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## Effect of zidovudine on fetal length & fetal weight of developing mice

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### Abstract

**Introduction:** Zidovudine was the first antiretroviral agent to demonstrate clinical efficacy in patients infected with HIV. Its currently widely used as a part of highly active antiretroviral therapy. The current study is done to see the effect of zidovudine on fetal length & fetal weight of swiss albino mice.

**Material & method:** Zidovudine was given to mice in doses of 50,100 & 150 mg/kgbw. Length & weight of fetuses were measured.

**Result:** Dose dependent decrease in fetal length & fetal weight was observed.

**Conclusion:** In this study we concluded that zidovudine is teratogenic to developing mice & should be cautiously used in clinical cases.

**Keywords:** Zidovudine, teratogen, HIV, fetal length, fetal weight

### Introduction

Zidovudine was the first antiretroviral agent to demonstrate clinical efficacy in patients infected with HIV and was introduced in 1987 for the treatment of AIDS [1]. Women of childbearing age represent an increasing proportion of HIV seropositive persons [2]. Although the drug crosses the placenta during first trimester [3], the drug is administered from 14 weeks of gestation because of its reservation as a potential teratogen [4].

Zidovudine belongs to a class of antiretroviral drug called as Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Zidovudine is a prodrug and must be phosphorylated in lymphocytes in order to exert its antiviral action. Zidovudine is first phosphorylated to their monophosphate by thymidine kinase, followed by a second rate-limiting phosphorylation step which is carried out by thymidylate kinase. The diphosphate product is further phosphorylated by the enzyme diphosphate kinase to yield deoxynucleoside-5'-triphosphate, the active form against HIV replication [5].

Looking at very few and inconclusive reports about the teratogenicity of zidovudine the present study has been undertaken. The aim of the present study is to see the effect of zidovudine on the development of mice, so, the drug has been given from day 6 to day 16 of the gestation, which is the period of organogenesis.

### Material and Method

The present study was conducted in the Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Adult female swiss albino mice weighing 20-25 gm (average age of 80-100 days) were used after approval of institutional ethical committee. These animals were obtained from animal house of Department of Anatomy, IMS, BHU Varanasi.

The animal house was maintained at an ambient temperature of 25+/- and 50-60% relative humidity with 12h: 12h light dark cycle. The animals were housed in polypropylene cages with husk bedding. They were fed on pelleted diet obtained from local Pashu Ahar Kendra and tap water, ad libitum.

The female mice in their pre-oestrous phase were transferred in the evening to the cages containing male mice in the ratio of 2:1. The presence of vaginal plug on the following morning indicated pregnancy and was designated as day zero (0) of gestation. In case of doubt the plug was examined microscopically for the presence of sperms. Each pregnant mice was separated out and housed individually in different cages.

The pregnant mice were divided into following groups  
 Group 1: control (given equivalent amount of tap water)  
 Group 2: Treated with Zidovudine 50mg/kg/bw from day 6 to day 16 of gestation.  
 Group 3: Treated with zidovudine 100mg/kg/bw from day 6 to day 16 of gestation.  
 Group 4: Treated with zidovudine 150mg/kg/bw from day 6 to day 16 of gestation.

Zidovudine was obtained from CIPLA industries, Goa. Each tablet contained 300 mg of the drug. Before treatment one tablet was dissolved in 25 ml of tap water. The animals were weighed and dose of the drug was adjusted in the proportion of 50 mg/kg bw for group 2, 100 mg/kg bw for group 3 and 150 mg/kg bw for group 4. Drug was administered by oral gavage. Control groups were similarly treated with the same volume of tap water on the same days of pregnancy. Food and water were given ad-libitum.

The mice of each group were sacrificed on day 19<sup>th</sup> of gestation by deep ether anesthesia and fetuses were collected after uterotomy. In this procedure the uterine horns were exteriorized after opening the abdomen by midline incision. The sacs were inspected for sites of resorption and viable fetuses were collected, blotted dry and weighed. Crown rump lengths (CRL) of the fetuses were recorded with the help of graph paper.

**Observation**

**Fetal weight**

On examination dose dependent decrease in fetal weight was

observed. The mean weight of fetuses of group-1 (control) was 1.27mg. While that of group-2 (50mg/kgbw) and group-3 (100mg/kgbw) was found to be 1.21mg and 1.07mg respectively. Weight of the fetuses of group-4 (150mg/kgbw) was greatly reduced with a mean weight of 0.21mg. On statistical analysis there was no significant difference in weights between group-1 and group-2 ( $p>0.05$ ), but a significant difference in weight was observed when weight of group-1 was compared to group-3 and group-4 ( $p<0.0001$ ). Among the treated groups (i.e group-2 v/s group-3 v/s group-4) there was significant weight reduction ( $p<0.0001$ ). (Table 1).



**Fig 1:** Dose dependent decrease in fetal length (from left to right: group 1, group 2, group3 & group4)

**Table 1:** depicting the effect of drug treatment on fetal weight in different groups

Dependent variable	Conditions			
	Group-1 (control) Mean (SD)	Group-2 (50mg / kgbw) Mean (SD)	Group-3 (100mg / kgbw) Mean (SD)	Group-4 (150mg / kgbw) Mean (SD)
Fetal weight (mg)	1.27 <sup>a</sup> (0.14)	1.21 <sup>A</sup> (0.09)	1.07 <sup>B</sup> (0.11)	0.21 <sup>C</sup> (0.31)

<sup>A, B, C</sup> – common superscripts show no significant difference (Post hoc using Tukey HSD)

**Fetal length**

On examination a dose dependent decrease in fetal length was observed. The mean length of group-1 was found to be 27.73mm, group-2 26.52mm, group-3 25.12mm and group-4 9.99mm.

On statistical analysis there was significant decrease in length

between group-1 and group-2 ( $p<0.05$ ). Highly significant decrease in length was observed between group-1 and group-3 ( $p<0.001$ ) and between group-1 and group-4 ( $p<0.001$ ). Among the treated group also there was significant decrease in fetal length ( $p<0.005$ ). (Table 2) (Figure 1)

**Table 2:** Depicting the effect of drug treatment on fetal Height in different groups

Dependent variable	Conditions			
	Group-1 (control) Mean (SD)	Group-2 (50mg/kgbw) Mean (SD)	Group-3 (100mg/kgbw) Mean (SD)	Group-4 (150mg/kgbw) Mean (SD)
Fetal height (mm)	27.73 <sup>a</sup> (1.40)	26.53 <sup>b</sup> (0.64)	25.12 <sup>c</sup> (0.56)	9.99 <sup>d</sup> (5.50)

<sup>a, b, c, d</sup> - common superscripts show no significant difference (Post hoc using Tukey HSD)

**Discussion**

Zidovudine is a prodrug which is first phosphorylated to zidovudine-monophosphate and then into zidovudine bi and tri phosphate. Zidovudine-monophosphate is found to be toxic to mitochondria and it induces degeneration in mitochondria leading to mitochondrial DNA depletion and hence death [6]. Zidovudine also binds with viral DNA as well as host DNA and prevents its chain elongation. This may also result in cell death of the embryo.

The critical period of zidovudine toxicity in murine embryos is between ovulation and implantation period and suggested that it directly suppresses cell division in the pre implantation

conceptus [7]. They further commented that exposure to zidovudine at any time before blastocyst formation results in immediate inhibition of cleavage and causes cell degeneration [7]. Inhibition of cleavage in a developing pre-blastocyst by zidovudine may prohibit development beyond blastocyst stage as a critical number of cells in inner-cell mass is required for further development [7].

On gross observation there was a dose dependent decrease in fetal weight and fetal length that was statistically significant. This could be explained on the basis of reports which have established that zidovudine exposure during first half of murine pregnancy results in decreased cell division and fetal

hepatic and bone marrow toxicity<sup>[8]</sup>. This may also be due to inhibition of DNA polymerase- $\gamma$ , the enzyme responsible for replication of mitochondrial DNA leading to mitochondrial depletion<sup>9</sup>. It has been seen that morphological maturation of mitochondria coincides with the blastocyst development and any insult during this period might induce maximum cytotoxicity leading to the death of embryo.

### Conclusion

On gross examination, there was dose dependent decrease in fetal weight and length. There was no significant difference in weights between group-1 (control) and group-2 but there was a significant weight reduction when group-1 was compared to group-3 and group-4. Among treated groups also there was significant weight reduction. Significant growth retardation (CR length) was also noted between the control and treated groups. The result was significant when compared among the treated groups.

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