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A Population Based Case-Control Study of Oral Moroxydine, an Antiviral Agent Treatment During Pregnancy

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Abstract: The data of the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities between 1980 and 1996 were evaluated. The objective of the study was to check the effect of oral moroxydine, a biguanide antiviral drug during pregnancy for birth outcomes. First, the prevalence of moroxydine use in the mothers of cases with and controls without congenital abnormalities was compared. Of 38,151 pregnant women who delivered newborn infants without any defects (control group), 14 (0.04%), while of 22,843 pregnant women who had fetuses or newborns with congenital abnormalities, 13 (0.06%) were treated with the oral tablet of moroxydine (POR with 95% CI: 1.6, 0.7-3.3). The teratogenic potential of oral moroxydine treatment cannot be excluded because a higher use of moroxydine during the second-third month of pregnancy was found in the mothers of multi malformed cases and of anencephalic fetuses, though these possible associations were based only on two-two cases. Second, control newborn infants without any defect born to mothers with or without moroxydine treatment were compared. A somewhat larger mean birth weight (3.532±426 vs. 3.276±511, adjusted t = 1.8; p = 0.07) and a reduction of low birth weight (0 vs. 9.2%) was found in control newborn infants of the mothers with moroxydine treatment. The weak teratogenic potential and some birth weight promotion effect of moroxydine treatment during pregnancy may deserve some attention.

Key words: Moroxydine, congenital abnormalities, birth weight, low birth weight, case-control study

INTRODUCTION

The objective of this project was to evaluate the potential embriotoxic-teratogenic and fetotoxic effect of all antimicrobial drugs used during pregnancy by the evaluation of birth outcomes: congenital abnormalities (CAs), gestational age (preterm birth) and birth weight (low birth weight) in Hungary. The possible reproductive effect of new drugs is checked before marketing in animal investigations followed by different clinical trials in the human being. However, the animal experiments cannot guarantee the exclusion of human teratogenic and fetotoxic effects of drugs due to species difference. In addition, clinical trials do not include pregnant women and in general the old drugs were not evaluated from this aspect. Thus the post-marketing surveillance of drug teratogenicity and fetotoxicity is important and our experiences have shown that it is feasible (Czeizel, 1999; Czeizel and Rockenbauer, 2001).

Some old drugs were withdrawn from the market and it means that experts lost their interest regarding their clinical and adverse effects. However, the recent studies of their chemical structures and their medical effects may deep in our knowledge in general. We presented here a study regarding moroxydine, a previous antiviral agent as an example for this concept.

Biguanide derivates have an antihyperglycemic effect, therefore some biguanides (e.g., metformin: N^1,N^1-dimethyl-biguanide) were used for the treatment of diabetes mellitus (Product Information, 1977). In addition, an inhibitive effect of heterocyclic guanidine derivatives for viral growth was found and it led the marketing one of the first antiviral drugs: moroxydine (N^1-N^1-anhydrobis-beta-hydroxyaetyl-biguanide-HCL) (ABOB, Flumidin®, Virustat®, Influmin®, Spenitol®, Morgalin®). The virostatic effect was explained by the inhibition of specific RNA-synthesis of viruses. First Schersten (1960) reported a beneficial effect of moroxydine (ABOB) for the treatment of herpes zoster, while Melander (1960; 1960) and Sjöberg (1960) found some preventive and suppressive effect of moroxydine (ABOB) for clinical influenza. Later, this drug was tested in patients with

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herpes simplex (Nasemann, 1962), measles and chickenpox (Kleinschmidt, 1962; Martinon and Baran, 1964) and different dermatological diseases (Rivoire, 1963; Duperrat, and Goudie, 1962) without real success. Moroxydine was the first antiviral drug in Hungary therefore several studies were published about its beneficial effects in different viral diseases (Farago and K. Bálint, 1969; Mészáros, 1970; 1976; Nagy, 1971; Ambro and Nagy, 1974)

The name of moroxydine is not mentioned in the well-known teratological textbook (Friedman and Dolifka, 1996; Shepard, 1998; Briggs *et al*., 1998). Thus, we evaluated the data set of the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (Czeizel *et al*., 2001), 1980-1996, regarding moroxydine use during pregnancy from two aspects. First, the prevalence of moroxydine use was compared between cases with different CAs and their matched controls in order to detect its possible teratogenic potential. Second, medically recorded gestational age and birth weight as a sensitive indicator of fetal development were evaluated in control newborn infants without CA born to mother with or without moroxydine treatment to analyze its possible fetotoxic effect.

MATERIALS AND METHODS

Cases with CAs were selected from the Hungarian Congenital Abnormality Registry (HCAR) (Czeizel, 1997) for the HCCSCA between 1980 and 1996. (The method of data collection was changed in the HCCSCA after 1996.) In addition, cases with Down syndrome were selected from the HCAR as patient controls for the HCCSCA. As population controls, in general, two newborn infants without CAs were selected for every case from the National Birth Registry of the Central Statistical Office matching according to sex, week of birth, and district of parents' residence. The exposure data were obtained (I) prospectively through antenatal care logbooks (it is available in 88.4% of cases, 93.8% of population controls and 90.8% of patient controls) and other medical records, in addition (ii) retrospectively by a structured questionnaire completed by mothers, (iii) finally regional nurses visited and questioned all non-respondent families of cases and patient controls, in addition 200 non-respondent population control families (Czeizel *et al*., 2003). Exposure information was available for 96.3% of cases (84.4% from mothers and/or medical records, 11.9% from visit), 83.1% of population controls (82.6% from mothers and/or medical records, 0.5% from visit) and 95.1% of patient controls (85.1% from mothers and/or medical records and 10.0% from visit) without mothers with wrong or unknown new addresses. Gestational age was calculated from the first day of the last menstrual period. The exposure to the moroxydine was mainly evaluated during the second and third months of pregnancy, i.e. the critical period for most major CAs. The details of the method have been described previously (Czeizel *et al*., 2001).

Moroxydine was available as tablet including 10 mg with 100 mg ascorbic acid and 1 mg methylhomatropine. The usual dose of oral moroxydine treatment was 3×3 tablets, i.e. 900 mg d^{-1} in the first three days, in addition 3×2 tablets, i.e. 600 mg in the next three days, finally 3×1 tablets, i.e. 300 mg in the last three days.

Maternal age, birth order, marital and employment status, acute and chronic disorders, and other medicine (drug and pregnancy supplements) uses were evaluated as potential confounders.

Statistical analyses were performed using the software package SAS version (SAS Institute Ins., Cary, North Caroline, USA). The prevalence of moroxydine treatment in cases with different CA groups was compared with the frequency of moroxydine treatment in their matched population controls, and adjusted prevalence odds ratio (POR) with 95% CI (confidence interval) were evaluated in an unconditional logistic regression model. Birth weight and gestational age were evaluated only in the subgroup of population controls with or without moroxydine treatment using adjusted Student's t test, because CAs may have a more drastic effect for fetal development than the drug studied. The prevalence of preterm birth and low birth weight in the treated and untreated population control subgroups was compared by the chi-square test and crude and adjusted POR with 95% CI was calculated.

RESULTS

The study period included 2,146,574 total births in Hungary, thus 38,151 population controls represented 1.8% of the Hungarian births during the study period between 1980 and 1996. Oral moroxydine was used by 14 (0.04%) population control mothers. The case group consisted of 22,843 malformed offspring (fetuses and newborn infants) and 13 (0.06%) had mothers who were treated by moroxydine during pregnancy (POR with 95% CI = 1.6, 0.7-3.3). Of 834 patient controls with Down syndrome, 2 (0.24%) had mothers with oral moroxydine treatment (POR 95% CI = 0.24, 0.05-1.05). Nearly all moroxydine treatments were medically recorded (12 in the case, 12 in the control and 2 in the patient control group) and used in the 1980s.

Table 1: The prevalence of moroxydine treatment during the entire pregnancy and the second-third months of pregnancy in different CA groups and adjusted POR with 95% CI for confounders

		Entire pregnancy				Second and third months			
Study groups	Grand total No.	No.	%	POR**	95% CI	No.	%	POR**	95% CI
Isolated CAs									
Neural-tube defects	1,202	2	0.2	4.8	1.1-21.1	2	0.2	10.6§	2.1-52.5
Cardiovascular CAs	4,479	2	0.0	1.3	0.3-5.7	2	0.0	3.3	0.3-37.7
Other isolated CAs	15,813	6*	0.0	1.1	0.4-2.8	4	0.0	2.3	0.5-9.5
Cases with multiple CAs	1,349	3	0.2	6.6	1.9-23.2	2	0.2	4.1	0.4-47.6
Total CAs	22,843	13	0.1	1.6	0.8-3.5	10	0.0	3.5	1.2-9.9
Total controls	38,151	14	0.0	referent		6	0.0	referent	

* hypospadias, microcephaly, eye CA (anophthalmia), clubfoot, limb deficiency (terminal transverse of right upper limb), poly/syndactyly

** POR adjusted for birth order, maternal age and employment status

§ crude POR; due to the model fitting it was not possible to adjust for birth order, maternal age and employment status

The gestational month distribution of moroxydine treatment was similar in the case and population control group ($p = 0.65$). Seven case and four control mothers had moroxydine treatment in the first month of gestation, and it was not continued after the diagnosis of pregnancy. However, the time of pregnancy diagnosis is in the second month of gestation, thus this exposure covered the critical period of most major CAs, i.e. during the second gestational month. Of two patient controls, one had mother with first month and one with third month treatment.

Potential confounders such as maternal age, birth order, marital and employment status, acute and chronic disorders did not show any difference between the case and population control groups. The main indication of moroxydine treatment was oral and genital herpes and influenza. Among other drugs, noraminophenazone (6 vs. 1) and penamecillin (6 vs. 1) were used more frequently by case mothers than by population control mothers (POR with 95% CI: 11.1, 1.1-112.0).

The distribution of CAs (including at least 2 cases) are shown in 13 cases (Table 1). The comparison of case mothers and their all matched population control mothers showed a higher prevalence of moroxydine treatment during the entire pregnancy in the group of neural tube defects. The mothers of two anencephalic fetuses were treated in the first month of gestation and it was continued in the 2nd gestational month, I. e. during the critical period of neural tube defects. Of three multi malformed cases, two had mothers with moroxydine treatment during the second and third months of pregnancy. A case born to mother with orofacial herpes and moroxydine treatment during the 2nd gestational month had polydactyly in hands, clubfeet and ear CAs while another case born to mother with herpes zoster and moroxydine treatment during the third gestational month had left renal agenesis and right hydronephrosis (or dysgenesis), in addition anal atresia, clubfeet and lung hypoplasia (this CA-pattern corresponds to the Potter sequence) but this multi malformed preterm girl (she was born on 31st gestational week) had also a complex cardiovascular CA (atrial septal defect, type II and patent ductus arteriosus). However, the latter complex cardiovascular CA might be connected with the preterm birth in the girl who died immediately after birth.

The mean gestational age was 0.4 week longer in population control newborn infants born to mothers with moroxydine treatment than in controls without this treatment (39.8±1.4 vs. 39.4±2.0; adjusted $t = 0.7$; $p = 0.47$). The mean birth weight was 256 g larger in newborn infants born to mothers with moroxydine treatment and the difference between the treated and untreated subgroups was near to the level of significance (3.532±426 vs. 3.276±511; adjusted $t = 1.8$; $p = 0.07$). These findings were in agreement with the somewhat lower rate of preterm birth (7.0% vs. 9.2%) and with no occurrence of low birth weight in the treated subgroups, while it was 5.7% in the untreated subgroup.

DISCUSSION

Present findings indicate some teratogenic potential of moroxydine treatment during the second and third month of pregnancy (POR with 95% CI: 3.5, 1.2-9.9). However, a higher rate of multi malformed cases was based only on two cases and the pattern of component CAs was different in these multi malformed cases, in addition the higher occurrence of neural-tube defects was also based on only two cases. On the other hand, there was a trend showing larger birth weight and the reduction of low birth weight in the newborn infants without CA born to mothers with moroxydine treatment. This trend may be connected partly with the longer gestational age, partly with a birth weight promotion effect of moroxydine.

The HCCSCA is the largest case-control data set of its type in the world, nevertheless the HCCSCA included only 29 pregnant women with oral moroxydine treatment. The small number of pregnant women with moroxydine

treatment is explained by the limited efficacy of the drug, its contraindication during pregnancy and the withdrawal of moroxydine from the market in the early 1990s.

As we mentioned previously, we did find any publication regarding the teratogenic potential of moroxydine. However, the possible teratogenic effect of biguanide derivates used for the treatment of diabetic pregnant women was studied. A partial placental barrier to metformin was observed (Product Information, 1977). Petterson *et al.* (1970) reported a child with multiple CA (micrognathia, gastroschisis and scoliosis) born to diabetic mother treated with insulin and another biguanide derivate: fenformin (phenyl-aethyl-biguanide) throughout pregnancy. Goetzee and Jackson (1984) treated 78 women with non-insulin dependent diabetes during the first trimester of pregnancy and they did not find any increase of CAs. On the other hand Tuchmann-Duplessis and Mercier-Parot (1961) administrated 550 to 1,000 mg kg^{-1} of metformin to rats by tube and find anophthalmia and anencephaly in a few fetuses. However, major CAs occurred in less than 0.5% of the fetuses suggesting that this biguanide derivate was not strongly teratogenic. Another animal experiment in mouse embryos did not indicate the teratogenic effect of metformin (Denno and Sadler, 1994). Nevertheless, it is worth mentioning that two anencephalic fetuses and one anophthalmic child were found in our data set.

In conclusion, the potential teratogenicity of biguanide derivatives cannot be excluded. On the other hand some birth weight promoting effect of moroxydine in pregnant women with viral diseases may deserve some attention.

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