Maternal-Fetal Pharmacology of Cefatrizine in the First 20 Weeks of Pregnancy

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To evaluate maternal-fetal pharmacology of cefatrizine (BL-S 640), a new oral cephalosporin, a single oral 1,000-mg dose was administered to 33 gravidas (8 to 20 weeks' gestation) at varying intervals within 46 h of an elective therapeutic abortion by hysterectomy or intra-amniotic prostaglandin F2α induction. Mean maternal serum concentrations at 1, 2, 4, and 8 h were 3.7, 7.9, 6.5, and 1.6 μg/ml; beyond a 3-h peak, a half-life of 2.4 h was determined. Cefatrizine placental half-life was 4.4 h. None of the 11 fetuses from a prostaglandin F2α abortion revealed cefatrizine activity; in contrast, 17 of 22 fetuses from a surgical abortion demonstrated cefatrizine concentrations in two or more samples. Fetal cefatrizine levels were less than 3 μg/g or μg/ml in kidney and urine, less than 2 μg/ml in serum and bile, and less than 2.5 μg/g in lung. After a single maternal dose, cefatrizine has a wide distribution in the fetus in the first half of gestation.

Cefatrizine (BL-S 640) is a new oral semisynthetic cephalosporin antibiotic that demonstrates not only the broad antimicrobial spectrum of other cephalosporins, but also more in vitro activity against various species of Enterobacteriaceae (11, 12, 15, 19).

Two reports indicate that as many as 16 to 41% of fetuses (8 weeks’ gestation to delivery) are exposed to antibiotics for treatment of an infection occurring during pregnancy (6, 7). These infections may involve the gravida alone, all or part of the intrauterine contents, or both the mother and fetus. One must extend the usual primary therapeutic concerns regarding the efficacy of the antimicrobial concentration at the specific site(s) of infection for the mother or fetus, or both, to include potential risks which may directly or indirectly affect the intrauterine passenger. These concerns may be as follows: an adverse maternal reaction with secondary fetal consequences; embryopathy; direct fetal toxicity as may be related to functional organ or metabolic development; and the placental role as a barrier or in concentration or clearance of an antibiotic for the fetus.

To date, most investigations regarding the maternal-fetal transfer of antimicrobial agents have been studied in fetal serum and amniotic fluid within hours of term delivery, except for the reports in early pregnancy by Philipson et al. (16) and Biró et al. (4). Their results reveal individual fetal pharmacological profiles for erythromycin and clindamycin (16) and ampicillin and carbenicillin (4). Pharmacological data or guidelines are rarely available to physicians who may use new drugs to treat infections in their gravid patients. This investigation was undertaken to determine the extent of the maternal-fetal transfer of cefatrizine and the distribution and concentrations of cefatrizine in the various tissues and body fluids of the conceptus after antibiotic administration to patients in the first 20 weeks of pregnancy.

MATERIALS AND METHODS

Patients. The patients in this study were 33 healthy gravidas at 8 to 20 weeks' gestation who were hospitalized for an elective therapeutic abortion between June 1975 and August 1976. After admission, an informed consent was obtained which met the requirements of the Research Committee of the Los Angeles County-University of Southern California Medical Center and the Department of Health, Education and Welfare.

Twenty-two patients, eight in the first (I) trimester and 14 in the second (II) trimester, were scheduled for an elective therapeutic abortion and sterilization by hysterectomy. Eleven patients in the II trimester received an intra-amniotic dose of 40 mg of prostaglandin F2α to induce abortion (Upjohn Co., Kalamazoo, Mich.). A single oral dose of 1,000 mg of cefatrizine was administered with 15 to 30 ml of

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water to the gravid patients at varying intervals within the 46 h before delivery. Thirty-three fetuses were available for study, 22 from a surgical procedure and 11 from prostaglandin \( P_2 \) induction. The "interval" was defined as the time between cefatrizine administration to the patient and the clamping of the uterine arteries at surgery or the time of expulsion of the fetus. Intervals varied from 1.9 to 22.7 h for the surgical patients and from 0.2 to 45.6 h for the patients receiving prostaglandin \( P_2 \).

Mean weights for the surgical patients in the I and II trimesters were 65.5 and 64.2 kg, respectively. These weights were not significantly different from the mean 59.9 kg for the patients receiving prostaglandin \( P_2 \).

Samples. Serum samples were obtained from 24 gravidas before the oral dose of cefatrizine and at 1, 2, 4, and 8 h after administration. Another maternal serum sample was taken at the time of delivery. Eight patients refused permission for venipunctures, and two patients allowed only the delivery time venipuncture to be performed. Samples of placenta, amniotic fluid, and cord serum were unavailable in the subjects receiving intra-amniotic prostaglandin \( P_2 \).

After surgery or prostaglandin-induced delivery, sterile technique was utilized to obtain samples of fetal tissues and body fluids. Only in the surgical cases was the placenta separated, weighed, and sampled. Fetal weight and measurements for crown-heel, crown-rump, and foot length were recorded. Samples of amniotic fluid, fetal blood, fetal bile, fetal urine, and fetal cerebrospinal fluid were obtained by needle aspiration. Fetal tissue samples of brain, lung, liver, and kidney were collected. All specimens were quick frozen and stored at \(-70^\circ C\) until time of cefatrizine assay. For technical reasons, sampling of the fetus was often incomplete, especially when less than 18 weeks' gestation.

Gestational age was determined from the first day of the last normal menstrual period. When the dates were uncertain, fetal measurements were utilized to estimate gestational age (9, 18).

Assay. Cefatrizine concentrations in maternal serum and fetal tissues and body fluids were determined in duplicate by an agar well microbiological assay described by Bennett et al. (2), with modifications described below (10). A 2-ml suspension of Sarcina lutea in 40 ml of AM-1 agar (no. 0293-91, Difco Laboratories, Detroit, Mich.) was plated on a sterile plastic plate (150 by 15 mm; Falcon no. 1058, Oxnard, Calif.). Under sterile conditions, each tissue sample was weighed and homogenized in a Ten Broeck tissue grinder with an equal weight of normal human serum (Flow Laboratories, Inc., Rockville, Md.). A pool of individual antibiotic-free fetal tissues or body fluids was used for the control blank and reference curve. A control blank, two standard reference curve points, and one unknown sample were plated in duplicate on each plate. Plates were incubated at 30°C for 18 h. Minimal detectable concentrations of cefatrizine in tissues and fluids with this method are as follows: 0.05 \( \mu g/ml \) or \( \mu g/g \) for maternal serum and fetal brain; 0.08 \( \mu g/ml \) for fetal serum; 0.1 \( \mu g/ml \) or \( \mu g/g \) for placenta, amniotic fluid, fetal bile, and fetal kidney; 0.2 \( \mu g/ml \) for fetal urine; and 0.5 \( \mu g/g \) for fetal lung. There was no microbiological inhibition of cefatrizine in concentrations of 0.1 to 12.8 \( \mu g/ml \) assayed with prostaglandin \( P_2 \) at 0 to 500 \( \mu g/ml \).

Analysis. A regression line, utilizing programs for the Hewlett-Packard HP-65 (Hewlett-Packard, Corvallis, Ore., a programmable calculator), was determined from individual cefatrizine concentrations in a tissue or fluid and extrapolated to a theoretical zero time \((T_0)\). The time at which the sample concentration was one-half the antimicrobial concentration at \( T_0 \) was defined as the half-life \( (t_{1/2})\) with the following equation: \( t_{1/2} = -\log e/\beta \), where \( \beta \) is the rate constant for decrease in cefatrizine concentration in tissues or fluids with time. The Hewlett-Packard HP-65 program for \( t \)-statistics for two means and the two-sample rank test (the Mann-Whitney U-test) was used to measure the significance of differences between any two groups of data. Significance levels were considered to be at \( P < 0.01 \).

RESULTS

None of the fetuses of the 11 patients receiving an intra-amniotic injection of prostaglandin \( P_2 \) demonstrated any detectable cefatrizine activity over the entire period (11 min to 45.5 h) of this study (Table 1). Consequently, the following report of results provides data accumulated in the study of only the 22 surgical patients and their fetuses (Table 2).

Maternal serum. Individual and mean maternal serum concentrations for the 22 surgical patients are represented in Fig. 1. Two-hour maternal serum values exhibited a wide range of values from 3.1 to 20.4 \( \mu g/ml \), and, similarly at 4 h, 3.9 to 18 \( \mu g/ml \). Peak serum concentration appears to occur between 2 and 4 h. Mean maternal serum concentrations were as follows: 1 h, 3.7 \( \mu g/ml \); 2 h, 7.9 \( \mu g/m\); 4 h, 6.5 \( \mu g/ml \); and, by 8 h, 1.6 \( \mu g/ml \). Serum half-life was found to be 2.4 h utilizing all values beyond 3 h \((r = 0.76)\). No significant difference was established for serum half-life between the I and II trimester patients; this allows a single line to represent the regression line for the 22 surgical patients.

Placenta. Cefatrizine activity was present in the first placental sample obtained 2 h after maternal drug administration (Fig. 2a). Beyond 17 h cefatrizine was no longer detectable. A peak placental concentration of 1.7 to 3.1 \( \mu g/g \) occurred between 3 and 5 h. Excluding the three high values that were outside 2 standard deviations between the 9- and 17-h intervals, a placental \( t_{1/2} \) of 4.4 h \((r = 0.72)\) can be determined for cefatrizine. Placental tissue concentrations were unrelated to simultaneous maternal serum concentrations and independent of gestational age.

Fetal serum. Cefatrizine was detected in fetal serum in levels below 1.7 \( \mu g/ml \) from 2.8 to
TABLE 1. Cefatrizine concentration after administration of a single oral 1,000-mg dose to 11 gravid patients (14 to 20 weeks' gestation) undergoing therapeutic abortion by intra-amniotic administration of 40 mg of prostaglandin F2

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Intervala (h and min)</th>
<th>Maternal serum at delivery (μg/ml)</th>
<th>Fetal tissues and body fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Kidney (μg/g)</td>
<td>Urine (μg/ml)</td>
</tr>
<tr>
<td>16</td>
<td>0:11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0:57</td>
<td>0.74</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1:29</td>
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<td>0</td>
</tr>
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<td>18</td>
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</tr>
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<tr>
<td>16</td>
<td>45:34</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Interval defines the time between drug administration and delivery.

22.6 h after maternal cephalosporin administration (Fig. 2b). No relationships to gestational age or concentrations of antibiotic in maternal serum or placenta could be found.

Fetal kidney. Independent of both gestational age and interval, cefatrizine activity in fetal kidney was present in concentrations less than 2.8 μg/g in 12 of 14 samples between 3- and 18-h intervals after maternal antibiotic administration (Fig. 2c). Two other samples beyond the 22-h interval contained no detectable antimicrobial levels.

Fetal urine. Only one I trimester fetal urine sample was collected. It contained a 1.5-μg/ml concentration of cefatrizine at a 3.6-h interval (Fig. 2d). This level is within the range of the
values (0.45 to 2.75 \( \mu g/ml \)) for the six older fetuses for the 4- to 17-h intervals. No specific relationships were found between fetal urine and the fetal kidney concentrations (Fig. 2d), but they were within the same range at the same intervals.

Fetal lung. Seven of the 18 fetal lung samples had cefatrizine concentrations of less than 2.5 \( \mu g/ml \) from the 3- to 17-h interval. No correlations were found for gestational age or concentrations in other fetal tissues and body fluids (Fig. 2e).

Amniotic fluid. Cefatrizine was first detected in amniotic fluid close to the 5-h interval. This was 1.3 h after it appeared in the fetal urine. Only one of eight I trimester amniotic fluid samples contained cefatrizine (Fig. 2f). Seven of 13 specimens from the II trimester demonstrated levels of less than 1 \( \mu g/ml \); all of these were between the 5- and 12-h intervals. Only two I trimester amniotic fluid samples were available from 5 to 12 h—the intervals when cefatrizine was present in II trimester samples—thus, no relationship of amniotic fluid concentrations to weeks' gestation can be made.

Fetal brain and cerebrospinal fluid. Only 2 of 19 fetal brain tissue assays revealed minimal cefatrizine antimicrobial activity (0.32 and 0.2 \( \mu g/ml \)) at approximately 3- and 14-h intervals. These were both in I trimester fetuses. At 3 h, one of the two corresponding cerebrospinal fluid samples had a 0.79-\( \mu g/ml \) cefatrizine concentration. One other cerebrospinal fluid sample from a 16-week fetus at 10.4 h demonstrated cefatrizine activity of 1.29 \( \mu g/ml \). Twenty-one other cerebrospinal fluids had no activity.

Fetal liver and bile. Cefatrizine was not found in 19 fetal liver samples. Three of five bile samples from fetuses of 19 and 20 weeks' gestation had cefatrizine concentrations of 1 to 1.6 \( \mu g/ml \) between the 6- and 12-h intervals (Table 2).

**DISCUSSION**

Most cephalosporin antibiotics have been empirically well accepted for treatment of infections occurring during pregnancy because of good therapeutic results (8) and lack of recognizable toxicity to mother or newborn infant. We found maternal serum levels of cefatrizine to be well within an achievable range for the treatment of infections caused by susceptible organisms (11, 12, 15, 19).

For healthy adult males receiving a 500-mg dose, Actor et al. (1) report a serum half-life of 1.4 h which is 1 h shorter than we found in our hospitalized gravid patients after they received a 1,000-mg dose. In contrast, another study by Del Busto et al. (5) of infected hospitalized patients who received multiple 500-mg doses, the curve of decreasing serum concentrations paralleled ours, indicating a similar half-life and concentrations at approximately one-half those found in our patients. Although early pregnancy is associated with significant increases in plasma volume (3) and similar increases in renal plasma flow and glomerular filtration (13), the pharmacokinetics are altered very little for the gravid patient, and changes in half-life and serum concentration may be related to an ambulatory or hospitalized state rather than pregnancy.

If fetal urine is the major contributor of cefatrizine to the amniotic fluid, why are cefatrizine levels in the amniotic fluid undetectable while those in fetal urine are still present? Perhaps this can be explained by the findings in a study by MacAulay and Charles (14), who found cephalothin in maternal serum only 10 min after injecting 500 mg into the amniotic sac of healthy gravidas in active labor. Cephalothin concentrations of 0.9 \( \mu g/ml \) were reached by 1 h in maternal serum and maintained for the 2 h of their study, demonstrating prompt uptake of cephalothin from the amniotic fluid.

Urinary recovery of cefatrizine in adults after an oral or intramuscular dose is less than 45% in 12 h and is significantly less than reported for either cephalxin or cefazolin (1); thus, other paths of excretion may be important. Bile is one other excretory path for cefazolin (17),
and we found the fetus at mid-pregnancy to be able to excrete cefatrizine into the bile 4 h after it appears in the fetal serum.

Philipson et al. (16) found mean concentrations of erythromycin and clindamycin in fetal tissue and fluids to be "considerably higher" after multiple doses as compared to single doses when administered to gravid patients in early pregnancy. Eight of his multiply dosed patients had abortions by saline infusion and nine had abortions by hysterectomy. The results from these two groups of patients were reported as a
single group. Although we anticipated pharmacological dissimilarities for the results from the surgical and prostaglandin-induced patients because of the uncertainty of the duration of fetal exposure to cefazolin, the complete absence of any detectable cefazolin activity in the prostaglandin-induced fetus was most unexpected. Our study, as that of Philipson et al. (16), indicates that perinatal pharmacological data vary greatly and are dependent on the design of the investigation. Our bias is that the best information for future clinical use of an antibiotic is gained from the gravid patient who elects a surgical termination of pregnancy. Single-dose studies are but the first step in healthy human volunteers, and further investigations are necessary to establish "safety for use in pregnancy" for the increasing number of antimicrobial agents available for treatment of the infected gravid.

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LITERATURE CITED