CLINICAL RESEARCH

Long term treatment with luteinising hormone releasing hormone agonists and maintenance of serum testosterone to castration concentrations

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Abstract

Serum concentrations of luteinising hormone and testosterone were measured by radioimmunoassay one, two, four, seven, and 24 hours after the subcutaneous administration of 500 µg of the luteinising hormone releasing hormone agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide or [D-Ser(TBU)⁶, des-Gly-NH₂¹⁰]LHRH ethylamide in patients who had previously received daily treatment with these peptides for 0, 1, 6, 12, 18, and 24 months. No increase in the serum concentrations of luteinising hormone or testosterone were detected at any time between one and 24 months' treatment. The data show that daily subcutaneous administration of the two luteinising hormone releasing hormone agonists used at the appropriate dose can maintain concentrations of serum androgens equivalent to those after castration during long term treatment.

Introduction

Since the observation of Huggins *et al* in 1941¹ the removal or blockage of testicular androgens by orchidectomy or oestrogens has been the principal form of treatment of advanced prostatic carcinoma.^{2,3} The psychological limitations of orchidectomy, however, are well recognised, and the high doses of oestrogens required for the complete inhibition of secretion of testicular androgens have serious cardiovascular side effects.^{4,5}

During the past five years potent agonists of luteinising hormone releasing hormone have been shown to inhibit serum testicular androgens to castration concentrations without side effects other than those related to hypoandrogenism—namely, hot flashes and decrease or loss of libido.⁶⁻¹³ It is important, however, that the inhibitory effect of these well tolerated peptides is maintained

during long term treatment. This is appropriate after the recent report of an increase of serum testosterone concentrations in three patients treated for six months with the luteinising hormone releasing hormone agonist ICI 118630 (Zoladex).¹⁴ About 450 patients at our clinic are treated with the luteinising hormone releasing hormone agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide and the antiandrogen flutamide. We present detailed results in 12 randomly chosen patients who had taken serum luteinising hormone and testosterone for up to two years, having received no previous hormonal treatment.

Patients and methods

Twelve previously untreated patients with clinical stage DII prostate cancer with bone metastases visualised by scintiscans of bone were studied on day 1 of treatment and after one, six, 12, 18, and 24 months' combination treatment with a luteinising hormone releasing hormone agonist and the pure antiandrogen flutamide (Euflex). The agonist used was [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide or [D-Ser(TBU)⁶, des-Gly-NH₂¹⁰]LHRH ethylamide (buserelin). Binding of receptors as well as in vitro and in vivo assays in the rat and acute and long term effects of these two agonists in man indicated similar potency and efficacy. A daily subcutaneous dose of 500 µg was given for one month followed by a 250 µg dose except on the days that serial blood samples were taken, when a 500 µg dose was given to provide a stronger stimulus and detect any escape of pituitary or testicular blockage, or both. Flutamide 250 mg orally was given every eight hours starting 24 hours before the first injection of the agonist.

Serum samples were taken at the time of injection of 500 µg luteinising hormone releasing agonist and one, two, four, seven, and 24 hours afterwards for measurements of serum luteinising hormone and testosterone concentrations by radioimmunoassay.¹³ Significance was assessed according to the multiple range test of Duncan-Kramer.¹⁵ All data are presented as means (SEM) of duplicate determinations for the 12 patients.

Results and discussion

The first administration of the luteinising hormone releasing hormone agonist caused about a fourfold increase in serum luteinising hormone concentrations measured one to 24 hours later ($p < 0.01$; fig 1(a)). Serum testosterone concentrations, however, increased slowly during the first 24 hours to a value 50% above concentrations in controls at 24 hours ($p < 0.05$; fig 2(a)). Serum luteinising hormone concentrations, measured by radioimmuno-

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assay, decreased to 45% of the control value at one month and to roughly 30% of the control value between six and 24 months' treatment ($p < 0.01$; fig 1(b)-(f)). Serum testosterone concentrations, however, decreased to 10% of those in controls at one month and remained at this low concentration thereafter ($p < 0.01$; fig 2(b)-(f)). The most important finding was that there was no increase in either luteinising hormone or testosterone concentrations after the subcutaneous injection of 500 µg of either luteinising hormone releasing hormone agonist used in our study.

Although in most studies the concentrations of serum testosterone measured 24 hours after administration of the luteinising hormone releasing hormone agonist are used as an index

FIG 1—Response of radioimmunoassayed serum luteinising hormone concentration to administration of the agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide or [D-Ser(TBU)⁶, des-Gly-NH₂¹⁰]LHRH ethylamide on first day of treatment and after one, six, 12, 18, and 24 months' daily treatment. Basal concentrations of luteinising hormone were 94.9 (12.7) ng/ml. Bars represent SEM.

FIG 2—Response of radioimmunoassayed serum testosterone concentration to administration of agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide or [D-Ser(TBU)⁶, des-Gly-NH₂¹⁰]LHRH ethylamide on first day of treatment and after one, six, 12, 18, and 24 months' daily treatment. Basal concentrations of testosterone were 11 (1.7) nmol/l (3.18 (0.49) ng/ml). Bars represent SEM.

Conversion: SI to traditional units—Testosterone 1 nmol/l $\approx$ 0.3 ng/ml.

of the efficacy of the peptides to inhibit testicular steroidogenesis, blood samples should be taken earlier to detect partial escape.¹⁶ When incomplete pituitary desensitisation is suspected, due to an inappropriate dose of the agonist, a lack of compliance, or use of a peptide with low activity, the increase in serum luteinising hormone and testosterone concentrations may be best seen two to seven hours after injection with a return to castration concentrations at 24 hours.¹⁶ Measurements of serum testosterone concentrations 24 hours after the subcutaneous administration of luteinising hormone releasing hormone agonists are thus a poor index of the efficacy of treatment with such agonists.

As there was no increase in serum luteinising hormone or testosterone concentrations measured two to three hours after injection in any of our 450 patients treated with a luteinising hormone releasing hormone agonist in combination with flutamide for up to three years, the increase in serum testosterone concentration seen in three of 10 patients treated for six months with ICI 118630 (Zoladex) by Kerle *et al* probably reflected a lack of compliance or a lower activity of the agonist used, or both.¹⁴ The availability of a depot formulation of the same peptide¹⁷ should eliminate the problem reported with its daily use.¹⁴

The use of the pure antiandrogen flutamide in association with a luteinising hormone releasing hormone agonist prevents any sign or symptom of disease flare seen in some cases when such agonists are used alone.¹⁸⁻²⁰ As studied in detail in the dog, the antiandrogen does not interfere with the changes in secretion of gonadotrophin induced by the agonist (Lacoste, Bélanger, and Labrie, unpublished observations). The antiandrogen thus takes advantage of the otherwise extremely well tolerated luteinising hormone releasing hormone agonists to achieve medical castration. The only side effects observed were hot flashes in about half the patients and a decrease or loss of libido in about three quarters.¹⁶ The data show that long term treatment with daily subcutaneous injection of potent luteinising hormone releasing hormone agonists at the appropriate dose maintains serum testosterone concentrations to castration concentrations.

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