PRELIMINARY STUDIES ON THE EFFECTS OF HALOPERIDOL ON OVULATION IN ANIMALS

by

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Introduction

A number of tranquillizers such as chlorpromazine, chlordiazepoxide, etc. are known to possess antiovulatory and antifertility activity, considered mostly as side effects of the drugs. Haloperidol (Searle, India) a butopyronon derivative is used frequently, as tranquillizer. It is quite likely that the compound also may share some of the common property of other tranquillizers. The present work was therefore undertaken to evaluate the antiovulatory as well as antifertility effects, if any, of the compound in experimental animals.

Materials and Methods

Oestrous cycles in rats: Periodicity of oestrous cycles was determined in each rat amongst a group of 50, weighing between 100 and 120 gms. by examining the vaginal smear daily for 3 consecutive weeks by the method of Burn (1950). When the periodicity was well established, 36 of them showing most regular cycles were selected and divided into 3 equal groups. The animals of the first 2 groups were treated orally with Haloperidol in doses of 1 and 2 mg/kg respectively for 10 consecutive days. Animals of the last group received only normal saline orally for the same period and served as control.

Vaginal smears of all of them were examined microscopically daily during the period of either drug or saline treatment and were extended till the normal cycles appeared again, after stopping drug treatment.

Oestrous cycles in Mice: In the next set of experiments, the effects of Haloperidol in doses of 1 to 2 mg/kg were studied on the oestrous cycles of 36 virgin mice, divided equally in 3 groups bred and reared in this laboratory, following the exact principle described above.

Effect of Haloperidol on the Induced Oestrous Phase of Rats

Five consecutive oestrous cycles were studied as before in virgin female albino rats weighing between 80 to 100 gms after they were reared to maturity. Thirty-six animals with regular cycles divided into 3 equal groups were taken. Two groups received oestradiol benzoate 50 μg/kg on the 1st day and 100 μg/kg on the 5th day of cycle intramuscularly by the method of Dasgupta (1955). When continuous oestrous phase was well established after a period of 2 to 3 weeks, Haloperidol in a dose of 2 mg/kg was administered orally to individual animal of 1 group for 10 consecutive days. The animals of the second group were kept for

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study of continuous oestrous phase alone and the animals of the 3rd group served as saline control. During this study 1 animal of each group was sacrificed and reproductive organs were studied macroscopically and microscopically.

Fertility in Mice: Effect of the drug on fertility in mice was studied by observing the mating behaviour and occurrence of pregnancy in the animals. Thirty-six female virgin mice were divided into 3 equal groups and drug in doses of 1 and 2 mg/kg orally, was administered to animals of first and second groups respectively. Animals of the third group served as saline control. Drug treatment was started 7 days prior to their exposure to males in a ratio of 2:1 and continued for another 7 days after exposure. The females were then separated from males and kept under observation for noting any evidence of pregnancy or birth of litters.

Mating test in Rabbits: Female rabbits usually accept males during oestrous only which occurs after every 22 to 23 days. Absence of mating during this period along with the presence of non-cornified cells in the vaginal smear is considered as an ovulatory phase in rabbits. To study the effects of haloperidol on the ovulatory vis a vis oestrous cycles in rabbits, 18 virgin female animals weighing between 1.2 to 1.5 kg were divided into 3 equal groups and their normal cycles were determined by vaginal smear method for 3 conscutive cycles. Animals of the first and second groups were then treated with the drug orally in doses of 1 and 2 mg/kg respectively for 10 consecutive days, prior to their expected date of beginning of the cycle, while the animals of the 3rd group were treated orally with water only for the same period and served as control. All the animals were then paired with males for next 14 days, after which they were withdrawn. Their vaginal smears were examined daily for possible presence of semen and cornified cells, absence of which was considered as an evidence of non-occurrence of ovulation or oestrous and vice versa. Drug treated rabbits, who were found to refuse males at this period were exposed to them for next consecutive cycles, till they were observed to accept mating readily. This period was considered as the time required for the return of normal oestrous cycle after drug treatment.

Artificial ovulation in rabbits: 18 virgin adult rabbits, reared in this laboratory, prepared as above were divided into 3 equal groups. Haloperidol in doses of 1 and 2 mg/kg were administered respectively to animals of the first and second groups for 10 consecutive days. Animals of the third group served as control and received only water orally for the same period. Artificial ovulation was stimulated by glass rod according to the method of Porter *et al* (1957) which was confirmed by vaginal examination method.

Observations and Results

It was observed in the present study that in normal rats, oestrous cycles occurred at regular interval of 3-4 days. Haloperidol disturbed this periodicity significantly. Treated animals remained in a non-oestrous phase during the course of drug administration while the control animals maintained the natural periodicity of the cycles. Furthermore cessation of drug administration failed to re-establish the natural periodicity immediately, which appeared gradually after an intervention of 3-4 irregular cycles in between, extending for a period of 15-20 days.

In mice also, Haloperidol effectively suppressed the oestrous and produced irregularity in the next 2 or 3 consecutive cycles as observed earlier in rats with 2 mg/kg dose.

Mating behaviour of mice and rabbits: In both the species of animals, it was observed that drug treated animals refused males and did not accept mating while the controls behaved in usual manner. When the animals of the former groups were exposed to males after varying intervals, they again started accepting the mating in the usual fashion as a consequence of which they became pregnant and gave birth to normal litters. These observations therefore, suggested that haloperidol, administered orally continuously for several days disturped the oestrous cycles in mice and rats and suppressed ovulation in rabbits.

Effect on the induced oestrous phase of rats: In rats in the induced oestrous state, vaginal smear, after a period of 2-3 weeks without Haloperidol pretreatment showed only cornified cells (100%). On the other hand, in drug treated group a mixed picture consisting of both cornified and non-cornified cells was obtained.

On histological examination of ovaries in the induced oestrous state, a cystic change was observed. In the Haloperidol pretreated group, though the cystic change was noted corpus luteum was absent.

Artificial ovulation in rabbits: Artificial ovulation could be induced in controls but not in Haloperidol treated animals. Signs of ovulation was detected by examination of vaginal smear.

Discussion

The present study showed that Haloperidol effectively inhibited the oestrous cycles in mice, rat and rabbits in doses of 1 and 2 mg/kg of body weight. The drug also suppressed the artificially induced ovulation in rabbits and modified the mating behaviour of normal animals. Occurrence of pregnancies in mice and rabbits were also suppressed by the drug. All these effects of the drug were of reversible nature as evidenced by the reappearance of normal oestrous cycle in all of them, after the withdrawal of the drug at an interval of varying periods. It thus appeared that Haloperidol possessed significant reversible antifertility property.

The site and exact mechanism of action of haloperidol are not known yet. As observed by its effect on oesterdiol induced continuous oestrous phase in rats, the drug might have some anti-oestrogenic activity which might explain its antiovulatory and antifertility actions. On the other hand dopamine blocking activity of the drug as suggested by Bhargava *et al* (1970) may play the important role. It has been reported earlier (Bhargava *et al*) that during ovulation dopamine level is raised and ovulation can be induced by intravenous or intracerebroventricular injection of dopamine in rabbits (unpublished observation). Therefore, haloperidol probably inhibited the ovulation by blocking the action of dopamine. These findings are still under investigations.

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