ZIPRASIDONE AS A POSSIBLE CAUSE OF CLEFT PALATE IN A NEWBORN

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SUMMARY
Use of antipsychotic medication during the entire course of pregnancy in patients suffering from schizophrenia is frequently necessary as discontinuation of therapy can lead to relapse of the illness which can be far more severe for the mother, but also for the fetus. That is the case why third generation antipsychotics, so called atypical antipsychotics, are also being used during the pregnancy, but their effects are not fully researched. Use of ziprasidone as a third generation antipsychotic, and its effects during the pregnancy in patients suffering from various mental illnesses is very rarely described in scientific literature. There is even fewer information regarding eventual adverse events of ziprasidone in newborn babies of mothers that have been treated with ziprasidone during the entire course of pregnancy.

This paper will be based around a case report of a female patient suffering from schizophrenia who has been treated with ziprasidone during the entire course of her pregnancy and whose newborn baby was diagnosed with a cleft palate (palatoschisis) at the time of birth.

Key words: ziprasidone – newborn - cleft palate

INTRODUCTION
Use of antipsychotic medication during the entire course of pregnancy in patients suffering from schizophrenia is frequently necessary as discontinuation of therapy can lead to relapse of the illness which can be far more severe for the mother, but also for the fetus. Choice of antipsychotic medication in this setting is a very complex process, especially when a newer medication is taken into consideration. Treatment with antipsychotic medication in pregnant women is a mutual problem of a psychiatrist, obstetrician, general practitioner and of the patient. According to the available literature, first generation antipsychotics, so called typical antipsychotics, are considered to be relatively safe when used by pregnant women. (Briggs 2002, Gentile 2008).

Lot less is known about newer antipsychotics and because of that fact it is not easy to predict their safety when used by pregnant women. Situation is quite similar when it comes to risks of prenatal exposure to atypical antipsychotics as there is not much data regarding it, especially when compared to typical antipsychotics, about which there is now sufficient data in medical literature. However, there is some data regarding newer generation antipsychotics and their effects in pregnant and lactating women. This data was published mainly for quetiapine and risperidone (Ratanyake & Libretto 2002, Tenyi et al. 2007, Coppola et al. 2007), but also for olanzapine and aripiprazole. (Mc Kenna et al. 2005, Yeshayahu 2007, Mendhekar et al. 2006a, Mendherkar et al. 2006b, Vermuri & Rasgon 2007).

Until 2009 there were no reports regarding effects of ziprasidone in pregnant and lactating women. However, during 2009 three case reports were published, but unlike other newer antipsychotics, there are still no complex studies or follow-ups on a bigger sample of patients. (Vaux & Jones 2005, Schlotterbeck et al. 2009, Fargo 2009).

According to epidemiologic data (mainly for USA), one of every 500 to 550 newborn babies is born with some form of a cleft lip or cleft palate. Genetic and external factors are the main causes. Cleft palate or cleft lip are hereditary in about 10% of cases. White women have a more frequent occurrence of isolated form of cleft palate. External factors associated with this defect are: smoking, alcohol, drugs, bad nutrition, lack of vitamins, various medications (antiepileptic medication, corticosteroids, etc.), while caffeine is still not a proven risk factor. (Panter et al. 1990, Knežević 2008, Holmes et al. 2008, Nguyen et al. 2009, Collier et al. 2009).

We found only one research paper that deals with the issue of antipsychotic medication and cleft palate defect. That research paper directly deals with chlorpromazine and cleft palate (Gentile 2008), while there is no available data regarding other antipsychotics, especially newer or atypical ones.

CASE REPORT
Patient is 33 years old, married, living with her husband at her parents, economical technician, but currently unemployed. Has a younger brother. Her uncle suffers from schizophrenia.
First problems started at the age of 15, while she was in high school. She was diagnosed with behavioral disturbances, and later with a personality disorder. She was hospitalized at the psychiatric clinic of KBC Rijeka on four occasions. First time was in 1998, while she was 22 years old because of various fears, projections, interpretations and depressive ideas. She was discharged with chlorpromazine and alprazolam in therapy. Second and third hospitalization were during 1999, while she was 23 years old, on both occasions because of attempted suicide, as she took big number of pills in order to commit suicide. Clinical picture was dominated by derealization and depersonalization phenomena, she was paranoid about her environment, along with marked erotization. Discharged with levopromazine and diazepam in therapy. Fourth and final hospitalization was during 2006, when she was admitted as manifestly psychotic (describes systematical paranoid ideas, religious delusions with a number of bizarre ideas, dominated by auditory hallucinations) which lead to the diagnosis of paranoid schizophrenia (F 20.0), according to DSM-IV and ICD-10. She was discharged with olanzapine and promazine in therapy.

During over a year of therapy with olanzapine she gained over 12 kilograms of body weight, which led to discontinuation of olanzapine and introduction of ziprasidone to therapy. Ziprasidone was titrated up to 120 milligrams daily, divided into two doses, along with fluvoxamine and diazepam. After eight months of ziprasidone therapy she lost 6 kilograms of body weight. She is satisfied with her psychical condition, started to date, met her future husband and got married.

In January of 2009, at the control examination, she mentions that she is pregnant and that she had her last menstruation in October of 2008, gynecological exam normal. Dose of ziprasidone was 120 milligrams until the first month of 2009, then 80 milligrams until the third month of 2009 and then lowered to 40 milligrams till childbirth.

Pregnancy was discussed in great detail with the patient, then her husband and mother. They were informed about the potential risks of pregnancy, possible deterioration of her psychical state and exacerbation of schizophrenia during pregnancy, childbirth and puerperium, along with genetic heritage of the illness.

With equal responsibility and burden we agreed to proceed with the pregnancy and its risks. Patient signed informed consent about the risks of pregnancy and possible risks connected with ziprasidone therapy during the pregnancy and that she voluntary agrees to continue the treatment during her pregnancy.

Patient was regularly attending gynecological control exams during her pregnancy, which was normal, without complications of any kind. She took ziprasidone every day during her pregnancy, with diazepam occasionally.

Patient gave birth on term to a baby girl, 50 centimeters long and 3070 grams heavy. However, cleft palate was diagnosed by a neonatologist and the baby was further examined by an otorhinolaryngologist and a pediatric dentist. Due to mother’s ongoing psychopharmaceutical therapy, ablationation was necessary, as well as bottle feeding of the child. No other member of the family was ever born with cleft palate or any other malformation. During her pregnancy the patient did not smoke, drink coffee, alcohol, nor took drugs or suffered from any form of physical illness. Ultrasound examinations were normal as well as karyotype analysis performed before the pregnancy.

DISCUSSION

When treating pregnant women suffering from schizophrenia we always have to consider which antipsychotic medication can be used during pregnancy. We have to use those medications that are least harmful for the mother and for the fetus, but that is not always possible in routine clinical practice. This case report illustrates this issue, as our patient came to see the psychiatrist when already three months pregnant. She was taking ziprasidone during the first trimester without consulting her psychiatrist first and it is well known that embryogenesis is at its peak right during the first trimester. During pregnancy it is recommended to use minimal and efficacious doses of antipsychotic medication. This was the case with our patient. Patient was informed about the possible risks of ziprasidone treatment during pregnancy but decided to continue with the treatment, and one of the results was cleft palate in her baby girl.

It is not entirely certain and proven beyond any doubt that cleft palate is a direct consequence of ziprasidone treatment during the entire pregnancy. Still, it is already known that some medication can cause cleft lip or palate in newborns. (Panter et al. 1990, Knežević 2008, Holmes et al. 2008, Nguyen et al. 2009, Collier et al. 2009). That is not the case with ziprasidone, or even for any atypical antipsychotic, but further research is needed. However, first generation antipsychotic medications are associated with this malformation, namely chlorpromazine (Gentile 2008).

All other possible causes of cleft palate were ruled out in this case (Knežević 2008), so there is
reasonable doubt that ziprasidone led to development of cleft palate. However, in this case we can only speculate about the complete mechanism for development of this malformation and keep in mind that so far there have been no reports of ziprasidone causing cleft lip or palate. Furthermore, there is one new report of combined treatment with 40 milligrams of ziprasidone and 60 milligrams of citalopram in a patient treated for psychotic depression during her entire pregnancy. That patient gave birth on term to a healthy baby girl (Fargo 2009). Vaux and Jones reported one case of particular interest, a case of embryopathy caused by ziprasidone and considered that ventricular arrhythmia and subsequent brain hypoxia lead to following malformations in the newborn: mild midface hypoplasia, hypoplastic nails, hypoplastic distal fingertips, bilateral 5th fingers clinodactyly, short fourth toes and symmetric growth deficiency (Vaux & Jones 2005).

CONCLUSION

Due to the fact that until now there have been only three case reports of ziprasidone use during pregnancy and lactation we believe that this report is very important for further research of effects of ziprasidone during pregnancy, as well as research of possible consequences to mother and fetus. That is especially interesting as cleft palate described in this case report is possibly caused by ziprasidone use during pregnancy, as all other possible causes were ruled out.

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