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Antiepileptic drugs and pregnancy

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Abstract

Background : Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness.

Methods and materials : Retrospective population based cohort study using administrative databases in New Zealand between 2008 and 2014. Women who had been pregnant were identified by the National Minimum Dataset and were linked to the Pharmaceutical Collection to obtain information on use of AEDs. Women aged between 15 and 45 years dispensed AEDs were identified in the Pharmaceutical Collection.

Results : There was an increase in the number of women of child-bearing potential prescribed AEDs, from 9 women per 1000 women in 2008 to 11.4 women per 1000 women in 2014. Women who had been dispensed an AED had an increased rate of spontaneous abortion 8.97 spontaneous abortions per 100 pregnancies, compared with, 6.31 per 100 pregnancies (risk ratio 1.42, 95% CI 1.40 to 1.44), and a decreased rate of pregnancy termination, 18.51 terminations per 100 pregnancies compared with 19.58 per 100 pregnancies (risk ratio 1.95, 95% CI 0.94–0.96).

Conclusion : Seizure symptoms can vary widely. Treatment with medications or sometimes surgery can control seizures for the majority of people with epilepsy. Some people require lifelong treatment to control seizures, but for others, the seizures eventually go away. Women who have epilepsy tend to have more seizures when they are pregnant. This is especially true in women who already have a lot of seizures. Epilepsy and the medicines to treat it can have many effects on the mother, the pregnancy, and the developing baby. Most women with epilepsy are able to have a healthy pregnancy and baby

Introduction

Epilepsy is one of the most common serious brain disorders, can occur at all ages, and have many possible presentations and causes[1]

Epilepsy is not a single entity but, instead, an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, or distorted perceptions that are of limited duration but recur if untreated [1] It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation[2]

Diagnosis of epilepsy remains clinical, and neurophysiological investigations assist with diagnosis of the syndrome. Brain imaging is making great progress in identifying the structural and functional causes and consequences of the epilepsies. Current antiepileptic drugs suppress seizures without influencing the underlying tendency to generate seizures, and are effective in 60–70% of individuals[1] Antiepileptic drug (AED) exposure during pregnancy increases the risk of major congenital malformations (MCMs). The magnitude of this risk varies by AED exposure [2]With early preconception counseling and close support in pregnancy, the vast majority of pregnancies in women with epilepsy are uncomplicated. The aim is to achieve the best possible seizure control without the occurrence of grand mal seizures using an antiepileptic drug with the lowest possible malformation risk. Due to the dose-related increase in malformation risk and other risks, especially with regard to children's cognitive development, the warnings for the regulation of valproic acid in women of reproductive age have been tightened. The pharmacokinetics of the antiepileptic medication (AED) during pregnancy requires regular serum level monitoring and early dose adjustmen [3]

pathophysiology of epilepsy as these diseases are caused by ion channel mutations. It begins with changes in nervous behavior associated with cardiac and atrial events ;

due to alterations in local ionic microenvironment which occur during focal epileptogenesis; intrinsic control mechanisms which serve to restrict seizure spread; neuronal characteristics which account for the differences in seizure patterns seen in infants and adults; and the possible long-term consequences of recurrent local neuronal hyperexcitability [4]

Antiepileptic drugs (AEDs) provide satisfactory control of seizures for most patients with epilepsy. The drugs have the remarkable ability to protect against seizures while permitting normal functioning of the nervous system [5]AEDs act on diverse molecular targets to selectively modify the excitability of neurons so that seizure-related firing is blocked without disturbing non-epileptic activity. This occurs largely through effects on voltage-gated sodium and calcium channels, or by promoting inhibition mediated by GABAA (γ-aminobutyric acid, type A) receptors. The subtle biophysical modifications in channel behaviour that are induced by AEDs are often functionally opposite to defects in channel properties that are caused by mutations associated with epilepsy in humans the are many drug such as Diazepam ,Phenobarbital , Ezogabine , Lacosamide , Lamotrigine
Levetiracetam [5] well be discus later on

Ppatient-,Choice of drug treatment is based on the classification of the seizures specific variables (for example, age, comorbid medical conditions lifestyle, and personal preference), and characteristics of the drug (such as cost and drug interactions). For example, focal-onset seizures are treated with a different set of medications than primary generalized seizures, although the list of effective agents overlap [1]

Use of certain antiepileptic drugs (AEDs) during pregnancy increases the risk for specific congenital malformations, such as , cleft lip and palate, Teratogenicity and cardiovascular malformations neural tube defects because of intrauterine valproate--or carbamazepine--exposure can be met by. Taking a careful history regarding .individual or family predisposition to defects or anomalies [6]

Women of childbearing potential with epilepsy require assessment of their antiepilepsy medications in regard to contraception and pregnancy planning. Several

antiepilepsy medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include *phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide*, and *clobazam*. These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patchring, implants, and oral tablets). Pregnancy planning is vital, as many antiepilepsy medications have the potential to affect fetal development an cause birth defects. All women considering nancy should be on high doses (1 to 5 mg) of folic acid prior to conception. *Divalproex* and barbiturates should be avoided.[1]

Aim of the report is to study the pathophysiology of epilepsy, mechanisms of action of antiepileptic drug and risk malformation of drugs during pregnancy.

Method and material

In the study included in this report they

Study population

Using the National Health Index (NHI) all records from the Pharmaceutical Collection were linked to the National Minimum Dataset (NMDS) to identify women with no pregnancy, a birth, spontaneous abortion or pregnancy termination, to create the following cohorts:

Women of childbearing age (15–45 years old)

i-women aged between 15 and 45 years old who were dispensed a study AED three or more times in a 12 month period between January 1, 2008 and December 31, 2014.

ii-estimated population of women in New Zealand aged between 15 an 45 years old

2- Pregnant women

A_women who had a spontaneous abortion or pregnancy termination between January 1, 2009 and December 31, 2014 who

i._ had been dispensed any AED included in the study in the preceding 3 months

ii _ had NOT been dispensed any AED included in the study in the preceding month

B- women in New Zealand who had a birth (including stillbirth) between January 1, 2009 and December 31, 2014 who
i-had been dispensed any AED included in the study in the preceding 9 months

ii-had NOT been dispensed any AED included in the study in the preceding 9 months

Every person in New Zealand has a unique NHI number, an alphanumeric identifier that is used in all interactions with the health system over their life. This number makes it possible to link an individual's health data across a range of databases. The recording of NHIs are reliable from 2008, with 97% of all
records containing an NHI therefore this study used data from the NMDS and the Pharmaceutical Collection between 2008 and 2014. Pregnancy outcomes starting from .January 2009 were used to ensure consistent NHI recording 9 months prior

The NMDS is a national collection of public and private hospital discharge information, including coded clinical data for both inpatients and day patients. Every hospital birth event (approximately 97% of births in New Zealand) is captured by the NMDS. The NMDS also contains information about pregnancy terminations and spontaneous abortions that are managed in public hospitals. The Pharmaceutical Collection contains claim and payment information from pharmacists for all subsidised community dispensing in New Zealand (100% of all subsidised .medicines), however not those dispensed in hospital.

All study data contained only encrypted NHI numbers and no identifying details such as name or address were used. Any women missing an NHI number or with more than .20% of their data missing were excluded.

Pregnancy outcomes
To capture pregnancy outcomes in the NMDS database ICD 10 codes for abortion, ectopic pregnancy and birth were used, grouped as follows: spontaneous abortions (O02 – O039), pregnancy terminations or induced abortions (O040 – O049), and births, including stillbirths (Z370 – Z375). Molar (O01) and ectopic pregnancies

(O00) were excluded. To help ensure validity of the data and minimise incorrect coding issues, women with maternity codes who were under 15 years old or over 55 .years old were excluded. Each pregnancy in the study time period was included

Abortions are defined in New Zealand as foetal loss usually during the first 20 weeks of gestation. Induced abortions (pregnancy terminations) are those initiated voluntarily with the intent of terminating a pregnancy. All other abortions are considered spontaneous abortions. The legal definition of stillbirth in New Zealand is a child born dead who weighs 400 g or more or who is born after 20 completed weeks .gestation

Assessment of AED exposure

In New Zealand, all AEDs are supplied by prescription and are subsidised if listed in the pharmaceutical schedule. The use of AEDs was defined as any prescription redeemed with drugs from the ATC code group Antiepileptics (N03AA) or subsidised under the "control of epilepsy" section of the schedule. This included the following medicines: carbamazepine, clobazam, clonazepam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, primidone, sodium valproate, topiramate and vigabatrin . Dispensing information about the use of AEDs which are not subsidised, such as pregabalin and oxcarbazepine, is not captured by the pharmaceutical collection.

We defined any dispensing of an AED within 9 months of a birth or stillbirth or within 3 months of a spontaneous abortion or termination as an exposure to an AED in pregnancy. The date the medicine was dispensed determined at which stage during the pregnancy the exposure to an AED occurred. Exposure to polypharmacy was recorded for women who were dispensed two or more AEDs in the same trimester. .[7]

Result

Women of child-bearing potential

Over the study period, the number of women of childbearing age (between 15 and 45 years) dispensed any AED increased, from 9 women per 1000 women in 2008 to 11.4

women per 1000 women in 2014 . During this time period, numbers of women dispensed sodium valproate or carbamazepine declined while the numbers of women dispensed lamotrigine, gabapentin, and levetiracetam increased. Prescriptions of AEDs to women of child-bearing age are most commonly provided by general practitioners, accounting for 60% of the prescriptions from 2008 to 2014

Pregnant women

individual women received an AED in the 9 months before a birth, or 3 months 2284 before a pregnancy termination or spontaneous abortion between 2009 and 2014. 311 women had two pregnancies over the study period and 59 women had three or more pregnancies over this period which resulted in 2728 pregnancies. Table 1 shows the maternal age characteristics. Women dispensed an AED during this period were more likely to be older than women who had not been dispensed an AED ($p < 0.05$)

Overall, women who had been dispensed an AED in the exposure period (within 9 months of a birth or stillbirth or within 3 months of a spontaneous abortion or pregnancy termination) had an increased rate of spontaneous abortion, 8.97 per 100 pregnancies, than those not dispensed an AED, 6.31 per 100 pregnancies (age-adjusted risk ratio 1.42, 95% CI 1.40 to 1.44). Women dispensed an AED had a decreased rate of pregnancy termination, 18.51 per 100 pregnancies compared with 19.50 per 100 pregnancies for women who had not been dispensed an AED (age adjusted risk ratio 0.95, 95% CI 0.94 – 0.96)

Analysis of pregnancy outcomes by AED, where women were only exposed to one AED during pregnancy and where there were 50 or more exposures, revealed no difference in the rate of spontaneous abortions between AEDs. Women that had a termination were more likely to be taking clonazepam, gabapentin or sodium valproate than lamotrigine or carbamazepine. Women that gave birth were more likely to be .taking carbamazepine or lamotrigine than clonazepam, gabapentin or sodium valproate

Overall use of AEDs by pregnant women increased slightly from 8.10 per 1000 births in 2009 to 9.18 per 1000 births in 2014. During this time, use of sodium valproate by pregnant women nearly halved from 2.24 women per 1000 births to 1.20 women per 1000 births while use of gabapentin (0.27 to 0.97 women per 1000 births), lamotrigine (1.10 to 1.79 women per 1000 births) and levetiracetam (from 0 to 0.83 women per 1000 births) increased among pregnant women

The majority of pregnant women dispensed AEDs during pregnancy are on monotherapy, only a small proportion (10.7%) were on AED polytherapy during pregnancy. In the time period from 2009 to 2014, of the women dispensed any AED during the nine months before birth, 171 (8.65%) were dispensed two different AEDs in the same trimester. 35 women (1.77%) were dispensed three AEDs and five (0.25%) women were dispensed four AEDs in the nine months before birth.[7]

Discussion

Managing epilepsy during pregnancy is to adjust the maternal and fetal dangers related with uncontrolled seizures against the potential teratogenic impacts of antiepileptic drugs (AEDs). A judicious approach requires information of such dangers as well as an understanding of the impacts of pregnancy on seizure control and of gestational impacts on AED mien. seizures are possibly perilous to the mother and, in spite of the fact that strict prove is missing, are by and large moreover expected to be more hurtful to the baby than are AEDs.[8] Levetiracetam is used during pregnancy, women should receive adequate amounts of folic acid (0.4–5 mg/day) and serum concentrations of levetiracetam should determined before conception if possible and during each trimester, especially during the middle of the third trimester, to assess therapeutic concentrations. The dose may need to be increased during the third trimester to provide concentrations consistent with those before conception. Woman should be informed that there appears to be a small chance of malformations with levetiracetam, but that the data are limited.[9] The drug is well absorbed orally and excreted in urine unchanged, resulting in few to no drug interactions[2] where as Rufinamide pharmacokinetics of AEDs in pregnancy and during lactation is important to enable optimal treatment. Gestation induced alterations in pharmacokinetics vary with the AED but also between patients and are difficult to predict. Therapeutic drug monitoring is, therefore, advisable during pregnancy and the use of the individual patient's Most common adverse effects are somnolence, fatigue, dizziness, dipolopia, nausea and ataxia. Rufinamide has shown promise as adjunctive treatment for Lennox-Gastaut syndrome and may have some role in localization related epilepsies as well.[9[

If possible, women already taking divalproex should be placed on other therapies prior to pregnancy and counseled about the potential for birth defects, including cognitive and behavioral abnormalities and neural tube defects. The pharmacokinetics of antiepilepsy medications and the frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and change during pregnancy[1]

Conclusion

In the discussion, the best antiepileptic drug during pregnancy is for(Levetiracetam) because it is the least fetal deformity and reduces epileptic seizures for the mother And also maintains the health of the mother and the baby

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