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REFERENCES

1. Ghose T K and Ghosh P, *J. Appl. Chem. Biotechnol.*, 1978, 28, 309.
2. Martin C, Negro M.J, Alfonso M, and Saez R., *Biotechnol. Bioeng.*, 1988, 32, 341.
3. De Padilla F H and Hoskins F. H, *J. Agri. Food Chem.*, 1968, 16, 735.
4. Updegraff D. M, *Biotechnol. Bioeng.*, 1971, 13, 77.
5. Ooshima H, Ishitani Y and Harano Y, *Biotechnol. Bioeng.*, 1985, 27, 389.
6. Ladisch M. R, Ladisch C M and Tsao G T, *Science.*, 1978, 201, 743.
7. Saddler J N, Brownell H. H, Clermont L. P and Levitin N, *Biotechnol. Bioeng.*, 1982, 24, 1389.
8. Ghose T. K, *Biotechnol. Bioeng.*, 1969, 11, 239.
9. Mandels M, Andreotti R and Roche C, *Biotechnol. Bioeng. Symp.*, 1976, 6, 21.
10. Gould J. M and Freer S.N, *Biotechnol. Bioeng.*, 1984, 26, 623.
11. Miller G. L, *Analyt. Chem.*, 1959, 31, 426.
12. Forney L. J, Reddy C. A, Tien M and Aust S. J, *J. Biol. Chem.*, 1982, 257, 11455.

Effect of Isoxsuprine Hydrochloride on Onset of Labour in Pregnant Rats.

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The effects on spontaneous labour of Isoxsuprine hydrochloride (I), a β_2 -adrenoceptor agonist¹ were studied on pregnant rats. Oral administration of (I) from day 13 to 21 of gestation in dose of 2.5 mg/kg/day or higher effectively delayed the onset of labour, slight increase in duration of parturition (DOP) and average weight of pup (AWP) were observed. No adverse effects on the gestating animals or fetuses were noted. The rat model appears to be a simple, reliable and cost-effective method for evaluating uterine relaxants.

IN our search for alternative animal models for evaluating uterine relaxants we chose the rat model as it appears to have number of advantages over the existing test systems^{2,3}. The period of second and third trimester of pregnancy when the incidence of premature labour is significantly higher⁴

was chosen for the present study. Instead of measuring uterine tone, the onset of parturition was noted to record the delay in labour. Other related parameters such as duration of parturition (DOP), average litter size (ALS), average weight of pup (AWP), the mortality of mother and fetus and bleeding at parturition were also noted.

§ For Correspondence

Table : Effect of Isoxsuprine Hydrochloride on Labour Parameters

| MEDICATION | MEAN GESTATION PERIOD±SD | DELAY IN ONSET OF LABOUR (h) | DOP±SD (h) | AWP± SD (g) | ALS± SD |
|-----------------|--------------------------------|---------------------------------------|----------------|-------------------|-----------------|
| Distilled water | 512.00±3.20 | ---- | 1.12± 0.01 | 6.26± 0.06 | 10.17± 0.750 |
| I (2.5mg/kg) | 530.01±1.29# | 18.09 | 1.34± 0.07# | 6.62± 0.09# | 10.00± 0.087 |
| I (5mg/kg) | 537.97±2.20# | 25.97 | 1.51± 0.03# | 6.47± 0.09# | 10.97± 0.081 |
| I (10mg/kg) | 543.63±1.06# | 31.63 | 1.83± 0.04# | 6.58± 0.05# | 10.83± 0.075 |

P < 0.001 and #P (Statistical significance evaluated by comparing control with treated using Pooled-t test.)

Holtzman-bred, Sprague-Dawley rats weighing between 200-220 g were used. A male rat was placed with two female rats at 14.00 h and removed at 20.00 h. Vaginal smears were taken at 08.00 h next morning. Pregnancy was confirmed by sperm positivity and 00.00 h of that day was considered as zero time for calculation of gestation period.

A total of twenty four pregnant rats were used in the study. The animals were housed in individual cages at constant temperature (24°) with cyclic light (14 h) and darkness (10 h). They were given food and water ad libitum. Animals were weighed daily till delivery and inspected hourly from day 21 of gestation. Duration of parturition was timed from birth of first pup until delivery of the entire litter. Litter size and average weight of pup and bleeding at parturition were noted for each animal. A stock solution containing 2 mg/ml of isoxsuprine HCl was prepared in distilled water.

The test animals were divided into four groups (six in each group), one control and three treated with 2.5, 5, 10 mg/kg/day of (I) and administered twice a day at 10.00 and 17.00 h orally on day 13 to 21 of

gestation. Animals in control group were given 0.25 ml distilled water at the same time.

The animals in control group delivered on day 22 while those in treated groups delivered on day 23 of gestation. The statistical significance was evaluated by subjecting the data to computer package BASICA and comparison was made by using Pooled-t test. Gestation period of the animals along with other labour parameters are given in the table.

The results indicate that administration of (I) orally during the second and third trimester of pregnancy in rats significantly increased the gestation period in a dose-dependent manner. This increase in gestation period can be attributed to the direct effect of (I) on uterine smooth muscles by stimulating the β_2 -adrenergic receptors. The suppression of uterine activity by (I) may help maintain the progesterone level for a longer period of time and can account for the delayed labour⁴. The maintenance of progesterone level can suppress the synthesis and secretion of oxytocin and delay the onset of parturition. This may explain the dose dependent increase in gestation period and the duration of parturition. The prolonged gestation led to increase in average weight

of pup. No mortality was seen throughout the study and no fetus was born dead. Bleeding at parturition was normal in treated animals and no visible side-effects were evident during the study. All the treated animals exhibited delayed labour and it was highly significant (more than 24 h) at a dose of 5 mg/kg/day and above.

The present study indicated that the rat model is a non-invasive and yet a reliable method for evaluation of the effects of uterine relaxants on various labour parameters, notably the delay on onset of labour. The evaluation procedures were also simple and cost effective.

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REFERENCES

1. Csapo, A. I. and Herczeg, J.; *Am. J. Obstet. Gynaecol.*, 1977, 128, 482.
2. Laurensen, V. H.; *Am. J. Obstet. Gynaecol.*, 1975, 121, 597.
3. Siimes, A. S. I. and Creasy, R. K. ; *Am. J. Obstet. Gynaecol.*, 1976, 128, 1003.
4. Caritis, S. N.; *Drugs*, 1983, 26, 243.

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