ORIGINAL RESEARCH PAPER

Anatomy

KEY WORDS: .

Prenatal olanzapine induced placental changes in Swiss albino mice

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ABSTRACT

Although Olanzapine, an antipsychotic is widely used in pregnancy , its safety profile is yet to be determined. We have therefore given Olanzapine to pregnant mice in different doses to see its effect on placenta of the embryo.

Material and Method : 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 placenta of mice embryos were dissected out, processed and were stained with H&E.

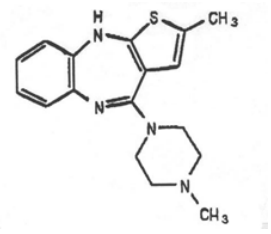
Results : The placenta of treated mice show thickening and hyalinization of trichorial placental membrane in a dose dependant manner. The placenta of 0.2 mg /kg treated mice showed degeneration of both spongiotrophoblast and trophoblastic giant cells . The placenta of 2mg/kg treated mice showed intense degeneration of spongiotrophoblasts and trophoblastic giant cells resulting in empty lacunar space and cellular debris .

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

Introduction

Existing and new symptoms of mental diseases are common in women in child bearing age[1,2,3]. These mental disorders if left untreated can result in harm to both mother and fetus[4,5]. It is estimated that almost 500,000 pregnancies are complicated by psychiatric illness worldwide[6]. Conventional antipsychotics used to treat these disorders causes congenital malformations in child and reduced fertility in mother[7,8]. Recently newer antipsychotics have been introduced to treated schizophrenia and other psychotic disorders . Also, the number of women suffering from schizophrenia , getting pregnant, is on rise[9,10,11,12].

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. Olanzapine is a yellow crystalline solid and practically insoluble in water. Its structure is as given below.



The pharmacological activity of olanzapine is due to its antagonistic effect on dopamine, serotonin and acetylcholine receptors and its pharmacological action parallels that of clozapine[13,14,15].Rapid placental transfer of olanzapine has been observed in animal and human studies.It has been classified as class C drug by FDA which means it has been found safe in animals but studies in human are inconclusive. Olanzapine has been shown to cause toxicity in humans invitro study. The toxicity is mainly by its genotoxic and cytotoxiceffects, its ability to cause mitochondrial DNA depletion and by metabolic disruption..

There is diemma on the use of olanzapine in pregnancy as the safety profile of this drug is not established. So, we have taken up the study to observe the effect of olanzapine on placenta of mice when given 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 respectively by gavage for the same period. On day 18th of gestation the female mice was sacrificed by cervical dislocation and uterotomy was done to extract the embryos.The placenta of the embryos were dissected out and kept in formalin for fixation. For histological study the placenta was processed, sections were cut at 8µm and stained with hematoxylin and eosin (H&E).

Results

GROSS EXAMINATION OF PLACENTA

The placenta showed significant reduction in weight in treated groups inboth low and high dose as compared to control group,which was statistically significant (P<0.05).

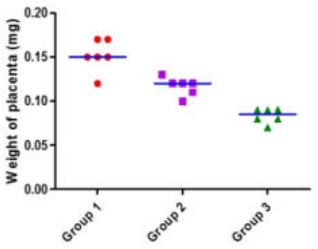
Weight of placenta

Group	MeanSD	p-value
Group 1	0.190.02	0.012
Group 2	0.140.01	
Group 3	0.080.06	

Group comparison

Group 1 vs Group 2	=	<0.05
Group 1 vs Group 3	=	<0.01
Group 2 vs Group 3	=	>0.05

Data



MICROSCOPIC STUDY OF PLACENTA

The normal mice placenta typically shows the following 4 layers from maternal to fetal side :

1) ***Basal zone***
It represents the maternal part of placenta. It is composed of cellular and fibrous tissue which continues into the metrial glands at the site of implantation. The mesometrialdecidual cells ultimately form only a thin layer at the base of placenta called decidua basalis, which is an important site of maternal angiogenesis. It is composed of three types of differentiated cells i.e. spongiotrophoblast, trobhoblastic giant cell and glycogen cells.

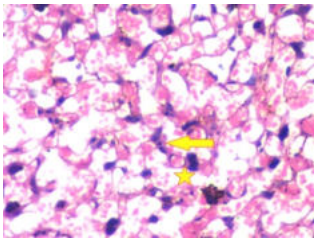
2) ***Junctional zone***
This shows few spongiotrophoblastic cells. The maternal blood passes through the spaces between these cells before entering the labyrinthine zone.

3) ***Labyrinthine zone***
It consists of maternal sinusoids and the trophoblastic septa which are composed of the trilamilartrobhoblastic epithelium and fetal capillary. The labyrinthine blood vessels are separated from the sinusoidal blood by the trichorial membrane which forms the placental barrier.

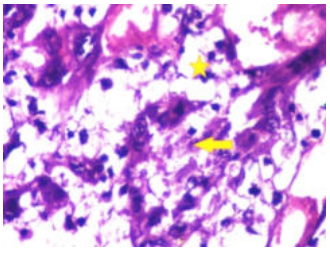
4) ***Chorionic plate***- it represents the fetal part of placenta

In low dose i.e. 0.2 mg/kg Olanzapine treated placenta there is considerable thickening of trichorial placental barrier. Also there appears to be disruption of maternal sinuses leading to vast spaces of maternal blood . In basal zone there seems to be degeneration of both spongiotrophoblast and trophoblastic giant cells giving rise to empty lacunar spaces

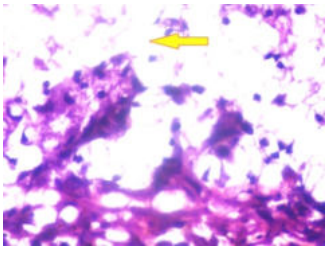
In high dose 2mg/kg Olanzapine treated placenta there is hyalinization and intense thickening of trichorial membrane and complete disruption of maternal venous sinusoids . Also in basal zone the spongiotrophoblast are vastly reduced with immense empty spaces. The cellular debris with degenerating cells are classically seen.



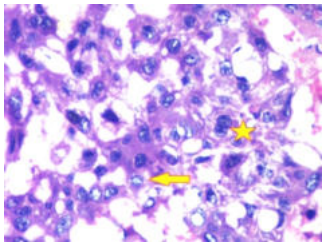
Photograph of basal zone of placenta of Control mice showing spongiotrophoblasts (⇦) and trophoblastic giant cells (☆) (H & E x 400).



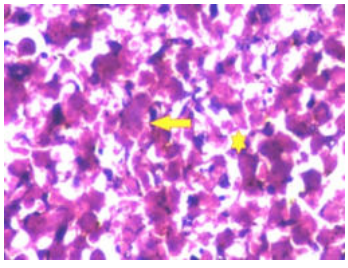
Photograph of basal zone of placenta of low dose treated mice showing degenerating spongiotrophoblasts (⇦) resulting in empty vacuolar spaces (☆)(H & E x 400)



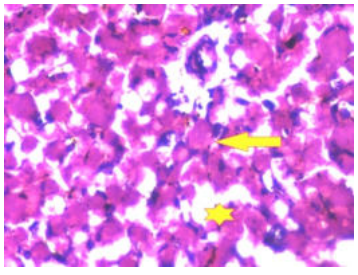
Photograph of basal zone of placenta of high dose treated mice showing complete disruption of spongiotrophoblasts and giant cells resulting in vacuolar spaces (⇦)(H & E x 400)



Photograph of labrynthine zone of placenta of Control mice showing trichorial barrier (⇦) and maternal sinus (☆) (H & E x 400).



Photograph of labrynthine zone of placenta of low dose treated group showing thickening of trichorial membrane (☆) and disruption of maternal sinus (⇦) (H & E x 400)



Photograph of labrynthine zone of placenta of high dose treated group showing hyalinization (⇦) and maternal sinusoid disruption (☆) (H & E x 400)

Discussion

Placenta of mice treated with Olanzapine shows thickening and hyalinization of trichorial placental barrier in labrynthine zone and degeneration of synctiotrophoblast and giant cells in basal zone. Also there appears to be disruption of maternal venous sinusoids leading to haemorrhage in the placenta . This could be explained by Olanzapine induced mitochondria dysfunction which leads to trophoblastic degeneration and death[16] (R.Ain et al 2006, S.Raha et al 2000).

Olanzapine has been shown to cause toxic effects on placenta by altering 5HT2A serotonin receptors in human trophoblastic cells which may cause deleterious effects on embryo[17]. These serotonergic receptors are crucial in regulating cellular proliferation, differentiation and migration[18]. Serotonin may also hinder estrogen synthesis which is vital for successful implantation and leptin expression[19,20]. Leptin is a key chemical which regulates fetal growth. So reduced estrogen synthesis and altered leptin expression may result in low placental weight and placental toxicity[21]. There might be an indirect role of olanzapine induced dopaminergic (D2) receptor antagonism on placental toxicity as dopamine has been found to promote growth in embryo.

Thus olanzapine causes toxic changes in placenta which might reflect on the developing embryo as intrauterine growth retardation. So caution should be exercised while prescribing this drug to pregnant ladies especially those who are predisposed to oxidative stress.

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. C. N. Soares, "DSM-V and reproductive-related psychiatric disorders: a closer look at windows of vulnerability," Archives of Women's Mental Health, vol. 13, no. 1, pp. 15–16, 2010
6. L. Levey, K. Ragan, A. Hower-Hartley, D. J. Newport, and Z. N. Stowe, "Psychiatric disorders in pregnancy," Neurologic Clinics, vol. 22, no. 4, pp. 863–893, 2004.
7. S. J.Menon, "Psychotropic medication during pregnancy and lactation," Archives of Gynecology and Obstetrics, vol. 277, no. 1, pp. 1–13, 2008.
8. H. Solari, K. E. Dickson, and L. Miller, "Understanding and treating women with schizophrenia during pregnancy and postpartum," Canadian Journal of Clinical Pharmacology, vol. 16, no. 1, pp. e23–e32, 2009.
9. ACOG, "Use of psychiatric medications during pregnancy and lactation," ACOG Practice Bulletin, vol. 111, pp. 1001– 1020, 2008.
10. E. Weiss, M. Hummer, D. Koller, H. Ulmer, and W. W. Fleischhacker, "Off-label use of antipsychotic drugs," Journal of Clinical Psychopharmacology, vol. 20, no. 6, pp. 695–698, 2000.
11. N. S. Philip, L. L. Carpenter, A. R. Tyrka, and L. H. Price, "Augmentation of antidepressants with atypical antipsychotics: a review of the current literature," Journal of Psychiatric Practice, vol. 14, no. 1, pp. 34–44, 2008.
12. G. Boonstra, D. E. Grobbee, E. Hak, R. S. Kahn, and H. Burger, "Initiation of antipsychotic treatment by general practitioners. A case-control study," Journal of Evaluation in Clinical Practice, vol. 17, no. 1, pp. 12–17, 2011.
13. 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.
14. 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
15. Borison, R. L. (1995) Clinical efficacy of serotonin-dopamine antagonists relative to classic neuroleptics. J. Clin. Psychopharmacol. 15(1 Suppl 1), 24S-29S
16. R. Ain, T. Konno, L. N. Canham, and M. J. Soares, "Phenotypic analysis of the rat placenta," Methods in Molecular Medicine, vol. 121, pp. 295–313, 2006.
17. C. Vaillancourt, A. Petit, and S. B´elisle, "Interaction of D2- dopamine receptor with two pertussis toxin sensitive G proteins in human placenta," Life Sciences, vol. 60, no. 16, pp. 1365–1375, 1997.
18. D. Hu and J. C. Cross, "Development and function of trophoblast giant cells in the rodent placenta," International Journal of Developmental Biology, vol. 54, no. 2-3, pp. 341–354, 2010.
19. J. A. Duffield, T. Vuocolo, R. Tellam, B. S. Yuen, B. S. Muhlhausler, and I. C. McMillen, "Placental restriction of fetal growth decreases IGF1 and leptin mRNA expression in the perirenal adipose tissue of late gestation fetal sheep," American Journal of Physiology, vol. 294, no. 5, pp. R1413–R1419, 2008.
20. Y. P. Gambino, J. L. Maymo, A. Perez Perez, J. C. Calvo, V. Sanchez-Margalet, and C. L. Varone, "Elsevier Trophoblast Research Award lecture: molecular mechanisms underlying estrogen functions in trophoblastic cells—focus on leptin expression," Placenta, vol. 33, pp. S63–S70, 2012.
21. H. Mise, S. Yura, H. Itoh et al., "The relationship between maternal plasma leptin levels and fetal growth restriction," Endocrine Journal, vol. 54, no. 6, pp. 945–951, 2007.