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Original Research Paper

Anatomy

EFFECT OF PRENATAL OLANZAPINE ADMINISTRATION ON BRAIN OF SWISS ALBINO MICE

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ABSTRACT

The women in child bearing age group are prone to develop symptoms of mental diseases . These symptoms shouldn't be ignored as the mental condition can affect the mother and fetus in an adverse way. One such condition is schizophrenia for which Olanzapine is given . This study aims to establish the safety profile of olanzapine when given to pregnant mothers.

Materials and methods : Olanzapine was given to pregnant mice in doses of 0.2mg/kg and 2mg/kg whereas tap water was given to control mice from 6th to 12th day of gestation. The female dams were sacrificed on 18th day of gestation by cervical dislocation and fetuses were dissected out by uterotomy. The brain of mice embryos were dissected out, processed and were stained with H&E.

Results: On gross examination of brain, the cerebrum was noticed to be reduced in size in both the treated groups. On histological examination, the cerebral cortex of treated mice shows deficient neuroblastic population due to increased necrosis and degeneration of these cells as well as decreased migration of neuroblast to cortical plate which was directly proportional to dose of Olanzapine.

Conclusion: Olanzapine causes a dose dependent insult on fetal brain when given to mother during period of organogenesis

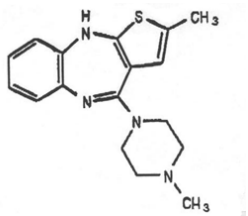
KEYWORDS :

INTRODUCTION

The women in child bearing age group are prone to develop symptoms of mental diseases [1,2,3]. These symptoms shouldn't be ignored as the mental condition can affect the mother and fetus in an adverse way [4,5]. Nearly 500,000 pregnancies are complicated by psychiatric illness worldwide[6]. Initially conventional antipsychotics were used to treat these mental disorders but they resulted in congenital malformations in child and reduced fertility in mother [7,8]. This led to the development of atypical antipsychotics which were devoid of these side defects. With the safer antipsychotics in the market the incidence of women, who are taking antispychotics , getting pregnant is on the rise . [9,10,11,12]

A lot of debate occurs over the prescribing practices for pregnant women with severe and persistent psychiatric disorders. The atypical antipsychotics have limited evidence for teratological risk, but are reports of altered fetal growth, both increased and decreased, with maternal atypical antipsychotic use. These effects may be mediated through changes in the maternal metabolism which in turn impacts placental function. The receptors which are targeted by atypical antipsychotics have also been found in the placenta ,proving that these drugs might have direct effects on the development and function of placenta.

The FDA approved **Olanzapine**, an antipsychotic drug manufactured by the Eli, Lily and company, in October 1996, for the treatment of psychotic disorders. It is a thieno-benzodiazepine analog with the chemical name of 2-methyl-4-(4-methyl-1- piperazinyl)-10 thieno [2,3-b][1,5] benzodiazepine. It is a yellow crystalline solid and is insoluble in water. Its structure is as given below.



In vivo studies proved that olanzapine is an antagonist of dopamine, serotonin, and acetylcholin. This receptor profile parallels that of Clozapine [13,14,15]. It has been observed in animal and human studies that olanzapine is transfereed via placenta rapidly. It comes undef category C drug by FDA which means it has been found safe in animals but studies in human are inconclusive. It has been observed in invitro studies that it is toxic to humans . Olanzapine owes its toxicity due to its ability to cause mitochondrial DNA depletion and metabolic disruption.

The safety profile of this drug is yet to be established in human beings . Thus in present work we intend to highlight the toxic effect of olanzapine on brain of the embryo when given to mother during pregnancy.

MATERIALS AND METHODS

This study was conducted on 27 swiss albino mice. Prior approval of institutional ethical committee was taken before the start of the present study. For this study swiss albino female mice were taken and kept with male mice for mating overnight in the ratio of 3:1.Presence of vaginal plug was considered to be the first day of gestation (GD 0). The pregnant female mice were divided into three groups for the present study. The first group was designated as control and was given tap water by gavage from day 6 to day 12 of gestation. The other two groups were given olanzapine in the dose of 0.2mg/kg and 2 mg/kg th respectively by gavage for the same period. On day 18 of gestation the female mice was sacrificed by cervical dislocation and uterotomy was done to extract the embryos.The brain of the embryos were dissected out and kept in formalin for fixation. For histological study the brain was processed, sections were cut at 8μm and stained with hematoxylin and eosin (H&E).

RESULTS

On gross examination of brain, the cerebrum was noticed to be reduced in size in both the treated groups. Brain of 2mg/kg (high dose) showed maximum reduction in its size with less marked sulci and gyri thus giving it more smoother appearance than the brain of control and 0.2mg/kg (low dose).

Microscopic structure of brain:

In cerebral cortex of brain of control mice the four layer arrangement from inner to outer aspect is classically seen (Fig A):

a) Ventricular zone – innermost layer near the ventricle
b) Subventricular zone
c) Intermediate zone
d) Cortical plate – outermost layer

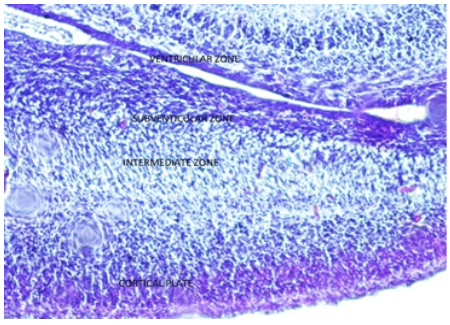


Fig. A: Photograph of cerebral cortex of brain of Group 1 (Control) mice showing all the four layers (H & E x 100).

In low dose 0.2 mg/kg Olanzapine treated mice there was deficient migration from subventricular zone to the cortical plate (Fig B).Also the density of neuroblasts were reduced . There was necrosis and degeneration of neuroblast .

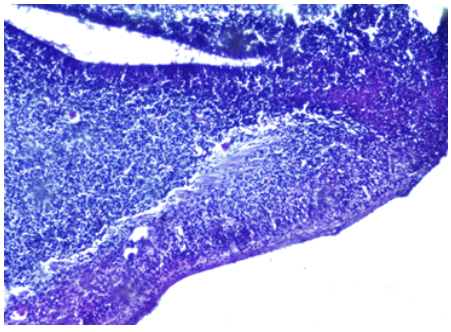


Fig. B: Photograph of cerebral cortex of brain of Group 2 (low dose)mice showing necrosis & disruption of neuroblast in cortical plate. (H & E x 100).

In high dose 2mg/kg Olanzapine treated cerebral cortex there is intense amount of degeneration and necrosis of neuroblasts in cortical plate and intermediate zone leading to complete loss of cytoarchitecture and typical laminar pattern (Fig C). There are vast amount of empty lacunar spaces giving rise to spongiform appearance of cerebral cortex.

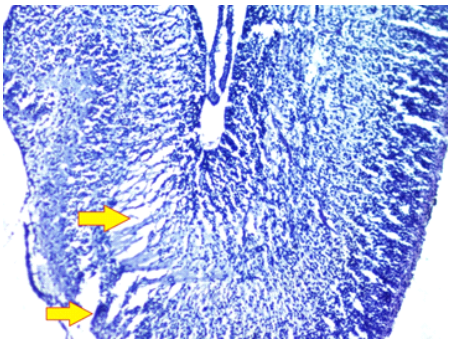


Fig. C: Photograph of cerebral cortex of brain of Group 3 (High dose) mice showing disruption & loss of cohesion of neuroblast in cortical plate & intermediate zone. (H & E x 100)

DISCUSSION

The cerebral cortex of treated mice shows deficient neuroblastic population due to increased necrosis and degeneration of these cells as well as decreased migration of neuroblast to cortical plate which was directly proportional to dose of Olanzapine. This could be explained on basis of increased level of reactive oxygen species in Olanzapine treated mice[16]. These reactive oxygen species from mitochondria as well as endoplasmic reticulum alters mRNA expression leading to defective protein synthesis [17]. A variety of these proteins are responsible for regulating cellular energy and providing vital energy to the brain for division and differentiation of neuroblast. This subsequently leads to increased apoptosis and neuronic degeneration.

Thus the physician and the mother have to balance the risks as of untreated psychiatric illness against the potential fetal toxicity associated with olanzapine.

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