OBSTETRICS

Pharmacodynamics of transdermal granisetron in women with nausea and vomiting of pregnancy

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BACKGROUND: Limited options exist for women with nausea and vomiting of pregnancy (NVP) who cannot tolerate oral intake. Transdermal delivery of granisetron, a 5-hydroxytryptamine-3 receptor antagonist, provides an effective alternative for such patients.

OBJECTIVE: The objective of this study was to evaluate the pharmacodynamics of granisetron administered intravenously (IV) and as a sustained release transdermal patch in women with NVP.

STUDY DESIGN: We recruited 16 women with singleton gestation between 12 0/7-18 6/7 weeks who were receiving treatment for NVP and had a Pregnancy Unique Quantification of Emesis and Nausea (PUQE) score of ≥6. All consenting subjects received 1 mg of granisetron as an IV infusion over 5 minutes and blood was obtained prior to the infusion and at 10, 20, 30, and 60 minutes and at 2, 4, 6, 8, 12, and 24 hours after the start of the infusion. After a minimum washout of 48 hours after initiation of IV granisetron, a 52-cm^2 granisetron patch (34.3 mg) was placed on the upper arm of all subjects for 7 days. Blood was drawn prior to patch placement and daily thereafter for 9 days. The subjects were evaluated daily. The PUQE score was obtained from these subjects prior to the IV infusion and daily for 2 days after and again prior to and daily for 9 days after patch placement.

RESULTS: Complete data were available in 15 women after IV administration and 13 women after patch placement. One woman stopped participation during the IV infusion while data were not available in 2 additional women after patch placement due to noncompliance. Peak plasma granisetron concentrations after IV and transdermal administration were similar (~10 ng/mL). Prior to IV administration of granisetron, the PUQE score was 8.6 ± 1.8 (mean ± SD). The PUQE scores were significantly reduced for the ensuing 2 days ($P < .01$). The PUQE score prior to patch placement was 7.6 ± 2.4. Scores were significantly ($P < .001$) reduced within 1 day of patch placement and stayed significantly reduced during the ensuing 6 days of patch placement. The patch was removed on the seventh day and PUQE scores increased significantly on the third day after patch removal. No serious side effects were reported either during IV administration or patch placement.

CONCLUSION: Granisetron significantly improved symptoms of nausea and vomiting as gauged by the PUQE score. After IV infusion the reduction in PUQE score was observed within 1 day. When granisetron was administered as a patch, benefit likewise was seen within 1 day suggesting rapid absorption of the medication transdermally. The beneficial effect of transdermal granisetron on the PUQE score persisted for the entire 7 days during which the patch was in place. In this small cohort, the granisetron patch appeared to be efficacious in reducing the symptoms of nausea and vomiting. The patch provides another option for treating this disorder and may be particularly useful in women who cannot tolerate oral medications.

Key words: 5-hydroxytryptamine-3 receptor antagonist, nausea and vomiting of pregnancy, Pregnancy Unique Quantification of Emesis and Nausea scores, transdermal

Introduction

Nausea and vomiting of pregnancy (NVP), to a variable extent, affects up to 90% of pregnant women.[1-6] As many as 2-5% of women with NVP demonstrate symptoms severe enough to require visits to the emergency room and subsequent hospitalization. Treatment of this disorder is generally ineffective as the pathophysiology of the disorder is not known.[7] In pregnant subjects, medical therapy is generally directed at symptomatic improvement particularly in reducing the nausea and vomiting symptoms and assuring adequate hydration. Among the antinausea and antiemetic medications currently available none has proven superior for NVP and substantial differences are evident in patient response and tolerance to these medications.[7] Confounding this wide variation in response is the inability of many women, particularly those with severe symptoms, to tolerate any oral medication.

The 5-hydroxytryptamine-3 antagonist ondansetron has been used to treat pregnant women with hyperemesis gravidarum with considerable success.[5] Use of ondansetron, however, is limited to those women who can tolerate oral medications. Granisetron (Kytril) another 5-hydroxytryptamine-3 receptor antagonist is a Category B drug and is Food and Drug Administration approved for treatment of chemotherapy and radiation-associated as well as postoperative nausea and vomiting. Transdermal granisetron (Sancuso) has proven effective in reducing chemotherapy-induced nausea and vomiting and is comparable in its efficacy to ondansetron for this indication.[8,9] Granisetron has been used in some pregnant women to treat itching from regional anesthesia during cesarean delivery and for postoperative nausea and vomiting.[10] Use of the granisetron patch offers an option not heretofore available to those pregnant women with severe signs and symptoms of nausea and hyperemesis. Limited data exist to describe the pharmacokinetics or pharmacodynamics of the granisetron patch in pregnancy. The purpose of this study was to evaluate plasma concentrations achieved with intravenous (IV) and transdermal granisetron and to assess the efficacy of transdermal granisetron in pregnant women with NVP.

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Materials and Methods

Study design

This study was performed under Investigational New Drug no. 114293 and was approved by the University of Pittsburgh Institutional Review Board. We recruited 16 women between 12 0/7-18 6/7 weeks' gestation with singleton gestation who were receiving treatment for NVP and had a Pregnancy Unique Quantification of Emesis and Nausea (PUQE) score of ≥6.[11] We excluded women with any medical disorder affecting absorption, metabolism, or elimination of the study medication and also excluded those with active hepatitis, HIV, or a serum creatinine >1.5 mg/dl. We also excluded those with uncontrolled hypertension; with a dermatologic condition that might affect absorption at the patch site; with an allergic or drug reaction to serotonin receptor antagonist; or concomitantly ingesting CYP 3A inhibitors such as erythromycin, ketoconazole, fluconazole, itraconazole, or voriconazole, or inducers such as rifampin, carbamazepine, phenobarbital, phenytoin, or St John's Wort. Each subject consented to be studied twice; once to receive IV granisetron in our clinical research center (CRC) and once to receive a patch designed to release granisetron slowly over a week. In the first study, subjects received 1 mg of granisetron as an IV infusion over 5 minutes and blood was obtained prior to the infusion and at 10, 20, 30, and 60 minutes and at 2, 4, 6, 8, and 12 hours after the start of the infusion. Subjects received 2 meals and snacks during their stay in the CRC. They were discharged home from the CRC after the 12-hour blood sample was obtained and they returned 24 hours after the start of the IV infusion for a final blood sample and the PUQE score was reassessed. A complete urine collection was obtained over day 1 and day 2 after the start of the IV infusion and PUQE scores were obtained. The second study was performed after a minimum of 48 hours but <5 days had elapsed after administration of IV granisetron. For the second study, a 52-cm^2 granisetron patch containing 34.3 mg of granisetron was placed on the upper arm and blood was drawn prior to patch placement and daily thereafter for a total of 9 additional days. A PUQE score was obtained prior to patch placement and daily for 9 additional days. The subjects were evaluated daily and questioned about side effects. Patch adhesion was also evaluated by the research staff. A 24-hour collection of urine was performed between days 2-3 or 3-4 after patch placement.

Other medications for treatment of nausea and vomiting were discouraged during the study but if any were taken, this was recorded. Blood was collected in heparinized tubes, centrifuged at 3000 rpm for 10 minutes at 4°C and the plasma frozen at −80°C until analyzed for granisetron using a high performance liquid chromatography-tandem mass spectrometry assay.

Statistical methods

As there were no data addressing the plasma concentrations of granisetron in pregnant women receiving transdermal granisetron, our sample size was selected to provide a reasonable determination of median values for the various pharmacokinetic parameters based on published pharmacokinetic data in nonpregnant volunteers. A similar coefficient of variation was seen with a sample size of 29.[12] Recognizing that a larger sample size would not reduce variance, we selected a sample size of 16 subjects to account for dropouts and noncompliance. For comparison of PUQE scores after IV or patch administration, we used both mixed models testing and repeated measures analysis of variance.

Granisetron assay

We developed and have reported an assay of granisetron and its major metabolite using high performance liquid chromatography-tandem mass spectrometry.[13] The lower limit of quantification on column was 0.06 ng/mL. Precision as measured by between and within run variation was 8.7-11 and 6.4-10 and accuracy between and within runs was 86-114% and 88-110%, respectively.

Results

Three subjects were withdrawn from the patch study, 2 for noncompliance and 1 due to worsening of long-standing reflux that necessitated an emergency department visit and led to an erroneous discontinuation of the patch by emergency department staff (Table 1).

Figure 1 depicts mean (±SD) plasma concentrations following IV infusion of 1 mg of granisetron over 5 minutes. Peak concentrations averaged 11.3 ng/mL. Plasma concentrations decreased rapidly with a half-life of 7.1 ± 4.6 hours.

Figure 2 depicts mean (±SD) plasma concentrations during 1 week of patch placement. Concentrations were near 10 ng/mL within 1 day (study day 2) of patch placement. Peak concentrations

TABLE 1
Summary of demographic characteristics of study cohort

Cases, n	16
Age, y	24.6 (5.9)
Race, n	
African American	12
Caucasian	3
Mixed race	1
Body mass index, kg/m2	26 (6.2)
Gestation at IV study, wk	15 (2.2)
Gestation at patch placement, wk	16 (2.4)

IV, intravenous.

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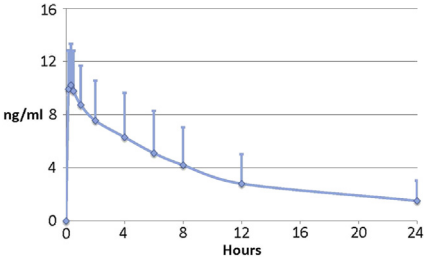
FIGURE 1
Granisetron concentrations after intravenous (IV) administration



Granisetron concentrations after intravenous (IV) administration. Values represent mean ± SD; 1 mg granisetron infused over 5 minutes at time 0. N = 15.

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