EURAP EXTENSION PROTOCOL N. 1

PHARMACOKINETIC EVALUATION OF NEW ANTIEPILEPTIC DRUGS DURING PREGNANCY AND THE PERINATAL PERIOD

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1. Introduction and rationale

The pharmacokinetics of many drugs undergo important changes during pregnancy, due to combination of factors such as modifications in body weight, altered plasma composition, hemodynamic alterations, hormonal influences, dietary factors (including folic acid intake) and contribution of the fetoplacental unit to drug distribution and disposition (1). While for older antiepileptic drugs (AEDs) these changes have been largely characterized, little information is available on the pharmacokinetics of new AEDs during pregnancy. At least for lamotrigine, preliminary observations do suggest that gestation and puerperium may be accompanied by marked changes in plasma drug levels and, possibly, dose requirements (2).

In a similar way, few data are available on transplacentar transfer of these drugs, on their degree of penetration into breast milk, and on their disposition in the newborn and the nursing infant.

It is clear that elucidation of these aspects is important for a safer and effective use of these drugs during pregnancy and for rational counselling concerning the possibility of breastfeeding.

The purpose of the present protocol is to obtain this information through collaboration with interested physicians and patients taking part in the European AED Pregnancy Registry (EURAP).

2. Objectives

The primary objectives of the study will be:

a) To collect information on the steady-state pharmacokinetics of new AEDs during pregnancy and puerperium;
b) To collect information on the excretion of these drugs in breast milk and neonatal exposure through nursing;
c) To collect information on the transfer of these drugs to the neonatal circulation via the placenta and through breast-feeding;
d) To collect information on the disposition of transplacentally acquired drugs in the newborn.

3. Study design

The study will use a non-randomized, open, prospective study design. It will not involve any change in the treatment that the patient is receiving or in overall clinical management.

The protocol involves three separate assessments:

a) Assessment of maternal pharmacokinetics
b) Assessment of drug excretion in breastmilk
c) Neonatal pharmacokinetics

IT IS NOT COMPULSORY TO TAKE PART SIMULTANEOUSLY IN ALL THREE ASSESSMENTS. PATIENTS OR INVESTIGATORS MAY ELECT TO PARTICIPATE IN ONE OR MORE OF THESE ASSESSMENTS, AT THEIR DISCRETION.

4. Eligibility criteria

4.1 Assessment of maternal pharmacokinetics

Patients (at least 15 patients/drug) will be enrolled according to the following inclusion criteria:
a) Women at any week of pregnancy (preferably in the first trimester) or on the day of delivery;
b) Maintenance treatment with any of the following drugs: gabapentin, lamotrigine, oxcarbazepine, topiramate, tiagabine, levetiracetam, vigabatrin or felbamate, either alone or in combination with other drugs;
c) Willingness to give written informed consent.

Associated medication or associated diseases do NOT represent an exclusion criterion.

4.2. Assessment of drug excretion in breastmilk

Patients (at least 15 patients/drug) will be enrolled according to the following inclusion criteria:
a) Women after at least 7 days after institution of breast-feeding;

b) Maintenance treatment with any of the following drugs: gabapentin, lamotrigine, oxcarbazepine, topiramate, tiagabine, levetiracetam, vigabatrin or felbamate, either alone or in combination with other drugs.
c) Willingness to give written informed consent.

Associated medication or associated diseases do NOT represent an exclusion criterion.

4.3 Assessment of neonatal pharmacokinetics

At least 8 neonates/drug will be enrolled according to the following inclusion criteria:
a) Neonates within 48 h of birth;
b) Born from mothers treated with any of the following drugs: gabapentin, lamotrigine, oxcarbazepine, topiramate, tiagabine, levetiracetam, vigabatrin or felbamate, either alone or in combination with other drugs;
c) Parental willingness to give written informed consent.

Associated medication or associated diseases do NOT represent an exclusion criterion.

5. Study procedures

5.1. Assessment of maternal pharmacokinetics

The protocol will involve collection of blood and urine samples on the following occasions:
a) at least once (and no more than twice) on each trimester of pregnancy (if enrolled sufficiently early to do so);
b) immediately after delivery (blood only, no urine on this occasion). At the same time, cord blood should also be collected;
c) about 4, 8 and 12 weeks after delivery.

For blood collection, the samples (6 ml) should be obtained into heparinized tubes after a constant interval (preferably 2-4 h) since the last dose of the drug. In any case, the precise time of collection and the time of the last dose must be recorded carefully in the CRF. The plasma should be separated within 4 h and stored frozen at -20oC until assay.

For urine collection, the woman should be asked to void her bladder just before taking the last daily dose on the day before blood sampling. A complete urine collection should then be obtained until the time of the next dose (urine should be voided just before the dose). Efforts should be taken to keep the urine collection period constant on all occasions. The total volume, the collection timing and the drug dosing timing should be recorded on the CRF. A 40 ml aliquot should be frozen within 6 h and stored at -20°C until assay.

5.2. Assessment of drug excretion in breast milk

One sample of breast milk (2 ml) should be collected at least 7 days after institution of breast-feeding. Collection can be obtained immediately before nursing at any time after drug dosing, but the times of collection and last drug dosing must be recorded carefully in the CRF. Immediately before collection of the breast milk, a blood sample should be obtained into a heparinized tube, the plasma should be separated within 4 h and stored frozen together with the milk sample at -20°C until assay.
If possible, a 0.3 ml of capillary blood should be collected by heel prick from the breast-feed infant about 2 hours after feeding (about 2 hours after collecting the milk sample). For sample collection, heparinized microtainers should be used. The plasma should be separated by centrifugation within 4 h and stored frozen together with the milk sample at -20°C until assay.

5.3. Assessment of neonatal parmacokinetics

One blood sample (6 ml) will be collected from the mother immediately after delivery, and a 2 ml sample of cord blood will be collected at the same time. Two additional capillary blood samples (0.3 ml) will be collected from the newborn by heel prick at the following times:

a) for gabapentin, vigabatrin, tiagabine and levetiracetam:
after approximately 12 and 24 h (for tiagabine an additional sample at 6 h);

b) for topiramate, felbamate and oxcarbazepine:
after approximately 30 and 60 h;

c) for lamotrigine:

after approximately 30 and 72 h.

For neonatal sample collection, heparinized microtainers should be used. The plasma should be separated by centrifugation within 4 h and stored frozen together with the milk sample at -20°C until assay. The precise time of collection must be recorded carefully in the CRF. Information on breast-feeding should also be collected.

6. Assay methods and pharmacokinetic analysis

The AEDs will be determined in plasma and urine using specific HPLC and/or immunological methods as appropriate. For lamotrigine and possibly other drugs, urinary metabolites will also be determined.

Plasma level/dose ratios and breast milk/plasma concentration ratios will be determined. Relationship between milk/plasma concentration ratio and time since last dosing will be assessed by Pearson's or Spearman's regression analysis. For neonatal samples, half-lives will be determined by linear regression on log-concentration vs time data pairs.

Most of the analyses will be descriptive. Comparisons of values obtained in different periods will be performed by ANOVA, paired Student's t-test or Wilcoxon's rank test as appropriate.

7. Data recording

All data, including demographic, sampling and drug dosing details will be entered in especially designed very simple Case Report Form (CRFs).
Information about therapeutic control and possible adverse drug effects will also be recorded.

8. Ethical aspects

The study will be conducted in compliance with the latest revision of the Helsinki's declaration. An informed consent form is attached. The study protocol will be submitted to Ethics Committees as appropriate and patients' confidentiality rights will be safeguarded according to national laws.

9. Publication policy

It is envisaged that results will be published in international journals. Each investigator providing samples for at least 4 fully assessable patients will be included as a co-author. Investigators providing less than 4 assessable patients will be acknowledged in the publication.

10. References

1. Perucca E. Drug metabolism in pregnancy, infancy and childhood. Pharmacol. Ther. 1987;34:129-143.
2. Tomson T, Ohman I, Vitols S: Lamotrigine in pregnancy and lactation. A case report. Epilepsia 1997;38:1039-41.

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INFORMED CONSENT FORM
(FOR ASSESSMENT OF MATERNAL PHARMACOKINETICS)

I, the undersigned ..... born in ..... on ..... give my consent to take part in the above evaluation.

The purpose of the evaluation is to determine whether pregnancy, delivery or the period after pregnancy interferes with the way my body absorbs and handles the medicines that I am taking. This information will be useful in the future to help other women who, like myself, are taking medicines during pregnancy.

My consent does not involves any change in my treatment or in the way the doctor will manage my pregnancy or my epilepsy. It will only involve collection of a small blood sample (6 ml) about every 3 months during pregnancy and after about 1, 2 and 3 months after delivery. I have been given written instruction of what I should do to help with the collection of these samples.

My doctor will collect medical information that may be shared with other research personnel. This information, however, will not be disclosed to third parties. No data that identify myself will be publicized, although law may require some information to be disclosed to health authorities.

My doctor has answered any question that I may have had. My consent is free, and I may withdraw it at any time without this affecting in any way my treatment or the relationship with my doctor.

Faithfully.

Date ..... Signed .....

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PHARMACOKINETIC EVALUATION OF NEW ANTIEPILEPTIC DRUGS DURING PREGNANCY AND THE PERINATAL PERIOD

INSTRUCTIONS FORM
(FOR ASSESSMENT OF MATERNAL PHARMACOKINETICS)

The purpose of the study in which I accepted to participate is to determine whether pregnancy, delivery or the period after pregnancy interferes with the way my body absorbs and handles the medicines that I am taking. Here are some answers to common questions that you may have.

Will this study affect my treatment?
No. There will be no change in the way your doctor treats you. Your doctor will do whatever is best for your health and for the health of your baby.

What am I expected to do to help?
We only need to obtain a few samples of blood and urine during and after your pregnancy. Your doctor will tell you when these are needed. Normally, blood and urine will be taken during your routine visits and should not involve any additional visit to the clinic.

How do I collect my urine the first time?
Precisely at the time you take your last epilepsy pills in the evening, empty your bladder, throw the urine away, and write the time here:

time: ...:.... date: ...../..../.....

Starting from this moment, all the urine produced until the time when you take your first epilepsy pills the next morning should be collected in a clean container kept at room temperature or in the fridge. Immediately before taking your first epilepsy pills in the morning, empty your bladder again and add this urine to the container. Write the time here:

time: ...:.... date: ...../..../.....

The collection is finished. Take the container and this form to your doctor.

How do I collect my urine the following times?
Repeat precisely the same procedure as the first time. Try to take always the evening and the morning pills at the same times of the day that they were taken the first time you did this urine collection. Keeping these times is important! Please write below the time you took the evening pills and you started your urine collection:

time: ...:.... date: ...../..../.....

Write below the time you took your morning pills and you stopped your urine collection:

time: ...:.... date: ...../..../.....

Do I take breakfast and my morning tablets before seeing the doctor for the blood sample?
Unless the doctor tells you differently, you should take your morning pills as usual. Your doctor will advice you whether to take your usual breakfast or not.

If you have any question, please feel free to call and ask your doctor.

Thank you for helping us with this work. It will be useful in the future to help other women like yourself.

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INFORMED CONSENT FORM
(FOR ASSESSMENT OF BREAST MILK EXCRETION)

I, the undersigned ..... born in ..... on ..... give my consent to take part in the above study.

The purpose of this study is to determine to what extent the medicines that I am taking to control my epilepsy pass into breast milk and to the baby's blood. While the benefits of breast-feeding generally outweigh any risk to the baby, this information will be useful to determine the degree of exposure of the baby's to different medicines.

This consent does not involve any change in my treatment and it does not affect my doctor's advice about the possibility of breast-feeding or my own decision to continue breast-feeding. It will only involve collection of a small sample of blood (6 ml) and milk (2 ml) once after breast-feeding has been established. One additional small blood sample (0.3 ml) will be taken 2 hours later from the baby to check the amount of medicines in his/her blood.

My doctor will collect medical information that may be shared with other research personnel. This information, however, will not be disclosed to third parties. No data that identify myself will be publicized, although law may require some information to be disclosed to health authorities.

My doctor has answered any question that I may have had. My consent is free, and I may withdraw it at any time without this affecting in any way my treatment or the relationship with my doctor.

Faithfully.

Date ..... Signed .....

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INFORMED CONSENT FORM
(FOR ASSESSMENT OF NEONATAL PHARMACOKINETICS)

I, the undersigned ..... born in ..... on ....., mother of ..... , born in ..... on ..... give my consent for the doctor to collect two small samples of blood (0.3 ml) from my baby within 72 hours of birth. I also give my consent to have a blood sample (6 ml) taken from myself at the time of delivery, and another sample taken from the discarded umbilical cord. The purpose is to determine whether the medicines that I am taking pass into the baby's blood and to assess the speed at which they are eliminated.

The information obtained will be useful in the future for the care of babies born from mothers who, like myself, had to take medicines during pregnancy. Apart from the samples, my consent does not involves any change in the baby's care. The amount of blood taken is small and will have no effect on me or the baby's well being.

The doctor will collect medical information about myself and my baby and this information may be shared with other research personnel. The information, however, will not be disclosed to third parties. No data that identify myself or my baby will be publicized, although law may require some information to be disclosed to health authorities.

My doctor has answered any question that I may have had. My consent is free, and I may withdraw it at any time without this affecting in any way my treatment, my baby's care, or the relationship with my doctor.

Faithfully.

Date ..... Signed .....