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Seizure control and pharmacokinetics of antiepileptic drugs in pregnant women with epilepsy

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Summary The main concerns associated with epilepsy during pregnancy consist of maternal and fetal risks from uncontrolled seizures, and harmful effects of the treatment on the development of the offspring. Although seizure control is maintained in the majority, worsening occurs in a fraction of childbearing women with epilepsy. As multiple factors associated with pregnancy may have a negative impact on epilepsy, a careful analysis of the situation should be performed in those who deteriorate. Emotional and behavioural influence, including insufficient sleep and treatment non-compliance, as well as physical factors, such as emesis and pelvic distortion, should receive attention.

The serum concentrations of almost all antiepileptic drugs decrease during pregnancy, particularly those which are metabolised by glucuronidation. The inter-individual variability is pronounced. In highly protein-bound drugs, such as phenytoin and valproate, unbound drug is less affected than total concentrations. Lamotrigine and levetiracetam concentrations may decrease by more than 50% in the course of pregnancy; monohydroxyoxcarbazepine by up to 30—40%.

Appropriate clinical follow-up tailored to individual needs and supported by therapeutic drug monitoring should be performed in pregnant women with epilepsy. Education concerning reproductive issues is an essential part of the epilepsy service to fertile women.

Introduction

Epilepsy is the most common neurological problem, which requires continuous pharmacological treatment throughout pregnancy. Among patients,

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as well as among health personnel, there is still often considerable uncertainty about the combination of pregnancy and seizure disorders, and how these two conditions may influence each other. The principal goal in the management of epilepsy during pregnancy is an optimal balance between maternal and fetal risks of uncontrolled seizures on the one side, and the risk of fetal exposure to antiepileptic drugs (AEDs) on the other. In particular, generalized tonic-clonic seizures should be avoided, as they may cause fetal anoxia and dangerous injuries due to blunt abdominal traumas.

Generally accepted guidelines for the treatment of epilepsy in pregnant women recommend monotherapy with the most effective AED for the woman's epilepsy type at the lowest effective dose. Valproate should be avoided if there are effective alternatives, due to potential adverse effects on the developing fetus.[1] Eager efforts to follow these recommendations may leave some childbearing women with a brittle seizure control. Minimal effective treatment as a starting point may possibly result in vulnerability to various potential pregnancy-related seizure precipitants (Table 1). Drug selection may be complicated in fertile women considering seizure type and epilepsy syndrome as well as the estimated teratogenicity and the neurodevelopmental risks in the offspring. The management of epilepsy may indeed be complex and demanding in females who wish to conceive.

Table 1 Factors which may influence seizure control during pregnancy

Behavioural factors
Emotions (positive/negative)
Psychosocial problems
Insufficient sleep
Fear of harmful seizures, particularly during labour and delivery
Concern for safety of breast-feeding
Misconceptions regarding the transmission of the disorder
Worries concerning adverse effects of AEDs on the developing fetus
Treatment non-compliance
Physical changes
Nausea and vomiting
Fatigue/exhaustion/pelvic distortion
Frequent awakenings/leg cramps
Altered hormone levels
Pharmacokinetic alterations of antiepileptic drugs
Reduced intestinal absorption
Increased volume of distribution
Altered drug protein binding
Enhanced metabolism
Increased renal clearance
Natural fluctuations of seizure frequency

Changes in seizure control during pregnancy

The effect of pregnancy on the course of epilepsy has been investigated in several studies, most of them in selected populations from specialist epilepsy clinics, probably including a preponderance of patients with difficult-to-treat seizure disorders. Schmidt[2] reviewed 2065 pregnancies reported until 1980 and concluded that the seizure frequency increased in 24%, decreased in 23% and remained unchanged in 53%. In a prospective study from 1983, 136 pregnancies were followed up. Seizure control was unchanged in 50%, deteriorated in 37% and improved in 13%.[3] Later studies have reported more or less similar findings.

Recently, a total of 1956 pregnancies in 1882 women from the EURAP pregnancy registry have been reviewed.[4] Due to lacking information from the pre-pregnancy period, seizure control during the second and third trimester was compared with that of the first trimester. Unchanged seizure frequency throughout all trimesters was reported in as many as 64% in this survey. A total of 58% remained completely seizure free throughout the observation period, 68% of those with generalized and 49% of those with partial epilepsies. Improvement during the course of pregnancy was reported in 16% and deterioration in 17%. Among the 42% who experienced seizures, 18% had generalized tonic-clonic seizures. Seizures during delivery were reported in 3.5% of women. There were 36 cases of status epilepticus (2%), but only 12 of them were convulsive. As mentioned above, almost 60% of the EURAP participants were completely seizure free during pregnancy, a fact that makes a marked bias towards difficult-to-treat seizure disorders in the study population less probable. In general, seizure control did not appear to be worse in those pregnancies, which resulted in miscarriages and stillbirths. Nevertheless, one case of status epilepticus was associated with a miscarriage.

All these various studies indicate that pregnancy does not appear to influence seizure control in most women. Those who are in remission have a low risk for recurrence during childbearing. Women who experience changes in seizure control can be divided in two approximately equally sized groups, those with improvement and those with deterioration. Intensified scientific focus on the group of women with deteriorated seizure control is now

warranted to identify clinical predictors for seizure increase in pregnancy.

Factors influencing seizure control in pregnancy

A range of relevant factors is listed in Table 1. Aspects other than drug-related changes have so far received relatively little attention. It should be kept in mind that many epilepsies seem to express an inherent tendency to episodic fluctuations of seizure frequency. Hence, apparent changes of seizure activity during the course of pregnancy may be due to the natural course of the epilepsy itself.

Non-pharmacokinetic factors

It is well known that the occurrence of seizures in people with epilepsy may be intimately related to feelings and thoughts.[5] Mood and behaviour of the expecting mother may be of significance. Pregnancy may have a major impact on the emotional status. ''Happiness is an anticonvulsant'',[5] sometimes quite a powerful one, whereas worries and psychosocial problems related to the pregnant state may contribute to deterioration. Lack of sleep is a major seizure precipitant in many patients. The fright for seizures causing harm to the mother and the fetus, particularly during labour and delivery, may be pronounced. Future risks during care of the newborn and limitations in the role as a mother may also represent a threat. Uncertainty concerning the safety of breast-feeding is prevailing. Misconceptions regarding the genetic transmission of the disorder to the baby are widespread. Medication noncompliance in the form of self-discontinuation of AEDs without medical consent is not uncommon due to maternal concern about the effects of the drugs on the health of the unborn.[6] Recurrence or worsening of seizures may be the result, a situation which requires appropriate counselling and guidance. Excessive nausea and vomiting during early pregnancy may also affect regular drug intake. Moreover, sleep may also be disrupted from physical factors, including leg cramps. Complications, such as pelvic distortion may add to the physical burden towards the end of pregnancy. All these unfavourable factors may occur in various combinations and should be considered in women experiencing seizure increase during pregnancy. Relevant issues should be addressed and discussed with the patient, appropriate measures to alleviate the problems should be undertaken and rational reassurance provided. Leave from work, domestic assistance, practical advice and social support may be helpful. Rest and protection from stress should be promoted. Patient education including preconception counselling is important. Factual knowledge about the disorder and its treatment in relation to reproduction may facilitate coping during pregnancy. Specially trained epilepsy nurses may play an active role in the management and support of these patients and should be readily available for contact. A close cooperation between professionals providing epilepsy service and obstetric care is often necessary. Pregnant women should be encouraged to share their worries. The problems should not be trivialized, but it should be emphasized that pregnancies are successful with healthy offspring in 90% of patients with epilepsy.[7] Table 1 may serve as a useful check-list for the follow-up during pregnancy, particularly when seizure control is incomplete.

The marked increases in sex hormone levels may also modify seizure activity. The hormonal influence may be twofold. Hormones may interact with the pharmacokinetics (PK) of AEDs. They may also have a direct pharmacodynamic effect on the seizure threshold. In animal and human studies, estrogens generally act as proconvulsants, whereas conversely, progesterone may have an anticonvulsant effect.[8] A massive and progressive increase in the concentrations of progesterone and estrogens take place during pregnancy. Possibly, some epilepsies may be vulnerable to the effects of estrogen, whereas others may be disposed to be influenced by progestins. It is not known whether the course of seizures during pregnancy may be predicted by the tendency to seizure increase in relation to the physiological hormonal fluctuations in the non-pregnant state, such as in so-called catamenial epilepsy. Since the estriol/progesterone ratio rises considerably during the last weeks of pregnancy,[9] a correlation between catamenial epilepsy and worsened seizure control could be hypothesized. To our knowledge, this has not been studied.

The induction of labour appears to be associated with withdrawal of the inhibitory influence of progesterone on the uterine contractility.[9] Several other factors, such as stress, pain, sleep deprivation, over-breathing and dehydration, may increase the tendency to seizures during partus. Nevertheless, most women with epilepsy will have an uneventful labour and a normal vaginal delivery. However, between 3.5 and 5% may have tonic-clonic seizures or even status epilepicus during labour or puerperium.[4] In one recent study, seizures during labour and delivery occurred in four of 32 (12.5%) patients categorized with primary generalized epilepsy, but in none of the 57 women with partial epilepsy.[10] If tonic-clonic seizures or even status epilepticus occur during labour, maternal hypoxia,

fetal hypoxia and acidosis may result. Women at risk for seizures should be followed closely around the time of term.

Pharmacokinetic factors

A range of physiologic changes during gestation may alter the PK of AEDs.[11] Increased plasma volume and/or increased total body water may lead to increased volume of distribution, and thus reduced AED serum concentrations. Increased plasma volume may also result in reduced serum albumin concentrations, which may affect AED protein binding and plasma clearance. Increased renal blood flow and glomerular filtration rate may reduce the serum concentrations of AEDs predominantly eliminated via the kidneys. Other factors, which may affect the PK of AED, are less well documented, e.g. changes in gastrointestinal motility/drug absorption, and altered biotransformation capacity. In the past three decades, several studies have been performed regarding the AED PK during gestation. Pregnancy-related changes may to some extent be predicted by the pharmacological properties of these drugs. However, the large number of factors, which may influence serum concentrations, as well as the marked inter-individual differences both in drug disposition and seizure control, make clinical reality anything else than simple. Co-medication with enzyme-inducing or inhibiting AEDs, which themselves may be subject to PK alterations, is a further complicating factor. Therefore, it is often difficult to anticipate whether pregnancy-related changes in AED PK will become clinically relevant in the individual patient or not.

A brief overview based on relevant literature on the PK interaction between pregnancy and frequently used AEDs is given below.

Phenobarbital (PB)

PB serum levels decrease during pregnancy. In a study by Yerby et al.[12] total serum concentrations declined by 55% with the sharpest fall during the first trimester. As protein binding is relatively low (40—60%), there was a similar decline in unbound levels (50%), but considerable inter-individual variations have been demonstrated.[13]

Phenytoin (PHT)

PHT serum levels decrease from the start of pregnancy and may fall by more than 60% in the third trimester, returning to pre-pregnancy levels within a few weeks after delivery.[14] However, a clear-cut relation between seizure control and total serum levels of PHT has not been established. This may be related to changes in its free fraction. PHT is highly protein-bound, which makes it susceptible to changes in plasma albumin concentrations. Accordingly, an increase in its free, unbound fraction and an increased plasma clearance of PHT during pregnancy, have been demonstrated. In one series, unbound PHT serum concentrations declined by only 18%, while total PHT declined by as much as 61%.[15,16] Enhanced hepatic metabolism of PHT to its main metabolite, 5-(4-hydroxyphenyl)-5-phenylhydantoin, seems to be the main cause.[17] However, one case report describes considerable intestinal malabsorption of phenytoin during pregnancy, with 56% of the dose appearing in the faeces, leading to a marked exacerbation of seizures and finally, status epilepticus.[18]

Carbamazepine (CBZ)

Plasma clearance increases during pregnancy with a maximum in the third trimester. The protein binding is 70%. Total CBZ serum concentration may decline by over 40%, but unbound drug has been reported to be less affected.[12] In one series, total CBZ levels were only 10% lower during the third trimester compared to baseline, whereas free concentrations were largely unchanged (4% lower).[15,16]

CBZ has a pharmacologically active metabolite, carbamazepine-10,11-epoxide. The ratio of the epoxide metabolite to CBZ serum concentrations usually increases during pregnancy, although not in a predictable manner. This has been attributed to both reduced biodegradation of the epoxide and to its enhanced formation from CBZ.[18]

Altogether, clinically significant changes do not appear to be common with CBZ during pregnancy.

Valproate (VPA)

Total VPA serum concentrations may decline by 50% and rise to pre-pregnancy levels within one week after delivery.[12] VPA is highly protein-bound and therefore susceptible to pregnancy-induced reduction in serum albumin concentrations. Accordingly, the unbound fraction has been shown to be inversely correlated to serum albumin concentrations. Since it is the free fraction of a drug, which is pharmacologically active, this may outweigh the decline in total VPA serum concentrations. It should also be kept in mind that the free fraction increases overproportionally with increasing total VPA serum concentrations. In nine pregnancies a decrease of 39% of total levels was found, while unbound levels increased by 25% at delivery. Dose increase had taken place in four of the patients.[12]

Lamotrigine (LTG)

LTG has a relatively low degree of protein binding (55%) and is unlikely to be significantly affected by

changes in serum albumin concentrations. However, LTG is extensively metabolised, mainly to LTG-N2-glucuronide by uridine-diphosphate glucuronosyltransferase (UGT). Its apparent clearance in the last trimester of pregnancy increases to at least the double compared to baseline, and the dose-normalized serum concentration may be reduced by 40—60% in the third trimester, returning to non-pregnant levels within 1—2 weeks postpartum.[19—23] The fall in LTG serum concentrations is considerably less pronounced in women on enzyme-inducing or inhibiting co-medication,[23,24] suggesting an enhanced rate of glucuronidation as the underlying mechanism. Accordingly, an increased LTG-N2-glucuronide/LTG serum concentration ratio has recently been demonstrated during pregnancy.[25]

Gabapentin (GBP) and pregabalin (PGB)
GBP and PGB are not metabolised and are eliminated unchanged through the kidneys. Theoretically, an increased glomerular filtration rate may therefore lead to reduced serum concentrations. However, no systematic studies on the PK of GBP or PGB during the course of pregnancy have been published.

Topiramate (TPM)
Only a small proportion of TPM is metabolised, and up to 40% of an oral dose is eliminated unchanged via the kidney. Thus, a pregnancy-related increase in renal blood flow might lead to an increased renal clearance and a decline in TPM serum concentrations. No studies on the PK of TPM during pregnancy have been published.

Oxcarbazepine (OXC)
After oral intake, OXC is quickly metabolised to the pharmacologically active, monohydroxycarbazepine (MHD-OXC), which is eliminated as a glucuronide. The protein binding of MHD-OXC is less than 50%. Only two small studies on the PK of MHD-OXC during pregnancy have been published so far. The serum concentrations of MHD were at least 36% lower during pregnancy, compared to pre- or post-pregnancy values, respectively.[26,27] As with LTG, an increased rate of glucuronidation may be the responsible mechanism.

Levetiracetam (LEV)
Protein binding is virtually non-existent. One third of an oral dose is metabolised in blood by hydrolysis, and two thirds are usually found unchanged in the urine. The apparent clearance of LEV increases significantly during pregnancy. Accordingly, case series have demonstrated reduced serum concentration/dose ratios as low as 50% of baseline.[28,29] The underlying mechanism is unidentified. Both increased peripheral hydrolysis and/or increased renal blood flow are possible.

Zonisamide (ZNS)
No systematic studies on the PK of ZNS during pregnancy have been published. ZNS is only 60% protein-bound and undergoes extensive biotransformation. Decreased serum albumin concentrations and increased glomerular filtration rate would not be expected to induce dramatic changes in the PK of ZNS. However, other pregnancy-related changes, like increased volume of distribution, might affect ZNS serum concentrations. Indeed, one case report describes an increase of the ZNS serum concentration after delivery, from 17.5 μg/mL to 23.3—25.5 μg/mL 9 days postpartum.[30]

Conclusion

Pregnancy does not influence seizure control in most women with epilepsy, but a minority experiences more seizures. Multiple mechanisms may contribute to deterioration. Pregnancy-related behavioural and physical factors may be of significance. Worries related to the disorder itself may have a real basis, but are often due to misconceptions and lack of factual knowledge. Appropriate patient education and counselling are crucial for confidence and treatment compliance during pregnancy.

The serum concentrations of most AEDs decline during pregnancy. In highly protein-bound compounds, unbound concentrations may be less affected than total levels. As yet, there is insufficient knowledge concerning many of the newer AEDs, but recent studies have demonstrated reductions of LTG and LEV concentrations exceeding 50%, and of MHD-OXC of 30—40%. The clinical consequences may be enhanced when AEDs with strong propensities to gestation-related changes are combined. Pre-pregnancy serum concentrations should be obtained and clinical follow-up during childbearing should be supported by sequential measurements. Dose adjustments should be performed according to individual assessments.

Conflict of interests statement

Brodtkorb has received speaker's honoraria and financial support for conference attendance from the following manufacturers of antiepileptic drugs, Pfizer, Novartis, Desitin, Glaxo Smith Kline, Janssen-Cilag and UCB. Reimers has no conflict of interests to disclose.

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