

TREATMENT OF PRECOCIOUS PUBERTY BY A LONG-ACTING GONADOTROPIN-RELEASING HORMONE ANALOGUE IN CHILDREN

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ABSTRACT

The GnRH analogue has been shown to be effective in the treatment of precocious puberty when given as a daily subcutaneous injection. We studied the effectiveness of a long-acting GnRH analogue, Triptoreline, for the treatment of central precocity, by suppressing gonadotropin and estradiol secretion in three children with true precocious puberty. One month after single dose intramuscular injection of depot GnRH analog Triptoreline, our patients showed significant decreases in serum estradiol and blunting of the responses of LH and FSH to GnRH test. No adverse effects were noted during the first six to eight months of treatment.

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INTRODUCTION

Puberty before the age of eight years in girls is considered precocious puberty. There are three major types: central, peripheral, and combined peripheral and central precocious puberty. Central precocious puberty is initiated by hypothalamic-pituitary-gonadal activation through a mechanism similar to that of normal puberty.¹

The discovery of the decapeptide structure of luteinizing hormone-releasing hormone (LHRH) led to the synthesis of agonistic analogues which far surpass the native molecule in potency and duration of effect. Chronic administration of these LHRH agonists in humans has been attended by an initial period of augmentation of pituitary gonadotropin secretion followed by a paradoxical refractoriness of the gonadotroph to further stimulation. This phenomenon has been termed a «desensitization» response.²

Monthly injection of depot GnRH analogue appears to be effective in suppressing gonadotropin and estradiol secretion, and may be a useful method for the treatment of children with central precocious

puberty.³ Triptoreline (Ipsen/Biotech, 30 Rue Cambonne, 75737 Paris cedex 15) is the D-Trp-6-LHRH analogue of GnRH.

It has been reported that daily subcutaneous GnRH analogue Leuprolide therapy is effective in the treatment of central precocious puberty in girls.⁴ Leuprolide acetate (TAP Pharmaceuticals, North Chicago, IL) has been shown to suppress gonadotropin and gonadal hormone secretion after an initial stimulation four weeks after therapy.⁵

One month after single IM dose of depot Triptoreline our patients' gonadotropin response to GnRH test and estradiol concentration in serum were suppressed. Their growth velocity and skeletal maturation slowed, and signs of pubertal development (breast and pubic hair) regressed in our three patients during the first 6-8 months of treatment. Most recently, evidence has been presented that a single monthly IM injection of depot GnRH analogue is as effective as daily SC dose in the treatment of precocious puberty.⁶

PATIENTS AND METHODS

Three patients with central precocious puberty were studied after informed consent was obtained from their parents. All of them had advanced bone age, height

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Precocious Puberty

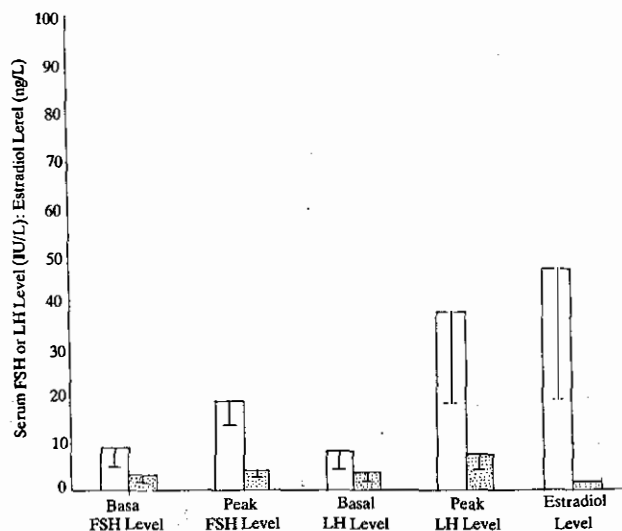


Fig. 1. Effect of a single IM dose of depot Triptoreline on basal serum FSH, LH estradiol levels and on the gonadotropin response to GnRH testing in our three patients. Heights of the bars are means, and one SEM below the mean is shown for each bar. □, pre-Triptoreline; ▨, 30 days after the first Triptoreline dose.

age, and pubertal development. Patients' height, weight, and pubertal changes were recorded at monthly intervals, and they received their injections in the hospital.

Depot Triptoreline was used as a single 50 mg/kg monthly deep IM injection. Basal serum LH, FSH, and estradiol levels and the changes in serum LH and FSH levels after GnRH testing (2 mg/kg; maximum, 100 mg) were measured before and one month after the beginning of monthly Triptoreline therapy. A radiograph of the left hand and wrist was obtained at six month intervals for bone age,⁷ which was assessed by a radiologist who had no clinical information about the patients. Serum LH, FSH and estradiol were measured by RIA, using commercially available kits (Coat-A-Count R, 5700 West 96th St, Los Angeles, CA 90045). In all three patients the diagnosis of central precocity was made after ovarian, adrenal, or clinically active central nervous system disease was excluded and serum pituitary gonadotropins in the pubertal range were documented. Our three patients had normal high resolution computerized tomography (HRCT) of the skull. They underwent adrenal and pelvic ultrasound with normal results. Thyroid tests and serum DHEA-S were within normal levels for age.

One of our patients had a history of meningocele without hydrocephalus and a history of head trauma with unconsciousness. The other two patients' history was unremarkable.

The stage of pubertal development was determined by the method of Tanner.⁸⁻⁹ In order to measure more accurately the breast size, we used a technique intro-

Table I. Decrease in breast size ("breast unit") after six months of monthly depot Triptoreline therapy
LBU, Left Breast Unit. RBU, Right Breast Unit.

Patient no.	pre-Triptoreline		6mo post-Triptoreline	
	LBU	RBU	LBU	RBU
1	90	90	64	49
2	76	76	72	72
3	143	132	110	121

duced by V.J. Capraro. This technique may be used to follow up the size of normal breasts. With a metric tape measure, the breast was measured from three o'clock to nine o'clock and from 12 o'clock to 6 o'clock. These two measurements are multiplied, yielding a figure called "breast unit".¹⁰ The significance of differences between means was calculated using paired t test.

RESULTS AND DISCUSSION

The patients were between 3.5-6 years of age (mean 4.8 years) and had idiopathic central precocious puberty. Bone age was greater than chronological age in all cases, and the mean bone age to chronological age was 1.2. Tanner stage was significantly advanced in our patients. Breast unit changes are shown in Table I.

Triptoreline resulted in marked suppression of GnRH-stimulated serum LH and FSH and a significant reduction in serum estradiol level. Figure 1 shows the results of GnRH testing before and after one month of treatment with a single injection of depot Triptoreline.

Peak FSH and LH levels were markedly reduced in all patients. Mean LH and FSH levels after GnRH stimulation markedly decreased (from 36.3 ± 23.6 to 4.6 ± 1.2 , and from 18.4 ± 5.6 to 2.03 ± 0.51 IU/L, mean \pm SEM, respectively), it was significant for FSH, $P < 0.02$.

Except mild menorrhagia during the first two weeks of therapy, no patient showed adverse local or other effects in 5-8 months of therapy. Longer follow up is necessary before a conclusion can be drawn regarding the efficacy of depot Triptoreline therapy in inhibiting precocious pubertal development and advanced bone age in such patients. Ultimate effects upon adult height are unknown, and the resumption of normal gonadotropin-gonadal axis has been demonstrated.

We conclude that depot Triptoreline may be a useful tool in the treatment of central precocious puberty.

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