Reproductive Toxicology 79 (2018) 79–83

Contents lists available at ScienceDirect

Reproductive Toxicology

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

Pregnancy outcomes after maternal betahistine exposure: A case series

Cuneyt Kemal Buharalioglu[a,*], Selin Acar[b,c], Hilal Erol-Coskun[b,c], Gözde Küçüksolak[b], Barış Karadas[b,c], Tijen Kaya-Temiz[b,c], Yusuf Cem Kaplan[b,c]

[a] Izmir Katip Celebi University Faculty of Pharmacy, Department of Pharmacology Izmir, Turkey
[b] Terafar - Izmir Katip Celebi University Teratology Information, Training and Research Center, Izmir, Turkey
[c] Izmir Katip Celebi University School of Medicine, Department of Pharmacology Izmir, Turkey

ARTICLE INFO

Keywords:
Betahistine
Pregnancy
Congenital abnormalities
Birth defects
Pregnancy outcomes
Antivertigo drug

ABSTRACT

Objective: To investigate the pregnancy outcomes of women who were exposed to betahistine during their pregnancies.
Methods: We identified and evaluated the outcomes of 27 pregnant women who were referred to Terafar (Teratology Information Service, Izmir, Turkey) for a teratological risk assessment.
Results: Of 24 pregnancies with known outcomes, 21 resulted in live births (including two pairs of twins) whereas two ended with miscarriage and three with elective terminations. Among the 20 live births for whom the malformation details were available, there were 17 normal outcomes, one major and two minor congenital malformations.
Conclusions: Despite a number of limitations, this case series may be of value regarding counseling pregnant women with inadvertent betahistine exposure. Further epidemiological studies with larger sample sizes and control groups are necessary to draw more definite conclusions.

1. Introduction

Betahistine is a histamine analog with a postsynaptic H_1 receptor partial agonist and presynaptic H_3 heteroreceptor antagonist properties. This multifactorial mode of action supposedly make betahistine a vestibular suppressant to restore proper balance and decrease symptoms of vertigo not only in Meniere disease [1,2] but also in vestibular migraine [3]. Although it has been commonly used in European countries since 1966 [4,5], betahistine has not been approved by the U.S. Food and Drug Administration [6]. In Turkey, it is available as a tablet form only with a recommended adult maintenance dose range of 24–48 mg daily.

Both vertigo and migraine are common in pregnant women. The Pacific Northwest pregnancy cohort study indicated that approximately one in four pregnant women had migraines and about 60% of pregnant women had experienced dizziness at some point in the first trimester. Among them, the most frequent symptom (35.7%) associated with dizziness was vertigo, while the second most frequent (21.4%) was deviated or unbalanced gait as well as unstable floating head sensation [7]. Probably stemming from the hormonal changes during the first gestational trimester [8], these complaints tend to seriously affect the quality of life and perceived wellbeing of the expectant mothers. Therefore, the possibility that pregnant women are being exposed to betahistine is not small.

Although betahistine has a good safety profile in general population [9,10], possible risks associated with its use during pregnancy are largely unknown. Studies with betahistine in pregnant rabbits failed to show any teratogenic effect [11] and evidence in humans is currently very limited. Betahistine is assigned to the category B in FDA risk categories, which were announced to be replaced by the new pregnancy and lactation labeling rule [12].

In order to expand the limited data and provide additional value to the clinicians assessing the possible teratogenic risks of inadvertent betahistine exposure during pregnancy, we aimed to evaluate and describe the pregnancy outcomes following maternal betahistine exposure by using the data from Terafar (Izmir Katip Celebi University Teratology Information, Training and Research Center, Turkey).

2. Methods

Terafar records were searched to retrieve pregnant women with a prospective referral for risk assessment regarding betahistine use during pregnancy between 2009 and 2017. The study has been approved by the Izmir Katip Celebi University Non-Interventional Studies Ethics Committee (02.06.2016, #156).

* Corresponding author at: Izmir Katip Celebi University University Faculty of Pharmacy, Department of Pharmacology, Balatçık Mahallesi Havaalanı Şosesi No:33/2 Balatçık 35620 Çiğli Izmir, Turkey.
E-mail address: ckemal.buharalioglu@ikc.edu.tr (C.K. Buharalioglu).

https://doi.org/10.1016/j.reprotox.2018.06.004
Received 7 March 2018; Received in revised form 30 April 2018; Accepted 11 June 2018
Available online 13 June 2018
0890-6238/

All relevant data regarding basic demographics, maternal characteristics, medical, obstetric and family history, medication and other exposures (e.g. drugs of abuse, herbal supplements, etc.) were recorded through face-to-face interviews using a detailed and structured questionnaire. For the timing of gestational exposure, the last menstrual period (LMP) date was determined by early ultrasound (USG) examination or maternal recall at the initial contact. To investigate the pregnancy outcomes, after the birth, a standardized follow-up telephone interview was conducted with the mothers/families, based on a structured questionnaire and oral informed consent was also obtained. This aimed to obtain the following information: Possible complications during pregnancy (e.g. preeclampsia, gestational diabetes etc.), further information in case of pregnancy loss, gestational age at birth, sex, birth weight and length, head circumference and Apgar scores. The survey also aimed to identify whether there had been any major or minor congenital malformations or any other adverse physical effects in the infant discovered either at birth, or during routine family physician visits.

In this study, the primary outcomes of interest were the rate and pattern, if present, of major congenital malformations. The secondary outcomes were the rate of miscarriage, elective termination, stillbirth, preterm birth and low birth weight. Major and minor congenital malformations were classified using the Malformation Coding Guides of European Surveillance of Congenital Anomalies (EUROCAT) [13,14] by three study authors (CKB, SA, HE-C) in an unblinded fashion. Any disagreements were resolved by consulting a fourth author (YCK). Miscarriage was defined as the spontaneous loss of a pregnancy $< 20^{th}$ week, elective termination was defined as the voluntary abortion for non-medical intent, stillbirth was defined as the birth with no signs of life $> 20^{th}$ week, preterm birth was defined as the birth $< 37^{th}$ week and low birth weight was defined as the birth weight < 2500 g at term. Due to inclusion of twin pregnancies in the study sample, the pregnancy outcome rates were calculated using the total number of exposed fetuses (n = 26) as the denominator.

3. Results

27 cases with an exposure to betahistine during pregnancy were identified in the period between 2009– 2017. The malformation rate calculations were restricted to first trimester exposures that resulted only in live births, due to the unavailability of data regarding major congenital malformations from the pathological examinations of miscarriages and elective terminations.

After excluding the cases lost to follow-up (n = 3), 24 betahistine exposures with known outcomes were included, including one live birth without available malformation data (Fig. 1). The median maternal gestational age at admission was 8 weeks (range: 4–25 weeks). Detailed maternal characteristics are presented in Table 1. Pregnant women with more than one chronic disease were considered in each disease category.

The patterns of exposure are presented in Table 2. The median daily dose of betahistine was 24 mg/day and the duration of exposure varied between 1 and 71 days of pregnancy with the oral route of administration in all of the pregnancies.

Child characteristics are presented in Table 3. In 24 pregnancies, two were twin pregnancies (one twin was missed abortus and the mother reported to have one umbilical artery in detailed USG). Therefore, for the calculation of percentages 26 exposed fetuses is used as the denominator. Of 26 fetuses with known outcomes, 21 (80.8%) were live births, two (8.3%) were miscarriages, and three (11.5%) were elective terminations. The median age of the children at the time of the follow-up was 23 months (range: 4–63 months). One infant was reported to have a low birth weight for gestational age, and seven other were reported to be born preterm. Among 20 live births with in utero exposure to betahistine during the first trimester, there were 17 (85%) normal outcomes, 1 major (5%) and 2 minor (10%) congenital malformations.

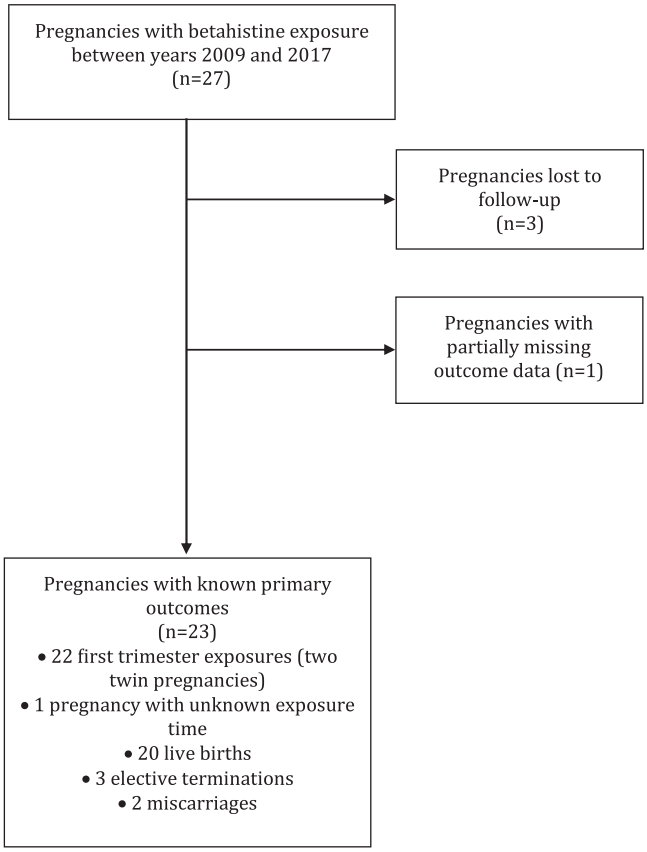

Fig. 1. Study flow diagram.

The infant with the only major congenital malformation, which was an intestinal malrotation, died at the 11^{th} day, postnatally (Case 10, Table 4). The two minor congenital malformations were a patent foramen ovale (PFO) in two female infants (Case 6 and Case 9, Table 4).

In terms of perinatal complications, one term infant (Case 6, Table 4) was diagnosed with both hypothyroidism and bronchitis 10 days after birth. One infant was reported to have cardiopulmonary arrest at birth. Following the recussitation she stayed in incubator for 9 days and survived.

In line with the FDA Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [15], a detailed descriptive analysis of the infants with congenital malformations including the high number of concomitant medication exposures is presented in Table 4.

4. Discussion

To the best of our knowledge, this is the first detailed case series investigating the outcomes of pregnant women exposed to betahistine during pregnancy. In 24 recorded pregnancies with betahistine exposure, the rates of major [our study with confidence intervals vs. background estimate: 5% (0.1–24.9) vs. 1–8% [16],] and minor malformations [10% (1.2–31.7) vs. 4% [17],] and low birth weight [5.3% (0.1–26) vs. 8.4% [18],] were comparable with the general population rates. However, elective termination [11.5% (2.4–30.2) vs. 4.7% [19],] and preterm birth rates [33.3% (14.6–57) vs. 12% [20],] were considerably higher. However, it should be highlighted that small sample size and data sampling limitations associated with Teratology Information Center surveillance methods discussed elsewhere [21] might have limited the precision of those estimates, therefore they should be cautiously interpreted. The only major malformation, in this study, was intestinal malrotation while the minor malformations were patent