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Effect of Norhydroxyprogesterone Caproate on Cervical Sperm Penetration and Secretion of Ovarian Steroids in the Human Female

LARS CARLBORG

From the Department of Obstetrics and Gynecology (Head: Prof. Carl Gemzell), University Hospital, Uppsala, Sweden

ABSTRACT

Compound SH 8.0582 (19-norhydroxyprogesterone 17α-caproate) is a depôt gestagen which in experiments on laboratory animals seemed to have a slightly higher inhibitory affinity for peripheral reproductive organs than for gonadotropin. In this study it was injected on day 5 of the menstrual cycle in healthy young subjects. The action was recorded by daily quantitative determination of sperm penetration in the cervical mucus. The influence on ovarian function was estimated by determination of urinary total oestrogens and urinary pregnanediol or plasma progesterone. Doses of 5 mg or more tended to prolong the cycle length, prevented cervical sperm penetration and decreased ovarian steroid secretion. Lower doses did not consistently influence any of these parameters. There was no certain specificity for the cervix.

INTRODUCTION

Compound SH 8.0582 (19-norhydroxyprogesterone 17α caproate) was synthesized by Schering AG, Berlin. In routine bioassays on laboratory animals it was found to possess a strong gestagenic action on peripheral reproductive organs and a mild suppressive action on pituitary gonadotropins. It was also found that the compound, when given intramuscularly in oil, had a more prolonged action than had progesterone or most synthetic derivatives of progesterone. The effect was estimated to last for about 14 days (unpublished data, Schering AG, Berlin). In the human, a single dose of 200 to 500 mg caused no changes in liver function or carbohydrate metabolism. To elicit a significant biological response in the endometrium, doses below 50 mg were sufficient (5). In post-menopausal women 40 to 200 mg reduced the gonadotropin output.

Therefore it was of interest to determine whether the compound would have a high affinity for the peripheral reproductive organs (interference with cervical sperm penetration) without disturbing the ovarian function (estimated by determination of oestrogens and progesterone in the human female). If this were the case the drug could possibly be used as a novel contraceptive injected early in the menstrual cycle.

MATERIALS AND METHODS

Regularly menstruating women between 20 and 30 years of age were chosen as test subjects. They had not used any hormonal contraceptives for at least 3 cycles before the experiments. The compound was given in oil in a single intramuscular injection on day 5 of the cycle at doses ranging from 2.5 to 20 mg.

Daily samples of cervical mucus were taken and tested for quantitative sperm penetration *in vitro* (2). The daily basal body temperature was recorded in all cycles.

The total urinary oestrogen excretion was measured on days 12 to 18 (1). The occurrence of ovulation was estimated either by determination of urinary pregnanediol excretion (3) on days 10 and 22, or by the determination of plasma progesterone concentration on days 9, 13, 17 and 23 (4).

RESULTS

20 mg (2 subjects): Bleeding was delayed by 17 days and an immediate thermogenic effect lasted for about 2 weeks. All hormone determinations were low. Sperm penetration tests were negative or became positive after 19 days.

10 mg (2 subjects): Bleeding was postponed by 5 days. With regard to temperature, sperm penetration, and hormone determinations, the data were similar to those obtained after the 20 mg dose.

5 mg (5 subjects): In one cycle, bleeding was delayed by 20 days but otherwise the cycle length was unaffected. Ovulation probably occurred in the remaining 4 cycles. No sperm penetration was found in 3 subjects and the last subject with unimpaired cervical function conceived and delivered a healty infant in due course.

3 mg (4 subjects): In this group all subjects had an untreated control cycle before the test period, and the determination of sperm penetration, urinary oestrogens, and plasma progesterone were within the normal range. Administration of the compound did not affect the length of the cycle and no major hormonal changes were detected. Only in 2 subjects was there a marked interference with sperm penetration. One subject with a positive sperm penetration conceived and delivered a healthy infant in due course.

2.5 mg (4 subjects): There was no interferance with cycle length and all cycles appeared to be ovulatory. However, in 3 cycles there was no sperm penetration.

DISCUSSION

Gestagens injected early in the menstrual cycle have been tried as a means of contraception (6, 7). The treatment generally resulted in amenorroea for 3 to 5 months. It is possible that the postponed bleeding could have been preceded by an ovulation—a situation which would reduce the reliability of the contraceptive method. The present study was undertaken to determine whether a long-acting gestagen (SH 8.0852) given early in the cycle would act as a contraceptive without impairing menstruation. The limited data show that doses as low as 5 mg did postpone the expected bleeding. After an interval of up to 2 weeks when a thermogenic action of the compound was manifest a positive cervical sperm penetration could be demonstrated.

Ovulation might possibly have occurred after the scheduled investigational intervals. The interest was thus focused on doses less than 5 mg. The data revealed that there was no consistent influence on cycle length, ovarian estrogen and progesterone production or inhibition of sperm penetration in the cervical mucus. The inability to act as a contraceptive at these doses was evidenced by two conceptions. To prevent sperm penetration, higher doses were needed but with the increased risk of disturbance of a menstrual rhythm.

It was shown that the lowest doses needed to interfere with cervical sperm penetration were also liable to postpone uterine bleeding and to interfere with ovarian steroid production. The mechanism for the latter phenomenon was beyond the scope of the study.

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Address for reprints:

Lars Carlborg, M.D.
Kliniken för gynekologisk radioterapi
Akademiska sjukhuset
S-750 14 Uppsala 14
Sweden