OBSTETRICS WORLD PREMATURITY DAY

Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation

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OBJECTIVE: The purpose of this study was to estimate pharmacokinetic parameters and to evaluate placental transport of 17-hydroxyprogesterone caproate (17-OHPC) in singleton gestation.

STUDY DESIGN: Sixty-one women who received weekly injections of 17-OHPC underwent 2 pharmacokinetic studies at 20 + 0 to 24 + 6 weeks' gestation (study 1) and 31 + 0 to 34 + 6 weeks' gestation (study 2); daily blood samples were obtained between injections. In 18 women, blood samples were obtained over a 28-day period beyond the last injection (extended study). Maternal and/or cord blood were obtained at delivery.

RESULTS: The half-life (median ± SD) of 17-OHPC was 16.2 ± 6 days. Concentrations of 17-OHPC were higher during study 2 than during study 1. Body mass index affected maternal 17-OHPC concentrations. Cord:maternal 17-OHPC concentration ratios averaged 0.2; 17-OHPC was detectible in cord plasma 44 days after the last maternal injection.

CONCLUSION: The apparent half-life of 17-OHPC is long, and pharmacokinetic parameters vary widely between subjects and are affected by maternal body mass index. The drug crosses the placental barrier.

Key words: cord blood, pharmacokinetics, placenta, preterm birth

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Seventeen-hydroxyprogesterone caproate (17-OHPC) reduces preterm birth rates in women with a previous preterm birth[1] but has not proved effective in women with multifetal gestation[2,3] or an ultrasonically identified short cervix.[4] The American Congress of Obstetricians and Gynecologists in a 2009 Committee Opinion recommended that this therapy be offered to all women with a previous preterm birth[5] and that more research be done with the pharmacology of 17-OHPC and other progestin preparations. Despite widespread clinical use, there are no reports that have described pharmacokinetics of 17-OHPC in singleton gestation, the plasma concentrations that are achieved during therapy for preterm birth prevention, and whether the medication is detectible in fetal blood. In this multicenter Obstetrical-Fetal Pharmacology Research Units Network study, we evaluated the pharmacokinetics and placental transport of 17-OHPC in women with singleton gestation who were receiving 17-OHPC because of a previous preterm birth.

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Materials and Methods

Study design

We recruited 61 women from 4 centers who were receiving or planned to receive 17-OHPC for the prevention of recurrent preterm birth based on a history of at least 1 previous spontaneous preterm (<37 weeks' gestation) birth. In keeping with clinical practice recommendations, all women who were receiving 17-OHPC began therapy between 16 0/7 and 20 6/7 weeks' gestation. Each subject agreed to participate in 2 pharmacokinetic studies lasting 7 days each. The first pharmacokinetic study (PK1) was scheduled to occur between 20 0/7 and 24 6/7 weeks' gestation after a minimum of 4 weekly

injections had been administered. The second pharmacokinetic study (PK2) occurred between 31 0/7 and 34 6/7 weeks' gestation. This second study evaluated possible gestational age-related changes in the pharmacokinetics of 17-OHPC. Eighteen women who completed PK2 agreed to have blood drawn an additional 7 times during the 28 days after the start of PK2 to determine the terminal disposition rate constant and apparent terminal disposition half-life (extended study). In these women, blood samples were obtained after the last injection on days 1, 2, 3, 4, 5, 6, and 7 as in all other subjects; however, in addition, blood was obtained on day 9, 11, 14, 17, 20, 24, and 28 after the last injection of 17-OHPC. For all subjects, when possible, blood was obtained at delivery from a maternal vein and the umbilical cord (artery or vein).

All subjects received their weekly 17-OHPC injections by the research staff up to the completed week 35 of gestation or delivery. The weekly injection times were scheduled within a 4-hour window of the initial injection time. The 17-OHPC was obtained from a central compounding pharmacy (Eminent Services Corp, Frederick, MD). At each weekly visit the site of injection was noted, and injection sites were alternated between the right and left hip/buttocks areas. A venous blood sample was obtained, and subjects were queried about side-effects, hospitalizations or episodes of preterm labor that required hospitalization or tocolytic treatment. Data that were recorded for each patient included maternal age, parity, self-reported race, body mass index (BMI), and gestational age at enrollment, at each blood sampling, and at delivery. Women who missed ≥1 injections were not included in the pharmacokinetic analyses. No attempt was made to alter or mandate clinical treatment of the subjects. The institutional review boards of each clinical site approved this study. This trial is registered at Clinicaltrials.gov (NCT00409825).

Sample analysis

For all 17-OHPC measurements, blood was collected in 10-mL tubes with ethylenediaminetetraacetic acid and centrifuged within 1 hour of collection at 3500*g* for 10 minutes. The supernatant plasma was aliquoted into 1-mL polypropylene tubes and frozen at –70°C until analysis of 17-OHPC by high performance liquid chromatography with tandem mass spectrometry as reported previously.[6] The standard curve was linear in the range of 1–200 ng/mL. The lower limit of quantitation for 17-OHPC was 1 ng/mL. Inter- and intraassay variability at 10 ng/mL was 7.9 and 5.2%, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters (Appendix) in each of the 2 pharmacokinetic studies and the extended study were estimated by the standard noncompartmental approach implemented in WinNonlin software (version 4.0; Pharsight Corp, Mountain View, CA). Maximum concentration and time to maximum concentration were determined from the observed data. The terminal disposition rate constant (λ_z) was determined by log-linear regression of terminal linear disposition phase with the data from the extended study. Half-life was estimated by 0.693/ λ_z. The area under the plasma concentration vs time curve (AUC^{t1}_{t2}) was calculated from time t_1 and t_2, which are time of consecutive doses (beginning at the end of a dosing interval). The apparent oral clearance (clearance/bioavailability) was estimated as dose/$(AUC)^{t1}_{t2}$, and the apparent volume of distribution (V_D/F) was calculated as dose/λ_z. AUC^{t1}_{t2} used the AUC data from PK2 and the terminal disposition rate constant from the second study in 18 subjects from whom samples were collected for up to 28 days after the last injection (extended study).

Statistical analysis

The primary outcome variable was the gestational change in AUC (0-7 days). The sample size estimate was based on the assumptions that gestational change in AUC (0-7 days) of 30% is clinically relevant and that the variance in 17-OHPC concentrations is similar to that reported in nonpregnant women by Onsrud et al[7] because there are no published data on singleton gestation. Based on these considerations, a total sample size of 47 women would be sufficient to detect such a difference, assuming a power of 0.8 and alpha of .05. We assumed a 25-30% dropout rate; therefore, the final sample size of 61 recruited subjects would be more than adequate for the evaluation of the outcome of interest. Secondary outcome variables included the pharmacokinetic variables that were described earlier (maximum concentration; time to maximum concentration; the minimum concentration at time zero, just before the next injection (C_{trough}); half-life; volume of distribution; apparent clearance) and maternal and cord 17-OHPC concentrations.

GraphPad Prism software (version 4.01; GraphPad Software, Inc, La Jolla, CA) was used for the performance of the statistical tests for significance. Pairwise group comparisons used nonparametric (Wilcoxon signed rank and Mann Whitney *U*) tests. Population medians in multiple groups were compared with Kruskal-Wallis 1-way analysis of variance with Dunn's posttest for multiple comparisons. We considered probability values of $< .05$ to be significant. All pharmacokinetic parameter results are reported as median (interquartile range). Demographic variables are reported as mean ±SD.

RESULTS

Demographics

The characteristics of the study population are summarized in Table 1. These 61 subjects each experienced 1-4 previous preterm births. Treatment with 17-OHPC started on average at 18 weeks' gestation, and subjects received an average of 6 injections by PK1 and 17 injections by PK2.

Noncompartmental pharmacokinetics

Figure 1 shows the mean (±SD) plasma concentration of 17-OHPC during each of the 2 pharmacokinetic studies. Only women who had received all their scheduled injections and remained undelivered through PK1 (20 6/7–24 6/7 weeks' gestation) and PK2 (31 0/7–34 6/7 weeks' gestation) were included in this analysis (n = 47). Ten subjects did not undergo PK2 because of preterm delivery (n = 6 women), study withdrawal (n = 3 women), or hospitalization (n =