with a line of best fit representing the PK curve for the study population. AUC0–inf, area under the curve (time 0–∞); Cmax, maximum concentration; Cl/F, apparent clearance; PK, pharmacokinetic; Vd/F, apparent volume of distribution.](image-url)
Conclusion

Acetaminophen PKs in maternal samples are consistent with values previously reported in pregnant women (Vd/F, 57.5 L; Cl/F, 28.8 L/h), except for a shorter half-life (84 vs. 114 minutes). They are also consistent with those described in healthy male volunteers in whom serum levels peak between 7.7 and 17.6 µg/mL and have a half-life of 1.5 to 2.5 hours. These values are similar to the peak concentration of 12.3 µg/mL and a half-life of 84 minutes seen in our PK model. Maternal and fetal acetaminophen levels are comparable as early as 30 minutes after administration, indicating rapid placental transfer of the drug. Notably, acetaminophen PKs in fetal samples closely parallels behavior of the drug in the maternal system. The time to peak concentration and half-life are similar, and the fetal AUC is nearly the same as maternal AUC (> 90%). The comparable concentrations of acetaminophen in the maternal and fetal compartments suggest that placental transfer is influenced primarily by rate of blood flow (“flow limited”) and not by transporters in the placenta (“diffusion limited”).

Fetal acetaminophen exposure has been associated with ADHD, DILI, and childhood asthma, though the threshold for these effects in the fetus is not known. An understanding of placental transfer kinetics is necessary to correlate maternal drug intake to fetal exposure and clinical outcomes. In this study, we have demonstrated that acetaminophen levels in the fetal compartment are nearly identical to maternal levels. The very high correlation between maternal and fetal levels suggests that maternal acetaminophen levels can be used as a surrogate for the extent of fetal exposure.

The modest sample size and lack of information on acetaminophen metabolites are the main weaknesses of the study. Although our findings do provide novel information on the PKs of acetaminophen in pregnant women and their fetuses, acetaminophen levels alone cannot provide precise estimation of fetal risk, as acetaminophen-mediated injury occurs when a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is formed. Saturation of the metabolic enzymes that inactivate acetaminophen leads to accumulation of NAPQI and subsequent adverse effects. Thus, future studies should assess NAPQI along with acetaminophen levels and utilize a larger sample size to permit a formal population PK analysis. In addition, our observation that transplacental passage of acetaminophen is “flow limited” is based on features of the maternal and fetal PK curves. Confirmation that acetaminophen does not interact with placental transporters may be obtained through ex vivo placental perfusion studies.

Although the current study suggests that fetal exposure to acetaminophen can be predicted using maternal drug levels, further study of acetaminophen metabolism to NAPQI in the fetus is clearly needed to better understand the risk of fetal harm after maternal acetaminophen use. However, our findings suggest that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus.

References
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