Is carbamazepine safe to take during pregnancy?

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Abstract

Question Some of my pregnant patients are afraid to take their antiepileptic drugs during pregnancy because of the known risk of malformations and the neurodevelopmental problems associated with valproic acid. Are there similar concerns with carbamazepine?

Answer Similar to valproic acid, carbamazepine increases the risk of neural tube defects; however, it does not increase the risk of other malformations. Carbamazepine is also not associated with an increased risk of developmental delay.

La carbamazépine est-elle sans danger durant la grossesse?

Résumé

Question Certaines de mes patientes enceintes ont peur de prendre leurs médicaments contre l'épilepsie durant la grossesse en raison des risques connus de malformations et de problèmes neurodéveloppementaux associés à l'acide valproïque. Y a-t-il des inquiétudes semblables avec la carbamazépine?

Réponse À l'instar de l'acide valproïque, la carbamazépine augmente le risque d'anomalies du tube neural; par ailleurs, elle n'augmente pas le risque de malformations et n'est pas associée à un risque accru de retard du développement.

For the past few decades, carbamazepine (CBZ) has been used as an effective treatment of seizures, bipolar disorder, and certain types of pain. Carbamazepine has been viewed by many as the antiepileptic drug (AED) of choice during pregnancy,[1] as there are more studies on the fetal outcomes associated with in utero CBZ monotherapy compared with other AEDs.[2] Treatment of active epilepsy is important during pregnancy because seizures can lead to falls, injury, and physical stress that can endanger the health of the woman and the fetus.[3] Carbamazepine has not been associated with increased risk of pregnancy complications such as cesarean section, preeclampsia, or premature delivery,[4] and its contributions to congenital malformations and neurodevelopmental anomalies have become clearer owing to recent large studies.

Congenital malformations

A 2008 review concluded that CBZ monotherapy has one of the lowest risks of teratogenicity among antiepileptic treatments.[2] The review summarized 9 studies that included women taking CBZ monotherapy as the exposed group. Six studies used epilepsy controls (n = 1613 for children born to epilepsy controls, n = 2533 for children exposed to CBZ monotherapy) and 3 used healthy controls (n = 2308 for children born to healthy controls, n = 542 for children exposed to CBZ monotherapy). Only 1 of the 9 studies had a relative risk ratio significantly greater than 1.0 for malformations when taking CBZ monotherapy compared with controls, and that was in one of the studies using healthy controls.[5]

Exposure to CBZ during pregnancy has been associated with an increased risk of neural tube defects (NTDs) (0.2% to 1% vs 0.1% in the general population),[6-8] and its association with other major malformations has been clarified in a recent systematic review of 8 studies.[9] The overall risk of all major congenital malformations was 3.3% with first-trimester CBZ monotherapy exposure (89 of 2680 exposed pregnancies, 95% CI 2.7% to 4.2%). The authors also conducted a case-controlled study using the EUROCAT database of 3 881 592 births and 98 075 major congenital malformations in Europe from 1995 to 2005. Within the database, spina bifida was significantly associated with exposure to CBZ monotherapy compared with no AED exposure (odds ratio [OR] 2.6, 95% CI 1.2 to 5.3), but the risk was significantly lower when CBZ was compared with valproic acid exposure (OR 0.2, 95% CI 0.1 to 0.6). Compared with no AED exposure, there was no significant association between exposure to CBZ monotherapy and total anomalous pulmonary venous return, cleft lip with or without cleft palate, diaphragmatic hernia, or hypospadias. Additionally, compared with other AED monotherapies (excluding valproic

acid), there was no significant association between CBZ exposure and either spina bifida or hypospadias, and the risk was actually lower for cleft lip with or without cleft palate (OR 0.1, 95% CI 0.0 to 0.6).

Neurodevelopmental deficits

Several early studies suggested increased neurodevelopmental anomalies in children exposed to AEDs in utero.[10,11] A 2010 meta-analysis of 7 studies analyzed full-scale, performance, and verbal IQ scores in 151 CBZ-exposed children, 58 unexposed children born to mothers with epilepsy, and 436 unexposed children born to mothers without epilepsy.[12] In 2 of the studies that used the Bayley or McCarthy IQ scales, which measure full-scale IQ only, there was no significant difference between the CBZ-exposed children and the unexposed children. In 3 other studies, when using the Wechsler IQ scale, there was a significant difference between the CBZ-exposed children and the children in the unexposed control group in performance IQ only; however, this significance disappeared when compared with the children in the epilepsy control group ($P<.002$). More current studies have confirmed that CBZ exposure does not significantly decrease average reported IQ,[13] fluency and originality,[14] and core language scores.[15]

Conclusion

There is a 2- to 10-fold increased risk of NTDs in women with epilepsy taking CBZ; however, the risks associated with CBZ are not as great as those associated with valproic acid. It is therefore important to discuss epilepsy treatments with women of childbearing age in the planning phase, so that they can begin early supplementation with 5 mg of folic acid and discontinue using valproic acid before pregnancy. Additionally, it is important to screen with a combination of a level 2 ultrasound and either maternal blood or amniotic α-fetoprotein testing at 16 to 18 weeks of gestation to rule out NTDs. Unlike valproic acid, CBZ does not appear to have adverse effects on neurobehavioural development.

Competing interests
None declared

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