Ex Vivo Human Placental Transfer of Trovafloxacin

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ABSTRACT

Objective: The purpose of this study was to determine the ex vivo human placental transfer of trovafloxacin from the maternal circulation to the fetal circulation.

Methods: Six placentas from uncomplicated, term, vaginal or cesarean deliveries were studied using the ex vivo isolated cotyledon perfusion chamber; ¹⁴C-antipyrine was used as a reference compound to determine the clearance index (CI) of trovafloxacin.

Results: The CI of trovafloxacin was 0.19 ± 0.13 at a mean trough concentration of 1.38 ± 0.22 µg/ml and 0.16 ± 0.10 at a mean peak concentration of 7.48 ± 2.3 µg/ml as determined by our newly developed high-pressure liquid chromatographic assay. Tissue concentration did not exceed maternal concentration, and there was little or no accumulation when the perfusion system was closed for 1 hr.

Conclusions: Trovafloxacin crosses the placenta by simple diffusion and does not accumulate in the media to any extent, nor does it bind to tissue or accumulate in the placenta. Infect. Dis. Obstet. Gynecol. 8:228–229, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS
maternal–fetal transfer; trovan; trovafloxacin

Trovafloxacin is a broad-spectrum antibacterial fluoronaphthyridone related to other synthetic fluoroquinolone compounds. There is a paucity of information on the placental transfer and accumulation of quinolone compounds in pregnant women because of the category C risk. The adverse reactions include possible skeletal malformations and increased gestational time. Additional serious adverse reactions in humans include potential hepatic malfunction, tendinitis, and tendon rupture. However, in reported cases of at least 32 women who received quinolone antibiotics in the first trimester of pregnancy, no congenital abnormalities were reported.¹ ² The results of these pregnancies were 21 normal births, 1 ectopic pregnancy, 4 spontaneous abortions, 5 terminations, and 1 unknown outcome. Because little or no information is available on the placental transfer of quinolone compounds, we used our ex vivo human placental model to determine the placental transfer of trovafloxacin.

MATERIALS AND METHODS

Laboratory-standard powder of trovafloxacin was a gift from Pfizer Pharmaceuticals (Groton, CT). The placentas used in this study were collected from term, uncomplicated, cesarean section or vaginal deliveries in accordance with the guidelines determined by the University of Texas Southwestern Medical Center Institutional Review Board. The placentas were collected in normal saline and were taken to the laboratory, where the fetal circulation was established within 15 min of delivery. The fetal artery and vein were cannulated with 3- and 5-French catheters, respectively. The isolated cotyledon was gently perfused with Eagle’s MEM and observed for leaks and loss of membrane integrity. Placental cotyledons that were noted to have fetal-to-maternal leaks were discarded. If there were no detectable leaks, the perfused cotyledon and adjoining tissue were transferred to a temperature-controlled chamber and perfused with

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drug-free media for 20 min to remove residual blood and stabilize the perfusion pressure in the fetal circulation. At the end of the 20-min stabilization period, the fetal pressure was 35 mmHg. If the fetal pressure exceeded 45 mmHg at a flow rate of 4.0 ml/min, the placenta was discarded. The maternal circulation was then established at 17 ml/min, and the complete perfusion system was stabilized for an additional 30 min. At this time, 0.1 mg/liter of $^{14}$C-antipyrine in Eagle’s MEM was added to the maternal circulation, and maternal and fetal samples were collected to determine maternal-fetal match, transport fraction, clearance, and clearance index as previously described. A transport fraction of >40% was representative of an acceptable maternal–fetal match.

Trovafloxacin was perfused into the isolated cotyledon at concentrations of approximately 1.0 µg/ml and 7.0 µg/ml to represent the trough and peak concentrations of the drug. Four milliliters of maternal and fetal perfusates were collected every 10 min for 1 hr with both the maternal and the fetal circulations open, at which time both the maternal and the fetal circulations were closed and the drug was allowed to accumulate for 1 hr, with samples collected every 10 min as previously described. All samples were frozen at 80°C until analysis.

The high-pressure liquid chromatographic (HPLC) assay of trovafloxacin consisted of all water-associated analytical equipment, which consisted of an M45 pump, 712B integrated sample processor, and a 486 variable wavelength detector. A 10-mm recorder (Linear, Inc., Houston, TX) was used to determine the peak height of the standards and samples. A phenomenex C$_{18}$ bond-a-clone column was used for compound separation. Other analytical conditions consisted of a sensitivity setting of 0.005 AU, a wavelength of 313 λ, a flow rate of 2.0 ml/min, a 50 µl injection, and a mobil phase of 550 ml H$_2$O, 450 ml methanol, and 40 µg/liter of penta sulfonic acid, pH 4.0. Within-batch and between-batch reproducibility studies were performed to validate the assay.

RESULTS

Reproducibility studies for the HPLC determination of trovafloxacin in the perfusates and tissue samples showed 95% reproducibility with a minimum sensitivity of 0.1 µg/ml (data not shown). The concentration and the clearance index of trovafloxacin revealed that the maternal–fetal transfer occurs by simple diffusion (Table 1). The accumulation of trovafloxacin in placental tissue was 0.10 ± 0.09 and 1.81 ± 1.1 µg/g at the low and high concentrations, respectively.

DISCUSSION

Trovafloxacin and other quinolones all basically have the same mechanisms of action. All quinolones exert their antibacterial action via inhibition of type II topoisomerase DNA gyrase. DNA synthesis and repair in the primate theoretically is unaffected by this mechanism. Quinolones in general are not recommended for use in pregnancy. Thus, the only time trovafloxacin is used is when alternate therapy was not adequate or when it was used inadvertently, prior to the diagnosis of pregnancy. Thus, these data are mainly for academic use but do provide the clinician with information that the drug does cross placental membranes by simple diffusion. With what is known about the uses of trovafloxacin in nonpregnant patients, it is unlikely that quinolone compounds will be used in pregnant patients.

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