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# The first clinical use of depot buserelin for advanced prostatic carcinoma

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**Summary.** The agonist analogues of the gonadotrophin-releasing hormone now provide an alternate medical treatment of prostatic cancer. For effect repeated administration is required, either by five or six times daily intranasal or once daily subcutaneous treatment. There is an obvious disadvantage to such regimens in elderly patients who may have difficulty complying with therapy. In order to circumvent these difficulties, sustained release formulations of the agonist analogues have been synthesized. We report the first clinical use of a long-acting formulation of *D*-Ser (TBU)$^6$-LHRH Ethylamide (buserelin) using a novel polymer material. Twelve symptomatic patients with previously untreated carcinoma of the prostate were treated with depot buserelin, administered once monthly. In all patients, depot buserelin suppressed serum testosterone into the range seen in castrate men at a rate equivalent to that provided by five times daily intranasal therapy. No significant increase in serum testosterone, luteinizing hormone or follicle-stimulating hormone concentrations occurred during the period of follow-up. Long-acting formulations of buserelin offer an advance in the management of prostatic cancer with agonist analogues of the gonadotrophin-releasing hormone.

## Introduction

In 1981, Redding and Schally described the inhibition of growth of an animal model of prostatic cancer by repeated administration of the *D*-Trp$^6$ agonist analogue of gonadotrophin-releasing hormone [3]. After initial observations of the acitivity of the agonist analogues of the gonadotrophin-releasing hormone in man [1, 5, 6], these compounds have entered widespread clinical trial. They have been found to be as effective as conventional therapies in the short-term control of carcinoma of the prostate [4]. However, in the long term it has been reported that the daily administration of the the agonist analogues of gonadotrophin-releasing hormone may not effectively suppress testosterone secretion in all patients [2]. This may be the result of escape of the pituitary-gonadal axis from inhibitory control, or represent poor compliance in elderly patients. In order to minimize the difficulties that may relate to the administration of treatment, depot preparations of the agonist analogues have been synthesized. We describe 12 patients with advanced prostatic cancer treated with monthly depot buserelin for periods of up to 8 months.

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## Patients and Methods

Twelve patients, aged 59 to 82 years (mean 71 years), who had not received any previous hormonal therapies were studied. Two men had locally advanced and 10 disseminated prostatic cancer. Each patient was treated with depot buserelin, in the form of a 5-mm tablet, inserted via a small skin incision into the subcutaneous tissue of the anterior abdominal wall at monthly intervals. Each depot preparation contained 5-mg buserelin in polyhydroxybutyric acid. Agonist was released over a 28-day period at an initial rate of 300 μg daily, a final rate of 30 μg daily and a mean daily rate of 150 μg (Hoechst data: available on application to J. S.) Treatment was maintained for 1–8 months (mean 3.9 months). Basal concentrations of serum testosterone, luteinizing hormone and follicle-stimulating hormone were measured prior to treatment and thereafter on days 1, 2, 3, 7, 14, 21 and 28 of treatment. Four hours after re-implantation of depot buserelin, serum concentrations of the gonadotrophins and testosterone were measurd. Concentrations of luteinizing hormone and follicle-stimulating hormone were measurd by specific double-antibody radioimmunoassay, using Medical Research Council Standards 68/40 and 78/549. Testosterone was measured by tritiated radioimmunoassay after ether extraction.

## Results

Details of the changes in serum concentrations of testosterone and the gonadotrophins are shown in Fig. 1. The concentrations of these hormones initially increased. After 1 month as compared to pretreatment, serum testosterone concentrations were significantly decreased ($P<0.001$: Student's t-test), as were follicle-stimulating hormone and luteinizing hormone ($P<0.01$ Wilcoxon's signed rank test). No significant rise in testosterone followed re-implantation, with mean concentrations pre-implantation of 1.6 nmol/l (range 1.4–1.9 nmol/l) and 4 h post-implantation of 1.6 nmol/l (range 1.4–1.8 nmol/l). Serum testosterone remained in the castrate range (<2.5 nmol/l) throughout the study period. No significant increase in follicle-stimulating hormone followed re-implantation, with mean levels

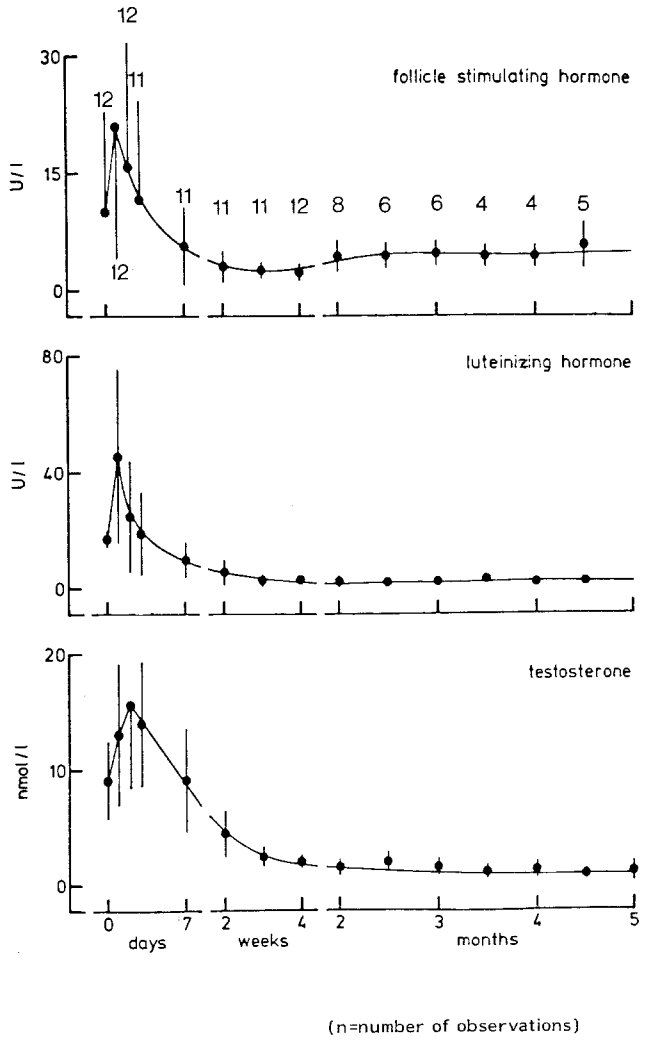


**Fig. 1.** Changes in serum concentrations of the gonadotrophins and testosterone with treatment with depot buserelin

pre-implantation of 3.3 U/l (range 2.3–5.7 U/l) and 4 h after re-implantation of 5.9 U/l (range 3.6–8.7 U/l). Basal concentrations of follicle-stimulating hormone rose from day 21, but this increase did not assume statistical significance. No significant rise in luteinizing hormone followed re-implantation, with mean levels prior to re-implantation of 2.2 U/l (range 2.1–2.4 U/l) and 4 h after re-implantation of 2.9 U/l (range 2.1–3.4 U/l). Basal concentrations of luteinizing hormone did not change significantly from day 28 for the remainder of the study. Two patients completely responded, 6 had partial responses, 1 stable disease and 3 patients did not respond to treatment, as assessed by National Prostatic Cancer Project Criteria.

## Discussion

This study has shown that a long-acting formulation of buserelin caused suppression of serum testosterone after 4 weeks' treatment into the range found in castrate men. This occurred at a rate equivalent to 200 μg five times daily intranasal therapy [6]. Serum testosterone concentrations remained suppressed for the duration of treatment. No significant increase in either the gonadotrophins or testosterone followed re-implantation of depot buserelin. Long-acting formulations offer an advance in the management of prostatic cancer with agonist analogues of gonadotrophin-releasing hormone. The use of such preparations facilitates compliance in elderly patients [7]. The possibility that sustained release of agonists provides more effective diurnal control of testosterone secretion than current daily regimens requires evaluation.

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