Reproductive Toxicology 26 (2008) 19–23

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

The safety of cetirizine during pregnancy
A prospective observational cohort study

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ARTICLE INFO

Article history:
Received 29 February 2008
Received in revised form 11 April 2008
Accepted 5 May 2008
Available online 13 May 2008

Keywords:
Pregnancy
Cetirizine
Antihistamines
Human
Teratogenicity
Fetal outcome
Birth defects
Cohort study

ABSTRACT

Objective: To assess the safety of cetirizine during pregnancy.
Study design: A prospective observational cohort study with data of the Berlin teratology information center from 1992 until 2006. Pregnancy outcome was compared between a cohort of pregnant women exposed to cetirizine during the first trimester ($n = 196$) and a control group not exposed to potential teratogens ($n = 1686$).
Results: Major birth defects were not more common in the study group than in the control group (OR 1.07; CI 0.21–3.59). We also compared the crude rate of spontaneous abortions (OR 0.97; CI 0.54–1.65), of preterm deliveries (OR 0.76; CI 0.35–1.5), and the birth weight of term newborns ($p = 0.13$).
Conclusions: This prospective observational study on cetirizine in pregnancy suggests that the use of cetirizine is relatively safe during the first trimester.

1. Introduction

Cetirizine is a non-sedating long-acting antihistamine with some mast-cell stabilizing activity. It is a metabolite of hydroxyzine. Cetirizine is used for the symptomatic relief of allergic conditions, such as rhinitis and urticaria [1]. Allergies are common in young and also pregnant women, but human pregnancy experience is so far limited.

No animal teratogenicity is described. According to the manufacturer administration up to 40, 180, and 216 times the human dose in pregnant mice, rats, and rabbits, respectively, did not produce an increase in congenital malformations in the offspring. In one published study, which we have examined only in abstract, there was no teratogenicity in rats or animals even at maternal toxic doses of 500 times the maximum human dose of cetirizine [2].

In 1997 Einarson et al. [3] published the first prospective cohort study on cetirizine and hydroxyzine in pregnancy. Among 39 cetirizine-exposed, 53 hydroxyzine-exposed pregnancies and a control group no significant differences were found in the pregnancy outcome concerning the rate of major or minor birth defects, fetal losses, mean birth weight, and gestational age at delivery. That was confirmed by the case series of Paulus et al. [4] who had collected 144 cetirizine-exposed pregnancies. Källén [5] published a study using the prospectively collected data of the Swedish Medical Birth Registry. He compared groups of antihistamines taken in early pregnancy concerning delivery outcome with all deliveries in the population. The two main antihistamine groups were drugs preferentially used for nausea and vomiting and drugs used for allergy. Cetirizine-exposed women ($n = 917$) were included in the allergy group. The percentage of infants with malformations was 3.16% in the general population and 3.95% after cetirizine, a difference which was statistically not significant.

With the evaluation of our data we wanted to assess the safety of cetirizine during the first trimester of pregnancy.

2. Materials and methods

Our prospective study enrolled women who or whose physician contacted our teratology information service (TIS) in regard to 1st trimester exposure to cetirizine between 1992 and 2006. A structured questionnaire for details of exposure was used at the first contact during (early) pregnancy and the following information was recorded before the pregnancy outcome was known: details of drug exposure (timing in pregnancy, dose, and duration), maternal demographics, medical and obstetric history. Approximately 8 weeks after the expected date of delivery, follow-up was conducted by mailed questionnaire with the woman or the woman's and/or baby's physician. This time was chosen to cover the results of the third pediatric check-up at the age of 6 weeks. (In Germany a pediatric examination program has been

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doi:10.1016/j.reprotox.2008.05.053

established that follows a detailed checklist of anatomical features and developmental milestones.) Furthermore, information about complications during pregnancy (i.e. infections, gestational diabetes, preeclampsia, etc.), details in case of pregnancy loss, gestational age at birth, sex, birth weight, length, head circumference, pH, and Apgar scores were obtained.

The women of the study group ($n = 196$) and their pregnancy outcome were compared with a control group ($n = 1686$) of pregnant women who had been counseled during pregnancy about exposures known to be non-teratogenic. Controls were enrolled in the same year as the exposed pregnancies. Data collection at first contact and follow-up were performed in the same way for both cohorts. In order to strengthen the statistical power we chose a more than 8 fold size of a control group compared to the experimental group.

The main point of interest was the rate of major birth defects, defined as structural abnormalities of medical, surgical or cosmetic relevance. All cases with congenital anomalies were classified according to Merks et al. [6] and Rasmussen et al. [7]. Secondary endpoints were the rates of miscarriage, stillbirth, preterm delivery (<37 weeks), gestational age at delivery and birth weight. In case of multiple pregnancies, each live-born was included individually in the analysis.

2.1. Statistical analysis

The birth defect rate was calculated using live births and fetuses with pathological examination. For calculating rates of major birth defects, genetic syndromes were excluded. Miscarriage rates were calculated per exposed pregnancies or controls respectively after exclusion of elective terminations of pregnancy (ETOP). We used two approaches: crude rates (no. of miscarriages/no. of exposed pregnancies, elective terminations excluded) and survival analysis. The latter was done by the newly introduced method by Meister and Schaefer [8] who modified the estimated cumulative incidences of spontaneous abortions based on the simple Kaplan-Meier approach for competing risks (live births, induced abortion). This method was first applied and described in a study on Vitamin K antagonists and pregnancy outcome [9].

For testing the categorical data, the Cochrane-Mantel-Haenszel-Test was applied. Continuous data were compared using ANOVA. Statistical analysis was performed with SAS Software Version 8.1.

3. Results

A total of 196 pregnant women with first trimester exposure (≤12 weeks after LMP) to cetirizine were enrolled in this study. The treatment indications ($n = 195$) were allergies in general ($n = 105$; 53.8%), allergic rhinitis ($n = 46$; 23.6%), urticaria ($n = 23$; 11.8%), asthma ($n = 9$; 4.6%) and others ($n = 12$; 6.2%). Among the latter there were two mothers who took an overdosage of cetirizine. One took 80 mg in week 7, the other 100 mg in week 10. The course of both pregnancies was uneventful and resulted in healthy infants at term.

78% of the women had started their therapy before week 5.0 after LMP. Approximately 50% of the patients continued cetirizine beyond week 7 and 25% beyond week 9. There were 163 women (83.2%) who took cetirizine only during the first trimester, one woman (0.5%) took it during the 1st and 3rd trimester, 11 (5.6%) during the 1st and 2nd trimester, and 21 (10.7%) throughout pregnancy. The median duration of cetirizine treatment was 6 weeks.

3.1. Maternal characteristics

Cetirizine-exposed women were more often smokers, and drank slightly more alcohol. Women in the control group had more previous pregnancies. The median gestational age at call was in both groups the 8th week. For further details see Table 1.

3.2. Pregnancy outcome

The rate of live births was similar in both groups. The gestational age at delivery and the mean birth weight of all and of term newborns did not differ between the two groups. The same applies for the lengths at birth and the head circumference. The rate of preterm children was higher in the control group (7.3% vs. 5.6%), but this does not reach statistical significance. We tested the rate of spontaneous abortion in the cetirizine and the control group by crude ratios, which was 8.9% and 9.1%, respectively (see Table 2). Due to spontaneous case reporting in observational investigations, study enrolment occurs at varying stages during (early) pregnancy. Considering such a "delayed study entry" we applied the survival analysis as a more appropriate approach and calculated 12% abortions in the cetirizine group and 18% in the control group, a non-significant difference.

The overall rate of birth defects was not significantly increased, nor was the rate of major birth defects (OR 1.07, CI 0.21–3.59; $p = 0.76$). In the study group there were 14 fetuses/children out of 12 pregnancies with birth defects. One twin pregnancy was electively terminated because of chromosomal anomalies (47, XXX), another twin pregnancy ended in late spontaneous abortion in week 18: The two fetuses showed craniofacial dysmorphias: retrogeny, oblique palpebral fissures, low-set ears, and hypertelorism. We classified 3 birth defects as major without a genetic background. These were an atrial septal defect and slight statomotor retardation in one case, club feet in a premature infant of the 32nd week (oligohydramnios not noted), and a boy with hydronephrosis on the right side requiring surgery plus a glandular hypospadias. Concurrent medication and details of all observed defects are shown in Tables 3 and 4.

Table 1
Maternal demographics and obstetric history

	Cetirizine (%)	Controls (%)
Exposed pregnancies	196	1686
Maternal age *n*=	193	1621
Median age	31	31
Interquartile range	27–35	27–34
Min, max	18–44	17–46
Smoking *n*=	190	1661
No	158 (83.2)	1501 (90.4)
≤5 cig/day	10 (5.3)	68 (4.1)
>5 cig/day	22 (11.5)	92 (5.5)
Alcohol *n*=	191	1663
No	180 (94.2)	1616 (97.2)
≤1 drink/day	7 (3.7)	44 (2.6)
>1 drink/day	4 (2.1)	3 (0.2)
Previous pregnancies *n*=	190	1666
0	88 (46.3)	679 (40.8)
1	56 (29.5)	576 (34.6)
2	20 (10.5)	251 (15.1)
3 or more	26 (13.7)	160 (9.5)
Previous parities *n*=	189	1662
0	100 (52.9)	848 (51.1)
1	56 (29.6)	589 (35.4)
2	23 (12.2)	166 (9.9)
3 or more	10 (5.3)	59 (3.6)
Previous miscarriages *n*=	189	1660
0	161 (85.2)	1394 (84)
1	23 (12.2)	194 (11.7)
>1	5 (2.6)	72 (4.3)
Previous ETOP[a] *n*=	189	1660
0	176 (93.1)	1539 (92.7)
1	11 (5.8)	98 (5.9)
>1	2 (1.1)	23 (1.4)
Previous children with birth defects *n*=	189	1658
0	188 (99.5)	1636 (98.7)
1	1 (0.5)	22 (1.3)
Gestational age at 1st TIS contact *n*=	196	1686
Median	8	8
Interquantile range	6–10	6–12
Min, max	3–36	3–39

[a] Elective termination of pregnancy.