Upsala J Med Sci 89: 147–150, 1984

A New Superagonist of GnRH for Inhibition of Ovulation in Women

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INTRODUCTION

Thousands of analogues of GnRH have been synthesized since the structure of this hypothalamic gonadotrophin-releasing hormone became known in 1971 (6). The purpose of this enourmous task has been: 1/ to develop more potent and long-acting molecules than GnRH itself for use in infertility and 2/ to develop antagonistic analogues of GnRH for use in contraception. The biological potency of the GnRH residue lies in the first part of the decapeptide. The amino acids histidine and tryptophan in positions 2 and 3 play a functional role in the biological activity of GnRH. The amino acids in positions 1 and from 4-10 seem to be involved in the binding to the GnRH receptor. Glycine in position 6 and 10 are most critical for preserving conformation.

Stimulatory analogues of GnRH have so far attracted most interest. Inhibitory analogues of GnRH with modifications at positions 2 and 3 have been produced but until recently they have not been potent enough to be of clinical interest. The most potent so-called superagonists of GnRH are modified at positions 6, 10 or both. The inital interest to use them in infertility for treatment of hypogonadal conditions have been more or less lost (4). Paradoxically, the superagonists were found to be anti-fertility by nature (2). Interest has therefore focused on their contraceptive potential (5).

We have recently concluded a long-term study using a superagonist for inhibition of ovulation in women (1). The results were very good and warrant further exploration of this new approach to birth control. Here we present the first results from a recently initiated contraceptive study with a more potent stimulatory analogue of GnRH (nafarelin acetate). The preliminary results show promise for an effective intranasal contraceptive method based on this GnRH analogue.

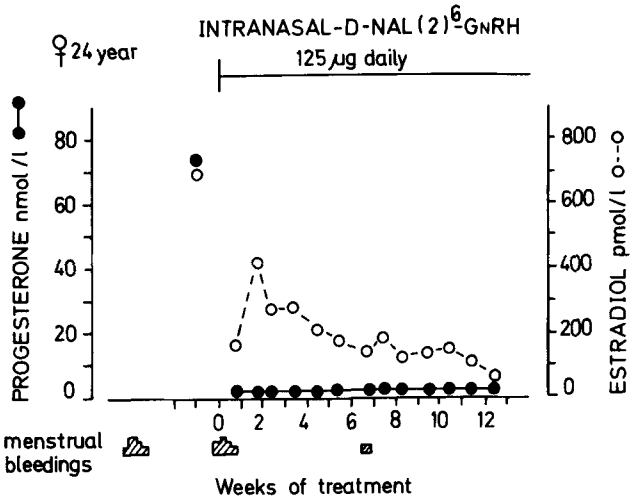

Fig. 1 Blood levels of progesterone and oestradiol before and after 12 weeks of daily intranasal treatment with 125 µg of nafarelin in a 24-year-old healthy volunteer.

PATIENTS AND METHODS

Twenty healthy regulatory menstruating women have started the trial. Before treatment normal ovulation was confirmed by clinical history, basal body temperature and postovulatory levels of progesterone in serum. Blood samples for assaying a wide range of metabolic parameters were obtained and will be assayed with post-treatment samples when the study is completed.

The GnRH superagonist (naferelin acetate (D-(Nal)2^6-GnRH (3), Syntex) was administered in a dose of 125 (n = 13) or 250 µg (n = 7) by a nasal spray device. Radioimmunoactive oestradiol and progesterone were weekly assayed by conventional radioligand procedures. The treatment was also monitored clinically by regular check-ups and daily recordings of the basal body temperature.

RESULTS

None of the 20 women had a normal ovulatory menstrual cycle during 57 treatment months. The bleeding pattern during the first eight weeks varied. Seven women had menstrual-like bleeding, eight oligomenorrhoea and five were amenorrhoeic.

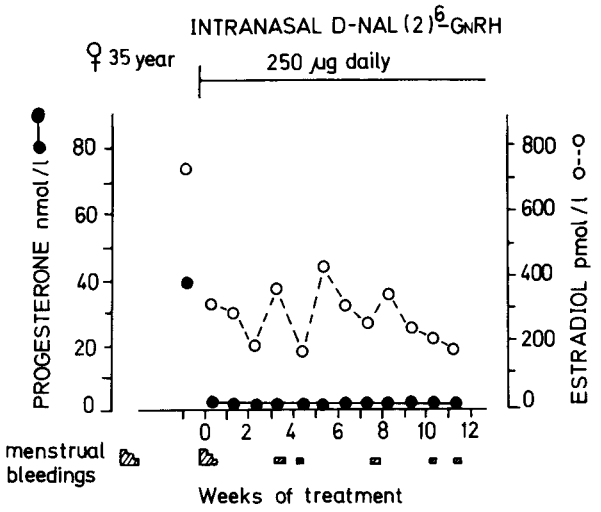

Fig. 2 Blood levels of progesterone and oestradiol before and after 12 weeks of daily intranasal treatment with 250 µg of nafarelin in a 35-year-old healthy volunteer.

One of the five women treated for more than 8 weeks had temporary hot flushes which were abolished when the daily dose was reduced to 125 µg. None of the volunteers had any clinical symptoms or signs of oestrogen deficiency. No pregnancy occurred during the study.

DISCUSSION

This preliminary study on women in reproductive age confirms that the new superagonist nafarelin is a potent anti-fertility drug with potential use for contraception in the future. Daily administration of the superagonist effectively inhibited normal ovulation. The intranasal route of administration was, despite short-lived nasal irritation, acceptable and practical for long-term use. No serious unacceptable bleeding disturbances occurred during the first months of treatment. Clearly, the bleeding pattern has to be evaluated during more prolonged treatment periods. More data will soon be available for possible dose adjustment.No pregnancies occurred when the women were relieved of their other non-hormonal contraceptives after four weeks of superagonist treatment.

The new potent superagonists of GnRH are of interest not only for contraception. The anti-reproductive properties of the agonist are of great interest for treatment of both malign (prostate, breast) and benign (leiomymata) tumours. There are other gynaecological disorders, such as endometriosis and the polycystic ovarian disease, which may benefit from superagonist therapy. Of special attraction is the possibility to treat precocious puberty with intranasal GnRH agonists in the future.

ACKNOWLEDGEMENTS

We thank Syntex for generous supply of GnRH agonist and Mrs Birgitta Bohman for expert secretarial assistance.

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