

Evaluation and significance of the degree of pituitary-gonadal inhibition during intranasal administration of buserelin

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Abstract. In 12 patients (11 girls, 1 boy) with central precocious puberty and 4 patients (3 girls, 1 boy) with idiopathic short stature treated for 1 year with a GnRH superagonist, buserelin (0.3 mg intranasally, 4 times a day), a variable degree of inhibition of sex steroid secretion and pubertal development was observed. Regression of breast or genital development required a daily dosage of buserelin $\geq 34 \mu\text{g}/\text{kg}$. After 3, 6, 9 and 12 months of treatment, the serum oestradiol level in the girls was positively related ($r = 0.69$) to basal serum LH measured at the same time and to change in breast development during the previous 3 months. In contrast, LH response to GnRH was very low in all the patients and not related to the degree of oestradiol inhibition. Height velocity and bone age velocity during the year of treatment showed no significant correlation with mean oestradiol level. Bone age velocity during treatment was inversely related to bone age at onset of buserelin. These data show that 1) the pituitary gonadal suppression during intranasal administration of buserelin is variable and dose-dependent; 2) gonadotropin response to GnRH is not a sensitive indicator of incomplete pituitary suppression during buserelin treatment; and 3) bone age velocity during treatment is more reduced the more advanced bone age is at onset of treatment.

Superactive analogues of GnRH induce a paradoxical central inhibition of the pituitary-gonadal axis (Sandow 1983); Yen 1983). On the basis of

this reversible inhibitory effect, GnRH superagonists were proposed as a treatment of central precocious puberty (Crowley et al. 1981). When compared with the previous therapies using medroxyprogesterone or cyproterone, GnRH superagonists were found to result in a more effective reduction of height velocity and bone maturation (Mansfield et al. 1983; Styne et al. 1985; Brauner et al. 1985; Roger et al. 1986; Pescovitz et al. 1986). Therefore, epiphyseal fusion was delayed and the adult height prognosis improved (Boepple et al. 1986). In most of these studies, beneficial therapeutic effects were obtained using injectable forms of GnRH superagonists providing serum concentrations high enough to suppress completely the pituitary-gonadal function. Intranasal administration of buserelin, a GnRH superagonist, results in low serum concentrations of the medication (Holland et al. 1986) and variable degree of pituitary-gonadal inhibition (Luder et al. 1984; Stanhope et al. 1985; Sizonenko et al. 1986; Rajfer et al. 1986; Bourguignon et al. 1987). In our experience, an incomplete inhibition of puberty during buserelin treatment was particularly obvious in a few patients with idiopathic short stature participating in a pilot study on the effects of buserelin on adult height prognosis. Therefore, data from these

patients were included in this study which was designed to evaluate whether the degree of sex steroid or pubertal development suppression during buserelin therapy was related to the inhibition of gonadotropin secretion and to height velocity and bone maturation.

Patients and Methods

Eleven girls and 1 boy with central precocious puberty (8 idiopathic, 4 organic) and 3 girls and 1 boy with idiopathic short stature were treated for one year using buserelin intranasally (1.2 mg/day divided into four doses). It should be noted that a uniform dosage was used in all the patients, since delivery of a fixed dose of 150 µg of buserelin by the nasal spray did not allow individual adjustment according to body weight. In patients with central precocious puberty, chronological age at diagnosis varied between 1.2 and 8.0 years (mean \pm 1 SD: 5.1 \pm 2.3). At the beginning of buserelin treatment, chronological age varied between 2.7 and 8.8 years (mean \pm 1 SD: 6.9 \pm 1.8) and bone age between 9.2 and 13.9 years (mean \pm 1 SD: 11.7 \pm 1.4) except in one patient with a markedly younger bone age of 3.6 years. This patient was not included in the study of bone maturation. Eight patients had been treated with cyproterone acetate for 1.0 to 4.0 years before receiving buserelin. In the five previously untreated patients, height velocity was 10.1 \pm 1.0 cm/year before buserelin therapy. Specific data on the patients with precocious puberty have been reported elsewhere (Bourguignon et al. 1987).

Patients with idiopathic short stature had parental heights within normal limits, normal birth weight for gestational age, normal karyotype, no evidence of chronic disease, and normal (i.e. > 10 ng/ml) GH responses to insulin or glucagon stimulation tests. At the beginning of buserelin treatment, genital development in the boy and breast development in the girls were at Tanner's stage 3. Their mean chronological age was 12.3 \pm 0.4 years, their bone age was 12.9 \pm 0.4 years and their height for bone age was -3.0 ± 1.1 standard deviation scores (SDS). These patients were followed for 1.0 to 3.4 years before treatment. During that time, mean height velocity (\pm 1 SD) was 5.1 \pm 1.1 cm/year and mean bone age velocity 1.3 \pm 0.3 year/year.

This study was approved by the University of Liège ethical committee and informed consent was obtained from the parents and the patients.

During the treatment, height was measured using a wall-mounted stadiometer. Breast development was rated according to Tanner (1962) and breast size was measured. An X-ray film of hand and wrist was obtained before treatment and after 6 and 12 months.

Bone age was calculated according to Tanner et al., rating 20 bones of hand and wrist (Tanner et al. 1975). SDS of height for chronological age or bone age were calculated according to Tanner et al. (1965). Serum measurements of oestradiol, dehydroepiandrosterone sulphate (DHEA-S), FSH and LH were obtained at 3, 6, 9 and 12 months of treatment. The response of FSH and LH (assayed with reference to MRC 68/39 and 68/40 standards, respectively) to 25 µg/m² GnRH (Bourguignon et al. 1982) was evaluated after 3 and 12 months of treatment. In the calculation of the correlation between oestradiol and breast development, data obtained during the first 3 months of treatment were not considered in order to exclude any change in pubertal size possibly related to the transient initial stimulation of FSH and LH or to cyproterone therapy in some patients. In the study of the correlation between oestradiol and height velocity, patients with idiopathic short stature were not included, since they differed from patients with precocious puberty in respect to their pre-treatment height velocity.

The patient groups were compared using the unpaired Student's *t*-test and correlations were studied by calculating the linear regression. Differences were considered to be significant at a *P*-level < 0.05.

Results

As shown in Fig. 1, the effect of buserelin treatment on breast development varied according to the dosage used. Progression or arrest of genital or breast development was noted in the 4 patients receiving a daily dose of < 31 µg/kg. Dosages between 31 and 34 µg/kg resulted in variable effects, whereas a regression was observed in all of the 8 patients receiving more than 34 µg/kg per day. As shown in Fig. 2, progression of breast development during buserelin treatment was associated with significantly increased serum levels of oestradiol (mean: 122.1 nmol/l). A positive linear correlation was found between oestradiol and LH serum concentrations in basal conditions. In contrast, no significant relationship was observed between oestradiol levels and LH responses to GnRH, most of these being below the prepubertal control range (1.0 to 6.5 IU/l). Serum oestradiol concentrations were not significantly related either to FSH basal concentrations or to FSH responses to GnRH, which were lower than in prepubertal controls (< 2.0 IU/l) in all the patients. There was no significant correlation between the dose of buserelin administered and serum levels of oestradiol and gonadotropins,

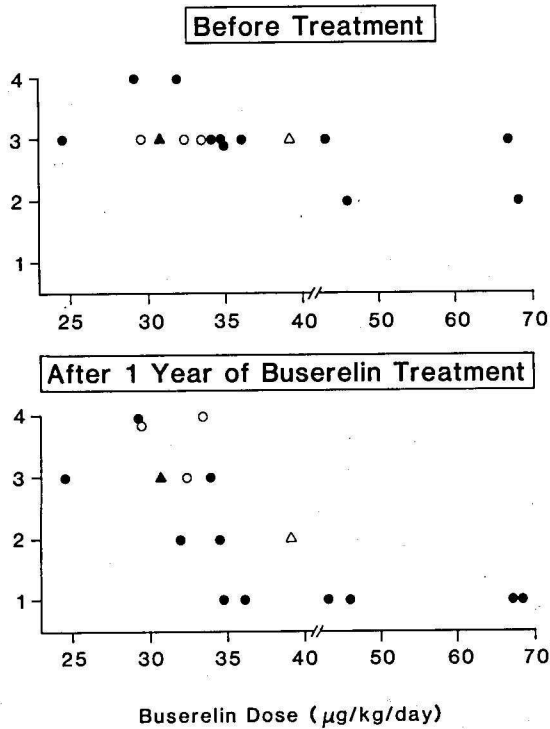


Fig. 1.

Tanner's stages of breast development (girls) or genital development (boys) in relation to the dosage of buserelin before (upper panel) and after 1 year of treatment (lower panel) in patients with central precocious puberty (CPP, ●, ▲) or idiopathic short stature (ISS, ○, △).

basally or in response to GnRH (data not shown). In girls with central precocious puberty, mean pre-treatment height velocity was $+3.2 \pm 1.6$ SDS. During buserelin treatment, their height velocity ranged between -1.9 and $+3.6$ SDS for chronological age (mean ± 1 SD: $+0.5 \pm 1.6$). When related to the mean oestradiol level obtained in each patient, height velocity showed a positive ($r = 0.45$) but not significant correlation. This might be due to the small number of observations. In the 3 girls with short stature, pre-treatment height velocity was $+0.3$, -0.3 and -0.4 SDS and decreased to -2.2 , -2.2 and -3.2 SDS during buserelin treatment. Bone age velocity (Δ bone age/ Δ chronological age, Δ BA/ Δ CA) during buserelin treatment was not significantly related to mean serum oestradiol level ($r = -0.22$, NS). In the 2 boys with central precocious puberty or idiopathic short stature, mean plasma testosterone level during buserelin treatment was 0.56 and 1.4 nmol/l, respectively (normal prepubertal range < 0.7 nmol/l), whereas their gonadotropin re-

sponses to GnRH were abolished (< 0.6 IU/l). Height velocity during treatment was -1.0 and -0.7 SDS respectively. As shown in Fig. 3, Δ BA/ Δ CA during buserelin treatment was inversely related to bone age at onset of treatment. Considering the small number of observations in different patients of both sexes, the linear regression was not calculated. Comparison with data (mean ± 2 SD) obtained in 22 hypopituitary boys studied during puberty (Bourguignon et al. 1986) suggests a similar decrease in bone age velocity in relation to bone age, although Δ BA/ Δ CA in buserelin-treated patients was lower than during puberty in hypopituitary patients. In patients with idiopathic short stature, Δ BA/ Δ CA was 0.69 ± 0.32 (mean ± 1 SD) when calculated after 2 years of treatment, the progression is bone age being more rapid during the second year than during the first year of treatment. No significant correlation was found between height velocity and serum levels of DHEA-S ($r = -0.21$, NS) or androstenedione ($r = -0.17$, NS).

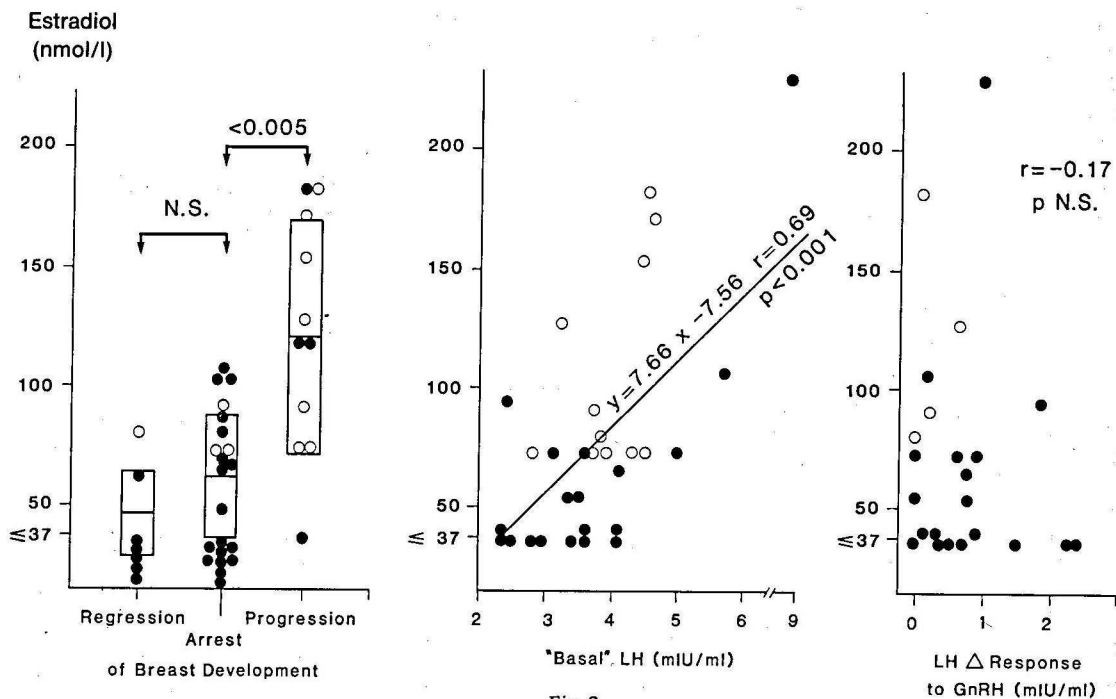


Fig. 2.

Serum levels of oestradiol obtained at 3, 6, 9 and 12 months during buserelin treatment (1200 μ g/day, intranasally) in girls with central precocious puberty (\bullet) or idiopathic short stature (\circ) plotted in relation to the change in breast development during the previous 3-month period (left panel) and serum LH concentrations measured at the same time, in basal conditions (middle panel) or as the increment in response to iv injection of 25 μ g/m² GnRH (right panel). Bars indicate mean \pm 1 sd.

Discussion

The observations reported in this paper have been made possible by the administration of a GnRH agonist, buserelin, in suboptimal conditions. The reason for the heterogeneous response to treatment may involve factors like dosage and route of administration (Rajfer et al. 1986; Monroe et al. 1986). In fact, a variable efficacy of GnRH agonists has especially been reported by authors using the intranasal route of administration (Luder et al. 1984; Stanhope et al. 1985; Brauner et al. 1985; Rajfer et al. 1986; Monroe et al. 1986; Bourguignon et al. 1987). The poor absorption of GnRH agonists through the nasal mucosa (Holland et al. 1986; Sizonenko et al. 1986) contributes to the importance of the dosage when treatment is given intranasally (Monroe et al. 1986). In these particular conditions we have shown that 1) the effect on pubertal development is dose-dependent; 2) the gonadotropin responses to GnRH do not discriminate patients incomplete-

ly suppressed from those fully inhibited; 3) bone age velocity is not significantly affected by the degree of sex steroid suppression, and 4) the major factor for a reduced bone age velocity is advancement in bone age at onset of treatment.

In order to examine consistently the importance of the degree of pituitary-gonadal inhibition by buserelin, we have considered together the data obtained in patients with central precocious puberty (Bourguignon et al. 1987) and limited observations in patients with idiopathic short stature. Both groups of patients were similar by their pubertal stage and their bone age at onset of treatment. In short stature patients, the interesting aspect was the obvious incomplete pituitary-gonadal suppression by the treatment, which may be related to the low doses of buserelin received by these patients. However, no significant correlation was found between buserelin dosage and oestradiol or gonadotropin serum levels. This might be explained by the non-linear relationship

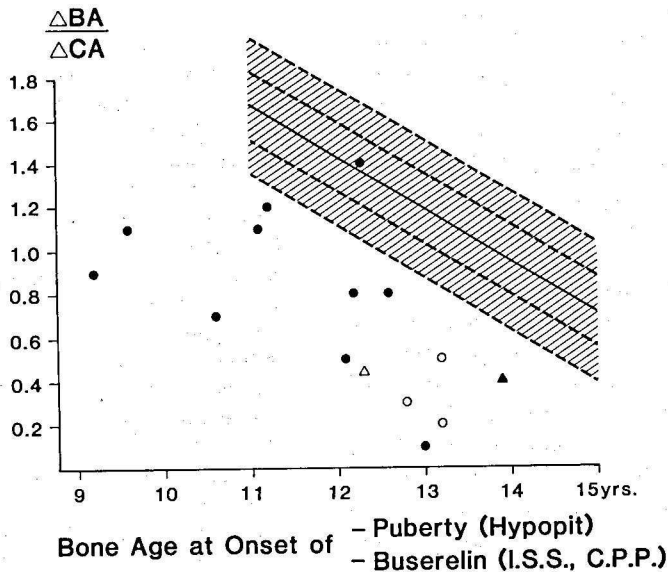


Fig. 3.

Individual symbols represent data from patients with central precocious puberty (●, ▲) or idiopathic short stature (○, △) in whom bone age velocity ($\Delta BA/\Delta CA$) during 1 year of treatment with buserelin is plotted against bone age at onset of buserelin treatment. The hatched area represents mean ± 2 SD of the regression line calculated in hypopituitary boys when bone age velocity during puberty is correlated with bone age at onset of puberty (Bourguignon et al. 1986).

between the dose of buserelin and the response to its administration. As far as the effects on growth are concerned, our results are very preliminary and cannot be compared with those in patients with precocious puberty, since pre-treatment growth velocity in the latter group was twice that seen in the former group of patients. Therefore, any formal consideration of GnRH agonist treatment in patients with short stature requires long-term and extended studies (Cutler et al. 1986). In precocious puberty, our limited number of observations might explain why the positive correlation between oestradiol and height velocity was not significant. In similar patients, Wierman et al. (1986) showed a correlation between DHEA-S levels and height velocity during GnRH agonist treatment. We found no such correlation.

Using GnRH agonists in very different conditions, several authors have shown the unequivocal abolition of FSH and LH responsiveness to synthetic GnRH, although they obtained variable clinical results (Luder et al. 1984; Stanhope et al. 1985; Bourguignon et al. 1987). This supports our conclusion on the low sensitivity of the GnRH

test in detecting incomplete suppression by the treatment. The GnRH agonist itself might provide an index of treatment adequacy since a dose-dependent response of the gonadotropins to the agonist has been observed during treatment (Monroe et al. 1986). Single determinations of serum oestradiol are useful, but may underestimate the steroid secretion according to the marked time-related fluctuations in serum oestradiol concentrations (Winter & Faiman 1973). Our data show that basal LH determinations may provide significant information when analysed as values obtained in a group of patients. In contrast, their analysis in individual patients will probably not be useful. Evaluation of suppressed LH pulsatility (Mansfield et al. 1983; Stanhope et al. 1985; Styne et al. 1985) requires prolonged serial sampling, which is not routinely feasible. In addition, the incomplete inhibition of sex steroid secretion may result from the rather high basal level of gonadotropin secretion (Santen et al. 1984; Bourguignon et al. 1987) without superimposed pulses. Recent studies have demonstrated increased levels of serum α subunit (Lahlou et al. 1986) and

urinary FSH (Morel et al. 1986) during GnRH agonist treatment. Further investigations of these parameters and others, like bioactive gonadotropins, are necessary to delineate the most sensitive monitoring of this treatment. A poor compliance could account for some of our data. However, this was not suggested by measurements of buserelin in urine performed in some of our patients (Sizonenko et al. 1986) and we excluded from this study 3 non-compliant patients.

When using GnRH agonists in paediatric patients, skeletal maturation is a major concern, since the aim is to optimize adult stature by delaying pubertal increase in height velocity and the concomitant acceleration in bone age velocity described by others (Buckler 1984). Previous investigators have reported a slow rate of bone maturation in patients well suppressed during GnRH agonist treatment (Mansfield et al. 1983; Styne et al. 1985; Brauner et al. 1985; Pescovitz et al. 1986; Boepple et al. 1986), whereas others have observed a less satisfactory inhibition of both pubertal growth and bone maturation (Luder et al. 1984; Stanhope et al. 1985). Accordingly, the rate of skeletal maturation was expected to depend on the degree of pituitary-gonadal suppression. Our data do not support this hypothesis. They show that bone age at onset of treatment is a major factor accounting for the slow rate of skeletal maturation. This is of therapeutic importance, since our data suggest that it may be worthwhile to consider treatment with GnRH agonist even in a patient with a bone age of 13 years. Interestingly, we came to a similar conclusion for the bone age at onset of testosterone treatment in hypopituitary boys (Bourguignon et al. 1986). Further studies are required on the rate of bone maturation in relation to different standards and in various disorders. Long-term evaluation in patients treated with GnRH agonists is also needed to establish the most appropriate therapeutic conditions and the absence of adverse reactions.

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