Reproductive Toxicology 50 (2014) 134–137

Contents lists available at ScienceDirect

Reproductive Toxicology

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

Use of ondansetron during pregnancy and congenital malformations in the infant

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ARTICLE INFO

Article history:
Received 11 August 2014
Received in revised form 17 October 2014
Accepted 20 October 2014
Available online 31 October 2014

Keywords:
Antiemetics
Cardiovascular defects
Congenital malformations
Meclozine
Nausea and vomiting in pregnancy
Ondansetron

ABSTRACT

The study investigates teratogenic risks with ondansetron (Zofran®). Data from the Swedish Medical Birth Register combined with the Swedish Register of Prescribed Drugs were used to identify 1349 infants born of women who had taken ondansetron in early pregnancy, 1998–2012. Presence of congenital malformations in the offspring was identified with three national health registers. In a Mantel–Haenszel analysis adjustment was made for year of delivery, maternal age, parity, smoking in early pregnancy and pre-pregnancy body mass index. Risks were expressed as odds or risk ratios with 95% confidence intervals.

No statistically significantly increased risk for a major malformation was found. The risks for a cardiovascular defect and notably a cardiac septum defect were increased and statistically significant (OR = 1.62, 95% CI 1.04–2.14, and RR 2.05, 95% CI 1.19–3.28, respective). The teratogenic risk with ondansetron is low but an increased risk for a cardiac septum defect is likely.

1. Introduction

Ondansetron (Zofran®) is a serotonin 5-HT3 receptor antagonist which is used as an antiemetic. Its original use was for nausea and vomiting after chemotherapy, irradiation or surgery, but an extended off-label use has occurred for hyperemesis and also nausea and vomiting (NVP) in pregnancy. The teratogenic risks when used in early pregnancy are not well known. The first report based on 176 exposures [1] found no significantly increased risk for a major malformation after ondansetron compared with other anti-emetics or non-teratogens. In a Swedish study from 2005 of antiemetic drugs during pregnancy [2], only 21 first trimester exposures were noted among nearly 30,000 women reporting the use of antiemetics. A retrospective case–control study from the National Birth Defects Prevention Study [3] found an association between maternal use of ondansetron and infant median cleft palate. In a case series of women treated with ondansetron [4], only seven treatments occurred during organogenesis, no infant was malformed. The largest studies so far have come from Denmark [5,6]. One of the studies [5] was based on 1233 first trimester exposures with 36 malformed infants (OR = 1.02, 95% CI 0.96–1.49). The second study [6] was based on 1248 first trimester exposures and found a major malformation risk of 1.3 (95% CI 1.0–1.7) and a congenital heart malformation risk of 2.0 (95% CI 1.3–3.1). In both studies exposure information was based on a National Prescription Registry and malformations were identified from inpatient registers.

Since our previously published study on outcome after antiemetics, the use of ondansetron for NVP has increased and we now have 1349 exposures in early pregnancy which makes it possible to study the presence of congenital malformations in the offspring.

2. Materials and methods

Two sources were used for the identification of women who used ondansetron in early pregnancy. One was the midwife interviews at the first antenatal care visit of the pregnant woman (usually during weeks 10–12) when she was asked what drugs she had used since she became pregnant [7]. The stated drug use was recorded in clear text and was later centrally transferred to ATC (anatomic, therapeutic, chemical) codes and entered into the Medical Birth Register [8]. This information was available for 1995–2012 but the first recorded exposure for ondansetron occurred in 1998 (Fig. 1) why the study period was 1998–2012. The material for 2012

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http://dx.doi.org/10.1016/j.reprotox.2014.10.017
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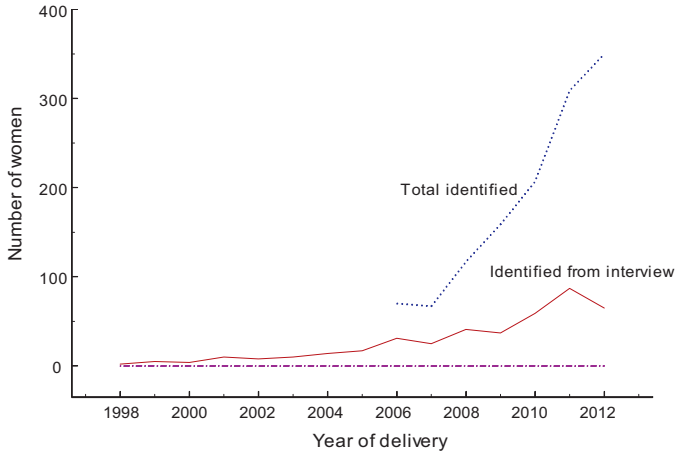

Fig. 1. Yearly number of infants exposed to ondansetron in early pregnancy as reported by the women at the first prenatal care visit in early pregnancy and after supplementation with data from the Prescription Register (total identified).

is not quite complete as data from one county is missing (approximately 2.3% of all to judge from 2011 data).

As ondansetron for NVP may be especially prescribed in association with the first antenatal visit, perhaps because the woman had already tried over the counter drugs like meclozine without enough effect, we also used the Swedish Prescription Register [9] in order to identify such prescriptions given during the pregnancy. This register was used for the period 2006–2012. Data from the register were linked to the Medical Birth Register using the personal identification number of the woman. This number also made it possible to compare the two sources of exposure information and to identify and remove duplicates.

The most used drug for NVP in Sweden is meclozine. This is an over the counter drug so its identification was restricted to the midwife interviews. Women using meclozine (1998–2011) were studied in order to evaluate a possible confounding by indication (NVP).

The presence of congenital malformations among the infants was ascertained from three sources: diagnoses given by the attending paediatrician in the Medical Birth Register, diagnoses reported to the Birth Defect Register (previously called the Register of Congenital Malformations), and discharge diagnoses from hospitalizations [10]. In order to reduce variability in registration some relatively common, clinically less significant malformations with a variable registration were excluded: preauricular tags, tongue tie, patent ductus in preterm infants, single umbilical artery, undescended testis, hip (sub)luxation, and nevus. The remaining malformations were called "relatively severe" but may contain a few minor or poorly specified conditions. This concept broadly corresponds to major malformations.

Odds ratios (OR) were calculated using Mantel–Haenszel analysis and approximate 95% confidence intervals (95% CI) were estimated using Miettinen's technique. When the expected number of malformed infants was less than ten, a risk ratio was instead determined as the quotient between the observed and the expected number with exact 95% CI calculated from Poisson distributions. In both types of analyses, adjustment was made for year of birth, maternal age, parity, smoking in early pregnancy, and body mass index. These data came from the Medical Birth Register and were mainly based on the midwife interviews.

3. Results

The total number of births in the study was 1,501,434 infants and 43,658 had malformations classified as a major, 2.9%. Among these, 14,872 had a cardiovascular defect (1%) and 10,491 a cardiac septum defect (0.7%), either a ventricular septum defect or an atrium septum defect or both.

Table 1
Distribution by pregnancy week (counted from last menstrual period) of the date of filling the first prescription for ondansetron.

Week	Number
<5	7
5	10
6	34
7	109
8	142
9	187
10	145
11	169
12	136

We identified 1349 infants, exposed in early pregnancy for ondansetron. Among them only 435 were identified from midwife interviews and 914 from the prescription register (excluding those who had also been reported in the interviews). Table 1 shows the pregnancy week of the first recorded filled prescription. Use of meclozine was reported by mothers of 41,388 infants.

Table 2 shows the presence of "relatively severe" congenital malformations among the infants exposed to ondansetron and Table 3 gives the risk estimates for groups of malformations with data for meclozine for comparisons. Among the 17 infants with septum defects, 13 had a ventricular septum defect, one an atrium septum defect, and three both a ventricular and an atrium septum defect. No infant had a cleft palate but one had a cleft lip/palate. Three had hypospadias (expected number 3.7).

In our material, the sex ratio after maternal use of ondansetron is 0.83 (95% CI 0.75–0.93) and that after meclizine is 0.92 (95% CI 0.90–0.93); excess of females.

4. Discussion

A very marked increased use of ondansetron in early pregnancy was seen which most likely is an expression of "off label" use at NVP. It appears that this use was higher in Denmark than in Sweden (Table 4). But because of a much larger study cohort than

Table 2
"Relatively severe" congenital malformations in infants exposed during early pregnancy for ondansetron.

ICD-code	Malformation	Number
Q063	Cauda equina malformation	1
Q210	Ventricular septum defect	12
Q211	Atrium septum defect	1
Q210 + Q211	Ventricular and atrium septum defect	3
Q210 + Q221	Ventricular septum defect + pulmonary valve stenosis	1
Q213	Tetralogy of Fallot	1
Q251	Coarctation of aorta	1
Q320	Tracheomalacia	1
Q375	Cleft lip/palate, unilateral	1
Q391	Esophageal atresia	1
Q400	Pyloric stenosis	1
Q412 + Q429	Ileum and colon atresia	1
Q423	Anal atresia	1
Q432	Colon dilatation	1
Q438	Unspecified intestinal malformation	1
Q540	Hypospadias	3
Q649 + Q669	Urinary tract malformation+ foot deformity	1
Q688	Musculoskeletal malformation, unspec.	1
Q690	Polydactyly fingers	1
Q714	Radius reduction	1
Q829	Unspecified skin malformation	1
Q848	Nail malformation	1
Q909	Down syndrome	1