Drug Saf - Case Rep (2017) 4:2
https://doi.org/10.1007/s40800-016-0044-6

CASE REPORT

Tracheo-Esophageal Fistula (TEF) in a Newborn Following Maternal Antenatal Exposure to Olanzapine

Vikas Maharshi[1,2] · Indranil Banerjee[2] · Pravesh Nagar[2] · Harmeet Singh Rehan[2]

Published online: 6 January 2017

Abstract There is a dearth of evidence on the safety of the use of antipsychotics during pregnancy. Olanzapine, a pregnancy category C drug, has no unequivocal evidence of harm to the fetus. Against this backdrop, we report the first case of a tracheo-esophageal fistula (TEF) in a newborn following maternal antenatal exposure to olanzapine. A 29-year-old woman with acute psychotic disorder had been treated with olanzapine for the last 7 years. Her first pregnancy, while taking olanzapine, resulted in a miscarriage at 4 months' gestation, following which she discontinued olanzapine. She reconceived after a few months and delivered a full-term normal child. However, due to the recurrence of psychiatric illness after her second pregnancy, she was prescribed olanzapine again, which was continued throughout her third pregnancy. The outcome of the third pregnancy was a full-term female baby with a TEF. The baby was managed surgically and discharged with satisfactory vital signs. Unfortunately, however, the baby did not survive beyond 11 months of age. Causality between antenatal maternal olanzapine exposure and TEF in the newborn was determined to be 'probable' (score +5) as per the Naranjo causality assessment scale. Greater knowledge of this potential teratogenicity caused by olanzapine is needed to reduce morbidity and mortality in newborns.

Key Points

Women with psychiatric diseases are treated with antipsychotic medication(s) with limited evidence to support the safety of their use during pregnancy.

Olanzapine, a second-generation antipsychotic, is a US Food and Drug Administration pregnancy category C drug with no unequivocal evidence of harm to the fetus.

We report the first case of tracheo-esophageal fistula as a possible teratogenic effect of olanzapine exposure.

Introduction

Women with psychiatric diseases may become pregnant and are treated with antipsychotics without any proven evidence of safety. Due to ethical issues, pregnant women are rarely included in clinical trials, leading to a dearth of data available on the safety of antipsychotic drugs in this population [1]. There have been reports of congenital anomalies in newborns of mothers exposed to antipsychotic medications during pregnancy [1–4]. Olanzapine, a second-generation antipsychotic, is a US Food and Drug Administration (FDA) pregnancy category C drug [3, 5] with no unequivocal evidence of harm to the fetus [3]. A literature search revealed that maternal exposure to olanzapine appears to be associated with lumbar meningomyelocele, dysplastic kidney, hip dysplasia, atrioventricular canal defect, club foot, microcephaly, ventricular septal defect, absent fingers, craniosynostosis, cleft lip, encephalocele,

✉ Vikas Maharshi
vikas.maharshi81@gmail.com

[1] Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India

[2] Department of Pharmacology, Lady Hardinge Medical College (LHMC), New Delhi 110001, India

aqueductal stenosis, etc. [1–4]. Given this perspective, the possibility of further teratogenic effects of olanzapine cannot be ruled out. In this case report, we report the first case of tracheo-esophageal fistula (TEF) as a possible teratogenic effect of olanzapine exposure.

Case Narrative

We report the case of a 29-year-old married woman with bipolar disorder with mixed episodes who had been treated with olanzapine in the psychiatric outpatient department of our institute (Lady Hardinge Medical College, New Delhi, India) for the last 7 years who delivered a full-term female baby with TEF in September 2013.

One week after her marriage in February 2008, the patient developed psychotic symptoms such as excessive talking, episodes of crying and laughing, and forgetting things frequently. Following initial unsuccessful local treatment, she was taken to the psychiatry department of a tertiary care hospital. After initial management of acute symptoms there, she continued her treatment from our institute, where she was prescribed olanzapine (Oleanz® 10 mg tablet orally once daily). In December 2008, she had a miscarriage at 4 months' gestation, following which she stopped taking the medication of her own choice. A careful history/enquiry from the parents failed to reveal any data available regarding congenital malformation of the aborted fetus. In 2009, she conceived again (it is noteworthy that the patient was not taking olanzapine during this pregnancy) and delivered a full-term healthy female child in January 2010. This child is presently healthy.

Eight months after delivery of this baby the patient had a recurrence of psychotic symptoms for which she was prescribed the same treatment. In December 2012, she conceived a third time but due to persistent psychiatric symptoms, olanzapine was continued throughout the pregnancy by the treating psychiatrist, who considered there to be a favorable benefit:risk ratio for the patient at that time. She received regular antenatal care and was compliant with all prescriptions and instructions, including prophylactic folic acid and two doses of tetanus toxoid. There was no history of maternal alcohol intake, smoking, or exposure to other potential teratogenic drugs or exogenous hormones throughout the pregnancy. All baseline hematological (hemoglobin 13.8 g/dL, total leukocyte count 6000/μL, platelets 2.3 lac/μL, etc.) and biochemical investigations (random blood sugar 98 mg/dL, blood urea 27 mg/dL, etc.) were within the normal limits. Tests for trisomy 21 and 18 (nuchal translucency scan and dual marker tests) and rubella were negative. No fetal abnormality was detected in abdomen ultrasonography in any trimester. In September 2013, she delivered a full-term female baby by vaginal delivery. Immediately after delivery, the baby experienced respiratory distress and excessive salivation, for which she was admitted to the neonatal intensive care unit. On examination, a red rubber catheter could not be negotiated beyond 10 cm in the esophagus. The chest X-ray was suggestive of TEF (Fig. 1); however, 2-dimensional echocardiography revealed normal cardiac structure and function. Other concomitant anomalies including vertebral, anal, renal, limb (components of VACTERL [Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb abnormalities]), eye, ear, and nasal defects were ruled out. The TEF was repaired using esophageal–esophageal anastomosis with a drainage tube in the fifth intercostal space. On the second post-operative day, there was excess serous discharge from the drainage tube. For this reason, cervical esophagotomy was performed and a gastrostomy was inserted for feeding purposes. The baby was discharged in a stable condition with advice for full breast milk feeding through gastrostomy, some required medications (multivitamin syrup, calcium, anti-emetic and antibiotics) for an appropriate duration, and regular vaccination. However, although the baby was well until this point, she was re-hospitalized at 11 months of age because of diarrhea and unfortunately died on 19 August 2014, probably because of widespread infection (no definitive record of the last hospitalization is available and a post-mortem was not performed).

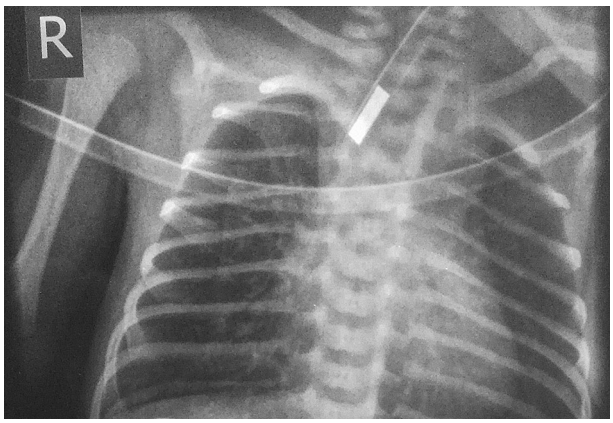

Fig. 1 Chest X-ray posteroanterior view of the newborn baby, who was born to a mother with antenatal exposure to olanzapine, suggestive of tracheo-esophageal fistula

Discussion

A number of drugs are clearly known to be associated with teratogenicity, such as thalidomide and isotretinoin, but the majority of drugs do not have conclusive data concerning their effect on fetal development and growth. Due to strict

ethical constraints, at-risk populations (including pregnant women) are not included in most clinical trials, limiting the availability of data on the use of drugs (including antipsychotics) in these populations [1], and thus spontaneous reporting of suspected adverse drug effects constitutes an essential tool for generating data on the safety of drugs, especially in the population of pregnant women.

According to a retrospective analysis of data from the Lilly Safety Database, of the 610 prospectively identified pregnancies exposed to olanzapine with an available outcome, there were 401 (66%) normal births, 60 (9.8%) premature births, 57 (9.3%) spontaneous abortions, 49 (8%) perinatal complications, 27 (4.4%) congenital anomalies (cleft lip, encephalocele, and aqueductal stenosis), and 16 (2.6%) other outcomes (post-perinatal condition, ectopic pregnancy, post-term birth, and still birth) [1]. Other reported congenital anomalies with olanzapine included meningocele, ankyloblepharon, hip dysplasia, acheiria, atrioventricular canal defect, and unilateral club foot [1, 6–8].

A link between teratogenicity and antipsychotics is also supported by the fact that these drugs readily cross the placental barrier [1, 4, 9], with 23.8% placental passage for quetiapine and 72.1% for olanzapine [2, 4, 9]. Newport et al. measured placental passage of medication from mother to fetus by measuring levels in the umbilical cord serum and found that olanzapine has the highest rate of placental passage, compared with haloperidol, risperidone, and quetiapine [3, 9].

The overall incidence of esophageal atresia/TEF ranges from one in every 2500 to 4500 live births [10]. However, a careful literature search revealed a paucity of data on the incidence of TEF in children born to women with psychiatric disease and the problem of confounding by indication cannot be ruled out. It has been proposed that antipsychotics interfere with the action of calmodulin, which has an important role in organogenesis [3]. Esophageal atresia and abnormalities of pharyngeal glands have also been proposed as being related to neural crest cells [11]. The drugs (olanzapine in this case) associated with such anomalies may be hypothesized to cause neural crest cell damage during early fetal development as a causative factor. Although the neural crest cell damage-related esophageal abnormalities in many cases are also associated with cardiovascular anomalies, these were absent in the present case.

We tried to establish the causality between the adverse outcome (TEF) and use of olanzapine during pregnancy according to the WHO-UMC (World Health Organization–Uppsala Monitoring Centre) adverse drug reaction causality assessment scale and the Naranjo causality assessment scale. Causality is 'probable' (score +5) as per the Naranjo scale, whereas it is 'possible' according to the WHO-UMC scale. One of the important reasons for lower scores of causality is the non-applicability of many questions in these scales. The current case report of TEF associated with antenatal olanzapine exposure demonstrates the need for large clinical studies to generate more conclusive data concerning use of this drug during pregnancy.

Conclusion

On the basis of the present case and the literature, it is suggested that antenatal olanzapine exposure may be related to the development of TEF in newborns. However, the present case report can only be considered as preliminary evidence and further observational prospective studies of women with antenatal exposure to olanzapine should be conducted to explore the strength of association between TEF and olanzapine. Knowledge of the teratogenic potential of a drug is essential to prevent/reduce the morbidity and mortality associated with a congenital anomaly (TEF in this case). Such post-marketing reports are effective tools to disclose the adverse effects of drugs, which are difficult to detect in clinical trials and may factually change the safety status of a drug.

Compliance with Ethical Standards

Conflict of interest Dr. Vikas Maharshi, Dr. Indranil Banerjee, Dr. Pravesh Nagar, and Dr. H. S. Rehan declare that they have no conflicts of interest.

Funding No financial support was received for the preparation of this manuscript.

Informed consent Written informed consent was obtained from the infant's father for publication of this case report.

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