PAPERS AND ORIGINALS

Debendox and congenital malformations in Northern Ireland

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Summary and conclusions

An investigation was carried out in Northern Ireland into the alleged association between fetal abnormalities and Debendox, an antiemetic drug used in pregnancy. During the period 1966-78 the total number of births each year and the overall incidence of congenital malformations per 10 000 births fell. The incidences of cleft lip, cleft palate, reduction deformities, and defects of the heart and great vessels fell from 1966 to 1976 but increased in 1977 and 1978. During the same period (1966-78) the number of prescriptions for Debendox issued by general practitioners increased more than fourfold.

These observations suggest that there is no relation between congenital malformations and the use of Debendox. This conclusion, however, does not take into account other drug- or environmental-related factors that may have resulted in a reduction in the number of congenital malformations and would hence have masked an increase associated with greater usage of Debendox. In particular, the amount of Debendox sold direct to the public without a prescription and the use of the drug by patients who were not pregnant could not be established. The amount of drug used in these ways is probably small, and it is difficult to see how it might influence the conclusions reached.

Introduction

Several reports have discussed a possible relation between fetal malformations and the administration of Debendox (dicyclomine hydrochloride 10 mg, doxylamine succinate 10 mg, and pyridoxine hydrochloride 10 mg), an antiemetic drug used in pregnancy.^{1,2} Donnai and Harris¹ described unusual fetal mal-

formations, including extrusion of abdominal contents and reduction deformities or total absence of a leg, in three children whose mothers had taken Debendox early in pregnancy (five and a half to six weeks after the last menstrual period). The authors did not necessarily associate the abnormalities with the drug. In 1976 the Committee on Safety of Medicines also reported reduction deformities in infants whose mothers had taken Debendox.³ A study by Shapiro *et al.*,⁴ however, on over 1000 women given doxylamine and dicyclomine in early pregnancy showed no increase in the incidence of abnormalities.

In 1980 the Committee on Safety of Medicines told the Minister of Health⁵ that there appeared to be no evidence to justify banning Debendox, although since 1963 the Department of Health has received 102 reports of fetal defects possibly associated with the drug.⁶ (Debendox was first marketed in the United Kingdom in 1958, and 200 000 women are estimated to take it each year.⁶) This statement followed reports in the press of Richardson-Merrell Inc being sued by an American couple whose 4-year-old son was born with a combination of limb abnormalities, absence of pectoralis major muscle, and pectus excavatum after the mother had taken Bendectin and other drugs during pregnancy. Bendectin is not identical with Debendox, as two years ago the United States Federal Drug Administration requested Richardson-Merrell to remove dicyclomine from the preparation as it contributed nothing to its effectiveness. A study carried out by the Centre for Disease Control, Atlanta, on Bendectin⁷ found no evidence to support allegations that it causes birth defects of the heart and limbs. Of 1183 women who gave birth to infants with birth defects, 121 women had babies with limb reduction defects, of whom 12 (9.9%) had taken Bendectin. This was similar to the 9.2% incidence of use of Bendectin among all 1183 women and the 10% incidence of use among mothers of children with neural tube defects or cleft lip and cleft palate. Rothman *et al.*⁷ reported that Bendectin was taken by 6.2% of mothers whose children had heart defects but by only 3.7% of mothers who had healthy children. Although the difference was statistically significant, the authors pointed out several methodological problems that should be considered in interpreting the data.

Against this background we investigated the relation between the use of Debendox and certain congenital malformations in Northern Ireland.

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Methods

Data on the total number of births (live births and stillbirths), total number of congenital malformations, and numbers of the specific congenital malformations of cleft lip, cleft palate, reduction deformities, and heart and great-vessel defects (see table I) were obtained from the *Annual Report of the Registrar General (Northern Ireland)* for 1966-73⁸ and from *Health and Personal Social Services Statistics for Northern Ireland* for 1974-6.⁹ The figures for 1977-8, which are unpublished, were made available by the Director of the Research and Intelligence Unit of the Department of Health and Social Services Northern Ireland. The incidences of all congenital malformations and of the specific malformations per 10 000 births (live births and stillbirths) were also determined for each year (see table II). Data on prescriptions for Debendox (see table III)—that is, the total number of prescriptions for Debendox and the total number of Debendox tablets prescribed in general practice—were obtained from the Central Services Agency, Belfast; the number of prescrip-

tions issued by general practitioners per 100 births (obtained by dividing the number of prescriptions for each year by the number of births for that year) and the number of tablets per prescription (obtained by dividing the total number of Debendox tablets for any one year by the number of prescriptions issued) were also calculated.

Results

Table I shows that from 1966 to 1977 the number of births declined from 33 778 to 25 747; 1978 showed a small increase. Table I also gives the numbers of all congenital malformations and of specific malformations in these years. As the number of births was not constant the incidence of congenital malformations per 10 000 births was determined. The incidence of all congenital malformations per 10 000 births (table II) increased from 354 in 1966 to 383 in 1971; from 1971 the incidence decreased irregularly to 333 in 1978. This

TABLE I—Numbers of births (live births and stillbirths), all congenital malformations, and specific malformations in Northern Ireland during 1966-78

Year	Total births	All congenital malformations	Cleft lip	Cleft palate	Reduction deformities	Heart and great-vessel defects	Total specific malformations
1966	33 778	1195	45	39	11	79	174
1967	34 009	1152	25	40	12	70	147
1968	33 714	1197	25	31	8	81	145
1969	32 930	1238	29	43	8	92	172
1970	32 551	1234	31	40	6	75	152
1971	32 227	1235	30	40	7	81	158
1972	30 428	1088	31	34	3	76	144
1973	29 589	865	26	33	2	56	117
1974	27 534	921	31	40	4	48	123
1975	26 505	840	27	26	5	57	115
1976	26 639	802	17	21	11	64	113
1977	25 747	862	37	31	5	102	175
1978*	26 483	882	22	22	28	77	149

*Provisional figures.

TABLE II—Incidences of all congenital malformations and specific malformations per 10 000 births in Northern Ireland during 1966-78

Year	All congenital malformations	Cleft lip	Cleft palate	Reduction deformities	Heart and great-vessel defects	Total specific congenital malformations*
1966	354	13.3	11.6	3.3	23.4	51.5
1967	339	7.4	11.8	3.5	20.6	43.2
1968	355	7.4	9.2	2.4	24.0	43.0
1969	376	8.8	13.1	2.4	27.9	52.2
1970	379	9.5	12.3	1.8	23.0	46.7
1971	383	9.3	12.4	2.2	25.1	49.0
1972	358	10.2	11.2	1.0	25.0	47.3
1973	292	8.8	11.2	0.7	18.9	39.5
1974	334	11.3	14.5	1.5	17.4	44.7
1975	317	10.2	9.8	1.9	21.5	43.4
1976	301	6.4	7.9	4.1	24.0	42.4
1977	335	14.4	12.0	1.9	39.6	68.0
1978†	333	8.3	8.3	10.6	29.1	56.3

*Discrepancies due to rounding error(s).

†Provisional figures.

TABLE III—Total number of prescriptions for Debendox issued by general practitioners in Northern Ireland, incidence of prescriptions per 100 births, and average number of tablets prescribed

Year	No of prescriptions for Debendox	No of prescriptions/100 births	No of tablets per prescription
1966	3 841*	11.4	42
1967	6 095	17.9	43
1968	7 716	22.9	45
1969	9 695	29.4	48
1970	11 190	34.4	50
1971	12 469	38.7	52
1972	13 618	44.8	55
1973	13 935	47.1	55
1974	13 571	49.3	57
1975	14 443	54.5	57
1976	14 329	53.8	57
1977	15 324	59.5	57
1978	15 954	60.2†	58

*Calculated from nine months' data.

†Provisional figures.

pattern, however, was not reflected in the incidences of cleft lip, cleft palate, reduction deformities, and defects of the heart and great vessels, specific congenital malformations mentioned elsewhere in association with Bendectin.² The overall incidence of these specific congenital malformations per 10 000 births showed a steady downward trend between 1966 and 1976 but a sudden rise to 68.0 and 56.3 per 10 000 births in 1977 and 1978 respectively, these incidences being higher than in any previous year. These figures are high because of the increased incidence of defects of the heart and great vessels in 1977 and 1978 (39.6 and 29.1 per 10 000 births respectively, higher figures than in any of the preceding years) and also because of the increased incidence of reduction deformities in 1978 of 10.6 cases compared with the previous highest figure of 4.1 cases per 10 000, in 1976.

Table III shows that the total number of prescriptions for Debendox increased progressively from 3841 in 1966 to 15 954 in 1978. The number of prescriptions per 100 births also increased dramatically, from 11.4 in 1966 to 60.2 in 1978. During the same time the number of tablets per prescription rose from 42 in 1966 to 58 in 1978.

Discussion

Congenital malformations in Northern Ireland are recorded by two systems administered by the Research and Intelligence Unit of the Department of Health and Social Services. These are the Registrar General's congenital malformation notification and the child health system. The congenital malformation notification registers at birth infants with malformations and operates through the chief administrative medical officer of each of the four Health and Social Services Boards in Northern Ireland. Information is collected on each malformed child from all stillbirths of 28 weeks' or more gestation and from live births and early deaths irrespective of gestational age. This system has operated since 1964. The child health system collects data from health visitors and other community health staff of the Boards. The register was extended in January 1971 to cover the whole of Northern Ireland and notes all stillbirths of 28 weeks' or more gestation and all live births irrespective of gestational age.

When the efficiency of these two Northern Ireland systems in recording neural tube defects was investigated for the years 1974-6¹⁰ the Registrar General's congenital malformation notification system identified 83.6% of all such defects whereas the child health system identified 63.3%. Both systems together accounted for 86.2% of all neural tube defects.

The data on congenital malformation presented in this paper were generated by the Registrar General's congenital malformation notification system alone for 1966-70, but from 1971 onwards data obtained through the child health system were also used. The coverage was improved further over the 1970s by including cases ascertained through other sources such as genetic counselling clinics and necroscopy records.

The results in this paper indicate that the number of births in Northern Ireland decreased from 1966 but increased slightly in 1978; during the same period the incidence of all congenital malformations decreased irregularly when expressed per 10 000 births. The overall incidence of the specified malformations of cleft lip, cleft palate, reduction deformities, and defects of the heart and great vessels, although decreasing from 1966 to 1976, showed a rise in 1977 and 1978 primarily due to increases in the incidences of heart and great-vessel defects and of reduction deformities. When the overall incidence of specific congenital malformations (table II) is compared with drug usage (table III) the incidence of these malformations over the years did not

appear to change while the use of Debendox rose more than fivefold, the number of prescriptions issued per 100 births rising from 11.4 in 1966 to 60.2 in 1978. This conclusion, however, does not take into account factors related to other drugs or the environment that may have caused a reduction in the number of congenital malformations and would hence have masked any increase associated with greater usage of Debendox. In particular, we could not determine the amount of the drug sold direct to the public without a prescription and use of the drug by patients who were not pregnant. Nevertheless, the amount of drug used thus is probably small and would be unlikely to influence the conclusion reached.

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ONE HUNDRED YEARS AGO Two cases carefully studied by Dr Naegli, and published in the *Swiss Medical Journal*, afford a striking illustration of the old warning not to bathe with a full stomach. The cases were those of two persons who died when bathing, and in whom the *post mortem* examinations revealed similar appearances, affording a certain evidence that death was due to the fullness of the stomach with food at the period of immersion. The first is the case of a lad, fourteen years old, who, on a holiday, after regaling himself with bread and sausages and a glass of beer, went into the river, with a comrade, for a swim in the evening; and was swimming gaily ahead of his friends, when suddenly, uttering only an indistinct sound, he sank below the surface; assistance was quickly at hand, and he was drawn out within three or four minutes after he had sunk. The physician was at hand at once, and the fullest hopes were entertained of being able to restore life, as the period of immersion had been so short, and the heart could still be heard to beat. Artificial respiration was at once employed, but without any success; then, without much delay, tracheotomy was had recourse to; but, on opening the larynx, instead of air rushing out with the well known sound, a stream of fluid food escaped from the wound. Every means was now attempted to remove by suction these foreign substances from the obstructed trachea, but uselessly; and, in spite of all endeavours, the lad could not be restored to life. A *post mortem* examination showed but few of the usual signs of suffocation from drowning, but the trachea was injected rosy red, contained small quantities of food, and the larger bronchi and bronchioles showed, in their lumen, small pieces of

potato entangled and obstructed; even sections in the periphery of the congested lung showed the remains of food in the larger bronchioles. The second case was one of a student aged 18, who went to bathe after an evening meal consisting of cheese, bread, and beer; and, soon after entering the bath, sank suddenly, uttering a dull gurgling sound, and was only recovered a quarter of an hour afterwards from the water, being then quite dead, and incapable of being restored to life. A *post mortem* examination showed, again, the larynx and air-tubes full of fluid contents of the stomach, the bronchi and larger bronchioles extending into the lung, being obstructed by small particles of cheese. These two *post mortem* examinations show that both of these unfortunate persons were suffocated by the food which had passed into their trachea and lungs when sinking; the explanation appears to be that the bathers had entered the water with a full stomach; that the pressure of the water on the abdomen, and the efforts in swimming, which not unfrequently produce in swimmers a slight feeling of seasickness, had induced nausea and vomiting. This had suddenly taken away their strength; they had sunk under the water, and, in sinking, had drawn in the food thrown up from the stomach and water into the larynx; the trachea had thus become obstructed by food; so that, even in the case of immediate help, which in this case was at hand, recovery could not be effected. The warning "not to bathe when the stomach is full of food" is certainly very strongly emphasised in these carefully observed and conclusive cases. (*British Medical Journal*, 1880.)