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Effects of Quetiapine on Neural Tube Development in the Early Stage of Chicken Embryos

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ABSTRACT

AIM: To investigate the effects of quetiapine exposure on neural tube development in early stage chicken embryos.

MATERIAL and METHODS: Eighty-four fertilised specific pathogen-free chicken eggs were divided into four equal groups (groups 1–4). Three experimental groups (groups 2, 3 and 4) and a single control group (group 1) were used. Each egg in group 2 (n=21) was injected with 20 µL of saline after 30 hours of incubation. Eggs in groups 3 and 4 were injected with 0.02 ml of a solution containing 400 and 800 µg of quetiapine dose, respectively. Incubation was continued until the end of 72 hours. All embryos were then removed from the eggs and histopathologically examined.

RESULTS: Normal development and the closed neural tubes were shown in 18, 16, 13 and 9 embryos in groups 1 2, 3 and 9, respectively, of the 84 embryos incubated. Open neural tubes were found in one, three and five embryos in groups 2, 3 and 5, respectively. Also, developmental anomalies were found in three, four, five and seven embryos in groups 1, 2, 3 and 4, respectively. Moreover, no significant relationship between NTD and quetiapine exposure had been found.

CONCLUSION: Quetiapine has no significant effect on the occurrence of neural tube defects in the chicken embryo model.

KEYWORDS: Quetiapine, Second-generation antipsychotics, Neural tube defect, Spina bifida, Chicken embryo

ABBREVIATIONS: NTD: Neural tube defects, **SGA:** Second-generation antipsychotics, **SPSS:** Statistical package for the social sciences

INTRODUCTION

Quetiapine is the most used second-generation antipsychotic (SGA) in the world. The reports from the last 10 to 12 years are indicating an enormous increase (up to 200%) of quetiapine use in pregnancy (12,22,27,28). The significant quetiapine indications are bipolar disorders and schizophrenia. The current spectrum is much broader as it is used as an auxiliary drug in conditions like insomnia and anxiety (27). As a result, many studies are investigating the potential effects of quetiapine on the foetus (5,9,10,16). In addition, many recent studies are suggesting that quetiapine use in pregnancy does not improve the risks of various congenital malformations. Concerning clinical practice, the idea of 'It is safe to use quetiapine in pregnancy' is widely accepted. However, cases also exist indicating many conditions related to prenatal exposure of quetiapine (9,16,25). It is too early to assume the safeness of such a drug based

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on studies considering that the first atypical antipsychotic was introduced into practice in 1951 and quetiapine in 1997 (13,18). Hence, the research on the potential dangers of new and widely used drugs is of vital importance. Interestingly, some studies also suggest that quetiapine has neuroprotective effects (1,34). This study decided to evaluate the potential impact of quetiapine on neural tube closure, which has never been investigated before, considering these data and clinical approaches.

MATERIAL and METHODS

This study was conducted in cooperation with Professor Dr. Mazhar Osman of the Neurosurgical Unit Research Laboratory of Bakirkoy, Mental Health and Neurological Diseases Training and Research Hospital. Fertilised, specific, pathogen-free *Gallus* chicken eggs were obtained from the Poultry Research Institute, Ankara, Turkey.

Incubation and Injection

Eighty-four fertile, specific non-pathogenic, domestic fowl eggs (*Gallus gallus*; Atabey®, Poultry Research Institute, Ankara, Turkey) were used in the study. The eggs were incubated at 37.5°C at 75% humidity. The eggs were sterilised with 70% alcohol and the outer shell was taped at the eighth stage of the Hamburger and Hamilton classification. A window was opened on the eggshell. Using a sterile Hamburger® syringe, 20 µL of fluid was administrated sub-blastodermically (Figure 1). The holes were closed with a drape and the eggs were then placed back into the incubator. The eggs were reopened after 72 hours of incubation (Hamburger Hamilton stage 12). The viability of the embryos was assessed by the presence of a heartbeat. The embryos were transferred into a Petri dish by microsurgically dissecting along the allantoic stalk (Figure 2). All the embryos were examined under a microscope (Leica DM 4000, Germany). Results were analysed in terms of neural tube closure (Figure 2).

Study Groups

Eggs were assigned to one of four groups. Three eggs were sacrificed in the determination of stage. Three experimental groups (groups 2, 3 and 4) and a single control group (group

Figure 1: Illustration of subblastodermic injection, and eggs covered with drape in the incubator.

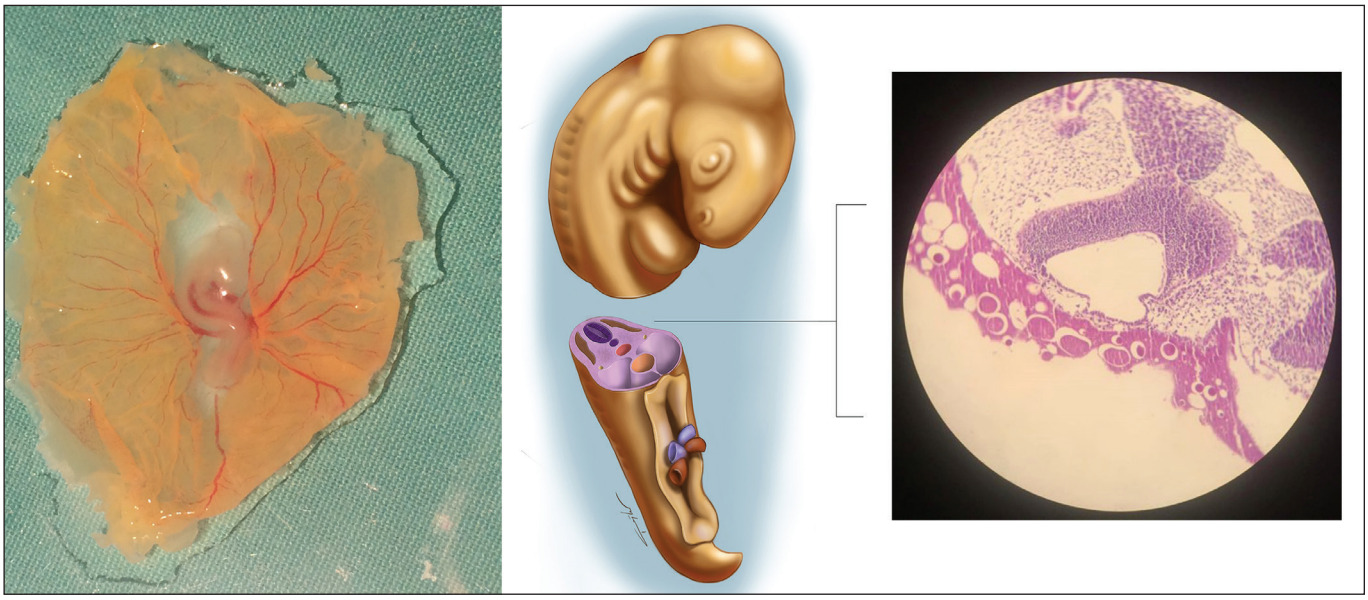

Figure 2: Re-opened embryo and light microscope image of opened neural tube.

1), each containing 21 eggs per embryo (Table I), were used in this study. Each egg in group 2 (n=21) was injected with 20 µL of 0.9% NaCl at the end of the 30-hour incubation. Eggs in group 3 were injected with 0.02 ml of a solution containing 400 µg of quetiapine (middle dose, 6 mg kg^{-1}). On the other hand, eggs in group 4 were injected with 0.02 ml of a solution containing 800 µg of quetiapine (high dose, 12 mg kg^{-1}).

Pathological Evaluation

Formalin-fixed, embryo tissue samples were embedded in paraffin. Briefly, the embryos were dehydrated using ethanol solutions. The embryos were incubated in xylene and then transferred into a paraffin embedding mixture after the dehydration. Tissue sections (5 µm thickness) were taken. Furthermore, the haematoxylin–eosin solution was applied to the tissue sections. Samples were evaluated under the microscope and assessed for the decomposition of somite pairs and neural tube continuity.

Statistical Analysis

Statistical evaluations were conducted using the Statistical Package for the Social Sciences (SPSS) V22.0 for Windows. The chi-square test was used to analyse group comparisons. A p value ≤0.05 was accepted as statistically significant.

RESULTS

Three (14%) and 18 (86%) embryos were undeveloped and intact, respectively, in group 1. Moreover, no embryo with NTD was noted in group 1. In group 2, 4 (19%), 1 (4.7%) and 16 (76.1%) embryos were undeveloped, developed NTD and intact, respectively. In group 3, 3 (14.2%), 5 (23.8%) and 13 (61.9%) embryos had NTD, undeveloped and intact (p=0.1455), respectively. In group 4, 5 (23.8%), 7 (33.3%) and 9 (42.8%) had NTD, undeveloped and intact, respectively (Table II). In addition, no significant relationship between NTD and quetiapine exposure had been found.

Table I: Distribution of Quetiapine Dosages in Different Groups

Group	Quetiapine Dosages
1	Control 1
2	Control 2 (injection of 20 µL of 0.9% NaCl)
3	Acceptable effective daily dose of quetiapine
4	Acceptable maximum daily dose of quetiapine

DISCUSSION

The worldwide incidence of NTDs ranges from 1 to 10 per 1,000 births (11,17,33). The average of this ratio in Turkey is about 3–5.8 per 1,000 births (29). Anti-epileptic drug use is one of the very well-known factors in NTDs aside from folic acid deficiency (7,11). Previous studies have repeatedly demonstrated the negative effects of maternal age and maternal diabetes exposure to various chemicals (food colours, additives etc.) on neural tube closure (3,24,26).

SGA is widely prescribed to women all over the world (2,30). Quetiapine is the most used SGA drug with a vast indication spectrum. Major depressive disorder, bipolar disorder schizophrenia, acute depressive episodes and manic episodes are the main indications (6). Moreover, quetiapine is commonly prescribed for anxiety and sleeping disorder and it is also used with mood stabilisers such as benzodiazepines (8,23).

No malformation pattern has been shown to link foetal exposure to SGA according to studies. Recent data are showing no improved congenital malformation risk (4,21). On the other hand, many case reports and previous studies, suggesting relationships with low birth weight, cardiac malformations, gestational diabetes etc. also exist (4,9,16,25). Still, quetiapine is a 'Pregnancy Category C' drug which means 'there are no adequate and well-controlled studies of quetiapine use in pregnancy'.

A daily dose of quetiapine changes between 400 and 800 mg per day in many indications. The main principle is not to harm the foetus while calculating the effective dose in pregnancy. Drug bioavailability also differs in pregnancy and the blood–placenta barrier is also an important factor in foetal exposure (21,31). The relatively low placental passage rate of quetiapine, among other antipsychotics, is suggested as another key point on its safety profile (20,21). Quetiapine use in pregnancy commonly continues under these terms (15,32).

The dosages of 400 and 800 mg kg^{-1} quetiapine in 20 µL saline were used in this study. As a result, no significant relationship between NTD and quetiapine use was found, but the correlation in numbers creates suspicion about a dose-dependent effect. Even though the idea of 'quetiapine causes NTD' is not being suggested, further studies, both clinical and embryological, are required. A higher dose could have been tested in this study with regard to the physiological changes in pregnancy (increased intravascular volume, cardiac output, glomerular filtration rate etc.) (31).

Table II: Distribution of Embryo Numbers in Terms of the Development of the Neural Tube

	Intact	Neural tube defect	Undeveloped	p1 value	p2 value
Group 1	18	–	3	1	0.23
Group 2	16	1	4	0.49	0.70
Group 3	13	3	5	0.34	0.51
Group 4	9	5	7	0.067	0.058

p1 value terms of NTD occurrence, p2 terms of any developmental defect (NTD + undeveloped) occurrence.

From a different perspective, but not applicable to this study, one of the well-known side effects of the atypical antipsychotics is weight gain and it is known that maternal obesity is a risk factor for NTD (14,19). Even indirectly, one can suggest that 'Atypic antipsychotics might cause NTD'. Thus, the absence of any direct effects on the embryo does not mean the drug is safe in terms of congenital malformations. This should always be kept in mind.

CONCLUSION

This study demonstrated no significant relationship between foetal quetiapine exposure and NTD occurrence in the chicken model of embryo development. Quetiapine is a widely used antipsychotic. In many circumstances, the treatments continue in pregnancy as well and, with reason, many studies exist about the foetal effects of quetiapine. Recent studies are indicating a safer profile for use in pregnancy. Nevertheless, many studies are suggesting that foetal exposure to quetiapine is related to many anomalies. It is not easy to interpret the data in these studies because many animal embryo models are insufficient to simulate a pregnancy environment. Thus, further phase-4 evaluations and experimental studies are needed.

DISCLOSURE

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REFERENCES

1. Aytar MH, Civi S, Kaymaz M, Ergun E, Kaymaz FF, Pasaoglu A: The effect of quetiapine on treatment of experimental acute spinal cord injury. Turk Neurosurg 28:105-110, 2018
2. Cabuk D, Sayin A, Derinoz O, Biri A: Quetiapine use for the treatment of manic episode during pregnancy. Arch Womens Ment Health 10:235-236, 2007
3. Canaz H, Alatas I, Canaz G, Gumussuyu G, Cacan MA, Saracoglu A, Ucar BY: Surgical treatment of patients with myelomeningocele-related spine deformities: Study of 26 cases. Child's nervous system: ChNS: Official Journal of the International Society for Pediatric Neurosurgery 34:1367-1374, 2018
4. Cohen LS, Goez-Mogollon L, Sosinsky AZ, Savella GM, Viguera AC, Chitayat D, Hernandez-Diaz S, Freeman MP: Risk of major malformations in infants following first-trimester exposure to quetiapine. Am J Psychiatry 175:1225-1231, 2018
5. Cohen LS, Viguera AC, McInerney KA, Freeman MP, Sosinsky AZ, Moustafa D, Marfurt SP, Kwiatkowski MA, Murphy SK, Farrell AM, Chitayat D, Hernandez-Diaz S: Reproductive safety of second-generation antipsychotics: Current data from the massachusetts general hospital national pregnancy registry for atypical antipsychotics. Am J Psychiatry 173:263-270, 2016
6. Damkier P, Videbech P: The safety of second-generation antipsychotics during pregnancy: A clinically focused review. CNS Drugs 32:351-366, 2018
7. Frey L, Hauser WA: Epidemiology of neural tube defects. Epilepsia 44 Suppl 3:4-13, 2003
8. Gjerden P, Bramness JG, Tvete IF, Slordal L: The antipsychotic agent quetiapine is increasingly not used as such: Dispensed prescriptions in Norway 2004-2015. Eur J Clin Pharmacol 73:1173-1179, 2017
9. Habermann F, Fritzsche J, Fuhlbruck F, Wacker E, Allignol A, Weber-Schoendorfer C, Meister R, Schaefer C: Atypical antipsychotic drugs and pregnancy outcome: A prospective, cohort study. J Clin Psychopharmacol 33:453-462, 2013
10. Huybrechts KF, Hernandez-Diaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, Cohen JM, Panchaud A, Cohen L, Bateman BT: Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry 73:938-946, 2016
11. Kaufman BA: Neural tube defects. Pediatric Clinics of North America 51:389-419, 2004
12. Kennedy D, Eamus M, Hill M, Oei JL: Review of calls to an Australian teratogen information service regarding psychotropic medications over a 12-year period. Aust N Z J Obstet Gynaecol 53:544-552, 2013
13. Komossa K, Depping AM, Gaudchau A, Kissling W, Leucht S: Second-generation antipsychotics for major depressive disorder and dysthymia. Cochrane Database Syst Rev 12:CD008121, 2010
14. Koren G, Cohn T, Chitayat D, Kapur B, Remington G, Reid DM, Zipursky RB: Use of atypical antipsychotics during pregnancy and the risk of neural tube defects in infants. Am J Psychiatry 159:136-137, 2002
15. Kulkarni J, Storch A, Baraniuk A, Gilbert H, Gavrilidis E, Worsley R: Antipsychotic use in pregnancy. Expert Opin Pharmacother 16:1335-1345, 2015
16. Kulkarni J, Worsley R, Gilbert H, Gavrilidis E, Van Rheenen TE, Wang W, McCauley K, Fitzgerald P: A prospective cohort study of antipsychotic medications in pregnancy: The first 147 pregnancies and 100 one year old babies. PLoS One 9:e94788, 2014
17. Lamers Y, MacFarlane AJ, O'Connor DL, Fontaine-Bisson B: Periconceptional intake of folic acid among low-risk women in Canada: Summary of a workshop aiming to align prenatal folic acid supplement composition with current expert guidelines. Am J Clin Nutr 108:1357-1368, 2018
18. Lopez-Munoz F, Shen WW, D'Ocon P, Romero A, Alamo C: A History of the Pharmacological Treatment of Bipolar Disorder. Int J Mol Sci 19(7):2143, 2018
19. McMahon DM, Liu J, Zhang H, Torres ME, Best RG: Maternal obesity, folate intake, and neural tube defects in offspring. Birth Defects Res A Clin Mol Teratol 97:115-122, 2013
20. Newport DJ, Calamaras MR, DeVane CL, Donovan J, Beach AJ, Winn S, Knight BT, Gibson BB, Viguera AC, Owens MJ, Nemeroff CB, Stowe ZN: Atypical antipsychotic administration during late pregnancy: Placental passage and obstetrical outcomes. Am J Psychiatry 164:1214-1220, 2007

21. Paulzen M, Goecke TW, Kuzin M, Augustin M, Grunder G, Schoretsanitis G: Pregnancy exposure to quetiapine - Therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood and obstetrical outcomes. Schizophr Res 195:252-257, 2018
22. Pinheiro EA, Wisner KL, Clark CT: Quetiapine dose adjustments in pregnant and postpartum women with bipolar disorder. J Clin Psychopharmacol 38:89-91, 2018
23. Pringsheim T, Gardner DM: Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: A descriptive study. CMAJ Open 2:E225-232, 2014
24. Ray JG, Wyatt PR, Vermeulen MJ, Meier C, Cole DE: Greater maternal weight and the ongoing risk of neural tube defects after folic acid flour fortification. Obstetrics and Gynecology 105:261-265, 2005
25. Reis M, Kallen B: Maternal use of antipsychotics in early pregnancy and delivery outcome. J Clin Psychopharmacol 28:279-288, 2008
26. Shaw GM, Quach T, Nelson V, Carmichael SL, Schaffer DM, Selvin S, Yang W: Neural tube defects associated with maternal periconceptional dietary intake of simple sugars and glycemic index. Am J Clin Nutr 78:972-978, 2003
27. Soeiro DESMG, Dias VV, Missio G, Balanza-Martinez V, Valiengo L, Carvalho AF, Moreno RA: Role of quetiapine beyond its clinical efficacy in bipolar disorder: From neuroprotection to the treatment of psychiatric disorders (Review). Exp Ther Med 9:643-652, 2015
28. Toh S, Li Q, Cheetham TC, Cooper WO, Davis RL, Dublin S, Hammad TA, Li DK, Pawloski PA, Pinheiro SP, Raebel MA, Scott PE, Smith DH, Bobo WV, Lawrence JM, Dashevsky I, Haffenreffer K, Avalos LA, Andrade SE: Prevalence and trends in the use of antipsychotic medications during pregnancy in the U.S., 2001-2007: A population-based study of 585,615 deliveries. Arch Womens Ment Health 16:149-157, 2013
29. Tuncbilek E, Boduroglu K, Alikasifoglu M: Neural tube defects in Turkey: Prevalence, distribution and risk factors. Turk J Pediatr 41:299-305, 1999
30. Uguz F: Prophylactic use of olanzapine and quetiapine from pregnancy to the postpartum period in women with bipolar disorder: A case series. J Matern Fetal Neonatal Med 30:2569-2571, 2017
31. Westin AA, Brekke M, Molden E, Skogvoll E, Castberg I, Spigset O: Treatment with antipsychotics in pregnancy: Changes in drug disposition. Clin Pharmacol Ther 103:477-484, 2018
32. Yaris F, Yaris E, Kadioglu M, Ulku C, Kesim M, Kalyoncu NI: Use of polypharmacotherapy in pregnancy: A prospective outcome in a case. Prog Neuropsychopharmacol Biol Psychiatry 28:603-605, 2004
33. Yerby MS: Clinical care of pregnant women with epilepsy: Neural tube defects and folic acid supplementation. Epilepsia 44 Suppl 3:33-40, 2003
34. Yilmaz MB, Tonge M, Emmez H, Kaymaz F, Kaymaz M: Neuroprotective effects of quetiapine on neuronal apoptosis following experimental transient focal cerebral ischemia in rats. J Korean Neurosurg Soc 54:1-7, 2013