ORIGINAL RESEARCH PAPER

Anatomy

KEY WORDS: Kidney, teratology, glomerulus, mesangial cells

NEPHROTOXIC CHANGES INDUCED BY PRENATAL ADMINISTRATION OF OLANZAPINE IN SWISS ALBINO MICE

Dr. Soumya Khanna Assistant Professor, Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005

Dr. Anand Mishra* Professor , Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005 *Corresponding Author

ABSTRACT

With the growing stress in lifestyle , women are becoming prone to develop mental illnesses, Psychiatric illness occurring during pregnancy if not treated may be associated with increased risks for mother (including self harm/suicide, self neglect and reduced compliance with prenatal and postnatal care) and risks for the child (impaired fetal development, infanticide and impaired mother child bonding). One such psychiatric illness is schizophrenia for which Olanzapine is given .This study aims to establish the safety profile of olanzapine on the kidney of fetus 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 kidney of mice embryos were dissected out, processed and were stained with H&E.

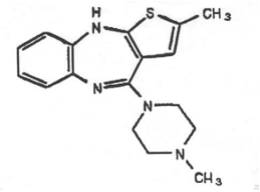
Results : on histological examination , There is dose related damage of glomerulus and mesangial cells in cortex and degeneration and disruption of tubules in the medulla of fetal mice treated with Olanzapine

Conclusion : Olanzapine causes a dose dependent damage to the fetal kidney when given to the mother during period of organogenesis.

INTRODUCTION

The biochemical and hormonal changes occurring in women of child bearing age make them susceptible to various mental illnesses. With the growing stress in lifestyle , women are becoming prone to develop mental illnesses. It has been observed that more than 500,000 pregnancies annually are complicated by psychiatric illness that either precedes or arises during pregnancy [1]. Psychiatric illness occurring during pregnancy if not treated may be associated with increased risks for mother (including self harm/suicide, self neglect and reduced compliance with prenatal and postnatal care) and risks for the child (impaired fetal development, infanticide and impaired mother child bonding) [2,3]. A significant decrease in fertility was reported in women using conventional antipsychotics [4]. on the other hand the newer atypical antipsychotics do not have this side effect. As a result , the number of women taking antipsychotics, who are becoming pregnant is on the rise .

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 have shown that olanzapine is an antagonist of dopamine, serotonin, and acetylcholine. This receptor profile is similar to that of Clozapine [5,6,7,8]. It has been observed in animal and human studies that olanzapine is transferred via placenta rapidly. It comes under 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 still a dilemma and needs to be solved . Thus in present work we intend to highlight the toxic effect of olanzapine on kidney 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 kidney 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

Microscopic structure of kidney

The kidney of developing mice classically shows these 3 layers :

1) **Nephrogenic zone :** This zone is principally composed of progenitor cells which will give rise to cells of glomerulus and medulla.
2) **Cortex** – Typically shows developing glomerulus and proximal and distal convoluted tubule. (Fig. A)

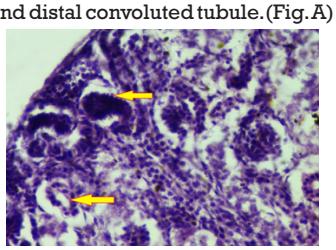


Fig. A: Photograph of kidney of Group 1 (Control) mice showing glomerulus & distal convoluted tubule in the cortex (H & E x 400).

3) **Medulla –** This zone shows Loop of Henle and collecting duct. (Fig B)

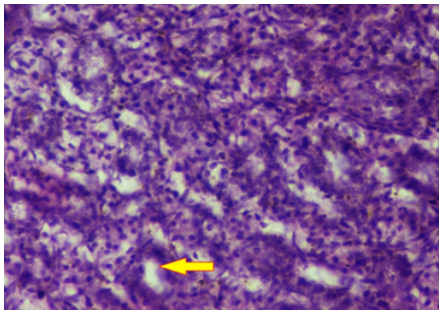


Fig. B: Photograph of kidney of Group 1 (Control) mice showing loop of henle in the medulla (H & E x 400).

In low dose (0.2 mg/kg) Olanzapine treated kidney there is degeneration and destruction of glomerulus and mesangial cells in the cortex. (Fig C) In the medulla there is disruption of tubules and haemorrhage

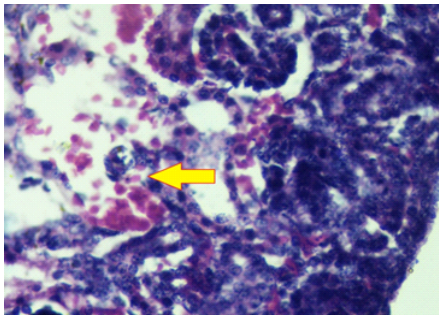


Fig. C: Photograph of kidney of Group 2 (low dose) showing necrosis & disruption of glomerulus & mesangial cells in the cortex . In the medulla there is disruption of tubules and haemorrhage (H & E x 400)

In high dose 2mg/kg Olanzapine treated kidney these findings are further exemplified. There is complete disruption of glomerulus and supporting cells giving rise to empty vacuolated spaces. Vast amount of degenerative cells with cellular debris can be seen (Fig D). In medulla there is degeneration of loop of henle leading to spongiform appearance appearance in It .

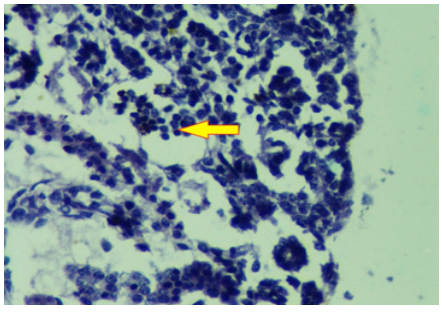


Fig. D: Photograph of kidney of Group 3 (high dose) showing complete disruption & necrosis of glomerulus & mesangial cells and spongiform in the cortex . In medulla there is degeneration of loop of henle leading to spongiform appearance appearance in It . (H & E x 400)

DISCUSSION

There is dose related damage of glomerulus and mesangial cells in cortex and degeneration and disruption of tubules in the medulla of fetal mice treated with Olanzapine. Gulec et al (2012) also noted altered glomerular structure, focal necrosis of cortex and medulla, increased thickness of basement membrane and loss of tubules on rats exposed to 0.5 mg/kg and 2.5 mg/kg Olanzapine for 6 weeks. This could be explained due to generation of reactive oxygen species like hydrogen peroxide, superoxide which are known to damage cell membrane, proteins and DNA leading to cellular degeneration. Also Olanzapine has a direct toxic effect on renal mitochondria again accentuating nephrotoxicity in the mice.

REFERENCES

1. P. Bebbington, G. Dunn, R. Jenkins et al., "The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity," International Review of Psychiatry, vol. 15, no. 1-2, pp. 74–83, 2003.
2. R. Zender and E. Olshansky, "Women's mental health: depression and anxiety," Nursing Clinics of North America, vol. 44, no. 3, pp. 355–364, 2009.
3. F. Akdeniz, "Female-specific health problems in mental patients," Current Opinion in Psychiatry, vol. 23, no. 4, pp. 378–382, 2010.
4. M. L. Figueira and S. Ouakinin, "Gender-related endocrinological dysfunction and mental disorders," Current Opinion in Psychiatry, vol. 23, no. 4, pp. 369–372, 2010.
5. Moore, N. A., Tye, N. C., Axton, M. S. and Risius, F. C. (1992) The behavioral pharmacology of olanzapine, a novel "atypical" antipsychotic agent. J Pharmacol. Exp. Ther. 262(2), 545-51.
6. Tye, N. C., Moore, N. A., Rees, G., Sanger, G., Calligaro, D. O. and Beaseley, C. M. (1992) Second International Conference on Schizophrenia., Vancouver, British Columbia
7. Borison, R. L. (1995) Clinical efficacy of serotonin-dopamine antagonists relative to classic neuroleptics. J. Clin. Psychopharmacol. 15(1 Suppl 1), 24S-29S
8. M. R. Baig, E. Navaira, M. A. Escamilla, H. Raventos, and C. Walss-Bass, "Clozapine treatment causes oxidation of proteins involved in energy metabolism in lymphoblastoid cells: a possible mechanism for antipsychotic-induced metabolic alterations," Journal of Psychiatric Practice, vol. 16, no. 5, pp. 325–333, 2010.