Oseltamivir and Its Active Metabolite Cross the Placenta at Significant Levels

To the Editor—Pregnant women are at increased risk for severe complications from influenza A H1N1 infection [1]. Early treatment with oseltamivir appears to reduce maternal morbidity and mortality [2]. The limited data available suggest that oseltamivir can be used without adverse pregnancy or fetal outcomes [3]. In fact, in ex vivo placental models, minimal or low transplacental transfer of oseltamivir and its active metabolite, oseltamivir carboxylate, was observed at normal therapeutic drug levels [4, 5]. In this letter, however, we describe a critically ill pregnant woman who was treated with oseltamivir in whom significant levels of the drug were detected in cord blood, indicating that oseltamivir crosses the placenta.

A 29-year-old woman, 29 weeks pregnant, was referred to an intensive care unit for respiratory failure requiring artificial respiration. She was diagnosed with pneumonia and treated with oseltamivir 75 mg twice daily, amoxicillin/clavulanic acid, and erythromycin. Subsequently, polymerase chain reaction (PCR) of a nasopharyngeal wash was positive for pandemic influenza A H1N1 (cycle threshold [Ct] value, 27.5). After 3 days the dosage of oseltamivir was increased to 150 mg twice daily. Six days after admission, PCR of the nasopharyngeal swab was still positive for influenza (Ct value, 36.2); PCR of maternal blood was negative, and the clinical situation had not improved. A cesarean section was performed and a girl of 1640 g was born; her Apgar scores were 7, 8, and 8 (at 1, 5, and 10 minutes after birth, respectively). She was transferred to the neonatal intensive care unit without signs of infection. PCR of a nasopharyngeal wash of the neonate and placenta was negative. The maternal condition improved after surgery. Three days later, a maternal nasopharyngeal swab also tested negative for influenza, and mother and child were discharged 13 and 14 days, respectively, after delivery.

The plasma concentrations of oseltamivir and its active metabolite were determined in maternal blood drawn just before the cesarean section and in venous umbilical cord blood after clamping of the umbilical cord, using a validated liquid chromatography–tandem mass spectrometry assay (Table 1). Samples were taken approximately 5 hours after the last dose of oseltamivir.

Our results show considerable levels (exceeding the 90% inhibitory concentration) of oseltamivir and oseltamivir carboxylate in the cord blood. Compared to ex vivo placental models [4, 5], we measured a higher fetal transfer rate of both substances (23.5% and 73.4%, respectively, versus 8.5% and 6.6% [5]). The high concentration of oseltamivir carboxylate in maternal blood might be due to the relatively high dose of oseltamivir (150 mg twice daily), whereas possible explanations for the larger fetal transfer rates can include alteration of the expression of multidrug resistance protein 1 [6], metabolism of the drug by the placenta, metabolization by the fetus, and/or fetal accumulation [4].

High concentrations of oseltamivir (carboxylate) may be beneficial for the fetus, as transplacental transfer of H1N1 has been reported [7]. However, it is unknown whether oseltamivir has toxic or teratogenic effects on the fetus. Therefore, we recommend that oseltamivir should only be administered to critically ill pregnant women.

Table 1. Oseltamivir and Oseltamivir Carboxylate Plasma Concentrations in Maternal and Umbilical Cord Plasma

<table>
<thead>
<tr>
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<th>Oseltamivir Concentration (ng/mL)</th>
<th>Oseltamivir Carboxylate Concentration (ng/mL)</th>
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<tbody>
<tr>
<td>Maternal</td>
<td>10.17</td>
<td>718.2</td>
</tr>
<tr>
<td>Cord</td>
<td>2.39</td>
<td>527.2</td>
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</tbody>
</table>

Notes

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