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Placental Transfer of Ondansetron during Early Human Pregnancy

Shing-Shun N. Siu,[1] *Matthew T.V. Chan*[2] and *Tze-Kin Lau*[1]

1 Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
2 Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

Abstract

Background and objective: Nausea and vomiting are common conditions that occur during early pregnancy and can be disabling. Ondansetron had been used in pregnant women when treatment with conventional antiemetics has failed; however, the safety and tolerability of this relatively new antiemetic drug during pregnancy is still uncertain. The objective of this study was to quantify the placental transfer of ondansetron in the first trimester of human pregnancy.

Patients and methods: This was a prospective, observational study. Forty-one patients who requested surgical termination of pregnancy at the first trimester were administered three doses of ondansetron 8mg before surgery. Maternal venous blood, coelomic fluid, amniotic fluid and fetal tissue were collected from each patient for analysis of ondansetron by liquid chromatography-mass spectometry.

Results: Ondansetron was found in all samples. Drug concentration in fetal tissue was significantly higher than that in the amniotic fluid and similar to that in the coelomic fluid. The median (interquartile range) fetal/maternal ratio was 0.41 (0.31–0.52) and there were no significant correlations between ondansetron concentrations in each compartment and gestational age.

Conclusions: A significant amount of ondansetron was present in all embryonic compartments. The developmental significance of this drug exposure requires further investigation, i.e. whole embryo culture.

Background

Nausea and vomiting in pregnancy (NVP) are common symptoms during the first trimester, affecting as many as 50–80% of pregnant women. Depending on its severity, NVP produce undue physical, psychological and economical burden to both the patients and their families.[1] A recent survey in North America revealed that 13% of patients experiencing NVP had considered termination of pregnancy because of intolerable symptoms.[2] In approximately 0.3–2% of all pregnant women, NVP result in dehydration and electrolyte disturbance, a condition known as hyperemesis gravidarum.[3] These patients required hospitalisation for fluid and electrolyte resuscitation; therefore, an effective treatment for NVP is of paramount importance.

To date, the exact aetiology of NPV and hyperemesis gravidarum is still unknown, thus treatment is limited to symptomatic relief. The use of simple natural remedies, including dietary adjustment and

change of lifestyle, is common advice given to women with NVP; however, the response is unpredictable. Many women with NVP will eventually require pharmacological treatment;[4] however, the use of medication in the first trimester of pregnancy poses great concern to both obstetricians and pregnant women.[5,6] Nonetheless, newer treatments have to be considered when NVP do not respond to conventional antiemetic therapy.

Ondansetron, a selective serotonin 5-HT_3 receptor antagonist, is known to be highly effective in relieving chemotherapy- or postoperative-related nausea and vomiting.[7] Several reports suggest that ondansetron is an effective treatment for hyperemesis gravidarum.[8-11] Koren and Levichek[6] recommended that ondansetron should be used when conventional antiemetic therapy fails; however, its teratogenic potential and the passage across the human placenta at an early stage of pregnancy are largely unknown. The aim of this study was to evaluate the placental transfer of ondansetron during the first trimester of human pregnancy.

Patients and Methods

Forty-one pregnant women who requested first trimester surgical termination of pregnancy under general anaesthesia because of psychosocial reasons were studied. All patients were assessed and counselled in the outpatient clinic at the Prince of Wales Hospital, Shatin, Hong Kong, by gynaecologists not involved in this study. Patients were only approached for consent to participate in this study after they had been admitted for surgery. Patients who had any medical disease or were taking any type of medication were excluded. The study was approved by the Clinical Research Ethics Committee and written consent was obtained from all patients.

Three oral doses of ondansetron 8mg (Zofran±, GlaxoSmithKline, Middlesex, UK)**1** were administered before surgery. The first and second doses were administered at 1400 hours and 2200 hours, respectively, on the day before surgery, and the third dose was administered 4 hours prior to surgery. This treatment schedule mimics the usual clinical regime. After induction of anaesthesia, fetal viability and gestation were confirmed by ultrasonography. Four types of biological samples were collected, as previously described:[12] (i) maternal venous blood was drawn immediately before induction of anaesthesia; (ii) coelomic and (iii) amniotic fluid were aspirated under transvaginal ultrasonography guidance before suction curettage; and (iv) fetal parts, most commonly limbs and the trunk, were identified, retrieved and washed with normal saline to remove maternal blood after the procedure. Surgical termination of pregnancy was performed in the usual manner using suction curettage.

Maternal plasma was separated by centrifugation at 1250 α *g* for 10 minutes. All samples were kept at −70≤C until analysis. The fetal tissues were weighed, mixed and homogenised in physiological saline and centrifuged to obtain a clear supernatant before analysis. Ondansetron concentration in all specimens was measured by the liquid chromatography-mass spectrometry system (Applied Biosystems/MDS Sciex, Toronto, ON, Canada). Ondansetron concentrations ranging from 0.1 to 100 ng/mL and fixed amounts of loxapine (internal standard) were spiked into the samples for calculating the calibration graphs. One millilitre of tissue or fluid sample, buffer, NaCl and ethyl acetate were added during the sample preparation. The ethyl acetate was evaporated under nitrogen gas and reconstituted with 100≥L mobile phase solution. Five microliters of the reconstituted sample was injected into the system for analysis. Ondansetron was analysed on a reverse-phase Hypersil BDS C18 column (ThermoQuest, Runcorn, UK).

The lower limit of detection was 0.025 ng/mL based on a signal-to-noise ratio of 3. Linear responses were obtained in analyte/internal standard peak height ratios for analyte concentrations ranging from 0.5 to 100 ng/mL with a correlation coefficient value of 0.99, and ranging from 0.5 to 80 ng/g with a correlation coefficient value of 0.9976 for fetal tissue. The mean extraction recovery of ondansetron was >90%. Accuracy ranges from 97.99% to

1 The use of trade names is for product identification purposes only and does not imply endorsement.

110.81% for concentrations from 0.5 to 80 ng/mL. The inter-assay coefficient of variation of the assay varied between 5.71% at 0.5 ng/mL, 5.11% at 2 ng/mL, 8.24% at 20 ng/mL and 7.88% at 80 ng/mL. The intra-assay coefficient of variation of the assay was 6.99% at 0.5 ng/mL, 4.16% at 2 ng/mL, 4.85% at 20 ng/mL and 2.07% at 80 ng/mL.

Statistical Analysis

Data were presented as median (interquartile range [IQR]). Intergroup difference was analysed using the Wilcoxon's signed rank test. To indicate the overall extent of placental transfer, the ratio of fetal tissue to maternal plasma ondansetron concentration (fetal/maternal ratio) was calculated. Ondansetron concentrations in various specimens and the fetal/maternal ratio were also compared with gestational age using the Spearman's rank test; p-values <0.05 were considered significant.

Results

The median (IQR) age and weight of patients was 34 (20–38) years and 55.2 (50.5–58.6) kg, respectively. Intraoperative ultrasonography confirmed live pregnancy in all women. The median (range) gestational age of pregnancy was 10.6 (9.3–12.1) weeks. The median duration from the last dose of ondansetron and the start of surgery was 4.2 hours (IQR 3–5 hours). Ondansetron was detected in all biological samples. Figure 1 shows the distribution of ondansetron concentration across the different maternal and fetal compartments. The median (IQR) total drug concentrations in maternal plasma, fetal tissue, coelomic fluid and amniotic fluid were 56.5 (38.7–67.5) ng/mL, 23.7 (12.9–27.1) ng/g, 17.6 (14.8–22.2) ng/mL and 11.9 (10.5–16.8) ng/mL, respectively. The average free ondansetron concentration in maternal plasma was 37% of the total drug concentration. The median (IQR) protein-free drug concentrations in maternal plasma and coelomic fluid were 19.1 (15.1–24.6) ng/mL and 7.6 (6.6–8.8) ng/mL, respectively. The total ondansetron concentrations between fetal tissue and coelomic fluid were similar ($p = 0.16$). There was also no significant difference between protein-free drug concentration in maternal plasma and total drug concentration in coelomic fluid ($p = 0.07$). No significant correlation was found between these drug concentrations and gestational age or the time interval between the last dose of ondansetron to the start of surgery.

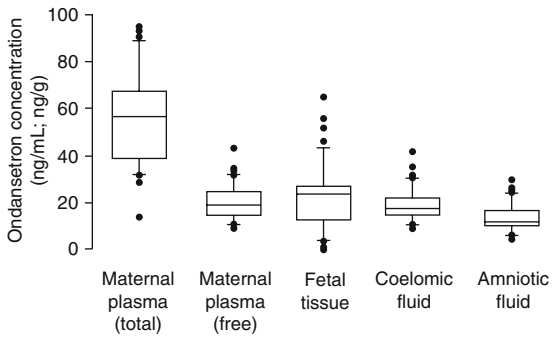

Fig. 1. Box plot showing ondansetron concentrations in each type of specimen. The central line in the box represents the median value, the lower and upper line the 25th and 75th percentile, respectively, whisker represents values <1.5 interquartile range (IQR) and ( ) represents values >1.5 IQR.

The median fetal/maternal ratio (IQR) was 0.41 (0.31–0.52) and the median (IQR) coelomic fluid/free maternal drug ratio was 0.94 (0.87–1.13). There was no significant relationship between these two ratios and gestational age.

Discussion

NVP are among the most common symptoms of pregnancy; no evidence-based management guidelines are currently available. Antihistamines, anticholine receptor antagonists, dopamine receptor antagonists and corticosteroids are commonly used at the physician's discretion. Magee et al.[4] reviewed the safety and effectiveness of these antiemetics and reported that only Diclectin± (a combination of doxylamine and pyridoxine [vitamin B_6]) and phenothiazines were proven to be well tolerated and effective. However, many patients did not respond to these conventional treatments and a more powerful antiemetic is required.

Ondansetron is highly effective in the treatment of chemotherapy-associated and postoperative nausea and vomiting.[7] An early pilot study showed that ondansetron was as effective as promethazine in the treatment of NVP.[13] Case reports indicated that

ondansetron was an effective option when conventional antiemetics failed.[8-11] One of the concerns in using ondansetron for the treatment of NVP is the uncertainty of its teratogenicity in human pregnancy, especially when prescribed during the first trimester, i.e. the organogenesis phase. Einarson et al.[14] reported an increase of fetal abnormality in an observational study evaluating the safety of ondansetron for NVP; however, this study had a small sample size, and the findings did not attain statistical significance.

In order to be teratogenic in human pregnancy, a drug must be able to pass through the placenta in early pregnancy in a concentration that is high enough to cause abnormal fetal development. No reports on fetal malformation after ondansetron administration during pregnancy were found in the medical literature. The apparent lack of teratogenicity may be due to pharmacokinetic factors or the intrinsic properties of ondansetron.

The present study evaluated placental transfer of ondansetron in early human pregnancy. Subjects were prescribed three doses of ondansetron, which was similar to the usual clinical regimen. Although the dose regimen will not have achieved a steady-state concentration, the median maternal ondansetron concentration (56.5 ng/mL) was similar to the reported steady-state concentration in nonpregnant subjects (42 16 ng/mL).[15] Furthermore, there was no correlation between maternal concentration and the time interval from the last dose of ondansetron to the start of surgery. These data suggested that the dosing regimen allowed adequate time for drug equilibration between maternal and fetal compartments. We believe our model provides a close estimation of ondansetron concentration in different fetal compartments after maternal exposure. Our study found that free ondansetron concentrations in maternal plasma were not significantly different from total drug concentrations in coelomic fluid, suggesting that free ondansetron readily passed through the human placenta in the first trimester. A significant amount of ondansetron was also found in fetal tissue and amniotic fluid. The ondansetron concentration was lowest in the amniotic fluid sample, while that in the fetal and coelomic fluid samples was similar. These findings suggest that the predominant route of drug transfer in early pregnancy is through the chorionic plate. Coelomic fluid is an ultrafiltrate of maternal plasma, while amniotic fluid is a combination of transudate from fetal skin and transfer from coelomic fluid.[16] On average, the ondansetron concentration attained in fetal tissue was 41% of the corresponding concentration in maternal plasma. The biological significance of this amount of ondansetron in the developing fetus requires further investigation. Previous *in vivo* animal studies in rabbits and rats showed no evidence of developmental abnormalities when they were fed ondansetron at the organogenesis stage,[17] even at a dosage that was 70-fold greater than that used in humans. However, these data cannot be extrapolated to humans because potential interspecies differences in pharmacodynamics, pharmacokinetics, drug metabolism and placental transfer have to be considered.

Currently, whole embryo culture is used to screen chemicals for their teratogenic potential; however, the major difficulty of this *in vitro* screening is to determine the most appropriate drug concentration to be used in the culture medium. Previously, this was estimated according to the maternal plasma drug concentration; however, maternal plasma is a poor predictor of the drug concentration in the developing embryo *in vivo* because of differences in placental transfer and plasma protein binding.[18]

In the past, placental transfer was rarely evaluated during the first trimester of human pregnancy owing to the ethical constraints and inaccessibility to the early human fetus. The placental transferal rate of a chemical is determined by its molecular weight, lipid solubility, ionisation and protein binding.[19] Unfortunately, there is no general formula to calculate the transferal rate based on these parameters. Recently, our group has successfully investigated the placental transfer of diclofenac[12] and naproxen[20] by sampling fetal tissue, coelomic fluid and amniotic fluid, using the method described in this paper (Patients and Methods section). This model provided information on the drug concentra-

tion in the three fetal compartments during early pregnancy, which could be used to determine the drug concentration used in whole embryo culture.

By combining the model we used to investigate placental transfer and whole embryo culture, we propose that this is the best available *in vitro* model to investigate the drug effect on an embryo and an early fetus. This model would provide the best estimation of teratogenicity of a drug when prescribed in early human pregnancy.

Conclusion

The present study has shown that ondansetron readily crosses the human placenta. Although the biological significance of those findings is still unknown, this study highlights the need for further evaluation and provides important information for further *in vitro* studies.

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Correspondence and offprints: Dr *Shing-Shun N. Siu*, Department of Obstetrics and Gynaecology, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong.
E-mail: nelsonsiu@cuhk.edu.hk