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Ondansetron Exposure Changes in a Pregnant Woman

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Abstract

Pregnancy results in many physiologic changes that can alter the pharmacokinetic profiles of medications used during pregnancy. One of the primary factors leading to these pharmacokinetic changes is altered activity of drug-metabolizing enzymes. Ondansetron is a substrate of cytochrome P450 (CYP) 3A4 (primary metabolic pathway), 2D6, and 1A2, all of which are altered during pregnancy. We evaluated the pharmacokinetics of ondansetron at three different gestational time points in a 26-year-old, pregnant, Caucasian woman with normal liver and kidney function, who was maintained on ondansetron 8 mg administered orally 3 times/day throughout her pregnancy. Serial plasma samples were collected from the subject over one 8-hour dosing interval at 14, 24, and 35 weeks' gestation (representing early-, mid-, and late-pregnancy time points, respectively). Ondansetron plasma concentrations were determined using liquid chromatography-tandem mass spectrometry. Ondansetron area under the plasma concentration–time curve decreased progressively across gestation (634 ng hr/ml in early pregnancy, 553 ng hr/ml in mid-pregnancy, and 387 ng hr/ml in late pregnancy), with a corresponding increase in apparent oral clearance (12.6 L/hr in early-pregnancy, 14.5 L/hr in midpregnancy, and 20.7 L/hr in late-pregnancy). The decreased area under the plasma concentration–time curve and exposure to ondansetron across gestation is likely due to increased activity of CYP3A4 and CYP2D6 during pregnancy. We were not able to study this patient during the postpartum period; however, as with other CYP3A4 and CYP2D6 substrates, the apparent activities of these isoenzymes are likely

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return to baseline. To our knowledge, this is the first report to describe ondansetron pharmacokinetics across gestation. Additional pharmacokinetic and pharmacodynamic data are needed to confirm our results and to evaluate clinical impact; however, in the meantime, clinicians should be aware of these pharmacokinetic changes in ondansetron exposure during pregnancy.

Keywords

ondansetron; pregnancy; pharmacokinetics

Pregnancy results in many physiologic changes that can alter the pharmacokinetic profiles of medications used during pregnancy. Changes in the absorption, distribution, metabolism, and elimination of many drugs have been reported during pregnancy.[1] One of the primary factors leading to changes in pharmacokinetics is altered activity of drug-metabolizing enzymes. In pregnancy, the apparent activities of cytochrome P450 (CYP) 3A4, 2D6, and 2D9, and uridine 5′-diphospho-glucuronosyl transferase (UGT) 1A4 are increased.[2, 3] Conversely, the apparent activities of CYP1A2 and CYP2C19 are decreased during pregnancy.[2, 3] We evaluated the pharmacokinetics of ondansetron, a substrate for CYP3A4 (primary metabolic pathway), CYP1A2, and CYP2D6[4] at three different gestational time points in a pregnant woman. This study was conducted in accordance with the Helsinki Declaration of 1975 and was approved by the institutional review board.

Case Report

A 26-year-old, pregnant, Caucasian woman was recruited for the study as part of the Obstetric-Fetal Pharmacology Research Unit Network project. She had normal liver and kidney function and was maintained on ondansetron 8 mg orally 3 times/day throughout her pregnancy. Serial blood samples were collected over one 8-hour dosing interval at time 0 and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing, at 14, 24, and 35 weeks' gsestation (representing early-, mid-, and late-pregnancy time points, respectively). Plasma concentrations of ondansetron were measured based on minor modification of a previously published liquid chromatography–tandem mass spectrometric assay[5] using a Waters Separation Module 2695 and a Waters Micromass Quattro micro triple quadrupole mass spectrometer (Waters Corp., Milford, MA) using positive electrospray ionization mode. Steady-state ondansetron peak plasma concentrations (C_{max}) and area under the plasma concentration–time curve from 0 to 8 hours ($AUC_{0–8}$) declined across gestation (Table 1, Figure 1). The apparent oral clearance (CL/F) increased across gestation (Table 1).

Discussion

Ondansetron is extensively metabolized in humans. Its primary metabolic pathway is hydroxylation, followed by glucuronide or sulfate conjugation.[6] Ondansetron is a substrate of CYP3A4, CYP2D6, and CYP1A2. Among these phase I enzymes, CYP3A4 is the primary enzyme responsible for hydroxylation of ondansetron.[4] Given that apparent CYP3A4 and CYP2D6 activities increase during pregnancy, we anticipated a change in exposure to ondansetron. Consistent with our expectation, the area under the plasma concentration–time curve, a measure of systemic exposure of a drug, decreased

progressively with time during pregnancy. We were not able to study this patient during the postpartum period; however, as with other CYP3A4 and CYP2D6 substrates, the apparent activities of these isoenzymes are likely to return to baseline.

Conclusion

To our knowledge, this is the first report to describe ondansetron pharmacokinetics across gestation. Additional pharmacokinetic and pharmacodynamic data are needed to confirm our results and to evaluate the clinical impact. In the meantime, clinicians should be aware of these pharmacokinetic changes in ondansetron exposure during pregnancy that may warrant dosing alterations.

Acknowledgments

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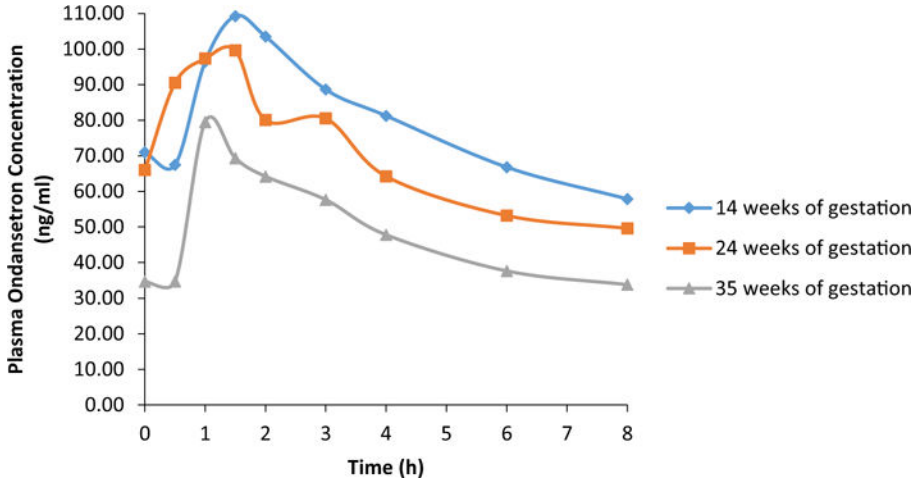

Figure 1.

Ondansetron plasma concentration–time profile in a pregnant woman at gestational weeks 14, 24, and 35.

Table 1

Pharmacokinetic Parameters of Ondansetron

Time Point	C_{max} (ng/ml)	$AUC_{0–8}$ (ng hr/ml)	CL/F (L/hr)
Early pregnancy (14 wks' gestation)	109	634	12.6
Mid-pregnancy (24 wks' gestation)	100	553	14.5
Late pregnancy (35 wks' gestation)	80	387	20.7

C_{max} = peak plasma concentration; $AUC_{0–8}$ = area under the plasma concentration–time curve from 0 to 8 hrs; CL/F = apparent oral clearance.