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Short communication

A pharmacological evaluation of a new 3-month depot preparation of buserelin for prostatic cancer

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Summary. A new slow-release formulation of buserelin given as a 3-month depot injection was evaluated in four patients with advanced prostatic cancer. Treatment was maintained for a mean period of 15 months. Steady-state urinary buserelin concentrations were reached by the beginning of the 3rd week of treatment and maintained until the end of the 3rd month. Serum testosterone remained suppressed in the castrate range for the duration of the study. This preparation offers an advantage for the patient and clinician over existing methods of gonadotrophin-releasing hormone (GnRH) analogue administration and will enter further clinical trial.

Introduction

Gonadotrophin-releasing hormone (GnRH) agonists were originally given five or six times daily as nasal spray insufflations or once daily as subcutaneous injections. These compounds provide an effective and safe alternative to orchidectomy and do not cause the cardiovascular toxicity brought about by oestrogen therapy [2]. To improve treatment, depot preparations were synthesized that are effective in suppressing testosterone if given once monthly [3, 4]. These peptide-delivery systems have been further improved and a new preparation, effective in suppressing gonadal steroid production in non-human primates has recently been developed [1]. We carried out a pharmacological and endocrine evaluation of this 3-month depot preparation in men with prostatic cancer.

Patients and methods

Four patients with metastatic prostatic cancer were studied. Each patient had previously been treated for a mean period of 1.8 years (range, 1–2.4 years) with depot D-Ser (TBU)^6-LHRH ethylamide (buserelin) given at an initial dose of 3.3 mg once monthly and then 6.6 mg every 2 months. All patients had shown a complete response to treatment that was maintained until the start of this study. Each 3-month depot implant consisted of a 1-cm-long core of lactide-glycolide copolymer containing 10 mg buserelin. Treatment was given by injection into the subcutaneous tissue of the anterior abdominal wall through a 14-gauge needle, and continued for a mean period of 15.7 months (range, 15–18 months).

During this period, urinary buserelin excretion was measured at weekly intervals. Buserelin was measured by double antibody radioimmunoassay (no cross-reactivity with GnRH or GnRH peptide fragments; assay sensitivity, 10 pg/tube; intra-assay precision, 11%; inter-assay precision, 17%; 1 ng/ml = 0.81 nmol/l) [4]. Testosterone was assayed using single antibody radioimmunoassay (significant assay cross-reactivity was obtained with 5-alpha-dihydrotestosterone 8%, 19-nortestosterone 47% and androstenedione 3%; assay sensitivity, 0.1 nmol/l; intra-assay precision, 5%–8%; inter-assay precision, 6%–8%). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by second antibody radioimmunoassay using MRC standards 68/70 and 78/549, respectively (significant cross-reactivity was obtained with hCG at 25% in the LH assay and 2% in the FSH assay; assay sensitivity, 1 IU/l for LH and 0.5 IU/l for FSH; intra-assay precision, 7%; inter-assay precision, 10%).

Results

Serum concentrations of testosterone, luteinizing hormone and follicle-stimulating hormone are documented in Fig. 1 and urinary buserelin levels are shown in Table 1. Serum testosterone was maintained in the castrate range <2.5 nmol/l) for the duration of treatment. There was no significant increase in serum levels of testosterone, luteinizing hormone or follicle-stimulating hormone during treatment. After an initial "release" burst, steady-state urinary concentrations of buserelin were reached at the beginning of the 3rd week of treatment and maintained until the end of the 3rd month. During the period of follow-up, two patients relapsed; their results are included in the study until further endocrine or cytotoxic therapy was instituted.

Discussion

This study has shown this depot preparation to result in sustained, controlled release of buserelin effective in maintaining castrate levels of serum testosterone for the duration of treatment. The four patients treated were the first in the world to receive this new, very long-acting depot preparation, whose release characteristics were

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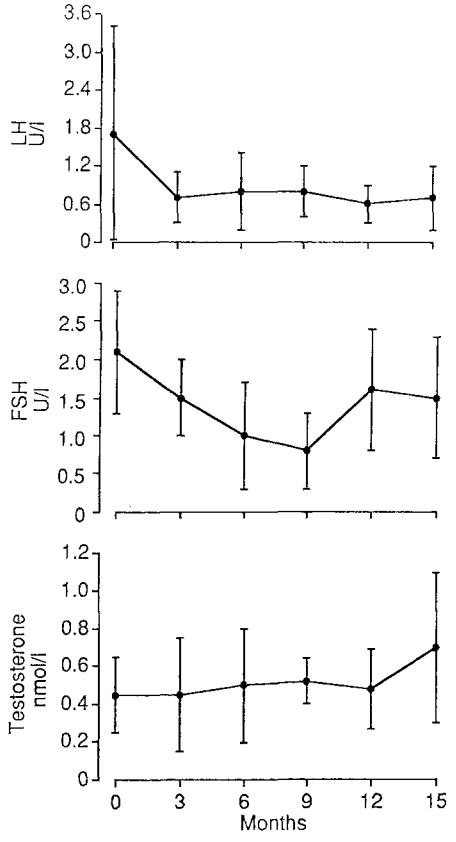

Fig. 1. Serum concentrations of luteinizing hormone (*LH*), follicle-stimulating hormone (*FSH*) and testosterone in patients with metastatic prostatic cancer after treatment with a 3-month depot implant of buserelin over 15–18 months (mean ±SE)

designed around the expected optimal outpatient attendance for clinical review. The use of this agonist depot will obviate the need for daily nasal spray or injections and has obvious advantages over 1-month depot treatment. Further clinical evaluation of this new preparation is currently proceeding.

Table 1. Urinary buserelin excretion (μg/g creatinine)

Day post-implant	Mean concentration l.c. (SEM)	Observations (*n*)
1	141.2 (106.4)	15
7	29.6 (21.2)	15
14	16.6 (11.4)	16
21	9.5 (5.9)	14
28	7.6 (5.1)	16
35	8.7 (11.6)	16
42	6.8 (5.4)	16
49	7.6 (6.4)	16
56	8.1 (6.1)	16
63	6.4 (5.2)	16
70	8.6 (6.7)	16
77	5.3 (4.1)	16
84	4.4 (2.8)	15

Summated results of four treatment cycles in four patients

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