



EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report

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BACKGROUND

All old-generation antiepileptic drugs (AEDs) are considered to be teratogenic and AEDs are among the most common causes of adverse effects to the foetus. The risks associated with the treatment of epilepsy during pregnancy is therefore of major concern to all women of childbearing potential with epilepsy. The information on the comparative teratogenicity of these AEDs in humans is, however, conflicting, mainly due to inadequate sample size and other methodological shortcomings of previous studies. The teratogenic potential of newer AEDs is even less known, a situation that prevents a rational approach to AED treatment in women of childbearing potential.

To address this problem, it is necessary to compile more information on outcome of pregnancies following maternal exposure to AEDs. Such information is needed to provide pre-pregnancy counselling concerning teratogenic risks, and possibilities for specific prenatal monitoring, including prenatal diagnosis of foetal disorders associated with specific medications. Given the current number of available AEDs and combinations, very large numbers of pregnancies have to be evaluated in order to establish the safety of each regimen. Large denominators are also needed because of the qualitative diversity of the main endpoint of outcome, major congenital malformations.

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal AED use have agreed on a prospective international multi-centre study of pregnancies with AEDs. Data from all participating groups are shared in a Central Registry of Antiepileptic Drugs and Pregnancy (EURAP). EURAP was established in the first centres in some European countries and has since then gradually expanded to include more centres and countries now involving also Asia, Oceania and Latin America.

OBJECTIVE OF EURAP

The primary objective of EURAP is to evaluate and determine the comparative risk of major foetal malformations following intake of AEDs (old and new) and their combinations during pregnancy.

METHODS

EURAP is a prospective observational study. Women taking AEDs at the time of conception, irrespective of the indication, may be included. To avoid selection bias, only pregnancies recorded before foetal outcome is known and within week 16 of gestation are included in the prospective risk assessment. Cases ascertained later in pregnancy are recorded as retrospective cases, as they may provide signals, but are not included in the comparative risk evaluation.

Information on patients' demographics, type of epilepsy, seizure frequency, family history of malformations, drug therapy and of other potential risk factors is obtained, and follow-up data are collected once at each trimester, at birth and at one year after delivery.

Networks of reporting physicians have been established in countries taking part in the collaboration. During the course of the pregnancy, and the follow-up time after delivery, the participating physician enters data into five Subforms (Subforms A-E) for each patient. Subform A is completed on enrolment of the patient, Subform B after the first trimester, Subform C after the second trimester, Subform D within three months after delivery, and Subform E within 14 months after birth. Immediately after completion, each Subform is submitted to the national coordinator for review. The national coordinator transfers the reviewed and accepted Subform to the Central EURAP Registry in Milan, Italy.

EVALUATION OF OUTCOME

The physician records descriptively abnormalities observed in the offspring. The final assessment and classification of the type of malformation is the responsibility of the Central Project Commission (CPC). In order to facilitate a uniform and objective assessment, reports of malformations are assessed regularly by an outcome assessment committee, which is kept blinded with respect to the type of exposure.

Outcome in relation to exposure to individual drugs or drug combinations will be assessed only after sufficient data is available for a meaningful statistical analysis. Determination of the sample size needed is complicated by lack of reliable information about the distribution of individual drugs and their combinations and about the incidence of the teratogenic event. Applying the general empirical rule that the ratio between the overall number of events (teratogenic events) and the number of explanatory variables (predictors) should be at least equal to 10, a total sample size of about 5,000 pregnancies would be needed to allow analysis of 25 predictors (different AEDs and other relevant risk factors) assuming an incidence of malformations in the order of 5%. For this reason, the present report does not include data on malformation rates in relation to specific AEDs.

INTERIM REPORT

The present report is based on data available in the Central Registry by November 30, 2002. At that time 31 countries had contributed cases to the Central Registry. Countries that had been active are listed in Table 1.

Table 1
Countries that have contributed with pregnancies reported to the Central EURAP Registry

Albania
Argentina
Australia
Austria
Chile
Croatia
Czech Republic
Denmark
France
Georgia
Germany
Hong Kong
Hungary
India

Israel
 Italy
 Japan
 Lithuania
 Macedonia
 Netherlands
 Norway
 Poland
 Portugal
 Scotland
 Slovakia
 Slovenia
 Spain
 Sweden
 Turkey
 United Kingdom
 Yugoslavia

The present report is based on only those pregnancies for which records are complete by November 30, 2002, excluding those reported who failed to meet inclusion criteria (n=34), drop-outs (n=18; withdrawal of consent or lost to follow-up) and those with Case Report Forms (CRFs) that need to be completed or corrected. Thus in total 2175 pregnancies are included in this report. Of these, 1568 (72%) are prospective, enrolled at the latest during the 16th gestational week. The following information will focus on data obtained from the prospective pregnancies.

The classification of the epilepsy among the prospective pregnancies is given in table 2. Epilepsy was the indication for treatment in all but 20 (1%) of the pregnant women.

Table 2.
 Classification of the epilepsy in 1568 prospective pregnancies

Epilepsy	Total	Percentage
Generalized	637	41%
Localisation-related	834	53%
Not ascertained	14	1%
Undetermined	51	3%
Missing data	12	1%
Not epilepsy	20	1%
Grand Total	1568	100%

The maternal age among prospective cases was 29.9±5.1 years (mean±SD), ranging 16-41 years. The pregnant women were of Caucasian ethnicity in 91% of the prospective cases.

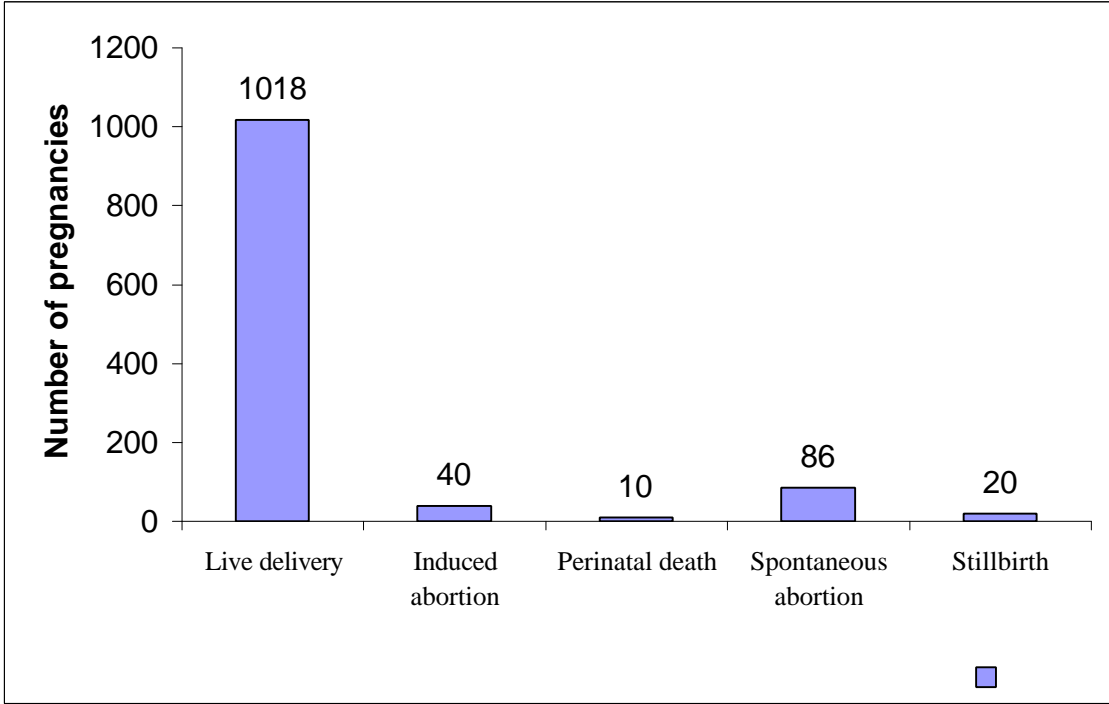
The number of the current pregnancy in the individual woman is presented in Table 3.

Table 3
Number of the pregnancy in prospective cases

Gravida	Total	Percentage
1st pregnancy	751	48%
2nd pregnancy	475	30%
3rd pregnancy	187	12%
4th pregnancy	80	5%
5th pregnancy	49	3%
> 5th pregnancy	26	2%
Grand Total	1568	100%

By the cut-off time for this analysis, 1174 (75%) of the prospective pregnancies had been followed until three months after delivery, (Subform D); whereas 578 (37%) had also completed the report on follow up one year after birth (Subform E). There were 20 stillbirths, ten perinatal deaths, 40 induced and 86 spontaneous abortions reported among the prospective pregnancies.

Figure 1
Outcome of prospective pregnancies



1460 of the prospective pregnancies had advanced to the stage when Subform B, and thus detailed data on drug exposure had been entered into the Central database. 1123 (77%) of the prospective pregnancies were using a single AED, 287 (20%) were on two AEDs whereas 50 (3%) took three AEDs or more. The exposure to the different AEDs in the prospective pregnancies is summarised in Table 4.

Table 4.

Number of prospective pregnancies with exposure to different AEDs in monotherapy and in combinations.

N° of AEDs	Type of AEDs	Total	Percentage
Monotherapy	carbamazepine	443	30%
	clobazam	3	0%
	clonazepam	11	1%
	ethosuximide	3	0%
	felbamate	2	0%
	gabapentin	12	1%
	lamotrigine	154	11%
	phenobarbital	100	7%
	phenytoin	33	2%
	primidone	11	1%
	valproic acid	290	20%
	vigabatrin	4	0%
	topiramate	8	1%
	oxcarbazepine	34	2%
	acetazolamide	2	0%
	barbesaclone	13	1%
	Two AEDs	barbesaclone + carbamazepine	2
barbesaclone + valproic acid		1	0%
carbamazepine + clobazam		12	1%
carbamazepine + clonazepam		9	1%
carbamazepine + lamotrigine		32	2%
carbamazepine + phenobarbital		21	1%
carbamazepine + primidone		3	0%
carbamazepine + topiramate		11	1%
carbamazepine + valproic acid		23	2%
carbamazepine + vigabatrin		8	1%
clobazam + valproic acid		2	0%
clonazepam + phenobarbital		4	0%
clonazepam + phenytoin		1	0%
clonazepam + valproic acid		7	0%
gabapentin + valproic acid		4	0%
lamotrigine + phenytoin		6	0%
lamotrigine + primidone		1	0%
lamotrigine + valproic acid		38	3%
phenobarbital + phenytoin		6	0%
phenobarbital + valproic acid		13	1%
phenobarbital + vigabatrin		2	0%
phenytoin + valproic acid		6	0%
primidone + valproic acid		3	0%
carbamazepine + gabapentin		6	0%
ethosuximide + valproic acid		1	0%
ethosuximide + lamotrigine		2	0%
carbamazepine + diazepam		2	0%
gabapentin + lorazepam		1	0%
clonazepam + lamotrigine		4	0%
lamotrigine + vigabatrin		1	0%
clobazam + phenytoin		2	0%
lamotrigine + phenobarbital		1	0%
oxcarbazepine + topiramate		2	0%
lamotrigine + oxcarbazepine	5	0%	

	gabapentin + lamotrigine	1	0%
	ethosuximide + phenobarbital	3	0%
	topiramate + valproic acid	4	0%
	carbamazepine + sulthiame	1	0%
	carbamazepine + oxcarbazepine	2	0%
	primidone + vigabatrin	1	0%
	lamotrigine + topiramate	4	0%
	clonazepam + oxcarbazepine	2	0%
	carbamazepine + phenytoin	4	0%
	clonazepam + vigabatrin	1	0%
	barbesaclone + phenobarbital	1	0%
	clobazam + lamotrigine	3	0%
	carbamazepine + levetiracetam	4	0%
	carbamazepine + tiagabine	1	0%
	phenytoin + sulthiame	1	0%
	lamotrigine + levetiracetam	4	0%
Three AEDs	barbesaclone + lamotrigine + phenobarbital	1	0%
	carbamazepine + clobazam + lamotrigine	4	0%
	carbamazepine + diazepam + valproic acid	1	0%
	carbamazepine + tiagabine + vigabatrin	1	0%
	clobazam + gabapentin + phenytoin	1	0%
	lamotrigine + phenobarbital + valproic acid	1	0%
	lamotrigine + primidone + topiramate	1	0%
	carbamazepine + clobazam + valproic acid	1	0%
	phenobarbital + phenytoin + tiagabine	1	0%
	carbamazepine + clobazam + primidone	1	0%
	carbamazepine + lamotrigine + primidone	1	0%
	lamotrigine + phenytoin + valproic acid	1	0%
	carbamazepine + topiramate + valproic acid	2	0%
	clonazepam + diazepam + phenytoin	1	0%
	oxcarbazepine + phenytoin + topiramate	1	0%
	barbesaclone + carbamazepine + valproic acid	1	0%
	carbamazepine + lamotrigine + valproic acid	4	0%
	clonazepam + lamotrigine + valproic acid	1	0%
	carbamazepine + clonazepam + topiramate	1	0%
	carbamazepine + phenobarbital + topiramate	1	0%
	carbamazepine + clobazam + vigabatrin	1	0%
	carbamazepine + gabapentin + topiramate	2	0%
	phenobarbital + topiramate + valproic acid	1	0%
	lamotrigine + phenytoin + vigabatrin	1	0%
Four AEDs	clobazam + lamotrigine + phenobarbital + valproic acid	1	0%
	clobazam + lamotrigine + topiramate + valproic acid	2	0%
	clobazam + lamotrigine + topiramate + vigabatrin	1	0%
	clonazepam + oxcarbazepine + phenobarbital + topiramate	2	0%
	carbamazepine + clobazam + phenobarbital + primidone + topiramate		
	clobazam + lamotrigine + phenobarbital + topiramate + valproic acid		
Five AEDs		2	0%
Missing data		2	0%
Grand Total		1460	100%

TERATOGENIC OUTCOME

A total of 63 cases with major birth defects have been identified in the prospective cohort. This includes eight cases of malformations among those with induced abortions, stillbirth and perinatal death. There are 16 additional cases with potential birth defects but for which further detailed information is necessary before final classification can be made. Sixty-three cases represent a malformation rate of 5% of all 1174 prospective pregnancies for which subform D (follow-up at three months after delivery) has been completed. The corresponding rate is 7% if the 16 potential cases were included. It should be emphasized that this is a preliminary classification of outcome based mainly on the follow-up three months after birth.

For reasons given above, outcome in relation to exposure to individual drugs or drug combinations will not be assessed or reported at this stage.

ANTICIPATED PROGRESS

So far, collaborators in 31 countries have contributed with cases to the Central Registry. Approximately 20% of all eligible pregnancies with antiepileptic drug exposure are enrolled in EURAP in Italy and Scandinavia, where the project was implemented first. However, many of the participating countries are at an early stage of EURAP and the enrolment rate is expected to increase gradually in these regions. In addition, networks are being established in other countries and several physicians in additional countries have expressed an interest in joining the collaboration. We therefore expect a continued increase in the enrolment rate, which at present is estimated to 120 new pregnancies monthly.

ORGANISATION, FUNDING AND SUPPORT

EURAP is a consortium of independent research groups working on a non-profit basis. The project is administratively organised by the Central Project Commission (CPC) with members representing different geographical areas and disciplines. EURAP is established and carried out under the auspices of the European Epilepsy Academy (Eurepa) and is endorsed by the Commission on Therapeutic Strategies of the International League Against Epilepsy. The project is supported by educational grants to the CPC from GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi-Synthelabo, UCB Pharma and Novartis. In addition, national and regional networks may receive support from other pharmaceutical companies.

APPENDIX

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