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The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study

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Objective Ondansetron (Zofran) is a drug used for the treatment of nausea and vomiting caused by cancer chemotherapy. Despite the fact that it is not indicated, women are being prescribed this drug for the treatment of nausea and vomiting of pregnancy (NVP). There is a paucity of information on fetal safety for this indication. The objective of this study is to determine whether this drug increases the baseline rate of major malformations.

Design A prospective comparative observational study.

Setting Teratogen Information Services (TIS).

Population Pregnant women.

Methods Our three groups included women who were exposed to ondansetron and women exposed to (1) other anti-emetics and (2) non-teratogen exposures. All of the women called either our NVP Helpline or TIS at The Motherisk Program in Toronto, Canada, or The Mothersafe Program in Sydney, Australia.

Main outcome measure Rates of major malformation.

Results We have completed 176 pregnancy outcomes in each group. In the ondansetron cohort, there were 169 live births, 5 miscarriages, 2 therapeutic abortions, 6 (3.6%) major malformations and the mean birthweight was 3362 g [SD 525]. There were no statistical differences in any of the study endpoints between the ondansetron and the comparison groups.

Conclusions This drug does not appear (although the sample size is limited) to be associated with an increased risk for major malformations above baseline.

INTRODUCTION

Nausea and vomiting (NVP) is the most common medical condition of pregnancy, affecting up to 80% of all pregnancies to some degree. In most cases, it resolves by the 16th week of pregnancy, although up to 20% of women continue to have symptoms throughout pregnancy. Severe NVP (hyperemesis gravidarum) affects less than 1% of women but can be debilitating, in the worst case scenario, requiring hospitalisation and rehydration of fluids.[1] Even less severe cases can have a significant impact on the quality of a women's life, affecting her occupational, social, domestic functioning and general wellbeing.[2] Although NVP affects such a significant number of pregnant women, it is largely ignored in terms of medical research and in the development of new treatment modalities. The drug of choice for treatment in Canada is Diclectin, the controlled release of doxylamine + vitamin B6[3]; however, in the United States, there is no drug approved by the FDA, since the removal of Bendectin 20 years ago due to unfounded fears that it was teratogenic.[4] Other modes of treatments have been used throughout the world, which include various antihistamines, phenothiazines, vitamin B6, metoclopramide and ginger with various levels of evidence of safety and efficacy.[5–9]

Despite the fact that ondansetron is not indicated for NVP and there are no studies examining safety in pregnancy, it has been used as a last resort and appears to be effective when no other treatments work. Recently, it was brought to our attention by American callers using our service that it has been used as a first line of treatment in the United States, with HMOs covering the cost.

A program of pre-clinical safety evaluation was undertaken, which involved a series of studies: single dose, repeat dose, reproduction, genotoxicity, oncogenicity, local irritancy and a hypersensitivity study. Ondansetron was found to have a very good safety profile and the only toxicity identified was associated with central nervous system activity when near lethal doses were administered. It was not genotoxic and had no reproductive or oncogenic potential.[10] The efficacy was also studied and it was found to be effective for the prevention of nausea and vomiting

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post-chemotherapy.[11] However, it was never intended or labeled as such to be a treatment for NVP. Consequently, there is a paucity of data in the literature on the safety of ondansetron for the treatment of NVP: there are three case reports[12] and one small study comprised of 15 subjects with severe NVP (hyperemesis gravidarum) who were compared with women taking promethazine.[13]

At The Motherisk Program, we established a Nausea and Vomiting Help Line in 1996, which is a toll-free line where women from all over North America can call for information about NVP. In an attempt to improve the quality of life of these women, we are continuing to investigate optimal treatment modalities. Several years ago, we found that a significant number of women calling our Helpline, many of whom were calling from the United States, had been prescribed ondansetron and were requesting information on the safety and effectiveness of this drug for NVP. We felt that if ondansetron is to be considered a useful drug for the treatment of NVP, the safety of this drug on the developing fetus must be examined first.

Our objective was to determine whether the use of ondansetron during pregnancy is associated with an increased risk for major malformations.

METHODS

Motherisk and Mothersafe are counselling services for pregnant and lactating women and their health professionals, where information is given on the safety/risk of drugs, chemicals, radiation and infectious diseases. Women who called either service, were taking ondansetron and were less than three months pregnant at the time of call (most were between 5 and 9 weeks of gestation) within a two year period were enroled. The comparison groups were enroled in the same fashion. Interviewers completed a standardised intake form that was used by both centres and the following information was collected whenever possible: the patients self-assessment of the severity of NVP, which was measured by the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring system recently created and validated by our team, where symptoms (nausea, vomiting and retching) are scored separately as reported by the women in the last 12 hours prior to their call,[14] and any concurrent anti-emetic or other medication. Two other groups of women were enroled concurrently: group 2, who also suffered from NVP but were not exposed to ondansetron, they had used other anti-emetics, which included Diclectin, metoclopramide, phenothiazines and ginger, and group 3, composed of women exposed to other drugs considered safe to use in pregnancy or those who had not used any medication.

The women were contacted 4–6 months after delivery to obtain outcome data using a standardised follow up form. Subsequent to the completion of the pregnancy follow up, the interviewer sent a letter to the caller's physician asking for verification of the information obtained from the mother concerning the baby's health. We compared basic characteristics of the women, which included age, smoking and alcohol status and gestational age at time of call. The three groups were analysed to determine rates of live births, miscarriages, therapeutic abortions, stillbirths, major malformations, gestational age at birth and mean birthweights.

Outcome endpoints of interest between the study and the comparison groups were compared using χ^2, Fishers exact and ANOVA statistical tests whenever appropriate. We obtained oral consent from each participant after the study was fully explained over the telephone and received ethics approval from our hospital's Research Ethics Board.

RESULTS

We were able to ascertain the outcomes of 176 women exposed to ondansetron who were all in the first trimester, most of whom were between 5 and 9 weeks of gestation and were using this drug for the treatment of NVP. All of the women in all three groups who were asked, agreed to participate and we enroled 188 in the ondansetron group. We were, however, unable to complete follow ups on 12 of the women because of the inability to contact them. There were no significant differences in the maternal characteristics between the exposed and comparison groups, their ages were similar and very few smoked cigarettes or drank alcohol during pregnancy (Table 1). In the ondansetron group, there were 169 live births, 5 miscarriages, the mean gestational age was 38.7 weeks [1.7] and the mean birthweight was 3362 [525] g. There were six major malformations: three cases of hypospadias, double urinary collecting system in kidney, mild pulmonary stenosis and a duodenal atresia. After the study was completed, a physician phoned to inform us (January 2004) that a patient of his, who was in our study and gave birth to a normal child, had a second child also exposed to ondansetron, born with a mild hydronephrosis.

In the comparison group (1), there were three major malformations, hydrocephalus, kidney anomaly and aortic stenosis, and in the comparison group (2), there were also three malformations, one case of hypospadias and two congenital heart defects. There were no statistically significant differences between the three groups in terms of live births, miscarriages, stillbirths, therapeutic abortions, birthweight or gestational age. (Table 2) The rate of hypospadias (3/169) live births in the ondansetron group was not statistically

Table 1. Maternal characteristics of the women ($n = 176$ in each group). Values are given as mean [SD] or n (%).

Outcome	Ondansetron	Other anti-emetics	Non-teratogen
Age	32.3 [4.4]	31.5 [4.3]	31.7 [4.4]
Smoking status	1 (0.5)	5 (2.8)	15 (8.5)
Alcohol use	2 (1.1)	1 (0.5)	3 (1.7)

Table 2. Comparison of pregnancy outcome among women exposed to ondansetron, other anti-emetic medications and non-teratogen drugs (n = 176 in each group). Values are given as mean [SD] or n (%).

Outcome	Ondansetron	Other anti-emetics	Non-teratogen	P
Live birth	169 (96.8)	160 (91)	162 (92)	0.68
Miscarriage	5 (2.9)	13 (7.5)	14 (8)	0.46
Stillbirth	0 (0)	1 (0.5)	0 (0)	0.70
Therapeutic abortion	2 (1.3)	2 (0.5)	0 (0)	0.89
Major malformation	6 (3.5)	3 (1.8)	3 (1.8)	0.52
Birthweight (grams)	3362 [525]	3372 [608]	3490 [606]	0.08
Gestational age at birth	38.7 [1.7]	38.7 [1.9]	39.4 [1.6]	0.57

significant from the combined controls (1/322, $P = 0.25$), however this sample size had only a 20% power to show the observed sixfold difference.

DISCUSSION

To our knowledge, this is the first study that examined the use of ondansetron in terms of safety during pregnancy. We were able to ascertain the outcomes of 176 pregnancies of women, all of whom were exposed during the first trimester of pregnancy in the period of organogenesis.

There were no statistical differences in the maternal characteristics of the women in the three groups and there were no statistical differences in any of the outcomes we examined. However, in the ondansetron group, there were three cases of hypospadias, which fit our criteria for major malformation because they required surgery. This is an increase in the rate of hypospadias in the general population (though not statistically significant), where this abnormality occurs in approximately 1 in every 300 males.[15] Of note however, none of these hypospadias were categorized as severe, two of the three were described by the child's attending physician in the report as minor and one was described as moderate. Our sample size lacked power to show this apparent sixfold increase in this anomaly, thus, was not statistically significant. This increase in the rates of hypospadias was not shown in animal studies.[10] More studies are required to achieve significant power to address any potential association between ondansetron and hypospadias.

Another interesting finding was the low rate (2.9%) of miscarriages in the ondansetron group compared with 7.5% and 8% in the comparison groups. This rate is considerably lower than is currently quoted in the literature, where many reports rely on approximate rates, rather than epidemiologic surveys. However, a recent study in Denmark did quote a 13% reported rate found in a surveillance study, which is twice as high as both of our comparison groups.[16] This low rate of miscarriages found in our study may confirm that NVP does have a protective effect in pregnancy, which we also found in our most recent study examining the safety of ginger for NVP in pregnancy, where there was an even lower rate of 1.6% in the women with NVP who had used ginger.[17] The finding of a protective effect of NVP has also been reported in other studies of NVP.[18] The confounding factor of this result however is that the rates of miscarriages in the second comparison group, which was comprised of other women with NVP who used other antiemetics. These were comparable with the third group of women who took other non-teratogen drugs or were not exposed to any drug, who also had relatively low rates compared with baseline. If NVP truly does have a protective effect, the rates of miscarriages in this group should have been similar to the ondansetron group rather than the non-teratogen group and there is no plausible explanation for this result.

A limitation of this study is the sample size, in which it has an 80% power to detect only a 3.5-fold increase in the rate of major malformations, with α of 0.05. Approximately 800 cases in each group would be required to detect a twofold risk of relatively common malformations and thousands of cases would be required to detect rare defects.

In summary, in our prospective cohort of 176 women who took ondansetron, all during the first trimester of pregnancy, there does not appear to be an increase in the rates of major malformations above the baseline. However, this is a small sample size and many more cases would be required to make a definitive conclusion. Nausea and vomiting can be a very debilitating and often ignored condition of pregnancy and this evidence-based information can be helpful to women and their health professionals when making a decision regarding treatment.

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