Clinical and Experimental Health Sciences

Effect of Zuclopenthixol Acetate on Neural Tube Development in Early Chick Embryos

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ABSTRACT

Objective: Neural tube defects are one of the congenital malformations of the central nervous system. Although the factors that cause the development of neural tube defects and their mechanisms of action are still not clearly explained, genetic predisposition, drug use and some environmental factors are thought to play a role. In this study, it was aimed to investigate the effects of zuclopenthixol acetate (ZA) on neural tube development in a chick embryo model.

Methods: Fourty specific pathogen-free (SPF) eggs were used in the study. The eggs were incubated for 28 hours and divided into four groups of 10 eggs each. At the end of the 28th hours, saline was injected to the control group, while ZA was administered subblastodermically to the experimental groups in 3 different doses (0.7, 1.4, 2.1 mg/kg). At the end of the 48th hours, all the eggs were opened and the embryos were dissected from the embryonic membranes and evaluated morphologically and histopathologically.

Results: When the study groups were evaluated according to the neural tube positions (open or closed), it was found that the neural tube patency increased depending on the ZA dose, which was statistically significant ($p < 0.05$). In addition, morphological developments of embryos were evaluated. Compared to the control group, a statistically significant decrease was observed in the mean somite numbers in all ZA-treated groups, while a significant decrease was found in the mean cranio-caudal length only in the high-dose group.

Conclusion: In this study, it was observed that neural tube and morphological development were adversely affected in the groups treated with ZA in the chick embryo model. It was shown that neural tube closure defects in embryos increased in direct proportion with ZA doses. However, we believe that it will not be possible to fully adapt the results of this study, which was carried out in the chick embryo model, to humans and that more comprehensive research should be conducted.

Keywords: Chick embryo, congenital malformations, neural tube defect, zuclopenthixol acetate

1. INTRODUCTION

The neural tube (NT) is the embryonic structure that forms to the central nervous system, which is made up of the brain and spinal cord. This structure begins to develop around the 17th day of fertilization (early week 3) and completes its development by the middle of the 4th week of embryonic development. Closure of NT begins in the cervical region. It continues uninterruptedly in the form of a zipper, in the cranial and caudal directions. Closure occurs in the midline at 23 days, in the anterior neuropore on 24-25 days and in the posterior neuropore on 25-26 days (1) Neurulation is the bending, elevation, fusion, and remodeling of the neural plate to form NT (2). Disruption of this process can result in neural tube defects (NTD) (3).

Anomalies that occur when the NT does not close are expressed as NTD (4). NTD is one of the congenital anomalies of the central nervous system that occurs during embryogenesis and is caused by the incompleteness of the morphogenetic process of NT closure (5). NTD occurs after NT does not close in the normal period (3rd and 4th weeks of intrauterine life) and as a result, permanent problems often occur (6). Incomplete closure of the cranial end of the NT causes anencephaly or exencephaly, while incomplete closure of the caudal end causes spina bifida of varying degrees (7).

Factors such as race, ethnicity, geographical location, and socioeconomic status are thought to be effective in the development of NTD. However, the etiology of NTD has not been clarified. It has been reported that many factors may lead to the development of NTD, including maternal exposure to hyperthermia and various chemicals during pregnancy, drug use, malnutrition or being obese, low folic acid levels, the presence of diabetes in the mother, and genetic factors (8).

The ideal situation to be achieved during drug therapy while pregnancy is to treat the mother's disease while protecting the fetus from the possible toxic effects of drugs.

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Therefore, it is important to determine the safety of drugs during pregnancy. However, the study of drug safety during pregnancy is fraught with ethical challenges, as it is not possible to study human embryos (9). It is not possible to access and examine the human embryo while it is in the neurulation stage. Therefore, different experimental models, including other mammals, amphibians, and birds, are used to study NT development (5). These models have advantages and disadvantages compared to each other. The fact that the developmental stages of the chick embryo resemble the neuronal and spinal development stages of the human embryo in the first trimester provides advantages for research (10). The ability of chick embryos to grow outside the uterus, the easy manipulation of embryos, and the ability to incubate many eggs and obtain many embryo samples are other advantages of working with a chick embryo model (11).

Some teratogens and drugs, which are thought to be harmful for the development of NT during pregnancy, have been investigated using various experimental methods (12,13). One of these teratogenic agents is zuclopenthixol (14). Zuclopenthixol is an antipsychotic drug with three different formulations (zuclopenthixol dihydrochloride, zuclopenthixol acetate, zuclopenthixol decanoate). It is used in agitation, acute and chronic schizophrenia, and similar psychoses, thought disorders, hallucinations, restlessness, mania, and other psychoses accompanied by aggression (15,16). It is licensed for use in doses of 50-150 mg in acute exacerbations. The chemical formula of ZA is $C_{24}H_{27}ClN_2O_2S$, its molecular weight is 443.04 g/mol (17).

Different experimental models are used in the literature to determine the teratogenic and toxic effects of various natural or artificial chemical agents and to determine safe dose ranges. The chick embryo model is one of these models. The neuronal and spinal developmental stages of the human embryo in the first trimester are like the early (first 7-day period) nervous system development stages in chick embryos (18). Therefore, chick embryos are one of the most suitable models that can be used to investigate neural developmental stages.

Antipsychotic drugs are among the drug groups that are risky to use during pregnancy. As far as we have investigated the results regarding the teratogenic and toxic effects of ZA, which is in this drug group, in the embryo as a result of its use in pregnant women, it is scientifically limited. Therefore, in our study, we aimed to examine the effect of different doses of ZA on NT development in the early chick embryo model.

2. METHODS

Permission was obtained from Afyon Kocatepe University Animal Experiments Local Ethics Committee for this study (Number: 49533702/104; Date: 24.08.2021).

2.1. Laboratory and Incubation Conditions

This study was conducted in Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Anatomy. Standardization in the incubator was determined as 37.5±0.5°C constant ambient temperature and 60±5% relative humidity. The incubator was run empty for one hour until the desired ideal ambient temperature and relative humidity were reached. Afterwards, the eggs were placed in the incubator with sharp ends pointing down in order to ensure the continuity of the embryos and to have them available at the times desired.

2.2. Experimental Animals

In this study, the eggs were procured from the Veterinarian Control and Research Institute, Bornova, Izmir, Turkey. 65±5 g in weight, specific pathogen-free (SPF) and day 0 fertilized eggs of white chickens.

2.3. Experimental Groups

In the study, 40 fertilized SPF eggs were randomly divided into 4 groups, with 10 in each group. The day they were incubated was considered day 0. Eggs were removed from the incubator at 28 hours after being placed in the incubator. Eggshell was sterilized with 70% ethanol. Under the light, the air sac of the egg was found and the middle point corresponding to this cavity was marked with a pencil. In the area of this sign, holes of approximately 2 cm were opened and injection was made with a Hamilton injector.

ZA was administered via the subblastodermic route in a volume of 30 µL in groups A, B, C and D by Hamilton microinjector (0.7 mg/kg, 1.4 mg/kg and 2.1 mg/kg in groups B, C and D, respectively). Group A served as the control group and was administered 30 µL 0.9% NaCl via the subblastodermic route. After the injections, small windows were sealed with cellophane tape. Then the eggs were hand-turned 180° and placed in the incubator.

2.4. Removal of Chick Embryos

Eggs were removed from the incubator at 48 hours of incubation. The eggshell was broken and only the yolk was placed in a glass container containing sterile ringer lactate or saline. The watch glass was placed in the cup to receive the blastoderm. Then, using fine forceps and fine-tipped scissors, the vitelline membrane was cut over the yolk. The vitelline membrane was separated from the yolk by carefully holding both ends, and the blastoderm adhering to the membrane was advanced in the liquid and placed in the watch glass. Embryos were examined under a light microscope.

2.5. Histological Tissue Follow-Up

Embryo samples obtained were taken into 10% formaldehyde for fixation. Tissues, which were kept in fixation solution for 72 hours, were washed in running tap water and passed through graded alcohol series. It was then cleared with xylol and embedded in paraffin. 5 µm sections were taken from embryos. Embryo sections were placed on the slide. Paraffin was cleaned with xylol. Then the slides were passed through

graded series of alcohol (100%, 96%, 80%, 70%, 50%) and washed in water. Sections were stained with Hematoxylin-Eosin (H&E) to determine the general histological structure. It was then passed through the increasing series of alcohols then xylol. Finally, it was closed with a coverslip using entellan.

2.6. Statistical Analysis

Analysis of all findings was performed using the Statistical Package for the Social Sciences (SPSS) 22.0 program. The data related to NT (open or closed) were analyzed by using c2 test. The somite number and crown–rump length were analyzed by using non-parametric Kruskal-Wallis tests. Dunn test were employed as *post-hoc* tests and $p < .001$ were considered significant.

3. RESULTS

Findings were evaluated according to Hamburger Hamilton staging. Embryos were removed from the eggs at 48th hour according to the normal developmental period. In a 12th stage embryo, the somite count was 16. Head continues to rotate to the left. The closure of the anterior neuropore completes the closure of the neural tube. Telencephalon begins to appear. Primary optic vesicles and optic sac are clearly visible. The heart takes a slight S shape. The head fold of the amnion occupies the entrance to the forebrain. In our study, we investigated the effect of different doses of ZA on the development of NT in chick embryos assumed to have reached the 48th hour and 12th stage.

Group A: Only saline injection was applied to the eggs in the control group. In this group, 10 embryos were evaluated. Embryos were examined morphologically and histopathologically. NT was found to be closed in all embryos and no developmental delay was observed. The head of the embryos had begun to turn to the left. Enlargement of the telencephalon was evident and Rathke's sac could be observed in some of the embryos. All these findings were compatible with stages 13 and 14 according to the Hamburger-Hamilton classification (19), and their developmental stages were normal. The mean cranio-caudal length of the embryos was 772.40±111.47 µm, and the mean somite number was 21.30±2.26.

Group B: Embryos in this group were injected with 0.7 mg/kg ZA. 3 out of 10 embryos evaluated morphologically had open NT. The NT of all the remaining embryos was closed and there was no developmental delay. The head of the embryos began to turn to the left. The anterior neuropore of embryos was closed. The telencephalon was beginning to appear. Primary optic vesicles were prominent. The heart took the shape of the letter S. When all these findings were observed, it was seen that the embryos were compatible with stage 12 according to the Hamburger-Hamilton classification (19). The mean cranio-caudal length was 736.20±87.56 µm, and the mean somite number was 15.9±0.74. It was observed that there was a decrease in both compared to the control group.

Group C: Embryos in this group were injected with 1.4 mg/kg of ZA. 4 out of 10 embryos evaluated morphologically had open NT. A slight cranial bending was observed in the macroscopic examination. The hindbrain was divided into 5 neuromeres. The anterior neuropore had begun to close. Optic vesicles were prominent. Development stage of all embryo, was stage 11 according to Hamburger–Hamilton embryonic classification (19) and were behind the normal developmental stage. The mean somite number of the embryos was 15.20±0.79, and the mean cranio-caudal length was 719.10±114.37 µm.

Group D: Embryos in this group were injected with 2.1 mg/kg of ZA. NT was open in 6 of the embryos. In the macroscopic examination, the brain vesicle, which is the first sign of cranial fold, was seen in the embryos. Optic vesicles were not clear. As a result of the study, these findings, which were seen in all the embryos that received high-dose injection, showed that the embryos were at stage 10-11 according to the Hamburger-Hamilton classification (19) and were behind the normal developmental stage. As a result of the macroscopic and morphological evaluation, the mean cranio-caudal length was 578.10±11.75 µm, and the somite number was 15.0±0.94. It was determined that there was a significant decrease in these parameters compared to the control group.

When the study groups were evaluated according to their NT positions (open or closed), it was found that NT patency increased depending on the ZA dose, which was statistically significant ($p<0.05$), (Figure 1). In addition, as a result of the morphological evaluation, it was determined that there was a decrease in the mean cranio-caudal lengths and somite counts of the embryos depending on the dose. Compared to the control group, a significant decrease was observed in the mean somite counts in all dose groups, while a significant decrease was observed in the cranio-caudal length mean values only in the high dose group ($p<0.001$, Table 1).

Table 1. *Statistical analysis between groups.*

Parameters	Group A	Group B	Group C	Group D	p
Open NT/Closed NT	0/10	3/7[a]	4/6[a]	6/4[a]	p = .036
Rate of Open NT/Total	0%	30%	40%	60%	
Somite Count	21.30±2.26	15.9±0.74[a]	15.20±0.79[a]	15.0±0.94[a]	p = .004* p < .001* p < .002*
Cranio-Caudal Length (µm)	772.40±111.47	736.20±87.56	719.10±114.37	578.10±11.75[a]	p = .004

**Kruskal-Wallis test*

a; A statistically significant difference was found when compared with the control group.

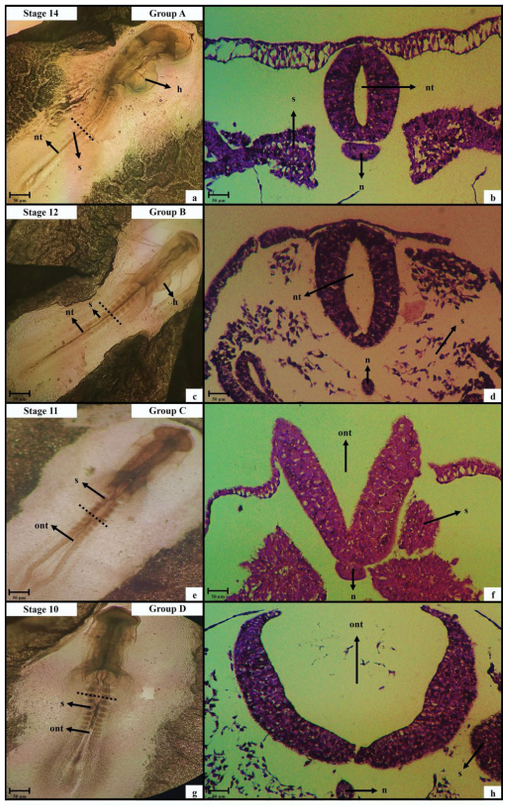

Figure 1. *Evaluation of embryos under the light microscope: (a) image of group A embryo under the light microscope; (b) cross section of an embryo (H&E, X20) after histological staining of group A embryos; (c)) image of group B embryo under the light microscope; (d) cross section of an embryo (H&E, X20) after histological staining of group B embryos; (e) image of group C embryo under the light microscope; (f) cross section of an embryo (H&E, X20) after histological staining of group C embryos; (g)) image of group D embryo under the light microscope; (h) cross section of an embryo (H&E, X20) after histological staining of group D embryos. nt: neural tube; ont: open neural tube; n: notochord; s: somites; h: heart; Group A: Control; Group B: ZA 0.7 mg/kg; Group C: ZA 1.4 mg/kg; Group D: ZA 2.1 mg/kg.*

4. DISCUSSION

In humans, between the 18th and 60th days of pregnancy, defects in nervous system development are more likely to occur. These defects occur as a result of problems occurring during the development of the NT or the reopening of the NT after completing its development (20). Different experimental models such as amphibian, mammalian, poultry, and computer modeling are used in the investigation of NT development.

The highest incidence of many psychiatric disorders in women, occurs during the reproductive years (21). In the literature, the status of being a parent of individuals with a diagnosis of psychiatric illness and the social and psychological status of individuals who have children have been examined. As a result of the studies, although there was a decrease in the fertility rate in psychiatric cases, it was determined that 36% of all individuals and 59% of women with a diagnosis of psychosis included in the study had children (21,22). It is very important to determine the drug safety of women with psychosis in terms of their desire to become a mother and to understand whether the drugs they should use (haloperidol, chlorpromazine, trifluoperazine, zuclopenthixol) have side effects in terms of mother and baby.

Antipsychotic medications may need to be prescribed for pregnant women in some cases. In these cases, the general health of the mother and the baby should not be adversely affected. However, there are no clear data on the potential effects of antipsychotic drugs on the infant. The available data on drug safety are limited, particularly for atypical antipsychotics (23,24). ZA is also in the antipsychotic drug group. Zuclopenthixol is a thioxanthene group neuroleptic drug. Its effect is fast and the duration of activity is 2-3 days. The fact that the side effects are low and mild, and that it can be administered with 48–72 hours intervals, has increased the use of the drug in recent years (25). Although there are various studies on the results of ZA use, no study on the effects of ZA on the fetus, especially on NT developing in the first trimester, was found as a result of the literature search conducted by us. However, animal reproduction studies of drugs in category “C” according to FDA have shown adverse effects on the fetus, and it has been reported that there are no adequate and well-controlled studies in humans. The study was planned in this direction and the effect of ZA on neural tube development in the chick embryo model was investigated.

In a study conducted in rats, the physiological effects of different doses of 3 long-acting neuropsychiatric drugs, including ZA (ZA doses: 0.5, 1 and 5 mg/kg), such as changes in body temperature, spontaneous cage activity and food intake were investigated. As a result of the study (5th-17th hours), food intake was significantly reduced in the medium and high dose ZA groups. In the high-dose ZA group, there was a significant decrease in body temperature at night. They explained that neuroleptics affect body temperature, spontaneous cage activity, and food intake, but that the effects are short-lived and do not have negative consequences for animals, and concluded that further studies are required (26). However, when the results of this study was evaluated in general, it was thought that the short-term negative effects that occurred in rats could also occur in humans after ZA use, and its use during pregnancy could harm the fetus. In our study, the doses to be applied to chick embryos were determined by considering the ZA doses used in rat studies (26,27).

Due to their small molecular size and lipophilic/lyophobic properties, antipsychotic drugs easily pass through the placenta and enter the fetal circulation. Maternal exposure to these drugs affects the fetal exposure level according to the placental crossing rate (28). Sadowski et al. observed in their study that fetuses exposed to antipsychotics were more likely to be premature (10.6%) compared to controls (4.3%) (29). In a study examining the potential relationship between the use of antipsychotic drugs during pregnancy

and gestational diabetes mellitus (GDM) and investigating the existing literature, it was stated that the use of first – and second-generation antipsychotic drugs did not pose a risk of GDM. As a result of the study, the use of ZA during pregnancy is not risky for GDM, but the effect of ZA on the fetus could not be examined (30).

In a study in which the neurodevelopment of 203 children whose mothers were exposed to typical antipsychotics during pregnancy, it was reported that there was no significant difference compared to the population in terms of IQ scores evaluated at the age of four. Major malformations were detected in babies whose mothers used haloperidol (2/78 (2.6%), flupentixol (5/101 (5%)) and zuclopenthixol (8/75 (10.7%)) (31,32).Use of both typical and atypical antipsychotics during late pregnancy may result in delayed development of the nervous system with an increased risk of perinatal complications, including extrapyramidal findings, respiratory distress, and seizures, which may inevitably persist up to 1 year of age (33). However, there is no general information in the literature on the increase of other malformations, although there is a potential concern about the occurrence of neural tube defects due to the use of antipsychotics during pregnancy (34). In addition to the use of antipsychotics, low diet, deficiency in vitamin intake, high maternal obesity rates and low serum folate levels in mothers with psychiatric disorders are thought to be effective in increasing the risk of NTD malformation (35). In a systematic study by Gentile et al., in which they investigated the safety of antipsychotic use in pregnant women, 419 pregnant women using antipsychotic drugs were examined. As a result of the examination, it was reported that a total of 26 congenital malformations with 4 neural tube defects were identified (36). When the results of our study are evaluated in line with this literature information, we think that ZA exposure negatively affects the development of the nervous system and therefore causes neural tube closure defects. It is seen that the concerns about fetal neural tube defects related to the use of antipsychotic drugs in the literature are supported by our study. Although this study was conducted in chick embryos, the results obtained are a reference study showing possible teratogenic effects that may occur with antipsychotic drug exposure in humans.

In a case report reporting the use of zuclopenthixol decanoate (ZD), a different form of ZA, during two consecutive pregnancies of a woman diagnosed with schizophrenia, it was found that a significant improvement was achieved in the clinical condition of the mother after the treatment. ZD was prescribed to the patient who stopped taking the drug on her own due to amenorrhea 6 months before the pregnancy due to compliance problems. Intramuscular (i.m.) depot ZD injection was planned to the patient as 400 mg every two weeks. The first unwanted pregnancy was diagnosed at the 13th week of pregnancy, approximately four and a half months after the start of ZD therapy. The patient was explained about the risks of using ZD during pregnancy. The patient decided to continue both pregnancy and drug therapy freely. The next drug dose was reduced to 200 mg and administered at monthly intervals. It was stated that both babies showed normal development. They reported that ZD is an option that can be used for pregnant women with psychosis, but large and controlled studies are needed to obtain a definitive result. In addition; it is understood that the mother has babies with normal development after ZD use, and that the use of the drug in controlled and certain doses does not have a toxic effect on both the mother and the fetus (37). As a result of our study, it was determined that the nervous system development of embryo was negatively affected depending on the ZA doses, and exposure to high doses of ZA delays fetal development. Therefore, we think that in cases where the use of ZA in pregnant women is necessary, it should be used by determining the dose that is controlled and appropriate for the clinical picture.

In the literature, it is thought that antipsychotic drugs block central dopamine (DA) receptors, leading to an accelerated cycle of DA and accumulation of acid metabolites in the brain (38,39). Although the pathophysiological mechanism of Neuroleptic Malignant Syndrome (NMS) is not known exactly, it is suggested that the blockade of dopamine receptors due to the use of antipsychotics causes this syndrome. NMS has been reported to be associated with both typical and atypical antipsychotics. However, a guideline was published by the American College of Obstetrics and Gynecology, which states that typical antipsychotics are safer than atypical antipsychotics in pregnant women (40). However, it has been stated that changes in the dose and route of administration of antipsychotic drugs increase the risk of NMS (41). We think that ZA, which we applied at different doses in our study, had a negative effect on the development of the nervous system regarding its effect on dopamine receptors.

In a study conducted in rats, it was determined that different doses of ZA (0.7 and 1.4 mg/kg intraperitoneal (i.p.)) increased the malondialdehyde level, decreased the glutathione level and produced a pro-oxidant effect (27). Many factors such as normal oxygen metabolism in living cells, environmental pollutants, radiation, various medical treatment methods and drug use trigger the formation of oxygen-derived free radicals. Antioxidants, which prevent oxidation caused by free radicals in the body and can stabilize this situation, come into play (42,43). In addition to this literature information, it has been determined that antioxidant defense mechanisms are impaired with the increase of oxidative damage due to the deterioration of the oxidant-antioxidant balance. As a result of this situation, it has been reported that nervous system development, membrane transport, mitochondrial energy production, gene expression and receptor-mediated phospholipid-dependent signal transduction may be affected (44,45). We think that neural tube closure defects and negative effects on embryo development observed as a result of our study may overlap with the results of these studies.

5. CONCLUSION

In our study, the possible negative effect of ZA, an antipsychotic drug, on the development of NT was investigated in the

chick embryo model. The effects of ZA on the development of embryos were associated with the injected doses, and it was determined that increasing doses of ZA administration caused midline closure defects during NT formation in early chick embryos during development. In addition, it was observed that the cranio-caudal length and somite counts decreased significantly in the C and D experimental groups compared to the control group, depending on the dose.

Consequently, our study has demonstrated that ZA exerts direct teratogenic effect on the process of NT formation of chick embryo in a dose-dependent manner. However, since we think that it will not be possible to fully adapt the results of this study, which was carried out in the chick embryo model, to humans, we believe that a more comprehensive study should be conducted.

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Research idea: GAK, EA, TE
Design of the study: EA, TE
Acquisition of data for the study: GAK, AS, YEK
Analysis of data for the study: EA, TE
Interpretation of data for the study: GAK, EA, TE
Drafting the manuscript: GAK, YEK, AE
Revising it critically for important intellectual content: AE, GAK, AS
Final approval of the version to be published: TE, EA, GAK

Data Availability Statement: *The datasets used and analyzed during the current study are available from the corresponding author upon request.*

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