VALPROIC ACID AS A HUMAN TERATOGEN

Elisabeth ROBERT
Institut Européen des Génomutations, 86,rue Edmond Locard
F-69005 Lyon, FRANCE

ABSTRACT: Anticonvulsants have been widely studied for a long time, and the risk increase was described as especially marked for facial clefts and heart defects. In 1982, we suggested a specific association between valproic acid and spina bifida. The origin of the observation is described, as well as the circumstances which resulted in the detection of this teratogenicity: the existence of a regional population-based registry, a special interest for spina bifida in the registry, the existence of a question on maternal epilepsy in the routine questionnaire, a high local prescription rate of valproic acid and the registry status as a member of the International Clearinghouse for Birth Defects Monitoring Systems. In a second part, a follow-up study is presented, which would suggest that the spina bifida association is stronger with valproic acid monotherapy than with valproic acid in combination with phenobarbital.

In a third part, the existence of specific links between valproic acid and defects other than spina bifida are discussed: on one hand the so-called "fetal valproate syndrome", on the other hand some major malformations, in the light of the literature and of a joint international study among six programs. The aim of this study is to compare the possible teratogenic specificity of various anticonvulsants, by looking for heterogeneity in drug-malformation distribution in a large sample of malformed infants with known maternal epilepsy, after stratification for program.

KEY WORDS: Birth defect, Teratogen, Valproic acid, Epidemiology, Anticonvulsants, Spina bifida

INTRODUCTION
Anticonvulsants are among the most extensively and carefully studied drugs
from the teratogenicity point of view. Evidence has then accumulated that epileptic women taking anticonvulsant medications during pregnancy deliver infants with malformations at a rate two to three times that of the overall population (Kalter and Warkany, 1983). The risk increase was first described as especially marked for facial clefts and cardiac defects. Other malformations were known to be probably more frequent in infants born to epileptic mothers than in other infants, but their low incidence rate combined with the moderate risk increase made that they were not especially remarkable in the data published. This paper will describe how a new specific association, that is between valproic acid and spina bifida, was detected. Then original data, an international collaborative study, as well as published papers involving valproic acid teratogenicity will be discussed.

MATERIALS AND METHODS

Detection of the drug teratogenicity

As most birth defects monitoring systems, our program, established in Lyon under the name of Institut Européen des Génomutations, was created to detect increases in the prevalence at birth of congenital defects and to conduct investigative studies to find the causes of detected increases (Robert et al., 1988). It has been one of the founding members of the International Clearinghouse for Birth Defects Monitoring Systems (Flynt and Hay, 1979). In this program, information is also collected on maternal exposures, and the routine data collection form includes a question on maternal epilepsy and its treatment. It is then theoretically also possible to observe associations between specific prenatal influences and birth defects. A special interest for spina bifida has existed in our registry since 1979, when I started my job of genetic counselling at the pediatric unit of the neurosurgical hospital in Lyon. This activity contains an interview of all mothers of liveborn infants operated upon for spina bifida. During these interviews, a form is routinely completed and is transmitted to the registry. About forty per cent of cases are notified more than once to the registry, which obtains data from multiple sources : infants can be notified, for instance, once by the obstetric unit, a second time by the pediatric unit, and a third time by the surgery unit.

Follow-up of the study

In the first report, information on the regional exposure rates to valproic acid among pregnant women with epilepsy was missing. To evaluate
this rate, a sample study made outside the birth defects registry examined the distribution of 113 anticonvulsant treatments in a Rhône-Alpes district population of pregnant epileptic women during the period 1976-1984 (Robert et al., 1986). This evaluation combined with the expansion of the collected data were used to re-examine the association previously suggested (Robert et al., 1984).

The Rhône-Alpes Auvergne registry material was updated at the end of 1987. It now contains 15,523 cases of malformed infants. Among them, 164 were born to epileptic mothers. This material was used to compare in utero exposures to valproic acid monotherapies with polytherapies including valproic acid. Minor anomalies like isolated facial dysmorphism, or foot malposition, were registered in the system up to 1984, but are no longer included since 1985. The ascertainment of the so-called "facial dysmorphology" cases in the birth defects registry was found to be strongly linked with drug use, as they were not recorded without drug use to any significant extent. Those considerations led us to disregard for this study, all the minor anomalies with antiepileptic exposure, including those notified before 1985. Cases where the drug use was unknown or where the epilepsy was not treated were also excluded from the study.

**Valproic acid and malformations other than spina bifida**

Our material with valproic acid was first updated in 1983 (Robert and Rosa, 1983) and efforts were made to assess the risk for congenital heart defects and facial clefts.

A study was set up to try to see whether specific drugs were linked to specific malformations (Källén et al., 1988). Data from six different registries (two in Italy, one in Spain, one in Sweden, one in South America and our registry in France) were retrieved, involving malformed infants with maternal epilepsy and use of anticonvulsant drugs. This material was divided into five groups according to malformations (facial clefts, congenital heart defects, hypospadias, spina bifida and other defects) and into five groups according to the treatment (phenobarbital/primidone, phenytoin, valproic acid, carbamazepine and other drugs). This study was made to look for heterogeneity in the drug-malformation distribution.

A review of the recent literature will be briefly made for the evaluation of the association between valproic acid and major malformations other than spina bifida, and the so-called "Fetal Valproate syndrome" (Di Liberti et al., 1984).
RESULTS

Detection of the drug teratogenicity

In September 1982, we presented our preliminary results at the annual meeting of the International Clearinghouse. Our first published report (Robert and Guibaud, 1982), stated that among 11 infants with spina bifida whose mothers had epilepsy, 9 had used valproic acid. This report concerned 3 years, the period from August 1979 to August 1982, and covered 220,000 births. Data collected and reported by members of the International Clearinghouse (Bjerkedal et al., 1982) showed that valproic acid exposed infants with spina bifida were only identified in France and Italy. The frequency of valproic acid use among mothers of infants with spina bifida in our region was much higher (6.2%) than the expected frequency (.7%). It was then very unlikely that the increased risk for spina bifida was due to maternal epilepsy. Using a case-control study design, the Italian IPIMC program team confirmed our results (Mastroiacovo et al., 1982). Dutch data (Lindhout and Meinardi, 1984) and more recently data gathered from several groups doing prospective studies (Lindhout and Schmidt, 1986) provided more arguments for a causal relationship between valproic acid exposure and spina bifida.

Since the registry now includes data on selective abortions after prenatal diagnosis of malformation, it has been possible to evaluate the regional impact of this new indication of prenatal diagnosis which is maternal treatment by valproic acid. Since 1983 up to June 1988, 118 amniotic fluid samples have been analysed because of a maternal valproic acid exposures (Guibaud, 1988). Four cases of spina bifida were detected and confirmed by ultrasonography. Selective abortions were notified to the registry, but not included in the tables. Two infants were born at term in 1986, whose mothers had not been informed, neither of the risk, nor of the possibilities offered by the prenatal diagnosis. In 1987, one such infant was born. In this last case, the prenatal diagnosis was made by ultrasonography early enough for a selective abortion, but the parents refused to interrupt the pregnancy.

Follow-up of the study

The monitoring system has registered 15,523 birth defects cases from 1976 up to 1987, including 337 spina bifida cases.

According to the above described criteria, among 164 cases of birth defects associated with maternal anticonvulsants exposure, only 112 were
classified as major malformations and included in the study.

Table 1 Distribution of maternal exposure to anticonvulsants among spina bifida cases and other defects in the birth defects registry

<table>
<thead>
<tr>
<th></th>
<th>SB</th>
<th>Other defects</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP alone</td>
<td>13</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>VP/PB</td>
<td>4</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>VP wo PB</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>AC wo VP</td>
<td>3</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>337(100.0%)</td>
<td>15,186(100.0%)</td>
<td>15,523</td>
</tr>
</tbody>
</table>

There is a very high risk increase for spina bifida cases to have been exposed to antiepileptic drugs: 6.2% against .6% for other defects. If we accept the etiological relationship between valproic acid and spina bifida, cases of valproic acid exposed spina bifida can be removed from the material, to see what remains: 3 spina bifida among 57 epileptics, against 316 among 15,411. There is still an estimated risk of about 3 (1 expected, 3 found), but this can be random.

Among the 113 newborns examined in the sample study (Robert et al., 1986), 8 had major malformations and will be excluded for this study, leaving 105 cases of anticonvulsant therapies during the first trimester of pregnancy, used as a control group.

Then, we can consider three different groups of infants born to epileptic mothers: spina bifida cases, other defects cases and controls. The first two groups only were retrieved in the birth defects registry. Regarding the valproic acid exposure, which can be divided into monotherapy and associations, we get the Table 2:
Table 2 Maternal exposure to anticonvulsants among malformed infants and controls

<table>
<thead>
<tr>
<th>Material in the birth defects registry</th>
<th>Control Sample (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB (%)</td>
<td>other (%)</td>
</tr>
<tr>
<td>VP monotherapy</td>
<td></td>
</tr>
<tr>
<td>13 (61.9)</td>
<td>13 (14.3)</td>
</tr>
<tr>
<td>VP/PB</td>
<td></td>
</tr>
<tr>
<td>4 (19.0)</td>
<td>19 (20.9)</td>
</tr>
<tr>
<td>VP wo PB</td>
<td></td>
</tr>
<tr>
<td>1 (4.8)</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>AC wo VP</td>
<td></td>
</tr>
<tr>
<td>3 (14.3)</td>
<td>54 (59.3)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>21 (100.0)</td>
<td>91 (100.0)</td>
</tr>
<tr>
<td>SB=spina bifida, VP=valproic acid, PB=phenobarbital</td>
<td>AC=anticonvulsants</td>
</tr>
</tbody>
</table>

The percentage of 61.9% of valproic acid monotherapies among spina bifida cases is high when compared with that in either the group of other defects (14.3%) or the control group (12.4%). The existence of only one spina bifida case with valproic acid combination without phenobarbital (valproic acid / carbamazepine) could have occurred because of its infrequent use in this population - only 5 such usages in the control sample.

Valproic acid and malformations other than spina bifida

Our study in 1983 suggested a moderate association with facial clefts and congenital heart defects. These results were not confirmed by an Italian case-control study (Mastroiacovo et al., 1983). The distributions in drug regimens shown in Table 2 between defects other than spina bifida and controls are comparable, with a valproic acid prescription rate around 40 percent. This is an argument against another specific teratogenic effect of valproic acid. It seems that the association suggested in 1983 was attributable to confounding from the increased risk for those defects due to maternal epilepsy and/or other anticonvulsants.

The international collaborative study described above (Källén et al., 1988) gave the following result: two associations got an odds ratio significantly above 1. One of them only involved valproic acid, obviously associated with spina bifida (the association was detected with part of this material). No other association was found with valproic acid.
Minor anomalies have often been reported in single case reports, once in a small cohort (Koch et al., 1983) but no comprehensive definition of a syndrome had been proposed until 1984, when Di Liberti et al. (1984) described a phenotype common to seven infants born to women treated with valproic acid during pregnancy. This concept of a fetal valproate syndrome was supported by a new prospective study including 19 patients (Ardinger et al., 1988), and a report of four additional cases (Winter et al., 1987). The described phenotype includes epicanthal folds connecting with infraorbital crease or groove, flat nasal bridge, small upturned nose, long upper lip and thin upper vermilion border, shallow philtrum, and downwardly turned mouth angles.

DISCUSSION

In 1982, the International Clearinghouse had planned a study on the teratogenic effects of infrequently used anticonvulsants. When this study was discussed during the London annual meeting, the participants were informed of the findings in the Rhône-Alpes program. The registry status as a member of the International Clearinghouse for Birth Defects Monitoring Systems had then a major role in the establishment of valproic acid as a human teratogen. This role was first to underline the interest and importance of the reported data. This membership gave us the opportunity to promptly collect the data from other member programs around the world, and to get an invaluable methodological support from experienced epidemiologists.

In an ideal world, where the whole population should be covered by birth defects registries with 100% ascertainment, where all the data is available, the association would have appeared earlier. In 1982, besides the publication by Gomez (1981), the manufacturer (Jeavons, 1982), as well as the WHO Committee on Drug Safety were aware of more than fifteen cases of coexistence between spina bifida and maternal valproic acid. If, as suggested by Jeavons (1982), the outcome of all pregnancies in women who had received valproic acid had been reported to Sanofi, it would have been another way to rapidly detect the association.

One of the main reasons why the drug teratogenicity was first detected in France is probably the high prescription rate observed in that country. In a recent joint international study of women with anticonvulsants in monotherapy (Bertolli et al., 1987), it could be noted that the drugs used in the various populations studied differ markedly. Thus, in France and Italy, valproic acid constitutes 19% and 14% of the monotherapies respectively, but
only 1% in Sweden. The rate of valproic acid use in mono- or in polytherapy among treated epileptic women was evaluated to 36% in the historical cohort study (Robert et al., 1986).

Table 2 compares the valproic acid use distribution among spina bifida outcomes with that in the control sample and that for other defect cases in the birth defects registry. The high proportion of valproic acid monotherapy among spina bifida cases contrasts with the use distribution among other defect outcomes in the birth defects registry, as well as the use distribution in the general maternal anticonvulsant sample. A similarly high proportion was found by Lindhout and Schmidt (1986) on a sample of six cases of neural tube defects. Furthermore phenobarbital, which increases valproic acid metabolism, was shown experimentally to drastically reduce the teratogenicity of valproic acid (Nau and Hendrickx, 1987). These elements constitute a good indication that the spina bifida association is stronger with valproic acid monotherapy than with valproic acid in combinations with phenobarbital. The infrequency of valproic acid combinations without phenobarbital can be noticed.

An interesting feature was noticed by Lammer et al. (1987) in their very complete teratogen update on valproic acid: yet no valproic acid-exposed infant with anencephaly has been reported. In fact, one such case was reported from Milan (Lindhout and Schmidt, 1986) we have been informed of two cases born in the West of France (Le MAREC, 1988). In one of these two cases, there was a family history of anencephaly.

Ardinger et al. (1988) suggested that certain major anomalies in the infant seem to be associated specifically to maternal valproic acid use. These include respiratory tract anomalies, limb anomalies, genital anomalies and cardiac defects. These considerations are based on limited series and there is up to now no clear indication that valproic acid is associated to any other specific major malformation than spina bifida.

Several authors have claimed the existence of anticonvulsant specific fetal syndromes - barbiturates facies, fetal trimethadione syndrome, fetal primidone syndrome, fetal hydantoin syndrome, and now the fetal valproate syndrome. There is considerable overlap between these syndromes, and frequently the children have been exposed to more than one drug, and most children exhibit some of the features. Among the seven infants reported by Di Liberti et al. (1984), two were born to mothers whose seizures resulted from traumaism. Since their facial dysmorphia was similar to that of the affected
children of mothers with idiopathic epilepsy, the authors conclude that the treatment most probably has caused the abnormalities. This can also be discussed, as every woman who experiences a skull traumatism does not develop an epilepsy, and one can think of a genetic susceptibility to epilepsy.

Many other perinatal anomalies like developmental delay and low birthweight have been associated with maternal valproic acid exposure, but only few facial characteristics described by Di Liberti et al (1984) seem to be treatment-specific, if any.

REFERENCES


