Hypotonia and poor feeding in an infant exposed to lamotrigine and valproic acid in utero

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Lamotrigine has been considered a safe new-generation antiepileptic drug during the perinatal period for both mothers and infants. Despite the concerns regarding its possible teratogenic effect, very limited data have been reported on the adverse effects of perinatal lamotrigine exposure. Herein, we report a case of an infant with hypotonicity and poor feeding who was exposed to lamotrigine in utero. The drug interaction probability scale indicated a probable relationship between sepsis-like symptoms and exposure to lamotrigine and valproic acid in utero in this infant.

Key words: lamotrigine, valproic acid, intrauterine period, exposure.

Lamotrigine (LTG) is one of the so-called new-generation antiepileptic drugs that is frequently used for the treatment of epilepsy and bipolar disorder in the perinatal period[1,2]. It has been shown that maternal plasma concentrations of LTG have been similar to those of cord blood in infants whose mothers were treated with LTG during pregnancy[3]. Despite the concerns regarding its possible teratogenic effect, very limited data have been reported on the adverse effects of perinatal LTG exposure[4]. Herein, we report a case of an infant with hypotonicity and poor feeding who was exposed to LTG and valproic acid in utero.

Case Report

A female infant weighing 2680 g was born by cesarean section due to breech presentation to a 31-year-old gravida 1 mother at 37 weeks of gestation at İhsan Doğramacı Children's Hospital, Hacettepe University. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. There was no maternal history of diabetes mellitus, hypertension or infection, with intact placental membranes during pregnancy. The mother had been on LTG and valproic acid polytherapy throughout pregnancy. She was taking 300 mg/day LTG and 400 mg/day valproic acid twice daily.

The physical examination of the infant in the delivery room was normal; however, hypoactivity, poor sucking and mild grunting were noted within the first hours of life. The respiratory rate was 48 breaths per minute. Intercostal and subcostal retractions were absent. A repeated physical examination revealed poor sucking, hypotonicity and hypoactive neonatal reflexes. The initial blood glucose level was 64 mg/dl. The infant was admitted to the neonatal intensive care unit (NICU) due to her clinical condition.

Intravenous dextrose and saline infusions were started. The white blood cell count was 6000/ mm^3 and immature/total neutrophil ratio was 0.12; C-reactive protein and serum procalcitonin levels were normal. Blood culture was negative, and chest radiography was normal. No antibiotic therapy was started.

Seventeen hours after delivery, maternal and infant serum LTG and infant valproic acid concentrations were obtained. The infant's serum valproic acid level was 42 mg/ml and the mother's was 52 mg/ml, both of which were within the therapeutic ranges. The infant's serum LTG level was 6.9 mg/ml, while the mother's was 3.0 mg/ml. The infant/maternal drug level ratio was 2.3. The aspartate aminotransferase and alanine aminotransferase levels were 40 U/L and 52 U/L, respectively.

On the third day of life, the infant's general condition improved gradually. Intravenous glucose infusion was stopped since the infant's feeding was active. Breastfeeding was not interrupted during or after the NICU follow-up. The infant was discharged in a healthy condition on the fifth day of life. During one year of follow-up, she was normal in all aspects.

Discussion

Lamotrigine (LTG) is a phenyltriazine antiepileptic drug structurally unrelated to conventional antiepileptic drugs. The drug is extensively metabolized by hepatic glucuronidation in the liver and is eliminated renally. The major metabolite is an inactive 2-N-glucuronide conjugate that accounts for 70% of the total metabolites in the urine[5]. The enzyme responsible for the reaction is uridine 5' diphosphate (UDP) glucuronosyltransferase (UDPGT). There are many factors that affect glucuronidation, including smoking, diet, concomitant drugs, ethnicity, hormones, genetics, and age. The half- life of LTG in non-pregnant adults ranges from 22.8 to 37.4 hours[6]. Glucuronidation of LTG may be induced or inhibited by the concomitant administration of other drugs[7]. Valproic acid inhibits hepatic glucuronidation and leads to a longer LTG half-life, up to 30-88 hours[5].

In the prospective study of Fotopoulou et al.[8] evaluating LTG concentration changes in women with epilepsy during pregnancy, neonatal and lactation periods, serum LTG clearance was increased with increasing gestational age. Thus, they offered an early prophylactic dosage increase in LTG, by average almost three-fold, in order to obtain therapeutic drug levels in pregnant women. Further, the median LTG concentration ratio of the umbilical cord blood to maternal serum was 1.01. In the short-term follow-up, they found no adverse effects in any of the infants.

In another study of 63 infants evaluating placental transfer of LTG, researchers found umbilical cord/maternal LTG concentration in a range of 0.40 to 1.38 (median 0.91) in monotherapy. In that study, maternal and umbilical LTG levels were increased and LTG clearances were decreased by about 65% with the concomitant administration of valproic acid with LTG (combined therapy). Furthermore, in combined therapy (valproic acid + LTG), maximum umbilical cord LTG concentration was 13.6 mg/ml, while it was found to be 4.5 mg/ml in monotherapy[9]. The study was a retrospective study, and the investigators did not report any side effects of the drug.

Lamotrigine (LTG) overdose results in minor clinical effects such as drowsiness/lethargy, vomiting and nausea in most of the adult cases. Serious clinical effects such as respiratory depression and coma from LTG toxicity are reported to be extremely rare in adulthood[10]. There is only one report of a serious adverse reaction in an infant exposed to LTG in the perinatal period. A 16-day-old, full-term infant experienced several mild apnea episodes due to maternal LTG monotherapy[4].

Considering the proposed pediatric therapeutic range[11] (1-5 mg/ml), the serum drug level (6.9 mg/ml) was high in our patient. The mother in the present case report was taking valproic acid in addition to LTG. Withdrawal symptoms of valproic acid are well known in the neonatal period. Irritability, jitteriness, abnormal tone, seizures, feeding problems, and hypoglycemia were described in the infants born to mothers who were on valproic acid treatment[12]. In these studies, hyper- rather than hypotonicity was the prominent feature reported[12,13]. In a prospective study consisting of 22 infants who were exposed to valproic acid in utero, withdrawal symptoms began 12–24 hours after birth and lasted two to seven days[13]. Hypoglycemia was not present in our patient, and symptoms of poor feeding, hypotonicity and mild grunting started within the first hours of birth. Furthermore, serum valproic acid concentration of the infant was 42 mg/ml 17 hours after delivery, which is in the range of therapeutic limits. According to the drug interaction probability scale, it is probable (total score of 5) that the poor feeding and hypotonicity were caused by exposure to LTG and valproic acid in utero in this infant[14].

Some factors in neonates, such as lower capacity for glucuronidation compared to adults and probable longer half-life of the conjugates because of immature renal function, make infants more susceptible to the harmful effects of this drug. This case is presented to draw attention to the side effects of maternal use of LTG and valproic acid concomitantly.

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