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Zidovudine and Efavirenz induced oxidative injury in brain of fetal mice

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Abstract
Introduction: Zidovidine (ZDV) and Efavirenz (EFZ) are anti HIV drugs widely used as combination chemotherapy to prevent maternal to child transmission. However the safety profile of these drugs has not been tested.
Materials and Method: MDA and Reduced Glutathione wer tested in brain of the fetal mice after they wer dissected out in control and other 3 treated groups given ZDV, EFZ and ZDV+ EFZ in dose of 50mg/kg.
Results: There is increased level of MDA and decreased levels of reduced glutathione in treated group as compared to the control and the maximum variation was seen in combination group.
Conclusion: Zidovudine and Efavirenz leaded to increased oxidative stress injury in brain of fetal mice and thus can lead to neurodegeneration.

Keywords: MDA, Reduced glutathione, oxidative stress, neuro degeneration

Introduction
Use of antiretroviral drugs during pregnancy has increased since the demonstration of reduction of mother to child transmission (MTCT) of HIV-1 first with Zidovudine monotherapy and more recently with highly active retro viral therapy regimens (HAART). Based on these recommendations many women are receiving HAART and may enter pregnancy already receiving multiple antiretroviral agents [1].
Zidovudine (3'-azido-3'-deoxy thymidine) also known as azidothymidine (AZT) is a thymidine analogue which is one of the drugs to have potent *in vitro* activity against replication of HIV in human T4 lymphocyte cell lines. Zidovudine is used for pre-exposure prophylaxis and post exposure treatment of mother to child transmission (MTCT) of HIV during pregnancy, labour and delivery and has been proved to be integral to uninfected sibling's prenatal and neonatal development. Zidovudine has been shown to reduce the risk of HIV transmission to as little as 8% when given in three part regimen post conception, delivery and six weeks post-delivery [2].
Efavirenz is benzoxazinone derivative (2H-3, 1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynl)-1, 4-dihydro-4 (tri-floromethyl)-(4S). Efavirenz is considered as preferred non-nucleoside reverse transcriptase as part of initial HAART therapy. In addition, Efavirenzy (EFV) is used with other antiretroviral (ARV) agents as part of an expanded post exposure prophylaxis regimen to prevent HIV transmission in health care workers and other individuals with non-occupational exposure to HIV [3].
However the safety profile of both the drugs have not been tested in pregnant women to brand them as safe in pregnancy. So we plan to carry out the antioxidant study in fetal mice to see the oxidative stress induced by these drugs.

Materials and method
Prior approval of Central Animal Ethical committee, IMS, BHU was taken before the start of this study. The study was carried out on Swiss Albino female mice of 3 months of age weighing 20-25 g, which were caged in air conditioned animal house of the Department of Anatomy. Female mice were kept in mating with male mice in the ratio of 2:1 overnight and were inspected next morning for the presence of vaginal plug. The day of vaginal plug seen was considered as day 0 of gestation (GD 0).

Weight of each female mice was taken on GD 0 and placed in an individual cage. Pregnant Swiss albino mice had been divided into following three groups--

Group I: Mice treated with distilled water

Group II: Mice treated with Zidovudine (ZDV) in dose of 50mg/kg

Group III: Mice treated with Efavirenz (EFV) in dose of 50mg/kg

Group IV: Mice treated with ZDV+EFV both in dose of 50mg/kg

On the 18th day of gestation, weight of mice of each group has been taken and then the mice were sacrificed by cervical dislocation. The foetuses were collected by laparotomy and their brains were dissected out for MDA and Reduced glutathione analysis by thiobarbituric acid (TBA) test and Beutler's method respectively

Result

Estimation of Malondialdehyde (MDA) in fetal brain was done in each group and there was a significant increase in MDA levels in fetal brain in entire treated groups as compared to the control. (P<0.001)

Table 1: Malondialdehyde (MDA) levels in fetal brain of mice in different group

Group	N	Mean (µg/ml)	Std. Deviation	Significance
1	6	6	0.63246	
2	6	8.5	0.54772	.017*
3	6	9.5	0.54772	.001**
4	6	11.5	0.83666	0**

Reduced glutathione (GSH) was also estimated in fetal brain of mice in different groups and it was observed that there is a reduction in levels of GSH in fetal brain in entire treated groups as compared to the control with the maximum reduction in GSH levels was observed in group IV.(P<0.001).

Table 2: Reduced glutathione (GSH) in fetal brain of mice in different groups

Group	N	Mean (µg/ml)	Std. Deviation	Significance
1	6	0.4767	0.01366	
2	6	0.3583	0.02483	.002**
3	6	0.2833	0.01211	0**
4	6	0.2283	0.01835	0**

Discussion

Zidovudine and Efavirenz are both reverse transciptase inhibitor which are used as combination chemotherapy to prevent maternal to child transmission [4]. Both the drugs were given individually as well as in combination in dose of 50 mg/kg to mice as it therapeutic plasma concentration falls at the same level as the plasma concentration therapeutic dose in human [5]. Both the drugs were given from 6 to 15 days of gestation in mice as this period is the period of organogenesis in mice and any insult by drug at this time may lead to congenital defects in mice.

Fetal brain MDA & GSH were estimated and it was observed that there was a significant increase in MDA level and reversely a significant decrease in GSH level in all the treated group with the maximum effect seen in Group IV. Increase in MDA & decrease in glutathione occurs in conditions of oxidative stress and therefore is suggested that an increase in ROS (reactive oxygen species) production also occur as an early event during ZDV & EFV exposure. The function of glutathione is to eliminate ROS demonstrated a decline in glutathione as early as day 6 after exposure [6, 7]. By day 15, there is 50% reduction in GSH level. GSH level reduction and MDA elevation can lead to increase level of ROS. ROS can damage and alter the function of DNA, protein and lipids thus leading to mitochondrial and cellular dysfunction.

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