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A teratological evaluation of anticonvulsant drugs

By

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Reviewing the important teratological data on anticonvulsants, the Hungarian experiences are reported. In the Hungarian Congenital Malformation Register use of the anticonvulsants diazepam and phenobarbiturates during pregnancy was determined in infants delivered with cleft lip with or without cleft palate, posterior cleft palate and, as a control, anencephaly and spina bifida. The teratogenic effect of diphenylhydantoin was confirmed, while that of diazepam and phenobarbital was not supported.

The incidence of epilepsy is usually estimated at 1%, but reliable epidemiological data show an incidence from 0.3 to 0.7% and a prevalence from 2 to 7%. According to Kurtzke [20], the incidence from birth to the age of 5 years is 0.5 to 1.5%, from 5 to 15 years, 0.25%, and beyond 15 years, 0.05 to 0.25%. Thus, it is not unusual for epileptics to seek advice regarding planned or already existing pregnancies.

The problems of family planning are the heredity of epilepsy and the possible teratogenic effects that might occur in epileptic pregnancies.

It was Meadow [24] who noticed that among the mothers of cleft lip and/or cleft palate babies, a higher than normal number had taken anticonvulsants during pregnancy. In the wake of this observation, many investigations were undertaken, the results of which are summarized in Table I. In infants born to epileptic mothers the incidence of congenital malformations was 6.4 to 6.7%, significantly ($p < 0.001$) higher than the 2.9% for infants born to non-epileptic women.

Among the epileptic pregnant women some had and some had not been treated during pregnancy. In the infants born to those reciving anticonvulsants during pregnancy the occurrence of congenital malformations was 7.4 to 7.8%, 2.5 times higher than the control figure ($p \ll 0.001$). On the other hand, in infants born to mothers who did not receive treatment during pregnancy, the occurrence of congenital malformations, 3.2%, did not significantly exceed the normal rate. Thus, the teratogenic effect of anticonvulsants would seem to be certain. However, those requiring treatment were in all probability suffering from

TABLE I

Teratogenic effects of anticonvulsants

Authors	Country	Control				
		N	CA		oral cleft	
			n	%	n	%
Janz and Fuchs [16]	GFR	—	—	—	—	—
Maroni and Markoff[23]	GFR	—	—	—	—	—
German et al [13]	USA	—	—	—	—	—
Elshove and van Eck [11]	Netherlands	11 986	221	1.8	32	0.27
Watson and Spellacy [30]	USA	50	0	0.0	0	0.00
South [36]	England	7 865	190	2.4	14	0.18
Speidel and Meadow [37]	England	483	7	1.4	1	0.21
Starreveld-Zimmerman et al [38]	Netherlands	—	—	—	—	—
Koppe et al [18]	Netherlands	12 300	426	3.5	21	0.17
Lowe [22]	Wales	31 877	877	2.8	50	0.16
Meyer [25]	GFR	—	—	—	—	—
Bjerkedal and Bahna [6]	Norway	112 328	2 471	2.2	1 797	1.60
Manson et al [29]	USA	50 591	1 240	2.5	76	0.15
Kuensberg and Knox [19]	Scotland	14 620	447	3.1	30	0.21
Niswander and Wertelecki [31]	USA	347 097	9 372	2.7	520	0.15
Millar and Nevin [26]	N.Ireland	32 227	1 235	3.8	70	0.22
Fedrick [12]	England	649	21[c] (36[d]	3.2 5.5)	0	0.00
Barry and Danks [14]	Australia	—	—	—	—	—
Annegers et al [2]	USA	84	0	0.0	0	0.00
Biale and Rhind [5]	Israel	—	—	—	—	—
Knight and Rhind [17]	Israel	—	—	—	—	—
Shapiro et al [35]	USA	49 977	3 216	6.4		
Total		672 134	19 723[c] (19 738[d]	2.9 2.9)	2 611	0.39

Abbreviations:

* = treated and non-treated epileptics
N = total
CA = Congenital anomaly
n = number

administered during pregnancy

Treated epileptics					Non-treated epileptics					Epileptics*				
N	CA		oral cleft		N	CA		oral cleft		N	CA		oral cleft	
	n	%	n	%		n	%	n	%		n	%	n	%
225	5^{1}	2.2	3	1.33	120	0	0.0	0	0.00	345	5^{1}	1.4	3	0.87
21	1^{0}	4.8	0	0.00	14	0	0.0	0	0.00	35	1^{0}	2.9	0	0.00
243[a]	13^{2}	5.3	1	0.41	—	—	—	—	—	—	—	—	—	—
65	10^{2}	15.4	5	7.69	—	—	—	—	—	—	—	—	—	—
51	3^{1}	5.9	0	0.00	—	—	—	—	—	—	—	—	—	—
22	2^{0}	9.1	2	9.09	9	0	0.0	0	0.00	31	2^{0}	6.5	2	6.45
365	17^{6}	4.7	3	0.82	62	0	0.0	0	0.00	427	17^{6}	4.0	3	0.70
281	22^{7}	7.8	9	3.20	16	0	0.0	0	0.00	297	22^{7}	7.4	9	3.03
125	11^{4}	8.8	1	0.79	67	2	3.0	0	0.00	192	13^{4}	6.8	1	0.52
134	9^{1}	6.7	1	0.74	111	3	2.7	0	0.00	245	12^{1}	4.9	1	0.41
199	37^{5}	18.6	5	2.51	124	4	3.2	0	0.00	323	41^{5}	12.7	5	1.55
378	17^{0}	4.5	4	1.06	—	—	—	—	—	—	—	—	—	—
205	11^{1}	5.4	3	1.46	101	3	3.0	0	0.00	306	14^{1}	4.6	3	0.98
48	5^{1}_{b}	10.4	0	0.00	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	413	17^{5}	4.1	3	0.73
110	7^{0}	6.4	2	1.82	—	—	—	—	—	—	—	—	—	—
198	15^{0}_{c}	7.6	1	0.51	19	2	10.5	0	0.00	217	17^{c}_{2}	7.8	1	0.46
—	$(28^{2}_{d}$	14.1)									$(30^{2}_{d}$	13.8)		
73	13^{0}	17.8	0	0.00	20	0	0.0	0	0.00	93	13^{0}	15.7	0	0.00
141	10^{6}	7.1	3	2.13	56	1	1.8	0	0.00	197	11^{6}	5.6	3	1.52
—	—	—	—	—	—	—	—	—	—	56	9^{2}	16.2	2	3.57
—	—	—	—	—	—	—	—	—	—	140	4^{3}	2.9	2	1.43
208	21	10.1			97	11	11.3			305	32	10.5	3	0.98
3092	22^{37c}	7.4	43	1.42	816	26	3.2	0	0.00	3622	230^{41c}	6.4	41	1.13
	$(242^{31}_{d}$	7.8)									$(243^{43}_{d}$	6.7)		

a = treatment unknown
c = diagnosed at birth
b = of 5 anomalies, 1 major, 2 minor and 2 questionable
d = diagnosed in later life
Index numbers above the figures indicate the number of congenital heart defects

more severe epilepsy, with frequent seizures and in worse somatic and mental condition. On the other hand, one could accept the argument that a treated woman who gave birth to a malformed infant might later have a healthy infant if left untreated during pregnancy [14]. In contrast, Shapiro et al [35], found no appreciable difference in the occurrence of defective infants born to treated vs. non-treated epileptic mothers.

When investigating the eventual teratogenic effect of anticonvulsants, two questions have to be elucidated, viz. (i) which are the malformations which will most frequently increase in number; and (ii) the difference in teratogenic effect between the different anticonvulsants.

(i) When treating an epileptic pregnant women the main malformation to be reckoned with is cleft lip and cleft palate [24]. As it is seen in Table I, the occurrence in the control groups was 3.39% (which is higher than the usual 0.2%), whereas in the infants born to epileptic mothers it was 1.13%.

On the other hand, among the offspring of women who during pregnancy had been treated with anticonvulsants, the point-prevalence at birth of cleft lip and cleft palate was 1.42% which represents a close to four-fold risk. Taking into consideration the normal prevalence at birth of these malformations, the rate of increase was at least 7-fold.

Congenital heart defects were also more frequent following anticonvulsant treatment during pregnancy; their frequency was nearly double the normal occurrence. Moreover, an increase in the frequency of multiple malformations may also be regarded as characteristic, with malformations of the bone structure, especially the digits, predominating. Most frequently afflicted are the fingers and the ulnar side [1, 3, 4, 10, 15, 21]. The frequent occurrence of mental backwardness and of its cause (genetic, teratogenic, social influence?) is a debatable point [12, 29].

Some authors found a higher perinatal mortality of infants born to epileptic women who had received treatment during pregnancy [20, 12, 6, 2, 37]; this, in addition to congenital malformations, may be related to an increased frequency of haemorrhage [30, 12] and intrauterine mortality.

The aim of the present work was to study the teratogenic effects of anticonvulsants as well as the differences between them.

Material And Method

In Hungary, nation-wide statistical data for congenital malformations have been kept since January 1, 1970, and by December 31, 1975, a total of 29,057 such infants, were on record in the Hungarian Congenital Malformation Register. The malformations were grouped in accordance with the 8th Revision of ICD. To study the possibility of a correlation between diazepam treatment during pregnancy and cleft lip and cleft palate [33, 34] we sent to the parents of every infant born with cleft lip and/or cleft palate and posterior cleft palate a questionnaire, in which we enumerated three groups of drugs. These were *(1)* the 10 most common sedatives, among them diazepam; *(2)* 6 anticonvulsants;

and *(3)* progestogen preparations for the protection of pregnancy. The mothers were asked to underline the drugs used during pregnancy and to indicate the weeks during pregnancy when these drugs were taken. The anticonvulsants were studied as having a supposedly positive teratogenic effect, while the progestogens for the protection of pregnancy were studied as having a negative effect.

As a control group, we selected babies with anencephaly and/or spina bifida. The reason we chose this group was that these malformations lend themselves to standard description, their reporting — similarly as that of cleft lip and cleft palate — may be considered 100% and the role played by the drugs under investigation has not yet come up in their aetiology.

Results

Results are shown in Table II. About 50% of the cases could be evaluated.

Table III shows the correlation between diazepam treatment during pregnancy and the 3 groups of malformations under investigation. In the cleft and/or cleft palate and the anencephaly-spina bifida groups the occurrence of diazepam treatment was practically the same, whereas in the posterior cleft palate group, insignificantly lower. Even when considering the critical period of the malformations no significant difference was found.

Table II

Cases in the Hungarian Congenital Malformation Register, 1970—1975, and evaluated cases

Type	Registered cases		Evaluated cases	
	No	%	No	%
Cleft lip and/or cleft palate	995	100.0	413	41.51
Posterior cleft palate	228	100.0	121	53.07
Anencephalyspina bifida	1476	100.0	843	57.11

Table III

Diazepam treatment during pregnancy in the 3 groups of congenital malformations

Congenital disorder	No	Time of drug administration							
		month of pregnancy					throughout pregnancy	unknown	total
		1	2	3	4—6	7—9			
Cleft lip and/or cleft palate	413	11 (2.66)	5 (1.21)	4 (0.97)	10 (2.42)	6 (1.45)	1 (0.24)	27 (6.54)	64 (15.50)
Posterior cleft palate	121	2 (1.65)	—	—	2 (1.65)	—	—	8 (6.61)	12 (9.92)
Anencephaly-spina bifida	843	7 (0.83)	15 (1.78)	15 (1.78)	27 (3.20)	13 (1.58)	8 (0.95)	43 (5.10)	128 (15.18)

Percentages in parentheses

TABLE IV

Anticonvulsant treatment during pregnancy in three congenital malformation groups (figures for barbiturates in parentheses)

Congenital disorders	No	Month of pregnancy					Whole pregnancy	Total	
		1	2	3	4—6	7—9		No	per cent
Cleft lip and/or cleft palate	413	1 (1)	1 (1)	— (2)	— (1)	—	9 (1)	11 (6)	(2.66)* (1.45)**
Posterior cleft palate	121	—	—	—	—	— (1)	1 (1)	1 (2)	(0.82) (1.65)
Anencephaly-spina bifida	843	— (1)	— (3)	— (2)	— (6)	— (1)	2 —	2 (13)	(0.23) (1.54)

* $x^2 = 15.9$; $p < 0.001$. ** $x^2 = 0.014$; $p < 0.10$

Data for anticonvulsant treatment during pregnancy are seen in Table IV. We evaluated separately the effects of diphenylhydantoin (DPH) derivatives, of phenobarbital and of other anti-epileptic drugs. In the case of phenobarbital no specific teratogenic effect could be proved, i. e. the frequency and the period of time when the drug had been administered, showed no deviation in the 3 types of malformations studied. In the case of the other anticonvulsants including the DPH derivatives, there were significant differences, as shown in Table V. Such treatment was significantly more common in the cleft lip and/or cleft palate group. The majority of the mothers had received treatment throughout pregnancy. Of the 121 and 843 pregnant women who gave birth to infants with posterior cleft palate and anencephaly-spina bifida, only one and two, respectively, had had anticonvulsant treatment during pregnancy. Thus, anticonvulsants seem to have a role in the aetiology of cleft lip and/or cleft palate.

Progestogen treatment showed an identical frequency in the 3 types of malformation.

TABLE V

Anticonvulsant treatment

Drug	Cleft lip and/or cleft palate	Posterior cleft palate	Anencephaly-spina bifida
Phenytoin	4	—	2
Phenacemide	1	—	—
Morfolep	1	—	—
Trimethadione	2	1	—
Mephenytoin	1	—	—
Primidone	2	—	—

DISCUSSION

The results seem to have proven the teratogenic effect of DPH. At the same time we have failed to find a teratogenic effect in the case of progestogen, in agreement with the data in the literature. Nor was there any evidence of a teratogenic effect of diazepam and of phenobarbital in the 3 types of malformations studied [9] including the earlier suspected cleft lip and cleft palate.

For the correct evaluation of the teratogenic effect it is necessary to separate the malformations of different aetiologies. Thus, isolated cleft lip and/or cleft palate have a multifactorial aetiology. One sign of genetic predisposition may be a cleft lip and/or cleft palate occurring in the first or second degree relatives. The aetiology of posterior cleft palate is not quite clear but the role played by teratogenic effects seems significant. On the other hand, cleft lip and cleft palate occurring with multiple malformations are different in aetiology; they may be associated with monogenic, chromosomal and teratogenetic syndromes.

Of the thus far registered 43 babies with cleft lip and cleft palate delivered by epileptic women, it was possible to ascertain the type in 33 instances; there were 24 isolated and 9 multiple cases. We must therefore expect a more frequent occurrence of both the isolated and the multiple type. The question needs, however, further studies.

Of the anticonvulsants we may attribute a mild teratogenic effect to DPH-derivatives. DPH penetrates well across the placenta, therefore its concentration is the same in the blood of the mother and the fetus [27, 28]. There are reports on the teratogenic effect of primidone, carbamazepine, trimethadione and paramethadione [4, 9, 13, 14, 21], but these observations are not yet sufficient to formulate a final opinion. The phenobarbiturates are unlikely to have a teratogenic effect, but their combination with DPH has been claimed to exert an increased teratogenicity [12, 22]. The majority of authors blames the absence of folic acid for the teratogenic effect of DPH. DPH has namely been shown to cause an acute folic acid deficiency which soon disappears on withdrawal of the drug. The correlation between folic acid deficiency and certain congenital disorders has been suggested by several studies [7, 39]. The reverse is also true: prolonged folic acid administration will neutralize the effect of DPH, and may thus cause a recurrence of seizures. In this way folic acid is a potential convulsant and its level in the epileptic focus is higher than in the rest of the brain [32].

There are several ways to interpret the increased frequency of congenital anomalies in the babies of treated epileptic mothers:

(i) the effect of anticonvulsants taken during pregnancy;

(ii) the effect of the epileptic condition;

(iii) some effects associated with epilepsy. The social standing of epileptics is usually below average and infections are therefore more frequent in them. Besides, their choice of sexual partners is limited and often disadvantageous, etc.

The first and second questions can be answered on the basis of the frequency of congenital disorders in the infants born to treated and non-treated epileptics. The significantly increased frequency in the former group points to the teratogenic effect of anticonvulsants. The third possibility must, however, also be taken into

consideration, at least as having a modifying influence.

In the course of pregnancy, anticonvulsant treatment must be continued. During pregnancy, almost one half of the epileptics has an increased tendency, to develop seizures [17] and the consequential reduction of placental circulation may cause fetal death or mental deficiency. Besides, a sudden cessation of drug treatment might elicit a status epilepticus fatal for both the pregnant woman and her fetus. If the seizures can be controlled by barbiturates, preference should be given to this group of drugs. Taking into account the critical period for congenital disorders caused by anticonvulsants, the period from the 4th to the 10th week of gestation may be considered dangerous.

As an additional treatment, folic acid and vitamin K are recommended. The former tends to diminish or inhibit the teratogenic effect, but will increase the tendency to seizures. Vitamin K is able to neutralize the coagulation defect resulting from anti-epileptic treatment [12, 30].

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