Case Report

DOI: 10.5455/bcp.20140714030311

Four Bipolar Cases Treated with Quetiapine During Pregnancy

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ÖZET:

Gebelik döneminde ketiapin ile tedavi edilen dört bipolar olgu

Bipolar bozukluğu tipik olarak adölesan ve erken erişkinlik döneminde yani reprodüktif dönemde başlayan bir hastalıktır. Bu nedenle üreme çağındaki kadın hastaların tedavisi, kullanılan psikotrop ilaçların birçoğunun teratojen olması nedeniyle önemlidir. Gebelikte klasik antipsikotik kullanımının konjenital malformasyon ve ölüm riskini artırmadığı ve doğum kilosunu etkilemediği bildirilmiştir. Bütün ilaçlar plasenta yoluyla bebeğe geçmekle birlikte, antipsikotikler içinde en az plesental geçiş gösteren ilaç ketiapindir. Deney hayvanlarında yapılan çalışmalarda teratojenik olmadığı yönünde sonuçlar elde edilmiştir. İnsandaki çalışmalar embriyonik/fetal risk değerlendirmesi açısından kısıtlı olmasına rağmen son dönemdeki çalışmalar, gebelik döneminde ketiapine maruz kalan bebeklerde doğum defekti görülme riskinin artmadığı ve diğer antipsikotik ilaçlarla karşılaştırıldığında gebelikte güvenilir olabileceğini göstermektedir. Bu yazıyla bipolar bozukluğu manik veya depresif dönemde ketiapin tedavisi alan dört gebe olguda teratojenite ve perinatal komplikasyon riski açısından herhangi olumsuz bir veriye rastlanmadığı ve gebelik döneminde ketiapin kullanımının güvenilir olabileceğini bildirilmektedir.

Anahtar sözcükler: bipolar bozukluk, gebelik, ketiapin

Klinik Psikofarmakoloji Bulteni 2014;24(4):391-5

ABSTRACT:

Four bipolar cases treated with quetiapine during pregnancy

Bipolar disorder is a disease that typically begins in adolescence and early adulthood, namely during the reproductive period. The treatment of female cases during their reproductive years is very important because of the teratogenic effects of psychotropic drugs. It has been stated that the use of classical antipsychotics during pregnancy was not associated with congenital malformations or low birth weight. While all drugs pass through the placenta, quetiapine shows the lowest degree of placenta transit of all the antipsychotics. Studies with animals have not showed any teratogenic effect. Even though studies with humans are very limited with respect to embryonic/fetal risk assessment, recent studies have shown no increased risk of birth defects in quetiapine exposed babies and when compared to other treatment alternatives, quetiapine can be used safely in pregnancy. In this article, we report that no negative data has been found in terms of teratogenicity or perinatal complications in the cases of four pregnant women being treated with quetiapine in the manic and depressive episodes of bipolar disorder and it is also reported that quetiapine can reliably be used during pregnancy.

Keywords: bipolar disorder, pregnancy, quetiapine

Bulletin of Clinical Psychopharmacology 2014;24(4):391-5

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Date of submission:
August 01, 2013

Date of acceptance:
July 14, 2014

Declaration of interest:
H.E.D., K.A., M.D., E.K.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Bipolar disorder (BD) is a disease that typically begins in adolescence and early adulthood, namely the reproductive period[1,2]. Although there are studies[3] indicating a reduction in the recurrence risk of BD during pregnancy, there are other studies that do not support this opinion, indicating an increase in recurrence risk and worsening of the disease course in this period in

which hormonal and lifestyle changes and restriction in the usage of psychotropic drugs occur[4,5]. BD's recurrance rate during pregnancy in three retrospective studies has been reported to be 45-52%[4,6,7]. In female patients with BD during pregnancy many psychotropic drugs should be used with caution due to their teratogenicity.

The pregnancy and the treatment of these patients during pregnancy must be planned in advance[8]. In addition, what is important in the first instance is the treatment of cases where there is an unplanned pregnancy. In these cases, the use of almost all psychotropic drugs must be stopped in the first trimester, during which organogenesis occurs because of the teratogenic effects on the fetus. A sudden stop of the drug use may cause aggravation of symptoms. Therefore, drugs may have to be resumed[9,10]. The affective and psychotic symptoms that may appear during pregnancy may pose a risk to the baby and the mother and result in morbidity[2,9].

It has been reported that in pregnancy the use of classical antipsychotic drugs does not increase congenital malformations and the risk of death before and after pregnancy, nor do they affect the birth weight[8]. It has been reported that the risk of the appearance of birth defect in the babies who are exposed to the atypical antipsychotics (AAP) like olanzapine, clozapine, risperidone and quetiapine does not increase but the data on the risk of teratogenity and perinatal complications associated with the use of AAP's are insufficient[1,8,11,12]. In a study carried out by Newport et al. in which the placental transition of antipsychotics was evaluated, the of drug concentration in umbilical cord plasma was found to be 72.1% of maternal plasma drug concentration for olanzapine and this maximum value was followed by haloperidol and risperidone respectively. It was observed that quetiapine had the lowest value of placenta transition with a rate of 23.8%[13]. Although studies conducted on humans are restricted in terms of the evaluation of the embrionic fetal risk, recent data shows that the risk of birth defects in babies who were exposed to quetiapine during gestation does not increase and quetiapine may be relied on during pregnancy compared to other antipsychotic drugs[13-17]. In studies conducted in experimental animals, there is some evidence of harm, such as an increase in delayed ossification in the skeletal system, a decrease in fetal weight and fetal and pup mortality[18]. In this article four pregnant patients who were monitored for a diagnosis of BD and were subjected to quetiapine treatment are presented and the results of treatment are discussed.

CASE 1

A.B is 21 year old and this was her first pregnancy. She had been diagnosed with BD for 6 years. The dose of lithium which was used by the patient, who was protected by an oral contraceptive drug and stated that she wanted to have a child, was gradually reduced and discontinued over two months and and drug free observation of the patient began. The patient became pregnant two months after the discontinuation of the drug. The results of a double scanning test in the 12th week and a triple scanning test in the 16th week were within the normal limits. Quetiapine at a dose of 200 mg/day was given to the patient, who entered into a depressive period, after explaining the potential risks and benefits to her. The Hamilton Depression Scale (HAM-D) score of the patient, which was 17 at the beginning of the treatment, dropped down to 11.5 after one week and to 2 after the subsequent two weeks. It was decided to return to the phase of drug free observation of the patient as a result of lack of any observable depressive symptom in the 35th week of the pregnancy of the patient, who had been treated with 200-600 mg/day of quetiapine for 19 weeks and becauseof the approaching day of birth. The patient, who was being regularly monitored gave birth to a healthy newborn.

CASE 2

C.D was 28 years old and this was her third pregnancy. The patient had been monitored for a

diagnosis of BD for 14 years. When it was found during routine monitoring that she was unintentionally pregnant (four months) she was supposed to be using lithium 120 mg/day, valproate 1000 mg/day and quetiapine 50 mg/day, but the patient had discontinued the use of the drugs after she had learned she was pregnant. She was hospitalized as a result of a manic episode which appeared in the 14th week of pregnancy. Haloperidol 10 mg/day was given to the patient together with 5 sessions of electroconvulsive therapy with anesthesia and myorelaxants. Subsequently the haleperidol was replaced with quetiapine after the development of extrapyramidal symptoms. The patient was taking quetiapine 600 mg/day upon leaving the hospital and had a HAM-D score of 3 and Young Mania Scale (YMRS) score of 0. The triple scanning test which was done in the 16th week a risk for trisomy 21 but no pathological findings were observed in the amniocentesis. Omega 3 (DHA-EPA) 3000 mg/day was added to the treatment in the 22nd week. After 18 weeks of treatment, quetiapine intake was discontinued at the 36th week of pregnancy. Quetiapine 200 mg/day was started as a result of the development of a depressive period in the 36th week of the pregnancy and following her remission within approximately two weeks quetiapine was discontinued in the 40th week of pregnancy and the patient gave birth to a healthy newborn.

CASE 3

The 36 year old patient E.F. had been diagnosed with BD 15 years ago. The patient, who was not making use of any birth control methods, was taking 600 mg/day of valproate, 50 mg/day of lamotrigine and 300 mg/day of quetiapine when she found out that she was 11 weeks pregnant. Intake of valproate and lamotrigine was halted by gradually decreasing the dose. At the 13 weeks, the double test was within normal limits. At 19 weeks, the quetiapine dosage was increased to 400 mg/day due to depressive symptoms (HAM-D score was 9). The ultrasonography (USG) examination at the 22nd week was normal. At the 30 weeks, haloperidol drops of 1 mg/day dosage were added to the treatment due irritability and the development of ideas that were evaluated as excessive. At 35 weeks, haloperidol was increased to 2.5 mg/day and quetiapine was decreased to 25 mg/day due to the development of psychotic symptoms. At 37 weeks, due to a decline in the symptoms, haloperidol dosage was decreased to 1 mg/day and continued until the last week of the pregnancy. The patient, who took 300-400 mg/day quetiapine for 36 weeks, gave birth to a healthy newborn at 39th weeks.

CASE 4

This 33 year old patient, G.H., who had 2 children had been diagnosed with BD 2 years previously. The patient was taking 1000 mg/day of valproate when she found out she was 4 weeks into an unintended pregnancy. Upon finding out about the pregnancy, the drug intake was gradually decreased until completely halted and the patient started taking omega-3 capsules 3000 mg/day. The USG, triple and quad tests of the patient at week 16 were evaluated to be normal. The patient, who was hospitalized with psychotic depression on week 28 of pregnancy, was started on 5 mg/day of haloperidol and 100 mg/day of quetiapine. The patient entered remission in approximately three weeks; the quetiapine dosage was reduced to 25 mg/day in the 36th week of pregnancy and the drug intake was halted at the last week of pregnancy. The patient gave birth to a healthy newborn at the 40th week.

DISCUSSION

In this study, no negative outcomes have been noted in terms of teratogenicity, perinatal and postnatal complications risks in four pregnant women taking quetiapine for the treatment of BD manic or depressive episodes.

Upon reviewing the literature, there is less information regarding risks relevant to exposure to AAPs in the prenatal period compared to classic

antipsychotics. In a study that researched whether AAPs caused an increase in malformation risk, 151 pregnancy cases who were exposed to clozapine, olanzapine, quetiapine and risperidone during pregnancy were compared to a pregnancy control group; no differences were found in the rates of spontaneous abortion, therapeutic abortion, low birth weight, stillbirth and malformation and it was reported that AAPs did not pose any risk of major malformation[14].

In a systematic review by Gentile et al., various major malformations that did not conform to a specific pattern were observed in 8 of 151 babies exposed to quetiapine in the prenatal period[19]. In a study investigating the effects of AAP exposure on the fetus during pregnancy, weight gain of pregnant women and other complications, it was observed that the 32 of 59 pregnant women were taking AAPs and had given birth. Twenty of them (8 olanzapine, 3 quetiapine, 9 risperidone cases) had babies without any malformation; spontaneus abortion occurred in 3 of the remaining women (1 olanzapine, 2 risperidone cases); 7 of the remaining women had therapeutic abortions (2 olanzapine, 2 quetiapine, 3 risperidone cases) and 2 women had stillbirths (1 quetiapine, 1 olanzapine case)[12]. On the other hand, there are also case reports and series indicating no major malformation and unexpected event in infants exposed to quetiapine during pregnancy[13-17]. The majority of the case reports indicating that quetipine was not the cause of increased birth defect risks, are associated with schizophrenia[15,20,21]; only one case was BD[17] and quetiapine was initiated during a manic episode. All four of our cases were BD cases and quetiapine was started during a manic episode in one of these and during depressive episodes in the rest. When considered from this point of view, it is safe to say that that our study provides more extensive information on BD patients who use quetiapine during pregnancy.

Upon reviewing the quetiapine doses that were used, the schizophrenic cases reported by Tenyi et al.[15], Taylor et al.[20] and Grover and Madan[21] have respectively used quetiapine doses of 300 mg/day, 300 mg/day and 250 mg/day. In the case reported by Çabuk et al.[17] which involved BD, the pregnant patient took 1200 mg/day of quetiapine. No perinatal and postnatal complications, psychomotor growth retardation, neuropsychiatric anomaly or teratogenic risk increase was noted in the mother or the baby in any of these cases. Our pregnancy cases, which involved BD patients only, have taken 50-600 mg/day doses of quetiapine and even though relatively higher dosages were utilized, no prenatal, perinatal and postnatal complications were seen.

The postnatal monitoring period for the cases reported in the literature was 1 month at the shortest and 2 years at the longest. The monitoring period in our cases was 1.5 years at the shortest and 2.5 years at the longest. This information indicates at the least that no complications relevant to quetiapine were seen in 2.5 years of monitoring in babies who were exposed to quetiapine during the intrauterine period.

The pregnancy period and the total time of exposure to the drug are among the most critical information elements in respect to exposure to the drug during pregnancy. Regarding patients diagnosed with BD, due to the fact that some of the pregnancies were unplanned and the patients were taking drugs when they found out about their pregnancy, the characteristics of the psychotropic drugs that were used are important. Our cases involve pregnant patients, two of whom started exposure in the 1st trimester, and the other two in the 3rd trimester and these patients were exposed to quetiapine for an average of 11-36 weeks; compared to the schizophrenic pregnant patients using quetiapine who were reported in the literature, these drug exposure times are shorter. The BD case reported by Çabuk et al. involved a patient who was exposed to quetiapine for 19 weeks, similar to our cases. Taking into consideration that quetiapine was used in all three trimesters in our cases, it is safe for us to say at least that the time during which quetiapine used and the trimester in which drug exposure occurred did not cause any complications for the four pregnancy cases that we have reported.

In conclusion, the information obtained during our study and from the literature shows that the use of quetiapine during pregnancy is safe and that no complications developed in the mother or the baby during the monitored period. However, the published data about anatomical malformations and long-term behavioral abnormalities are insufficient in children exposed to AAP drugs by in-utero. Our knowledge about the fetal safety of AAP drugs used in pregnancy is mostly retrospective and cases reports are based upon the results of some open studies. Large volume prospective cohort studies are required in order to obtain relevant and reliable information.

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