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Pharmacokinetics and endocrine effects of the LHR analogue buserelin after subcutaneous implantation of a slow release preparation in prostatic cancer patients

J. H. M. Blom[1], W. H. Hirdes[1], F. H. Schröder[1], F. H. de Jong[2,3], D. J. Kwekkeboom[3], A. J. van't Veen[4], J. Sandow[5], and B. Krauss[5]

Departments of [1]Urology, [2]Biochemistry (Chemical Endocrinology) and [3]Medicine, Erasmus University, Rotterdam, and [4]Medical Department, Hoechst Holland n. v., Amsterdam, The Netherlands
[5]Department of Pharmacology, Hoechst AG, Frankfurt, Federal Republic of Germany

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Summary. The pharmacokinetics and endocrine effects of the LHRH analogue buserelin [D-Ser(TBU)^6-LHRH], released from biodegradable implants, were studied in 14 patients with stage C and D prostate cancer. Six patients received a subcutaneous implant of 3.3 mg buserelin monthly, and 8 patients received a subcutaneous implant of 6.6 mg buserelin every two months. Serum levels of buserelin decreased rapidly immediately after implantation. After 1–2 weeks a more gradual decline occurred, while in the two-monthly treated group a third phase of the elimination curve started after 5 weeks. Mean serum buserelin levels just before the next implantation in the two groups were not different. Urinary excretion of buserelin followed the same pattern. Serum LH levels in both groups became non-detectable 2 weeks after the first implant. This decrease of LH levels was accompanied by a suppression of serum testosterone to concentrations below 1 nmol/l (castration level). Side effects were not different from those observed with the intranasal application of buserelin. It is concluded that the subcutaneous application of buserelin is an easily administered form of treatment which has more profound and more reliable endocrine effects when compared with the intranasal administration of the drug. The greatest advantage of the new preparation is that the intervals between applications may be prolonged to at least 2 months.

Key words: Metastatic prostate cancer – LHRH analogues – Implant preparation

Introduction

LHRH analogues have been found to be as effective as conventional forms of androgen suppressing therapy in metastatic prostate cancer [2, 4, 5, 6, 7]. These drugs have found wide acceptance in daily urological practice, because they lack the cardiovascular risks of estrogens and the psychological disadvantages of surgical castration [2, 10].

Buserelin [D-Ser(TBU)^6-LHRH] is a highly active analogue of LHRH (luteinizing hormone-releasing hormone). This peptide causes paradoxical suppression of the pituitary release of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) after an initial increase of the secretion of the gonadotrophins [1, 6, 7]. Presently buserelin is administered as a nasal spray, which produces a reliable and consistent suppression of LH, and therefore of androgens in peripheral plasma. However, the spray has to be administered several times daily, which may lead to problems in patient compliance, especially in the elderly men. To minimize the difficulties that may relate to the administration of treatment, an implant preparation of the LHRH analogue buserelin has been developed. The first clinical use of implant buserelin was described by Waxman et al. [14]. Implant preparations of other LHRH analogues are presently subject of several studies [3, 4, 12].

In the present study the pharmacokinetics of an improved implant preparation were investigated during 6 months and the reliability in suppressing plasma testosterone of implant preparations acting during one and two months was assessed.

Patients and methods

Patients

Between March 1987 and December 1987 twelve patients with histologically proven prostate cancer were staged clinically and found to have metastatic carcinoma. One of the patients had cytologically proven metastases only to the para-iliac nodes, all other patients had distant metastases to the bones. Beside these twelve

patients two other patients, who already were using the nasal formulation of the LHRH analogue buserelin for metastatic prostate cancer for more than three years, were switched to the subcutaneous application. So, fourteen patients, aging between 53 and 79 years (average age 65.4 years) were randomly allocated to either of the treatment regimes, i.e. 3.3 mg of buserelin ($n=6$) or 6.6 mg ($n=8$). One of the patients decided to stop treatment after one month. Another patient showed progression of disease and died of prostate cancer before the end of the 6 months period of pharmacokinetic investigation, which made him not evaluable for the duration of the whole study. Both patients however, could be evaluated for the first implant period. Twelve patients completed the whole pharmacokinetic evaluation.

The study protocol was approved by the medical ethical committee of the Academic Hospital Rotterdam. Written informed consent was obtained.

Buserelin application

After one week of treatment with cyproterone acatate (50 mg three times daily) the patients received either 3.3 mg or 6.6 mg of buserelin given in 75:25 polylactide-glycolide co-polymer formulation by subcutaneous implantation in the anterior abdominal wall under local anaesthesia. The implantation was repeated every month for the patients who received a 3.3 mg implant and every eight weeks for the patients who received a 6.6 mg implant. The treatment with cyproterone acatate was continued until the second implantation of buserelin. The local application was very well tolerated and none of the patients showed local allergic reactions or local infections. Systemic side effects never necessitated discontinuation of treatment.

Laboratory examinations

The pharmacokinetic investigation was done by determination of serum and urinary buserelin levels. The endocrine effect of the treatment was evaluated by estimations of peripheral levels of LH and testosterone.

Laboratory examinations were performed weekly starting one week before the first buserelin implant until the end of the sixth month. Furthermore blood and urine samples were taken directly before and 4 h after each implantation of buserelin and on day 2, 3 and 5 during the first week. Conservation of blood and urine samples for buserelin estimation was achieved by addition of Bacitracin to the samples (final concentration 10^{-3}M). Samples were stored at −20 °C.

Buserelin was measured by specific radioimmunoassay in unextracted serum and urine [8]. After iodination by the chloramine-T method, resulting in a specific activity 800-1,000 μCi/μg, the (mono-^{125}I-Tyr^{5}) buserelin fraction was used for the radioimmunoassay. The buserelin antiserum (AS-639) was raised in rabbits against a buserelin/thyroglobulin conjugate. Sensitivity of the assay was 10.6 pg/tube (minimum detectable dose), the interassay coefficient of variation was 17.2% (34 assays), and the intra-assay coefficient of variation was 6–8%.

Serum Testosterone was estimated by a radioimmunoassay using the antiserum described by Verjans and associates [13] after extraction of the plasma. The interassay coefficient of variation amounted to 9.7% for samples containing less than 2 nmol/l; the minimum detecable concentration was 0.2 nmol/l.

For LH determinations an immunoradiometric assay (IRMA), which specifically measures LH (supplied by IRE-Medgenix, Brussels), was used. The interassay coefficient of variation was 13.6% for samples less than 2 I.U./l. The minimum detectable concentration was 0.5 I.U./l. LH was expressed in terms of the MRC 68/40 reference preparation.

Table 1. Buserelin levels in serum (ng/ml)

Day of treatment	Dose unit 3.3 mg (mean ± S.E.)	Dose unit 6.6 mg (mean ± S.E.)
1	4.29 ± 0.25	9.36 ± 0.66
8	0.81 ± 0.07	1.86 ± 0.18
15	0.49 ± 0.06	0.95 ± 0.08
22	0.41 ± 0.50	0.85 ± 0.06
29	0.38 ± 0.40	0.83 ± 0.08
36		0.86 ± 0.08
43		0.70 ± 0.08
50		0.51 ± 0.07
57		0.43 ± 0.08

Table 2. Buserelin excretion (μg/g creatinin)

Day of treatment	Dose unit 3.3 mg (mean ± S.E.)	Dose unit 6.6 mg (mean ± S.E.)
1	165.50 ± 15.70	201.10 ± 0.66
8	16.64 ± 1.11	24.40 ± 0.18
15	9.28 ± 0.77	13.90 ± 0.08
22	6.92 ± 0.55	11.90 ± 0.06
29	7.04 ± 0.68	12.10 ± 0.08
36		11.52 ± 0.08
43		9.18 ± 0.08
50		6.11 ± 0.07
57		4.93 ± 0.08

Results

Table 1 shows buserelin levels in the serum for the two dosage groups. In the group of patients who received. 6.6 mg buserelin per 2 months the serum levels of buserelin reached an initial value which was twice as high as in the group of patients who received 3.3 mg buserelin per month. At the end of the two months period the serum level of buserelin in the high dose group was equal to that after four weeks in the group of patients who received 3.3 mg buserelin.

A similar situation was found for the urinary buserelin excretion (Table 2). In the group of patients who received 6.6 mg buserelin per 2 months the initial excretion was higher than in the group of patients who received 3.3 mg buserelin per month, but at the end of each period the values were no longer different. The data have been visualized in Fig. 1. The halflife of buserelin elimination (release rate) is composed of three components, an early rapid phase, a second pronounced plateau phase, and a third slow elimination phase, corresponding to biodegradation of the implant material.

Plasma testosterone levels in the two groups of patients are indicated in Fig. 2. There was no difference

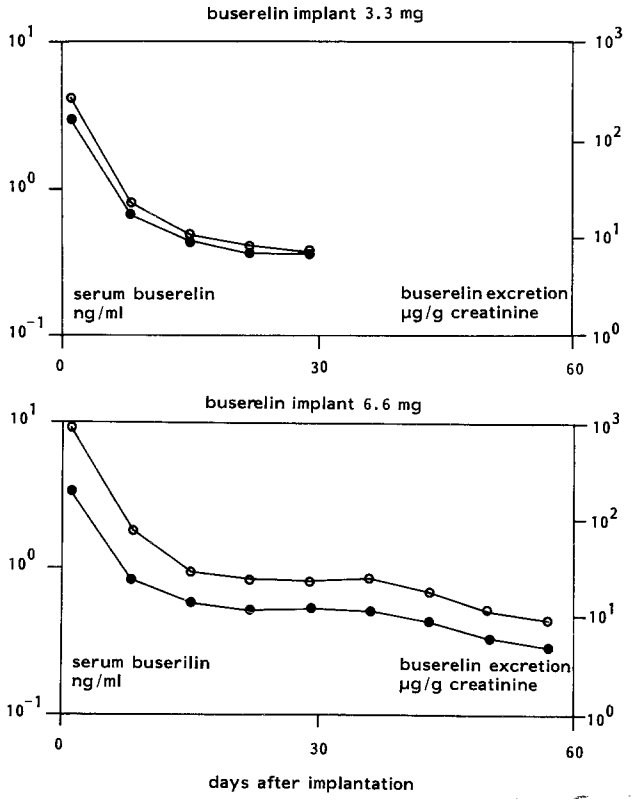


Fig. 1. Serum buserelin levels (O-O-O-O) and urinary buserelin excretion (●-●-●-●) for the 3.3 mg implants (upper panel) and for the 6.6 mg implants (lower panel)

Fig. 2. Serum testosterone levels for the patients receiving a 3.3 mg buserelin implant and for those receiving a 6.6 mg implant

Table 3. Plasma LH levels (I.U./l)

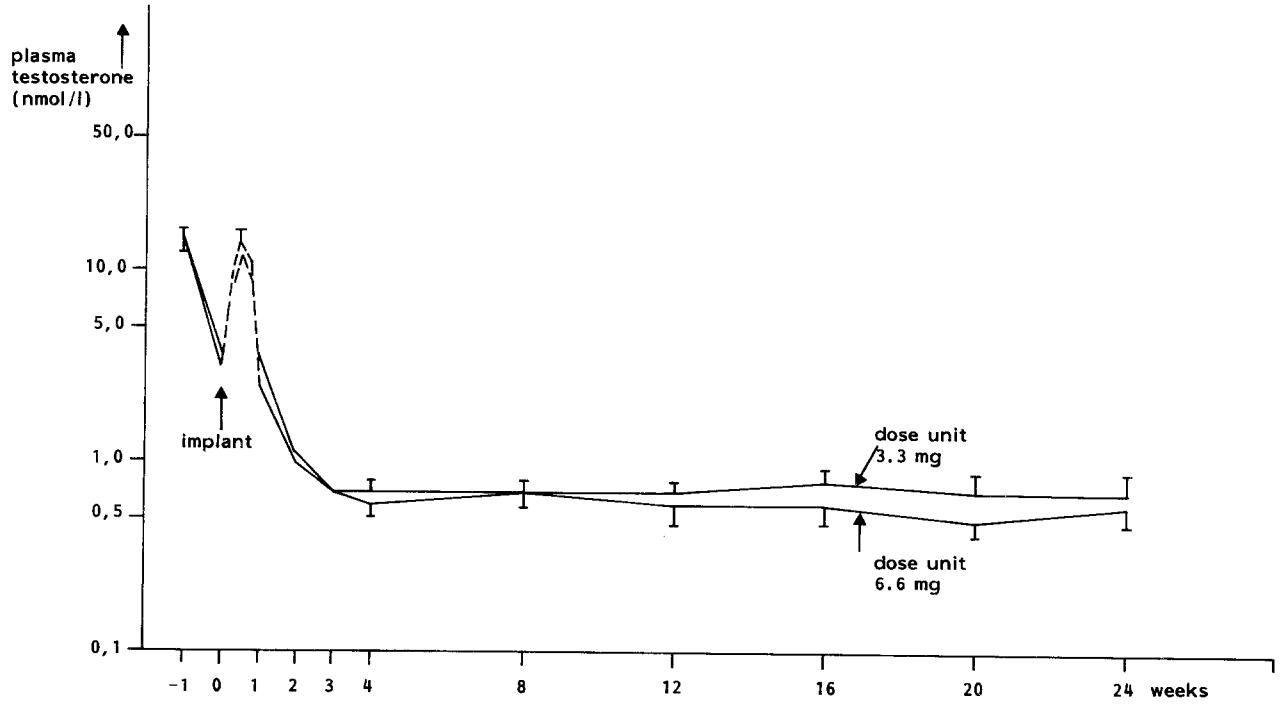
Day of treatment	Dose unit 3.3 mg (mean ± S.E.)	Dose unit 6,6 mg (mean ± S.E.)
−7	7.9 ± 1.62	10.6 ± 7.05
1 before implant	2.8 ± 0.64	4.0 ± 2.03
1 4 h after implant	35.9 ± 11.4	32.9 ± 15.40
2	26.7 ± 3.82	23.4 ± 9.54
3	8.9 ± 1.56	10.6 ± 3.64
5	4.7 ± 1.02	5.4 ± 2.19
8	2.2 ± 0.18	2.8 ± 1.23
15	0.8 ± 0.28	1.13 ± 0.18
>15	< 0.5	< 0.5

in testosterone levels whether the patients received 3.3 mg of buserelin every month or 6.6 mg every 2 months.

Plasma LH values are given in Table 3. After two weeks of treatment plasma LH levels were below 0.5 I.U./l and remained below that level during the whole period of pharmacokinetic study.

The clinical response on treatment was also studied in the patients, but this is not subject of this report.

Side-effects of treatment with buserelin included loss of erectile potency and hot flushes. In almost all patients the frequency and the intensity of hot flushes diminished in the course of time. Only in one patient the intensity of the hot flushes remained rather severe during the whole treatment, but it was not severe enough to cause discontinuation of the treatment. Incidence and severity of side effects ob buserelin were studied and described in detail in a previous study [9].



Discussion

Repeated administration of LHRH analogues results in a reliable and profound suppression of serum testosterone levels in men with metastatic prostate cancer [1, 2, 4, 5, 9, 10, 11]. This treatment has been shown to be safe and without major adverse reactions [2, 9]. There are no apparent drug-related thromboembolic or cardiovascular complications. In the meantime much experience has been gained with LHRH analogues in the treatment of prostate cancer. Besides daily subcutaneous injections administration of the drug by means of a nasal spray is recognized as an effective route of drug administration. However, implant preparations might offer advantages over the nasal spray or daily subcutaneous injections in terms of patient compliance and convenience. Therefore a biodegradable sustained release formulation of buserelin was developed. This study shows that the present formulation is capable of suppressing plasma testosterone levels to castration levels for at least 28 days in case of the 3.3 mg preparation of buserelin, and that even with a two-monthly injection of 6.6 mg of buserelin testosterone suppression to castration level can be reached. The testosterone levels observed in this study are significantly lower than those obtained with the intranasal application, which we reported earlier [9]. This is most likely due to a more pronounced suppression of peripheral LH levels obtained with the implants (D. J. Kwekkeboom et al. to be published). It is concluded that monthly implants of 3.3 mg or two monthly implants of 6.6 mg buserelin offer a reliable, minimally interventional treatment for prostate cancer. The procedure of application is safe and the tolerance of the implant is good. Especially the two monthly implants have the advantage of a low frequency of buserelin application.

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Jan H. M. Blom, MD
Department of Urology
Erasmus University
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands