

Case Report

Teratogenicity with Olanzapine

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ABSTRACT

Olanzapine, a 2nd generation antipsychotic, is in use in the clinical practice for nearly a decade and a half now. It is classified as a category C drug with very few reports of its toxic effects on the fetus. In general, the risk benefit analysis warrants its use in pregnancy. We report a case of microcephaly and anophthalmos associated with the use of olanzapine in pregnancy. Although a causal role cannot be unequivocally proven, it calls for larger studies to explore this issue.

Key words: Olanzapine, pregnancy, teratogenicity

INTRODUCTION


Prescribing psychotropic medication in pregnancy is a complex issue involving assessment of the risk of leaving an untreated psychiatric illness with its attendant complications versus the risk of adverse effects on the fetus. Most of the 2nd generation antipsychotics have been in use since the 1990s. Olanzapine, one of the 2nd generation antipsychotics, is a category C drug and there is no unequivocal evidence of harm to the fetus. Here, we report a case of microcephaly with anophthalmos in a patient who was treated with olanzapine for unspecified non-organic psychosis. To the best of our knowledge, such a complication has not been reported earlier.

CASE REPORT

Ms. A, a 25-year-old married lady presented in the hospital's Walk-in clinic with the symptoms of

suspiciousness and hearing voices. The symptoms had been present for about 5 years. She was very irritable and was unable to sleep. She also suffered few episodes suggestive of dissociative spells in which she would call herself "Goddess Kali." There was also occasional history of disinhibition in the form of taking of her clothes in front of her family members.

Detailed evaluation revealed delusions of persecution and second person auditory hallucination. There were no features suggestive of a mood disturbance or organicity. She was diagnosed as having unspecified non-organic psychosis on International Classification of Diseases, tenth edition.^[1] Olanzapine was started and gradually increased to 15 mg/day. The psychotic symptoms were controlled over a period of 2 months with olanzapine. After 1 month of treatment with olanzapine, the patient became pregnant (this was her first pregnancy) and sought consultation for safety of medications during the 2nd month of gestation. Considering the severity of the symptoms in the past and duration of illness, on mutual discussions, it was decided to continue olanzapine. She was referred to the obstetrics service of the hospital to keep a close watch for any untoward event. She followed-up there regularly as advised by the obstetrician. A discussion with the consulting obstetrician and review of records revealed no major untoward event during pregnancy. Careful history revealed absence of fever, rashes or other skin lesions. Antibody titers for herpes

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simplex, varicella, cytomegalovirus, toxoplasma and rubella were conducted and found to be normal. Fasting and postprandial blood glucose levels performed at the time of first consultation and repeated in the 2nd and 3rd trimesters were found to be in the normal range. On follow-up, the fetus was detected to have microcephaly on ultrasonography. No other major anomalies were detectable.

Ms. A delivered a female baby weighing 3.4 kg with microcephaly and congenital anophthalmos (bilateral) at full term. The head circumference was 30.5 cm at birth, which falls below the third percentile.^[2] The baby was seen at department of pediatrics, genetics and ophthalmology. B scan ultrasound revealed absence of ocular tissue. No additional causative factors could be elicited despite the above mentioned specialist referrals. However, detailed imaging and genetic investigations could not be done due to cost limitations. She was not on any other medication known to cause teratogenicity during the period. There was no history of any substance use or family history of congenital anomalies. Patient had adequate nutrition and rest during her pregnancy. There was no history of trauma or exposure to radiation either. The history was corroborated by the patient's mother as well as husband. Although this adverse event scored only three on the the Naranjo *et al.* adverse drug reaction probability scale,^[3] the lower scores were due to non-applicability of some questions to this situation. For instance, the issue of improvement on discontinuation of drug or administration of antagonist obviously does not apply to this case. Similarly, re-administration and replication of the adverse effect also cannot be done in this case for ethical reasons.

DISCUSSION

Olanzapine is considered pregnancy category C drug. One study involving pregnancy outcomes in 151 patients on different atypical antipsychotics (60 were on olanzapine) did not find any statistically significant differences in various pregnancy outcomes between the exposed and comparison groups, except the rate of low birth weight, which was 5 times higher in the exposed babies and a higher rate of therapeutic abortions. One case of encephalocele with cleft lip and aqueductal stenosis was reported in a patient on olanzapine.^[4] Arora and Praharaj^[5] reported a case of meningocele and ankyloblepharon in the child of a patient on olanzapine. Reis and Källén^[6] reported craniosynostosis and ureteral reflux in one, an upper limb reduction defect in a second and a ventricular septal defect and upper gastrointestinal tract malformation in the third infant whose mothers were exposed to olanzapine during pregnancy. Our patient, however, had a normal birth weight. Another study^[7] on 37 prospective and 11

retrospective pregnancies with exposure to olanzapine did not find any increase in the rate of spontaneous abortion and malformation compared with the general population. Of the prospective pregnancies, 84% had normal delivery and postnatal course. The remaining 16% suffered problems such as prematurity, postmaturity and low or high birth weight. At least two of the mothers were noted to have gestational diabetes. Newport *et al.*^[8] measured placental passage of medication from mother to fetus by measuring levels in umbilical cord serum and documented neonatal outcomes in 54 women followed through pregnancy. They concluded that olanzapine has the highest rate of placental passage, compared with haloperidol, risperidone and quetiapine. Neonates exposed to olanzapine showed trends toward lower birth weights and more neonatal intensive care unit admissions than neonates exposed to other antipsychotic medication. Some authors have reported varying results among pregnant women treated with olanzapine^[9] while others have not reported any harm to either mother or fetus.^[10] To the best of our knowledge, this is the first report of microcephaly along with anophthalmos following intranatal exposure to olanzapine. We made attempts to rule out alternative causes and several of the causes that are responsible for baseline rates of congenital anomalies were ruled out. Our patient was continuously exposed to olanzapine even before conception until birth of the infant. Authors^[5] have earlier hypothesized that this may increase the risk as the early developmental period is crucial for organogenesis. They also highlighted that many negative studies had olanzapine exposure after the 8th week of pregnancy. Thus, we hypothesize that early and sustained exposure to olanzapine may impair embryonic development in ways that may not occur with shorter or later periods of exposure. Calmodulin antagonism during early development has been proposed as a possible mechanism for antipsychotics in general; although, its specificity to olanzapine is unclear.^[11] However, our report by virtue of being a case report has its obvious limitations of not being able to conclusively prove a causal link. Furthermore, for reasons mentioned earlier, some of the investigations could not be performed. The largest of the studies in pregnant women so far had only 60 patients on olanzapine. Whether these studies had sufficient power to detect risk of congenital anomalies is debatable. Careful studies are therefore needed to clarify the situation. The purpose of this case report is more to stimulate further research in this direction.

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