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SHORT COMMUNICATION

Fetal exposure to lamotrigine and quetiapine in two consecutive pregnancies

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Abstract We present the case of two healthy infants born to a bipolar female maintained on low-dose lamotrigine and quetiapine.

Keywords Pregnancy · Lamotrigine · Quetiapine · Bipolar disorder

Introduction

When necessary, the use of lamotrigine in pregnant patients with bipolar disorder is generally accepted as safe (Reimers 2014; Gentile 2006). While there is limited data on the safety of atypical antipsychotic use during pregnancy, the addition of such medications may be necessary to maintain mood stability. Our literature review found no reports on the concomitant use of lamotrigine and the atypical antipsychotic quetiapine during pregnancy; thus, we present the case of two infants exposed in utero to lamotrigine and quetiapine without major congenital malformation (MCM) or apparent neurodevelopmental delay.

Case report

Two infants were born vaginally at term, 21 months apart, to an otherwise healthy mother in her late 20s with bipolar disorder. The mother had been stabilized prior to pregnancy and was continued on the same regimen of lamotrigine (100 mg/day) and quetiapine (25 mg/day). The mother was treated with folate (2 mg/day) starting 2 months prior to each conception and was continued on this dose throughout the first trimester of pregnancy. Combination acetaminophen, butalbital and caffeine, and promethazine were required to treat a recurrence of migraine headaches during both pregnancies. The mother denied use of tobacco or alcohol during either pregnancy and had normal screening laboratory workups and normal routine pregnancy surveillance.

The first child was born healthy appearing on physical exam, with 1 and 5 min Apgar scores of 8 and 9, respectively. Birth weight was 3234 g and length was 53.34 cm, values that fall within appropriate for gestational age (AGA) parameters. No abnormal muscle movements, apneic events, or respiratory depression were noted during routine nursery stay, and mother and child were discharged from the hospital on infant day of life number 2. State-mandated newborn screening (NBS) labs were performed though no lamotrigine level was obtained. NBS results revealed an abnormal thyroid stimulating hormone (TSH) level of 27 μIU/mL (reference range <25 μIU/mL), necessitating retesting on day of life 11. Retest resulted in a TSH of 4.43 mIU/mL and free thyroxine (fT4) level of 2.34 ng/dL, both within normal limits. Due to concerns regarding drug passage into breast milk, the mother elected to formula feed the infant. By 2 years of age, the child was meeting all age-appropriate developmental milestones and was reported not to have any mental or verbal delays.

The second child also appeared healthy upon physical examination with 1 and 5 min Apgar scores of 8 and 9, respectively. Birth weight was 3564 g and length was 52.07 cm (AGA). Again, no abnormal muscle movements, apneic events, or respiratory difficulties were noted at birth or during nursery stay, and routine NBS labs were performed revealing no abnormalities. No lamotrigine level was obtained. A mild

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heart murmur was noted on the first day of life, but mother and infant were discharged from the hospital on day of life number 3, after the infant passed routine congenital heart disease four-extremity pulse-oximetry screening. No imaging workup was required. Per pediatrician's records, the murmur had resolved by day of life 15. After discussion of possible risks and benefits with the newborn's pediatrician, the mother elected to breastfeed this child. The second child was also noted to be meeting all age appropriate developmental milestones at routine 2-month well child check.

Discussion

The risks associated with untreated or undertreated maternal illness during pregnancy may, in some instances, outweigh the potential iatrogenic risks to the patient's developing fetus (Gentile 2006; Larsen et al. 2015). The decision to commence or continue psychopharmacological treatment in pregnancy must therefore be made on a case by case basis, and the provider necessarily be familiar with the dangers to the fetus of each medication prescribed.

It has been documented that use of lamotrigine during pregnancy increases the risk for numerous MCMs (i.e., cleft palate, skeletal deformities, genitourinary abnormalities, and gastrointestinal abnormalities) (Morrow et al. 2009), and there is concern that its use may lead to lowered IQ when folate dosing is neglected prior to conception.

Two recent reviews of lamotrigine registries indicate no increased risk for facial cleft or club foot in particular, and that the risk of MCMs in general appears to be between 2 and 3 %, the same as in untreated populations (Dolk et al. 2016; Epstein et al. 2014). It has been suggested that rates for MGM may be slightly higher (up to 5.5 %) when doses of greater than 200 to 300 mg/day of lamotrigine are used (Morrow et al. 2009; Tomson et al. 2015), but the data are conflicting at best (Epstein et al. 2014). Some data appeared to indicate that mothers who used folate prior to conception had children with IQs up to seven points higher at 6 years of age than those who did not use folate (Meador et al. 2013), but these findings were not replicated (Baker et al. 2015).

While lamotrigine has been shown to have little antifolate activity (Morrell 2002), it may affect placental folate transport (Rubinchik-Stern et al. 2015), and thus, it is recommended that mothers on lamotrigine be supplemented with anywhere between 0.4 and 5 mg a day with folate, as our patient was (Gandelman-Marton and Neufeld 2013). When dosing lamotrigine, the provider must also consider that lamotrigine clearance can be markedly increased during pregnancy, particularly in the first trimester. One study noted a decrease in blood lamotrigine levels by up to 40–60 % (Tomson et al. 2013). Lamotrigine levels appear to return to a pre-pregnancy state starting around 1.5 weeks post-partum (Clark et al. 2013). Drug level monitoring and lamotrigine dose changes are sometimes necessary in pregnant patients with epilepsy (Reimers 2014), but it is unclear whether or not women with bipolar disorder would require this as well, given that they are often maintained at much lower doses. Lamotrigine levels in the neonate at time delivery appear to be, on average, 66 % of mother's blood level (Clark et al. 2013) and can drop precipitously after birth. This in turn may predispose the infant to withdrawal seizures, as was noted in one case report (Vieker et al. 2009).

The risks associated with the use of second generation antipsychotics (SGAs) in pregnancy are much less clear, with one study reporting a 3 % increased risk of MCM, 5 % increased risk of preterm delivery, 5 % increased risk of being small for gestational age, and an overall risk of lower birth weight in infants with in utero exposure to second generation antipsychotics when compared to an unexposed population (Coughlin et al. 2015).

One meta-analysis revealed that congenital heart defect was the most prevalent MCM associated with SGA use (but with an ARD of just 0.01 compared to non-exposed fetuses); it also revealed that preterm fetuses delivered an average of only 0.21 weeks earlier and had birth weights an average of 57.89 g lower than matched controls (Coughlin et al. 2015). Although these risks were statistically significant, they represent a very small number of affected infants, and the studies referenced in this protocol did not exclude infants exposed to other pharmacological agents, illicit substances, tobacco, or alcohol.

There has been documentation of abnormal muscle movements and respiratory distress in newborns exposed in utero to second generation antipsychotics (Kulkarni et al. 2015); however, these potential withdrawal symptoms were not present in either infant in our case study.

Conclusion

Current evidence indicates that lamotrigine use during pregnancy is fairly safe, but there is a paucity of convincing evidence for the use of SGAs in pregnancy. To date, there is no literature to support the concomitant use of lamotrigine and quetiapine for maintenance of mood stability in pregnant patients with bipolar disorder. We therefore have presented the case of two healthy infants born without any evidence complications after continuous exposure in utero to the combination of lamotrigine and quetiapine. This information, in combination with current literature base, can assist providers in making well-informed, individualized decisions with their patients who are or desire to become pregnant.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

Baker GA, Bromley RL, Briggs M et al (2015) IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 84(4):382–390. doi:10.1212/WNL.0000000000001182

Clark CT, Klein AM, Perel JM, Helsel J, Wisner KL (2013) Lamotrigine dosing for pregnant patients with bipolar disorder. Am J Psychiatry 170(11):1240–1247. doi:10.1176/appi.ajp.2013.13010006

Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH (2015) Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. Obstet Gynecol 125(5):1224–1235. doi:10.1097/AOG.0000000000000759

Dolk H, Wang H, Loane M, Morris J et al (2016) Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies. Neurology 86(18):1716–1725. doi:10.1212/WNL.0000000000002540

Epstein RA, Moore KM, Bobo WV (2014) Treatment of bipolar disorders during pregnancy: maternal and fetal safety and challenges. Drug Healthc Patient Saf 7:7–29. doi:10.2147/DHPS.S50556

Gandelman-Marton R, Neufeld M (2013) Epilepsy in pregnancy. Harefuah 152(8):473–476, 498

Gentile S (2006) Prophylactic treatment of bipolar disorder in pregnancy and breastfeeding: focus on emerging mood stabilizers. Bipolar Disord 8(3):207–220

Kulkarni J, Storch A, Baraniuk A, Gilbert H, Gavrilidis E, Worsley R (2015) Antipsychotic use in pregnancy. Expert Opin Pharmacother 16(9):1335–1345. doi:10.1517/14656566.2015.1041501

Larsen ER, Damkier P, Pedersen LH, Fenger-Gron J, Mikkelsen RL, Nielsen RE et al (2015) Use of psychotropic drugs during pregnancy and breast-feeding. Acta Psychiatr Scand Suppl 445:1–28. doi:10.1111/acps

Meador KJ, Baker GA, Browning N et al (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 12(3):244–252. doi:10.1016/S1474-4422(12)70323-X

Morrell MJ (2002) Folic acid and epilepsy. Epilepsy Curr 2(2):31–34

Morrow JI, Hunt SJ, Russell AJ et al (2009) Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 80(5):506–511. doi:10.1136/jnnp.2008.156109

Reimers A (2014) New antiepileptic drugs and women. Seizure 23(8):585–591. doi:10.1016/j.seizure.2014.05.004

Rubinchik-Stern M, Shmuel M, Eyal S (2015) Antiepileptic drugs alter the expression of placental carriers: an in vitro study in a human placental cell line. Epilepsia 56(7):1023–1032. doi:10.1111/epi.13037

Tomson T, Landmark CJ, Battino D (2013) Antiepileptic drug treatment in pregnancy: changes in drug disposition and their clinical implications. Epilepsia 54(3):405–414. doi:10.1111/epi.12109

Tomson T, Xue H, Battino D (2015) Major congenital malformations in children of women with epilepsy. Seizure 28:46–50. doi:10.1016/j

Vieker S, Thiel M, Längler A (2009) Neonatal seizures caused by lamotrigin withdrawal? Z Geburtshilfe Neonatol 213(2):62–63. doi:10.1055/s-0029-1214404