REPRODUCTION IN RABBITS GIVEN ALTHESIN

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(Received 10th January 1973)

An ideal anaesthetic should not possess hormonal activity nor should it interfere with the processes of reproduction. Althesin, a new intravenous anaesthetic, contains two steroids, alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione) and alphadolone acetate (21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione) in 20% aqueous Cremophor EL (Badische Anilin und Soda Fabrik). Cremophor EL is polyoxyethylated castor oil, a non-ionic surface active agent. Althesin contains 9 mg alphaxalone and 3 mg alphadolone acetate/ml. The only endocrinological activity noted for Althesin has been a weak anti-oestrogenic effect in mice (Child, English, Gilbert & Woollett, 1972). Experiments have been undertaken to investigate whether the anaesthetic has any adverse effects on reproduction in rabbits. The results of similar studies on mice and rats have already been described (Child et al., 1972).

Rabbits of the Dutch breed were used. Each doe was mated two or three times in the course of a few hours (Day 0 of pregnancy) with a buck of proven fertility. The mated does were individually housed in wooden breeding hutches and provided with nesting material well before parturition.

Althesin was administered intravenously either once daily throughout pregnancy (0.2 ml/kg body wt) or on Days 26 to 31 of pregnancy (0.6 ml/kg body wt). Because of restricted breeding accommodation, the experiment had to be conducted in two parts. In the first part, twenty-eight nulliparous rabbits were used and the control animals received 20% aqueous Cremophor EL. The second part of the experiment employed fifteen multiparous animals and the control animals received 0.9% saline. Control injections (0.2 ml/kg body wt/day) were given intravenously throughout pregnancy. As the two parts of the experiment yielded similar results, they have been summed.

All the offspring were weighed weekly from weaning to 11 weeks of age. They were then culled to retain one male and two females from each litter; these were weighed weekly up to 21 weeks when the females were mated with their male sibling. Details of the ensuing pregnancies were recorded.

The sleep duration of the pregnant does receiving Althesin increased as gestation proceeded. Of the group receiving 0.2 ml/kg/day throughout pregnancy, sleep increased from 10.3±0.8 min on Day 1 to 13.5±1.3 min on Day 28 (significant, P<0.05) and, for the does receiving Althesin only for the final 6 days (0.6 ml/kg/day), sleep increased from 28.3±1.3 min on Day 26 to 34.3±2.8 min on Day 30 (not significant, P>0.05).

There was no significant difference in the growth rates of the pregnant does injected with either dose of Althesin compared with those of the control animals.
The reproductive performance of rabbits given Althesin in pregnancy is given in Table 1. The proportion of pregnant to mated does was not significantly altered by Althesin ($\chi^2 = 1.16$) nor did the anaesthetic affect gestation length, litter size or the ratio of weaned offspring to those born.

The growth of the offspring from weaning to maturity (Text-fig. 1) was similar in all groups, irrespective of the maternal treatment. The fertility of the offspring (i.e. number pregnant out of number mated) agreed with that of the
treated mothers (Tables 1 and 2). The maternal treatment also had no significant effect on the gestation length, litter size at birth or the ratio of young weaned to the number of young born.

The increase in the amount of sleep recorded as pregnancy progressed has also been observed in mice and rats given Althesin (Child et al., 1972). There seems little doubt that Althesin or its component steroids can pass the placental barrier in the rat, the ewe and woman. Card, McCulloch & Pratt (1972) demonstrated the presence of radioactivity in the fetuses of rats which received $^{14}$C-labelled Althesin. G. S. Dawes (personal communication) has demonstrated respiratory, cardiovascular and EEG changes in the fetuses of ewes which received the anaesthetic. Downing, Coleman & Meer (1973) have concluded, from the results of their use of Althesin in human obstetrics, that 'it does cross the placental barrier and in high doses it will achieve levels in the foetus that may cause significant neonatal depression'. The small increase in the duration of sleep of pregnant animals dosed with Althesin may therefore be a function of the increase in absolute dosage (administered on a body weight basis) and percentage transfer across the placental barrier.

As in the rat and mouse (Child et al., 1972), Althesin did not induce premature parturition in does at the large near-lethal dose given during the last days of pregnancy. This contrasts with the effect of hydrocortisone (Wagner, 1971) and dexamethasone (Kendall & Liggins, 1972), each of which triggers parturition in the rabbit when administered intramuscularly near the end of pregnancy.

As the work was carried out between August and January, the overall figure of 78% for the ratio of pregnant to mated does seems satisfactory. Napier (1963) estimated that 60% of mated does actually became pregnant. The values obtained for gestation length and for numbers in the litters at birth agree well with those of Adams, Aitken & Worden (1967), who cite 31-0±0-8 days and 6-3, respectively, for untreated animals, showing that our rabbits, with or without Althesin, behaved normally.

Reliable estimates of the fetal sex ratios could not be made because the young were not sexed until weaning. Adams et al. (1967) emphasized that 'when only a few litters are considered, the sex ratio may show wide variations', and some

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**Table 2. Reproductive performance of offspring from rabbits given Althesin in pregnancy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. pregnant/ no. mated</th>
<th>Group mean ± S.E.</th>
<th>No. of offspring weaned/no. of offspring born</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gestation length (days)</td>
<td>No. in litter at birth</td>
</tr>
<tr>
<td>Control *</td>
<td>7/8</td>
<td>30.9±0.5</td>
<td>5.3±0.2</td>
</tr>
<tr>
<td>Althesin †</td>
<td>7/7</td>
<td>31.4±0.5</td>
<td>4.9±1.0</td>
</tr>
<tr>
<td>Althesin ‡</td>
<td>5/7</td>
<td>31.2±0.4</td>
<td>5.4±1.0</td>
</tr>
</tbody>
</table>

* Six does received 20% aqueous Cremophor EL, five does received 0.9% saline; 0.2 ml/kg/day intravenously throughout pregnancy.
† 0.2 ml/kg/day intravenously throughout pregnancy.
‡ 0.6 ml/kg/day intravenously on Days 26 to 31 of pregnancy.
of the does (especially among the sibling matings) cannibalized and ‘scattered’ their young during the neonatal period. Althesin had no significant effect on this behaviour. The reason for the overall lack of maternal care is thought to be because the does, most of which were primigravid, were disturbed after giving birth, when the litter size was being assessed (Hafez, 1970).

It is concluded that Althesin produces no adverse effects on reproduction in the rabbit, nor does it affect the reproductive capacity of young born to treated does.

REFERENCES


