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EFFECT OF NAPROXEN ON FERTILITY IN MALE RATS

by

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Abstract

The antifertility effects of naproxen, a prostaglandin synthesis inhibiting drug, were investigated in male rats. A dose of 14 mg/kg/day administered orally for 7 days caused a significant reduction in fertility which was reversible after withdrawal of the drug. It is suggested that the main cause for the antifertility effect is a change in fertilizing capacity of sperm brought about either by a change in semen biochemistry or by a physiological and/or ultrastructural lesion of sperm resulting from reduction in prostaglandin levels.

Introduction

The presence of prostaglandins has been demonstrated in seminal plasma of many species[1,6,9] including that of man[2,3,5,10]. Prostaglandins have been reported to be low in seminal plasma of men with otherwise unexplained infertility[2,3,5]. The prostaglandin synthesis inhibiting drug aspirin has been shown to suppress the level of prostaglandins in human semen[4]. Furthermore, fenclozic acid, another prostaglandin synthesis inhibitor has been shown to induce temporary sterility in male rats when administered orally[12]. These observations suggest that other prostaglandin synthesis inhibitors might warrant investigation as potential male contraceptive agents.

The present study reports the effects observed on fertility when naproxen was administered orally to male rats. Naproxen is a non-steroidal anti-inflammatory drug which blocks biosynthesis of prostaglandins[7] as does aspirin and fenclozic acid.

Materials & Methods

Animals

Healthy, sexually experienced, laboratory bred mixed strain rats (males weighing 250 - 275 g and females weighing 200 - 225 g) were used. They were housed in a well ventilated animal house at a temperature of 28 - 30C with a natural photoperiod (approximately 12 h. light and 12 h. dark daily). All rats recieved food (Rat pellets, Moosajees Ltd. and green leaves) and water **ad libitum**.

Preparation and administration of drug

Naproxen was administered by oral gavage as anaqueous suspension made in 1% methyl cellulose (methyl cellulose, low substitution, B. D. H. Chemicals Ltd. U. K.)

Six rats in each group received daily doses of 1 ml methyl cellulose (Group I, control), 7 (Group II), 14 (Group III) or 21 (Group IV) mg/kg of drug consecutively for 7 days between 10.00 and 12.00 hrs.

Fertility trials

A sexually experienced pro-oestrous female rat was paired with each of the males in the 4 groups 7th day prior to treatment, on the last day of the treatment and on the 7th day following the cessation of treatment. The behavioural response of the male to female was noted 3-5 hr. later. Vaginal smears were taken to confirm normal regular oestrous cycle and to check insemination. If sperm were present in the vaginal smears on the morning following pairing, their numbers in vagina were estimated. The number of morphologically abnormal sperms present was also simultaneously counted. In the absence of sperm daily smearings of the females were undertaken to check for pseudopregnancy. The females were sacrificed 10-12 days coitum and the numbers of implantation site present in the uterine horns were recorded.

Autopsy

Any animal which was found dead during the period of investigation was subjecetd to autopsy and the state of the major abdominal viscera and reproductive organs were examined grossly.

Statistics

The significance of differences in fertility between treated and control groups were analysed using Mann-Whitney non parametric test, taking P 0.05 as significant.

Results

The food intake and general health of the rats remained normal except in animals in group IV where mild to moderate suppression of food consumption, signs of stress and deterioration of health were evident during the drug treatment. Two rats of this group died on day 4 of the treatment period and autopsy revealed servere lesions in the stomach and in the small intestine. This was also accompanied by peritonitis. Organs of the reproductive system however, appeared normal.

Results of the fertility trials are given in Table I. Fertility of all rats in the four groups was normal prior to any treatment regimen. In group I neither the administration of the vehicle (1% methyl cellulose) nor its withdrawal produced a significant effect on fertility. In group II, one rat became sterile during treatment but fertility was restored to normalcy subsequent to withdrawal of the drug.

No depression in fertility was evident in other rats. In group III, two rats become infertile and another two became subfertile (less than 4 embryos) while the rest were practically unaffected. However, when this group is considered as a whole, the antifertility effect was significant (p 0.05, Mann Whitney test). In this group, fertility reached normal values at post treat-

ment matings. None of these three treatments had any marked effects on 1.) libido, as was evident by vigorous courtship and normal mating behaviour of the males, 2.) ejaculatory mechanism, as indicated by high vaginal sperm counts (5.25 - 7.87 million), and 3) morphology of sperm in vaginal smears, as judged by light microscopy. On the other hand, in group IV marked suppression in libido was evident in three rats since they failed to mate successfully as indicated by the absence of pseudopregnant state in the paired females. The other rat however, displayed normal sexual drive and produced 5 embryos. Libido and fertility became normal following the withdrawal of treatment.

Discussion

The results of the present study demonstrate that oral administration of naproxen, a prostaglandin synthesis inhibiting drug, to male rats at a dose of 14 mg/kg/day for 7 consecutive days caused a significant depression in fertility which was reversible following the withdrawal of treatment. A lower dose (7 mg/kg/day) was ineffective in suppressing fertility while the higher dose (21 mg/kg/day) produced undesirable side effects and was found to be toxic; two rats of this treatment group died on day 4 and at autopsy ulceration of the gastrointestinal tract and peritonitis were evident. Gastrointestinal lesions are a common side effect observed in prostaglandin synthesis inhibiting drug therapy[9]. Although the other four rats survived they were lethargic and showed a marked reduction in their disposition to court and to mate. There is no conclusive evidence for the precise mechanism of the antifertility action of the drug observed at the effective dose. However, many possibilities merit consideration. The rapid onset of the antifertility action during treatment together with the equally rapid reversibiilty following the withdrawal of naproxen strongly suggest that the drug acts on a post-testicular site/s. Since, sexual drive seemed unaltered as judged by vigorous courting and mating behaviour exhibited by the treated males this may indicate that the androgen output from testes is not altered markedly. Male libido is androgen-dependent[11] and the testes is the main source of androgens[11]. The vaginal sperm count of the females paired with treated males at the effective dose always had sperm in normal numbers and thus an action of the drug through an inhibition of the ejaculatory mechanism can be ruled out. On the countrary, naproxen has been shown to induce ejaculatory disturbances in man[13]. but this may well not be so with rats. Therefore, the antifertility effect observed in rats could be attributed to the suppression in the fertilizing potential of sperm possibly resulting from a physiological and/or ultrastructural lesion of sperm. Such a lesion could be brought about by a reduction in prostaglandin content in seminal plasma which, though not assessed, could have resulted from the prostaglandin synthesis blocking activity of the drug. A similar mechanism of action has also been proposed for antifertility effects observed in male rats following oral administration of fenclozic acid [12]. However, the possibility of naproxen molecules *per se* exerting an antifertility effect on extragonadal sperm cannot be excluded.

It seems therefore, that prostaglandin synthesis blockers represent a new group of drugs worthy of further investigation with a view to their development as potential male contraceptive agents.

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Table 1. Fertility performance of male rats prior to, insert comma during and following oral administration of naproxen for 7 days.

Group	Number of implantations		
	Pre treatment	*Treatment*	*Post treatment*
I(1% methyl cellulose)	6	7	7
	8	8	8
	10	9	10
	9	9	8
	8	8	8
	8	8	10
II (7 mg/kg Naproxen)	5	5	7
	9	7	10
	8	7	8
	10	0	5
	7	7	6
	9	6	9
III (14 mg/kg Naproxen)	9	9	9
	9	0	8
	8	0	7
	9	3	8
	9	4	8
	10	6	9
IV (21 mg/kg Naproxen)	8	a	a
	8	a	a
	9	N.M.	7
	10	N.M.	6
	6	N.M.	5
	8	5	8

N.M. - Mating did not take place at this pairing.

a - no pairings were undertaken as the male was found dead.

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