TOXIC NEONATAL EFFECTS FOLLOWING MATERNAL CLOMIPRAMINE THERAPY‡

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ABSTRACT

Clomipramine is a chlorinated tricyclic antidepressant commonly used in the treatment of depression (1). The drug is widely prescribed in Europe and Canada and has been recently approved for use in the USA. Its safety during pregnancy and breastfeeding, however, has not been fully established. Very few reports on its effect on the fetus and neonate have been published (2,3).

We report a case of a mother treated with clomipramine during pregnancy, and the side effects observed in the infant. The correlation between plasma clomipramine concentrations in the baby's blood and clinical effects are described. Subsequently, we present the pregnancy outcome of five prospectively collected cases. (Key Words: tricyclic antidepressant; clomipramine; in utero toxicity; pregnancy; milk; human.)

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CASE REPORT

A 27 year-old woman who suffered from unipolar depression was treated throughout pregnancy with clomipramine 125 mg/d. No other medications or drugs of abuse were reported to be used by this woman. A baby boy was born at term by vaginal delivery weighing 3300 g with Apgar scores of 6 at 1 and 5 min. At birth, meconium stained fluid was found in the trachea. Initial examination of the neonate revealed no dysmorphology, normal blood pressure, and respiratory rate of 70/min with grunting and mild retractions. Neurological evaluation revealed mild hypotonia and a tremor. Electrocardiogram was normal and so were serum creatinine, electrolytes, glucose and calcium. Blood gas values were consistent with a respiratory acidosis and chest radiography noted air trapping. The baby was transferred to the neonatal intensive care unit for treatment. At 12 h of age the infant presented with jitteriness. The respiratory distress, hypotonia and jitteriness resolved spontaneously by 6 days of age. During this period the baby was fed only with formula. At 7 days of age the baby was started on breastfeeding and remained asymptomatic. Maternal and neonatal blood, and breastmilk were obtained at delivery and 4, 6, 10, 14, and 35 days after birth for determination of clomipramine concentrations by fluorescence polarization immunoassay (TDx system, Abbott Park, IL). The lowest limit of sensitivity was 20 ng/mL and the coefficient of variation 5.5% within run and 7.7% between runs at concentrations of 100 ng/mL. Table 1 summarizes the concentrations measured. Clinically significant clomipramine plasma concentrations were found in all maternal samples and in the neonatal samples obtained during the first few days. The concentration of clomipramine in the baby’s blood decreased with a half life of 92.8 h, as determined during the first week by least squares regression analysis. The mother continued to be treated with clomipramine at 125 mg/d for a week and then the dose was increased to 150 mg/d. Simultaneous plasma and milk samples obtained between 10 and 14 h after the daily dose at steady state gave milk/plasma ratios between 0.8 and 1.6. Despite institution of breastfeeding at day 7 the infant remained asymptomatic and the plasma clomipramine concentrations did not increase, remaining at the lowest detectable level.
TABLE 1
Clomipramine concentrations (ng/mL) in maternal and neonatal samples

<table>
<thead>
<tr>
<th>day</th>
<th>maternal dose(mg/d)</th>
<th>maternal plasma(ng/mL)</th>
<th>maternal milk(ng/mL)</th>
<th>milk/plasma ratio</th>
<th>neonatal plasma(ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>at birth</td>
<td>125</td>
<td>474.4</td>
<td>----</td>
<td>266.6</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>125</td>
<td>211.0</td>
<td>342.7</td>
<td>1.62</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>125</td>
<td>208.4</td>
<td>215.8</td>
<td>1.04</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>150</td>
<td>355.0</td>
<td>269.8</td>
<td>0.76</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>150</td>
<td>364.8</td>
<td>305.4</td>
<td>0.84</td>
</tr>
<tr>
<td>35</td>
<td></td>
<td>150</td>
<td>509.8</td>
<td>624.2</td>
<td>1.22</td>
</tr>
</tbody>
</table>

PROSPECTIVE STUDY

The Motherisk Program is an antenatal counselling service for drug, chemical and radiation exposure during pregnancy and lactation (4). After the expected date of confinement a follow up interview with the mother and a report by the pediatrician caring for the child yield details on the course of pregnancy, labor, and postnatal health.

Since the inception of the program in September of 1985, we have prospectively followed five women taking clomipramine during pregnancy. One of the women elected to have a therapeutic abortion at nine weeks of gestation. Of the four liveborn, three fetuses were exposed to the drug throughout pregnancy at daily doses between 75-250 mg/d, whereas in the fourth case the mother discontinued it after realizing she was pregnant. All four babies were born at term with no evidence of congenital malformations. One of the three babies exposed to the drug throughout pregnancy exhibited mild hypotonia during the first weeks of life. Another such baby needed oxygen for 1.5 days for transient tachypnea. No other causes for these signs, such as perinatal complications or other drug or chemical use, were identified in these cases.
Clomipramine (Anafranil) is a tricyclic antidepressant widely used in treating depression with obsessive or phobic features (1). Clomipramine is readily absorbed from the gastrointestinal tract and is extensively demethylated by first pass metabolism in the liver. The metabolites are excreted in the urine either free or in a conjugated form. Clomipramine and desmethylclomipramine are extensively bound to plasma and tissue proteins. In adults, clomipramine plasma half life ranges from 22 to 84 h (5). During the last 15 years only five cases of newborn babies affected by maternal clomipramine have been reported (6-8). Ben Musa et al. (6) described a baby exposed in utero to clomipramine who became jittery on the second day of life with associated hypoglycemia and feeding problems. Plasma clomipramine levels were < 20 ng/mL but the corresponding levels of its active metabolite, chlordesipramine were 116 and 96 ng/mL. Ostergaard and Pedersen (7) presented two babies with respiratory distress, hypotonia and feeding problems. Cowe et al. (8) hypothesized that the adverse effects are part of a withdrawal syndrome rather than side effects of the drug. Singh et al. (9) described a full term baby with tachypnea, intermittent hypertonia and marked diaphoresis. All symptoms disappeared within 10 days. Fears of exposure to the drug through milk led these authors not to initiate breastfeeding.

In our case report, the baby’s clinical picture included respiratory distress, tachypnea, hypotonia and jitteriness. While it is possible that the respiratory symptoms could be attributed to the mild meconium aspiration syndrome, the hypotonia and jitteriness were more likely caused by the drug. This clinical picture is similar to the adverse effects seen in adults with an overdose, though in our infant it was observed at plasma levels below the reported adult therapeutic range (200-500 ng/mL). Because the TDx method does not detect the active metabolites of clomipramine it is possible that neonates accumulate these metabolites, and the measured clomipramine levels underestimated the amount of active drug they were exposed to, as shown by Ben Musa (6).
Two of the three babies followed in our prospective study, who were exposed to clomipramine throughout pregnancy, exhibited signs consistent with adverse effects of the drug (hypotonia in one and transient respiratory distress in the other).

In the present case report the clomipramine plasma concentrations in the baby decreased significantly by the sixth day parallel to the disappearance of the symptoms. These suggest that the symptoms were directly caused by the drug and not due to a withdrawal syndrome. The baby was fed with breast milk from day 7; despite continuation of mother treatment producing clomipramine drug levels within the therapeutic range, only very low neonatal clomipramine concentrations were found, and the baby remained asymptomatic. These suggest that clomipramine is safe during breastfeeding. Comparison of maternal and neonatal plasma clomipramine concentrations reveals that the baby achieved about 6% of the maternal levels due to breastfeeding. The elimination half life of clomipramine in the baby was 2-3 fold slower than in adults (5), reflecting a lower metabolic clearance rate, or a larger distribution volume or both.

Although data are insufficient to rule out human teratogenicity and developmental safety of tricyclics, these drugs do not appear to be associated with appreciable increase in teratogenic risk.

Our data suggest that babies exposed in utero to clomipramine should be followed carefully during the neonatal period. If signs consistent with clomipramine toxicity become evident, determination of drug levels in the blood may assist in the differential diagnosis. On the other hand we have not found any evidence to justify cessation of breastfeeding in mothers treated with clomipramine.

If we assume the baby consuming about 1000 mL of breast milk a day and based on the clomipramine concentration found in mother’s milk (624.2 ng/mL) when treated with 150 mg daily dose, the baby will receive about 0.4% of the maternal dose. Although no dosing recommendations are available for newborns, the dose the child will receive through breastmilk will produce levels much below the therapeutic. The American Academy of Pediatrics considers clomipramine compatible with breastfeeding (10); yet, other sources consider breastfeeding to be contraindicated for patients using
this class of medications (11). To the best of our knowledge this is the first report containing specific data on neonatal clomipramine exposure through breastmilk and its apparent safety.

REFERENCES


