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DESVENLAFAXINE INDUCED CONGENITAL MALFORMATIONS IN SWISS ALBINO MICE

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ABSTRACT

Desvenlafaxine is a bicyclic phenylethylamine compound which inhibit neuronal uptake of 5-HT and norepinephrine,with significantly lower in vitro affinity for norepinephrine. This drug is used for the treatment of depressive disorder. In the present study, desvenlafaxine is administered by oral gavage at the dose of 80mg/kg body wt from gestational day(GD) 1 to 18.The control group was treated with equivalent amount of tap water for the same duration of gestation. The fetuses were collected on GD 19 after uterotomy and observed for gross malformations if any. Desvenlafaxine treated mice showed significant weight reduction and severe hemorrhagic patches in different parts of the body. Similarly, malrotated, flexed and extended limbs were also observed in the fetuses of treated groups. These results suggested that desvenlafaxine induce teratological changes in Swiss albino mice.

Key words: Teratolgy, Phenylethylamine, Antidepressants

Desvenlafaxine is one of these antidepressants classified as atypical antidepressant. It is bicyclic phenylethylamine compound and is structurally and chemically unrelated to other available antidepressants and anxiolytics including other antidepressants classified as SNRIs[1]. Desvenlafaxine succinate (DVS;Prestiq) is an extended-release formulations of the succinate salt of O-desmethylvenlafaxine(ODV), the principal active metabolite of venlafaxine. Venlafaxine is metabolized to desvenlafaxine by cytochrome P450 2D6(CYP2D6). Desvenlafaxine is not metabolized by CYP2D6 and is excreted unchanged or after conjugation. The SNRIs are also sometimes referred to as dual reuptake inhibitors as they are mediated by concomitant blockade of neuronal serotonin(5-HT) and norepinephrine uptake transporters. The drug has weak binding affinity for the dopamine transporter and does not cause substantial changes in extracellular dopamine concentration. Desvenlafaxine is more potent inhibitors of 5-HT reuptake than of NE reuptake.[1,2,3] Decreased presynaptic serotonin and norepinephrine uptake increase the synaptic concentration of these neurotransmitters. These effects are thought to be responsible for desvenlafaxine's antidepressant efficacy.

Desvenlafaxine is a novel drug, classified as pregnancy category C, indicating that there are no adequate and well controlled studies in pregnant women and that the drug should be used during pregnancy only if it is clearly needed. [4] In humans, desvenlafaxine when taken in the third trimester of pregnancy can cause serious neonatal complications like respiratory distress, cyanosis, apnea and seizures. [5] Desvenlafaxine is excreted in breast milk and may cause adverse effect in infants who are breast-fed. [6] The highest doses of desvenlafaxine, 80 mg/kg(V 80), reduce the food intake of pregnant rats, resulting in different rates of body weight gain during treatment.[7] Vulnerability of pregnancy to mood disorders such as panic disorders was recognized only recently. [8,9]

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Table 1: Weight of fetus

Group	Mean±SD	p-value
Group I	1.53±0.38	
Group II	1.18±0.07	0.032
Group III	0.85±0.06	

Table 2: Length of fetus

Group	Mean±SD	p-value
Group I	29.16±2.56	
Group II	25.33±1.36	0.001
Group III	16.33±2.80	

Pharmacological therapy of depression or anxiety during pregnancy creates the clinical dilemma of exposing the unborn brain to psychoactive drugs. Since the developmental toxicology of this drug is not studied much so we have taken this work to study deleterious effect of this drug on development.

MATERIALS AND METHODS:

The present study was conducted in the Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, and Varanasi. Adult female Swiss albino mice weighing 25-30 gm were used after approval of institutional ethical committee. The animal house was maintained at an ambient temperature of 25±2 ^{0}C and 50-60% relative humidity with 12h light dark cycle each with free access to food and water. The animals were housed in polypropylene cages with rice husk

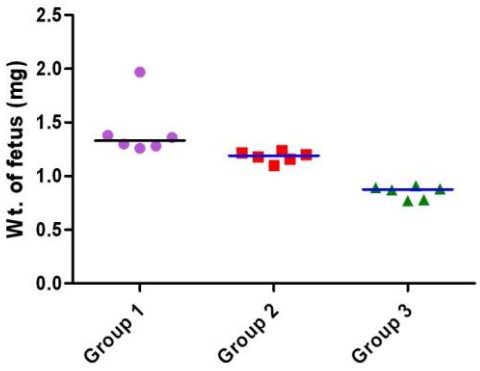

Fig. 1 : Comparision of fetal weight

bedding. The female mice 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. The animals were divided into three groups. Group 1 mice termed as control received distilled water. Group 2 mice received desvenlafaxine (IPCA, Mumbai) orally at a dose of 80mg/kg body weight from GD 1 to GD 6 and group 3 mice received the same drug from GD 1 to GD 18. There were 6 mice in each group. Mice of each group were sacrificed on day 19th of gestation by deep ether anesthesia and fetuses were collected after uterotomy. The collected fetuses were blotted dry and weighed. Crown rump lengths (CRL) of the fetuses were recorded with the help of graph paper and were examined for external abnormalities if any including cleft palate.

The data were expressed in a form of Mean±SD and analyzed by applying ANOVA test using SPSS software.

RESULTS

There was significant difference between the groups in the fetal weight ($p<0.05$). The lowest fetal weight was observed for group 3 and highest for group 1 (Table 1 and Fig. 1). Although the fetal weight was decreased in treated groups as compared to control, but the difference between group 1 and 2 was non-significant($p>0.05$) while

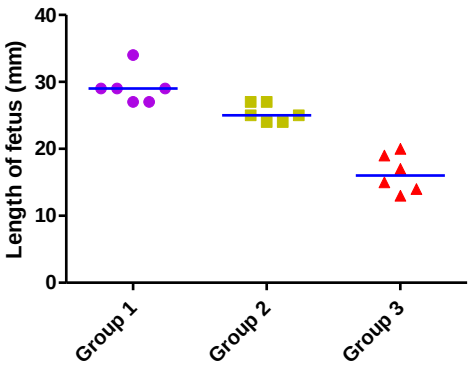

Fig. 2 : Comparison of fetal length

that between group 1 and Group 3 was significant ($p<0.05$). Similarly, although the fetal weight of group 3 was lower than that of Group 2, but they were not statistically significant ($p>0.05$).

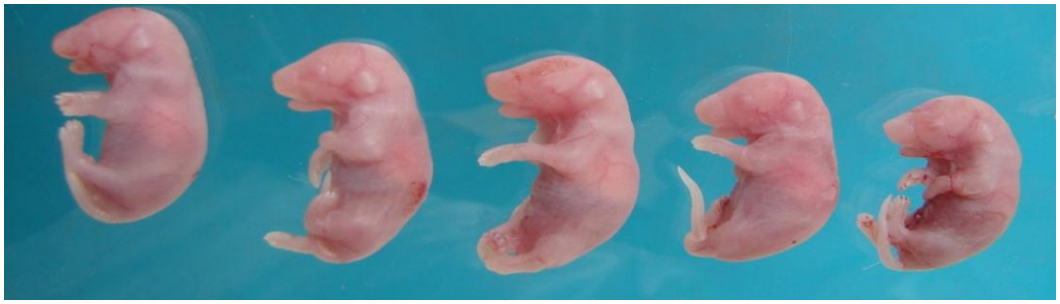

Fig. 3: Feuteses of group 1

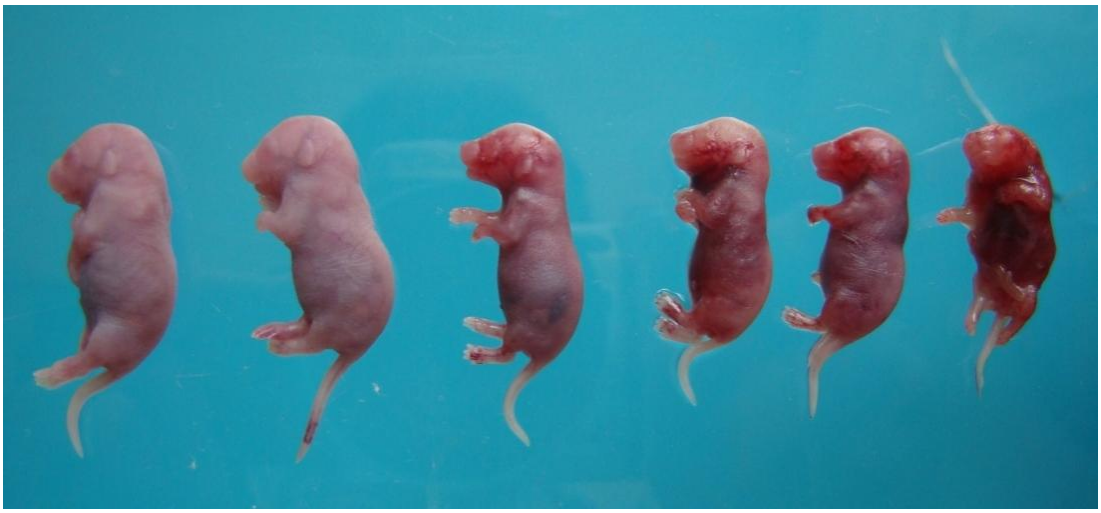

Fig. 4; Fetuses of group 2

Mean crown-rump length also significantly differed between the groups ($p<0.05$). The maximum crown-rump length was observed for group 1 and minimum for Group 3 (Table 2 and Fig. 2). The fetuses of group 2 showed significant ($p<0.05$) growth retardation when compared to the fetuses of group 1. the fetuses of group 3 also followed similar trend and showed highly significant ($p<0.01$) growth retardation when compared with fetuses of group 1 and significant ($p<0.05$) growth retardation in comparison to group 2.

In control group, no malformation of fetuses was observed (Fig. 3). In fetuses of group 2, malrotated or extended forelimbs were seen. Some of the fetuses also showed hematoma over the snout and anteriorly shifted eyes along with periocular edema (Fig. 4). In fetuses of group 3, severe hemorrhage was observed all over the body of fetuses including limbs and tail. Malrotated, flexed and extended fore- limbs were seen. Some of the fetuses also showed skin tag near the cervical area. A few fetuses showed constricted hemorrhagic ring on the hind limb (Fig. 5).

DISCUSSION

O-desmethylvenlafaxine(ODV), or simply desvenlafaxine, the primary active metabolite of venlafaxine, was introduced in 2008 as desvenlafaxine succinate, a sustained-release formulation for the treatment of depression.[4] Since this drug is an active metabolite of venlafaxine and has similar pharmacological activity to that of venlafaxine[1]. In vitro studies indicate that desvenlafaxine is somewhat more potent for blockage of norepinephrine transporters than the parent drug and the succinate salt was chosen to enhance bioavaiability[4]. According to a report published in drug monograph metabolism of desvenlafaxine in human was similar to that in mice, rats and dog[10].

There are large number of women who suffers from depression are of child-bearing age. When a depressed woman becomes pregnant, she may

continue the drug as 50% of the pregnancies are unplanned [11]. The current study showed that desvenlafaxine reduce the birth weight as well as the length of the fetus and induce some congenital malformation in offspring when the drug was given during early pregnancy and the magnitude of congenital malformation as well as birth weight and length becomes more severe when the drug

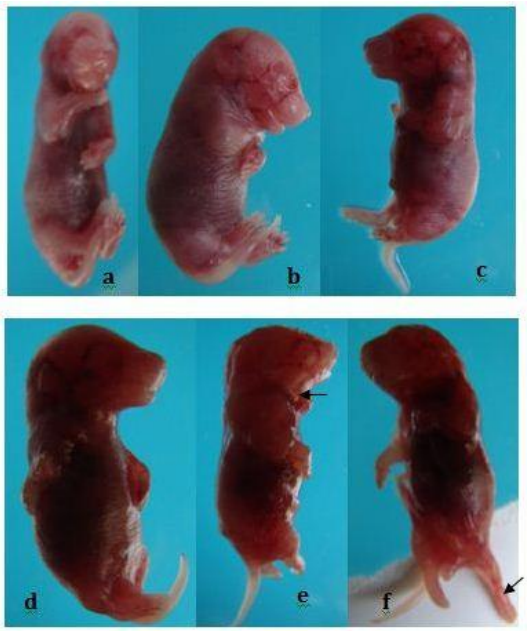

Fig. 5; Fetus of group 3, showing flexed neck, globular flattened snout flexed and medially rotated forelimb, slightly extended forelimb and open mouth(a),open eyelids surrounded by haemorrhagic sports, congested cranial and facial veins and congested veins of the paws(b), extensive hemorrhage around head, neck, ventral surface of the body and hind limbs(c), extended forelimb and flexion deformity of hind limbs (d), anteriorly shifted eyes surrounded by hemorrhage extended forelimb and extensive hemorrhage all over the body and skin tag (←) seen in the anterior cervical region(e),extensive hemorrhagic constriction ring present in the hind limb (←)(f).

was given throughout pregnancy. da-Silva *et al.* (1999) also reported reduced birth weight in the offspring when the drug was introduced during the third week of gestation[7].

Bioavailability of desvenlafaxine after oral administration is 80%[3] and placental passage of antidepressants has also been documented [5,6]. Antidepressant and metabolite concentrations were detectable in the umbilical vein blood in 87% of the samples collected [6]. The drug is metabolized principally through O-glucuronidation pathway as well as through oxidative metabolism like N-methylation, hydroxylation, and formation of N-oxide. The metabolites of the drug formed during oxidative N-demethylation, hydroxylation process and accumalation of the unchanged des-venlafaxine, des-venlafaxine-o-glucuronide conjugated and unconjugated N-desmethyl metabolite may increase the oxidative stress resulting in the damage such as subcutaneous hemorrhage and congenital malformations which was seen in the present study.

It has been postulated that, at clinically relevant doses, acute treatment with SSRIs and SNRIs do not acutely elevate extracellular 5-HT levels in terminal brain areas[2]. However chronic antidepressant treatment, such as desvenlafaxine, causes immediate increase in extracellular 5-HT in the presence of SSRI or SNRI, probably mimicking their long term effect. [12-17.] The uninhibited increase in serotonin and nor-epinephrine will probably down regulate its receptors and ultimately decrease its production. As these neurotransmitters are important for homeostasis and for normal developmental process, its transient or permanent deficiency may contribute to various defects as observed in this study.

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