EFFECT OF LYSERGIC ACID DIETHYLAMIDE ON OESTRUS CYCLE AND OFFSPRING IN RATS

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Summary: Lysergic acid diethylamide (LSD-25) was studied for its effect on oestrus cycle and offspring in rats. The drug in a single dose of 5 μg/kg sc did not produce any alteration in the normal four day oestrus cycle of rats. Though an oral dose of 200 μg/kg given in early pregnancy did not produce any change in either litter size or foetal mortality rate, 100 and 200 μg/kg sc given at a similar period of pregnancy decreased litter size, produced stunted foetuses, increased foetal mortality rate and the number of resorptions as evidenced by increase in vascularity and beading in the uteri of drug treated females. No unusual specific deformities were noticed in either live or dead foetuses.

Key words: lysergic acid diethylamide, foetal mortality, rate, litter size

INTRODUCTION

Cases of malformation in infants born of lysergic acid diethylamide (LSD-25) users have been reported (3, 9, 12, 13, 21). The drug is reported to produce teratogenicity in mice (4) rats (1, 2) and hamsters (11, 14). Other workers did not observe any teratogenic effect either in rats (20) hamsters (7) or rabbits (10). The drug is also reported to cross the placental barrier (14).

It is, therefore, apparent that the influence of LSD-25 on offspring and genetics is a much controversial subject and offers a wide field for further study in the light of the agent being unduly misused. The present study reports the effect of LSD-25 on oestrus cycle, conception and offspring in rats.

MATERIALS AND METHODS

Laboratory bred albino rats of proven fertility weighing 130-150 g were used. Each treatment group consisted of ten rats and a corresponding number of saline controls. They were housed in single cages except at the time of mating and were allowed food and water ad libitum.

Drugs: LSD-25 was obtained from Sandoz Ltd. as a pale yellow amorphous readily soluble powder. Stock solution of 1 mg/ml was made in pyrogen free distilled water and was stored for not more than four days at a time. Solution for injection was made daily from the stock and was given in the volume 0.5 ml/100 g body weight.

Effect of LSD-25 on oestrus cycle: The oestrus cycle of female rats were studied by taking daily vaginal smears and staining with haematoxylin. Only animals having two normal four day
cycles were used for the subsequent studies. After a single subcutaneous injection of 5 μg/kg of the drug, daily vaginal smears were studied for two weeks.

**Effect of LSD-25 on offspring when administered prior to mating:** Male and female rats were injected 5 μg/kg of the drug subcutaneously for three days prior to mating with untreated females and males respectively. The presence of the vaginal plug indicated successful mating. The pregnant animals were separated, kept in individual cages and weighed daily until littering. The litters were examined as to litter size, any foetal abnormality gross or otherwise, number of stillborn and foetal deaths within one week.

**Effect of LSD-25 on offspring when administered early in pregnancy:** Adult male and female rats were mated for two days in the ratio 1:1. The pregnant rats were separated and housed in single cages. Each group was treated on the 4th day of pregnancy with: LSD-25: 5, 10, or 200 μg/kg sc. In addition, 5 animals were treated orally with 200 μg/kg.

Daily weights were recorded and the animals were allowed to proceed to term. Litter were examined as mentioned earlier. Animals which failed to deliver on the expected date were autopsied a few days later, and their uteri and ovaries examined.

**RESULTS**

LSD-25 in the dose of 5 μg/kg sc did not produce any change in the normal four day oestrous cycle of rats. No significant change either in average litter size or foetal mortality rate was seen when either males or females were treated with 5 μg/kg sc of LSD-25 prior to mating. All foetuses of the male treated group were normal whereas in the female treated group one was shunted weighing only 2.5 g (average normal weight 10.0 g) and one was macerated.

**TABLE I:** Effect of LSD-25 on the offspring of rats. LSD-25 was given to either parent prior to mating and to females on the 4th day of pregnancy.

<table>
<thead>
<tr>
<th>Group and treatment</th>
<th>No. of rats used</th>
<th>No. that littered</th>
<th>Mean litter size ± S.E.</th>
<th>Percentage foetal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Males prior to mating saline control</td>
<td>10</td>
<td>10</td>
<td>8.0 ± 0.59</td>
<td>8.4</td>
</tr>
<tr>
<td>LSD-25 5 μg/kg sc</td>
<td>10</td>
<td>10</td>
<td>7.7 ± 0.93</td>
<td>9.87</td>
</tr>
<tr>
<td>2. Females prior to mating saline control</td>
<td>10</td>
<td>10</td>
<td>6.5 ± 0.65</td>
<td>12.91</td>
</tr>
<tr>
<td>LSD-25 5 μg/kg sc</td>
<td>10</td>
<td>10</td>
<td>6.2 ± 1.45</td>
<td>19.20</td>
</tr>
<tr>
<td>3. 4th day of pregnancy saline control sc</td>
<td>10</td>
<td>10</td>
<td>7.2 ± 0.47</td>
<td>15.27</td>
</tr>
<tr>
<td>LSD-25 100 μg/kg sc</td>
<td>10</td>
<td>10</td>
<td>6.7 ± 1.13</td>
<td>19.42</td>
</tr>
<tr>
<td>LSD-25 200 μg/kg sc</td>
<td>10</td>
<td>10</td>
<td>6.4 ± 0.97</td>
<td>*34.36</td>
</tr>
<tr>
<td>Saline control orally</td>
<td>10</td>
<td>10</td>
<td>5.3 ± 0.27</td>
<td>*37.58</td>
</tr>
<tr>
<td>LDS-25 200 μg/kg orally</td>
<td>5</td>
<td>5</td>
<td>7.0 ± 0.71</td>
<td>11.40</td>
</tr>
</tbody>
</table>

*P < .01

Oral administration of drug sc produced interesting findings. The 200 μg/kg dose-related increase in weight range from 1 to litter, though the all these rats showed beaded arrested. In the g another one three were noted. Postmortem

Our data show cycle in rats, 5 μg/g foetus. The line of drug sc could damage in human in vivo could necromice treated with
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When LSD-25 was given to females on the 4th day of pregnancy the observations were as follows: The 200 μg/kg s.c. dose significantly (P < 0.01) reduced the mean litter size. A dose-related increase in the foetal mortality rate was also observed. The increase with 100 μg/kg s.c. were statistically significant (Table 1). 8.7% of born foetuses were stunted with a weight range from 2.0—3.5 g (Fig. 1); otherwise they did not show any gross pathology. An interesting finding was that, with the higher doses of LSD-25 given s.c. 40% of the animals failed to litter, though they did become pregnant as evident from the autopsy findings. The uteri of all these rats showed increased vascularity and thickened endometrium. In some, the uterine horn showed beaded appearance (Fig. 2); obviously the growth of the embryo must have been arrested. In the group receiving 200 μg/kg s.c., one mother died four days after littering and another one three days after injection of the drug. In the latter, bleeding from the vagina was noted. Postmortem examination showed thickened and haemorrhagic uterus.

Oral administration of the drug (200 μg/kg) did not produce any significant change in the litter size, or foetal mortality and only one out of the 41 foetuses born was stunted (Table 1).

DISCUSSION

Our data suggest that 5 μg/kg of LSD-25 s.c. did not affect the normal four day oestrous cycle in rats, 5 μg/kg (s.c) dose given to either parent prior to mating also did not affect the foetus. The linear increase in foetal mortality rate seen with 5, 100 and 200 μg/kg doses of drug s.c. could have been due to the drug producing chromosomal damage. Chromosome damage in human leucocytes in vitro and vivo has been reported (6, 8, 15, 21) but these effects in vivo could not be reproduced by others (5, 16, 18, 19). Meiotic chromosome damage in mice treated with high doses of LSD-25 has also been observed (17).
Alexander, et al. (1, 2) reported an increase in the proportion of deaths during gestation, abortions, resorptions, runting, still births and offspring mortality even with a single dose of 5 μg/kg of LSD-25. In our study, though this dose did not produce any effect on offspring, higher doses of 100 and 200 μg/kg (sc) significantly increased the foetal mortality. Autopsy of non-littering females showed increased vascularity of uteri, thickened endometrium, and arrest of foetal growth. These are in accord with those of Alexander et al. (1, 2). We did not interrupt pregnancy after treatment but the animals were permitted to come to term. Auerbach and Rugowski (4) who interrupted pregnancy on the 7th day in mice observed a

six-fold increase in the number of deaths and indicate any specific pathologic effect on the foetus. However, detailed pathologic examination was not done.

No conclusion could be drawn from our present study even 200 μg/kg of LSD-25 orally, particularly in litter size, and increased foetal mortality. The activity of a drug in our studies in humans being compared to those in rat and hamsters, human foetuses are considered to be a more sensitive test system for the activity of a drug.

The authors thank Dr. Hoffman and Professor V. Iswariah, Howrah for their suggestions.

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A six-fold increase in the number of deformities in the CNS of embryos. Our studies did not indicate any specific pattern of damage to organs except that some animals were stunted. However, detailed pathological work may reveal changes which we were unable to detect.

No conclusion on the teratogenic potential of LSD-25 can be drawn from our study. 5 µg/kg of LSD-25 orally would be the dose comparable to human consumption. In the present study even 200 µg/kg orally did not produce any offspring damage. Only subcutaneous administration of 100 and 200 µg/kg doses produced increase in off-spring mortality, decrease in litter size, and increase in the number of resorptions. These doses are far in excess of the comparably human doses customarily employed for self medication. Moreover, toxic activity of a drug in one species need not imply toxic activity in other species. Detailed studies in humans being LSD-25 chronically and the effects of the drug on pregnancy and human foetuses are essential. However, caution is indicated in the indiscriminate use of the drug.

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REFERENCES


DEVELOPMENT OF REPRODUCTIVE METHODS

U. K. S.
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Summary: In vitro: progesterone, norethindrone, NEA showed sufficient and found to be much over a period of th been developed an pregnancy has been referred.

Key words: re

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