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Responses to the Antagonistic Analog of LH-RH (SB-75, Cetrorelix) in Patients With Benign Prostatic Hyperplasia and Prostatic Cancer

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ABSTRACT: Among new highly potent antagonistic analogs of luteinizing hormone-releasing hormone (LH-RH), containing neutral hydrophilic D-ureidoalkyl amino acids such as D-Cit and D-Hci at position 6 and free of edematogenic and anaphylactoid reactions, Ac-D-Nal(2)[1], D-Ph(4Cl)[2], D-Pal(3)[3], D-Cit[6], D-Ala[10] (LH-RH) (SB-75; Cetrorelix) was shown to be one of the most powerful. In this trial, we evaluated the response to 500 μg SB-75 given every 12 hr subcutaneously (sc) for 4 weeks in 11 patients with benign prostatic hyperplasia (BPH), and 6 weeks in 6 prostatic cancer patients (2 stage C, 4 stage D2). In patients with BPH presenting with prostatism and urinary outflow obstruction, there was a noticeable clinical improvement after the first week of SB-75 administration. This improvement continued during the course of treatment. Before therapy with SB-75, the serum levels of prostate-specific antigen (PSA) (6.73 ± 1.46 ng/ml), acid phosphatases, total (12.67 ± 1.15 U/l), and prostatic (2.27 ± 0.34 U/l), were mildly elevated, but declined to normal values at 4 weeks: (2.13 ± 0.59 ng/ml; $P < 0.01$), (7.68 ± 0.89 U/l; $P < 0.01$), and (1.39 ± 0.18 U/l; $P < 0.01$), respectively. Mean prostatic volume assessed by ultrasonography showed a significant decrease in all patients from 67.84 ± 8.86 to 37.92 ± 8.52 cm^3; $P < 0.01$, which represents a reduction of 44%. In patients with prostate cancer, after the first week of therapy with SB-75, we observed a significant decrease in bone pain, relief in urinary outflow obstruction, and reversal of the signs of prostatism. Subjective improvement continued during the following weeks of treatment, so that the patients no longer needed analgesics. PSA, acid, and alkaline phosphatases gradually fell, achieving nearly normal values at 6 weeks. Initial serum testosterone levels in BPH and prostatic cancer patients were within normal limits, but during treatment with the antagonistic analog SB-75, fell to castration values. A major fall in free testosterone levels was observed after the first dose; the maximal inhibition was seen after 6–12 hr, with a simultaneous decrease in levels of both gonadotropins. Our results show that antagonist SB-75 can be safely administered for prolonged periods of time. The rapid shrinkage of the prostate and concomitant improvement in obstructive symptoms of prostatism obtained with antagonistic analog SB-75 in patients with BPH may decrease the morbidity of prostatic surgery and offer a therapeutic alternative in men who are considered poor surgical risks. Antagonist SB-75 could also be useful for the treatment of prostatic cancer, but further studies are required.

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INTRODUCTION

The variety of clinical applications of luteinizing hormone-releasing hormone (LH-RH) analogs is steadily expanding. Chronic administration of potent long-acting LH-RH agonistic analogs leads to pituitary desensitization and inhibition of sex steroid levels, and is being used for treatment of precocious puberty, endometriosis, uterine myomas, benign prostate hypertrophy, and hormone-dependent malignant neoplasms, especially those of prostate, breast, ovary, and pancreas [1–8].

The development of antagonistic analogs of LH-RH is also actively proceeding [1,2,3,9]. Since 1973, a series of LH-RH antagonists have been synthesized and tested in animals and human beings [1,2,3,9]. The first clinical study with the antagonistic analog D-Phe^2, D-Trp^3, D-Phe^6-LH-RH demonstrated that a single injection can suppress gonadotropin levels and the response to exogenous LH-RH [10]. However, early analogs had a low potency and side effects due to histamine release have been observed with most LH-RH antagonists with D-Arginine or other basic residues in position 6 [1,2,3,9,11]. The allergic reactions produced by these early antagonists delayed their clinical use in humans. During the past few years, new potent antagonistic analogs of LH-RH with various structural modifications and low histamine releasing effects have been synthesized by several groups [12–16]. Highly active LH-RH antagonists containing neutral hydrophilic D-ureidoalkyl amino acids such as D-Cit and D-Hci at position 6, and free of edematogenic and anaphylactoid reactions, were synthesized by our group and tested in vitro and in vivo [12,13]. Among these analogs [Ac-D-Nal(2)^1, D-Phe(4Cl)^2, D-Pal(3)^3, D-Cit^6, D-Ala^{10}] LH-RH (SB-75; Cetrorelix) was shown to be one of the most powerful [12]. Furthermore, SB-75 showed practically no release of histamine from peritoneal mast cells in vitro [12]. Our previous studies showed that the intravenous (iv), subcutaneous (sc), intramuscular (im) administration of antagonist SB-75 to climacteric women and normal men caused inhibition of serum LH and follicle stimulating hormone (FSH) levels [17]. Dose responses were obtained to 75, 150, 300, 600, and 1,200 μg of SB-75 given as a single injection. Maximal inhibition was observed 6–12 hr after administration. Normal men, with a mean age of 24 years, showed an 80% fall in serum total and free testosterone levels 12 hr after sc administration of 300 μg SB-75 [17]. In view of these encouraging results, we decided to evaluate the antagonistic LH-RH analog SB-75 in patients with benign prostate hyperplasia (BPH) and advanced prostatic cancer.

PATIENTS AND METHODS

Eleven patients with symptomatic BPH and six with biopsy proven prostatic cancer (two stage C, four stage D2) volunteered for this study. Patients with BPH received 500 μg of the antagonistic analog every 12 hr by the sc route for 4 weeks. Prostatic cancer patients were treated with the same regimen for 6 weeks. All patients had severe urinary symptoms. The prostatic cancer patients also had bone pain and elevated levels of prostate-specific antigen (PSA), acid, and alkaline phosphatases. None of the patients had received any specific drug therapy previously. This study was conducted as an open label. The patients were admitted to the Endocrinology Department of the Hospital de Especialidades, Centro Medico La Raza del Instituto Mexicano del Seguro Social in Mexico, D.F. Informed consent was obtained from all the patients after the therapeutic options available had been explained. The study was approved by the Hospital Ethics and Scientific Research Committee (protocol 92-690-753).

In order to assess local or systemic reactions, the analog was first diluted using Evans solution and carefully administered by scratch testing in the forearm starting with 1:10,000 and afterwards using 1:1,000, 1:100, and 1:10 dilution. Eventually the undiluted analog was applied intradermally in a concentration of 300 μg/ml. Local and systemic reactions, including blood pressure, respiration, heart frequency, and pulse were monitored carefully. We did not observe any adverse local or systemic reaction. On the basis of our previous studies on dose responses in climacteric women and normal men, it was decided to use 500 μg every 12 hr. An indwelling, iv catheter was placed in a vein in the antecubital fossa; blood samples were taken 15 min prior to and immediately before administration of the antagonistic analog (time 0) and then every 2 hr up to 12 hr. After centrifugation, serum was separated and frozen for radioimmunoassays (RIA). RIA kits for LH, FSH, and PSA were obtained from CIS Biointernational (Paris, France), and for total and free testosterone from Diagnostic Products Corporation (Los Angeles, CA). The gonadotropin results are expressed as international units (IU/L) of the second international reference preparation of human menopausal gonadotropin (2nd IRPHMC). Total testosterone was expressed in nmol/L, free testosterone in pmol/L, and also as the

TABLE I. Changes in Prostatic Volume, Serum PSA, Acid Phosphatases, Testosterone, LH, FSH Levels, and 24-hr Urinary Frequency (Diurnal/Nocturnal) in 10 Patients With BPH After 4 Weeks of Treatment With 500 μg b.i.d. of the Antagonist SB-75

	Prostatic ultrasound (20–25)[a] (volume cm^3)	PSA (0–1.9)[a] ng/ml	Serum acid phosphatases		Serum testosterone		LH (0–5.3)[a] IU/l	FSH (0–6)[a] IU/l	24-hr urinary frequency (diurnal/nocturnal)
			Total (2.17–10.53)[a] (U/l)	Prostatic (0.25)[a] (U/l)	Total (10.4–34.6)[a] n mol/l	Free (41.6–138.6)[a] pmol/l			
Pre	67.81 ± 8.86	6.73 ± 1.46	12.67 ± 1.15	2.27 ± 0.34	19.03 ± 1.07	60.70 ± 8.59	5.06 ± 0.71	6.9 ± 0.8	15.1 ± 2.60 (8.72/6.36)[b]
Post	37.92 ± 8.52*	2.13 ± 0.59*	7.68 ± 0.89*	1.39 ± 0.18*	5.78 ± 2.04*	14.18 ± 5.02*	1.67 ± 0.6**	1.68 ± 0.54**	5.81 ± 0.62*** (4.27/1.54)[b]

[a]Normal range.
[b]ratio diurnal/nocturnal.
*$P < 0.01$.
**$P < 0.05$.
***$P < 0.001$.

percentage of maximal inhibition. The intra- and interassay coefficients of variation for each assay were less than 9%. Before treatment, baseline ultrasound of the prostate was performed in each patient. Subsequently, prostatic volume was measured every 2 weeks by suprapubic transvesical ultrasonography using a General Electric RT-3600 unit with a sectorial scanner and a 3.5 mHz probe. Prostate volume was calculated by planimetry [18]. The safety of the analog was tested on days 1, 3, 5, 14, and 28 by clinical examination and laboratory tests, which included the assessment of blood hemoglobin levels, leukocyte total counts and differential, platelets, urea, creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline and acid phosphatases, and total bilirubin. In urine, protein, glucose, urobilinogen, epithelial cells, erythrocytes, and leukocytes were also measured. Hormonal evaluation of 12-hr serum levels of testosterone (total and free), LH, and FSH was done on the same day. The urinary symptom scores were determined from weekly interviews. Scores ranged from 0–4 (0 = asymptomatic; 4 = severely symptomatic). Those scores included urinary flow, dribbling, and 24 hr diurnal/nocturnal frequency of urination.

The antagonistic analog was synthesized and provided by Asta-Medica, Frankfurt/M, Germany. For injection, the analog was dissolved in a 5% mannitol solution and then was sterilized in an autoclave for 15 min at 18 psi and 120°C. For the injection, each dose was diluted to one milliliter.

Statistical Tests

Unless otherwise indicated, all group values are expressed as the mean ± SEM. The data were analyzed by Student's paired *t* test.

RESULTS

BPH Patients

Table I shows the mean changes in prostatic volume, the laboratory data, and 24-hr urinary frequency (diurnal/nocturnal) in 10 patients before treatment, and after 4 weeks of sc administration of 500 μg b.i.d. of the antagonistic analog SB-75. After the first week of SB-75 administration, we observed improvements in urinary flow, and reversal of the signs of prostatism with a significant decrease of the 24-hr, frequency (diurnal/nocturnal). This improvement continued during the following weeks of treatment. At 4 weeks, urine flow became practically normal, the frequency being reduced from 15.1 ± 2.60 to 5.81 ± 0.62/day ($P < 0.001$).

Before therapy, the serum acid phosphatases (total and prostatic) were mildly elevated (12.67 ± 1.15 U/L and 2.27 ± 0.34 U/L, respectively), but declined to normal values 4 weeks after treatment was started (7.68 ± 0.89 U/L and 1.39 ± 0.18 U/L, $P < 0.01$), respectively.

Seven patients showed a progressive decrease of serum total and free testosterone levels after administration of the first dose of the antagonistic LH-RH analog SB-75, and remained at subnormal levels following 4 weeks of therapy. In 4 patients, castration values in total and free testosterone were seen after the first dose, and in seven patients, on the fifth day of the antagonistic analog administration (Fig. 1).

Maximal inhibition of LH and FSH levels was seen at 6–12 hr, with a simultaneous decrease of both gonadotropins (Fig. 2). At 4 weeks, LH and FSH levels showed a significant decrease from 5.06 ± 0.7 IU/L to 1.67 ± 0.6 IU/L, $P < 0.05$, and from 6.9 ± 0.8 IU/L to 1.68 ± 0.54 IU/L; $P < 0.05$, respectively. In 4 patients

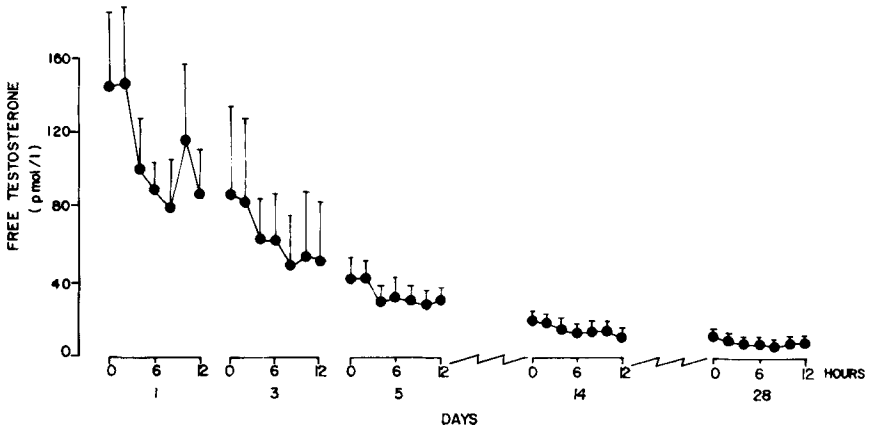

Fig. 1. Inhibition of serum-free testosterone levels after sc administration of 500 μg of the antagonistic LH-RH analog SB-75 every 12 hr in seven patients with BPH. Vertical lines indicate ± SEM.

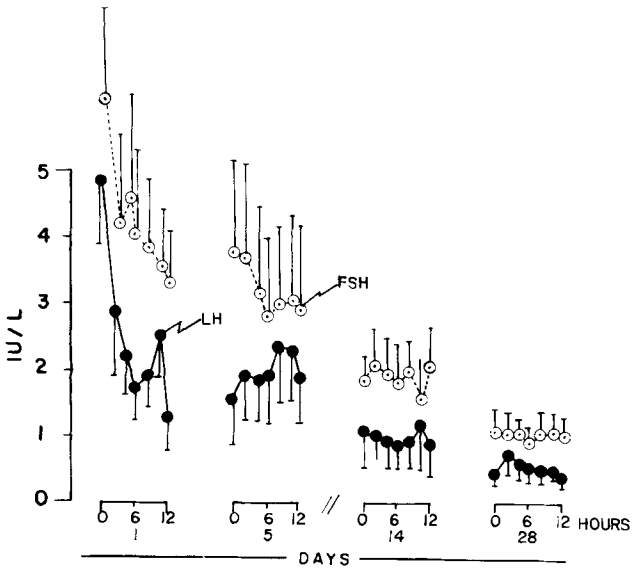

Fig. 2. Inhibition of serum LH and FSH levels after sc administration of 500 μg of antagonist SB-75 every 12 hr in seven patients with BPH. Vertical lines indicate ± SEM.

(no. 1,2,5, and 11), free testosterone remained at borderline values before and during treatment (Fig. 3).

Irrespective of the inhibition or the lack of suppression of the serum testosterone levels, all the patients showed a significant decrease in the prostatic volume obtained by ultrasonography from 67.81 ± 8.86 cm^3 to 37.92 ± 8.52 cm^3, which represents a reduction of 44.51 ± 8.87%. The group in which testosterone was inhibited showed a reduction from 67.82 to 37.93 cm^3 (44%) and the group in which it was not suppressed demonstrated a decrease from 64.38 to 34.97 cm^3 (46%). Figure 4 shows individual changes in the prostatic volume. The serum PSA decreased from 6.73 ± 1.46 ng/ml to 2.13 ± 0.59 ng/ml ($P < 0.01$) (Table I).

At the end of the study, a transurethral prostatectomy was performed in 4 patients. Three patients remained only on observation. No increase in the prostatic volume by ultrasonography was seen for up to 52 weeks in the patient who was observed for the longest time (Fig. 5).

Blood cell count, chemistry, and electrolytes were within normal limits before and during treatment. All patients reported an increase in appetite, and no symptoms of flare-up were noted. Some patients developed hot flashes and impotence during treatment, but only one BPH patient (case 8) discontinued the antagonistic analog after 2 weeks because of occurrence of impotence. No other side effects were recorded during acute or chronic administration of antagonist SB-75.

Prostatic Cancer Patients

Table II shows the mean changes in serum phosphatases, PSA, testosterone, and 24-hr urinary frequency (diurnal/nocturnal) in six patients before and after 6 weeks of administration of the antagonistic analog SB-75 (500 μg b.i.d.).

After the first week of treatment with SB-75, we observed a significant decrease in bone pain, relief of urinary flow obstruction, and reversal of signs of prostatism. Subjective improvement continued during the following weeks of treatment and ultimately the patients no longer needed analgesics. Acid and alkaline phosphatases gradually fell, achieving next to normal values after 6 weeks. After 6 weeks of administration of SB-75, PSA levels reached normal levels in two stage C patients. Initial serum testosterone was within normal limits, but fell to subnormal levels during treatment with the antagonist. A major fall was observed in free testosterone beginning with the

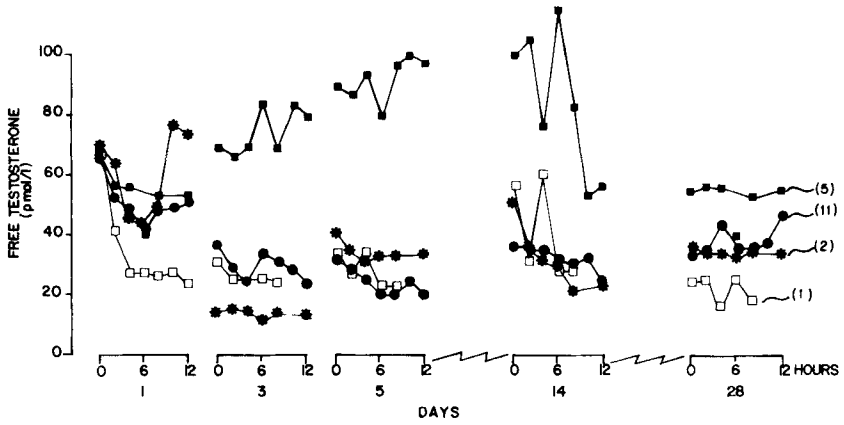

Fig. 3. Serum levels of free testosterone in four patients with BPH which remained within normal limits during the administration of 500 μg antagonist SB-75 every 12 hr, in spite of the decrease in the prostate volume and reversal of the signs of prostatism. (Numbers in parentheses are the patient numbers.)

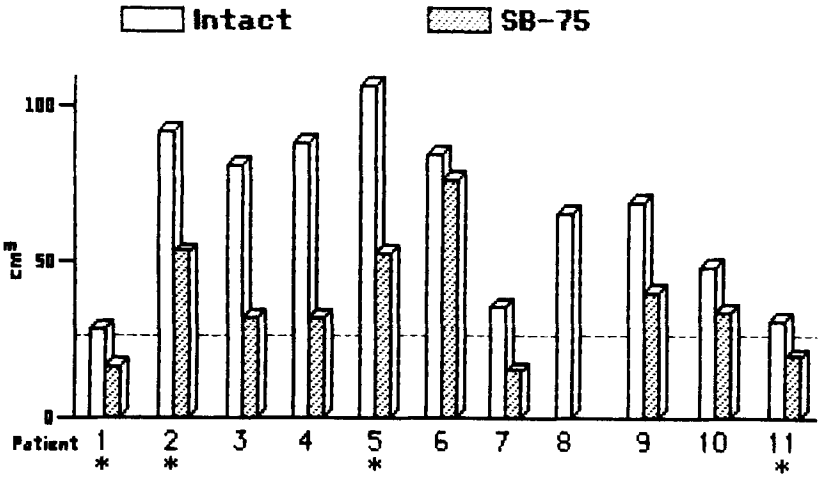

Fig. 4. Decrease in the prostatic volume as measured by ultrasonography in 11 patients with BPH after the administration of 500 μg of the antagonist SB-75 every 12 hr for 4 weeks. In patients 1,2,5, and 11, serum testosterone levels remained within normal limits. (Dashed line represents the normal volume.)

first dose, and maximal inhibition was seen after 6–12 hr. Three of 6 patients showed castration levels after the first day, and the other three after 2 weeks of therapy. A persistent inhibition of serum testosterone levels in a patient with prostatic cancer stage D2 after administration of SB-75 can be seen in Figure 6. A significant and progressive decrease in prostatic volume was obtained during the second week of treatment in the 2 patients with stage C cancer. The pretreatment volumes were 51.3 and 49.6 cm^3 and, after 6 weeks of therapy, decreased to 9.28 and 7.49 cm^3, respectively, which represents a reduction of more than 80%. In the 4 patients with stage D2 cancer, the pretreatment prostatic ultrasonography showed a small volume due to previous prostatic resection, and no significant changes were observed during the therapy.

DISCUSSION

The marked and selective inhibition of pituitary and gonadal function that occurs after chronic administration of super active, long-acting agonistic analogs of LH-RH has led to a new and important approach to the treatment of sex hormone-dependent tumors, especially prostate cancer, as well as precocious puberty, endometriosis, and uterine leiomyomas [1–8, 19,20]. While repeated administration of agonists is required to inhibit LH and FSH release and reduce the levels of sex steroids, similar effects can be ob-

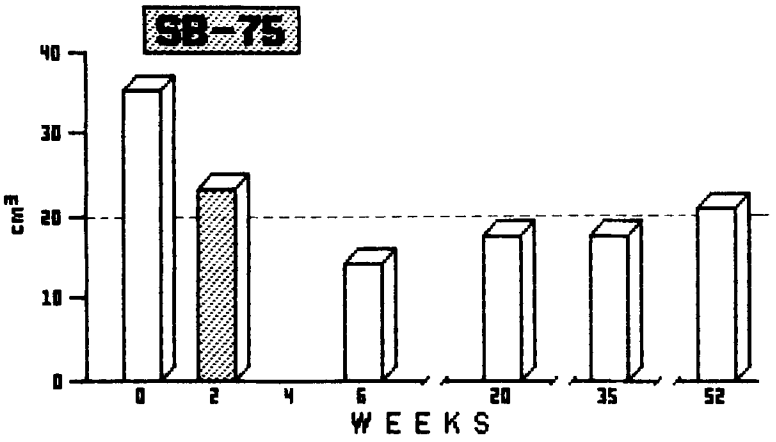

Fig. 5. Prostatic volume by ultrasonography before, during, and after sc administration of antagonist SB-75 in a 62-year-old patient with BPH. SB-75 was given at the dose of 500 μg b.i.d. during weeks 1 to 4. (Dashed line represents the normal volume.)

TABLE II. Changes in Serum Phosphatases, PSA, Testosterone and 24-hr Urinary Frequency (Diurnal/Nocturnal) in Patients With Prostatic Cancer After 6 Weeks of Treatment With 500 μg b.i.d. of Antagonist SB-75

		Phosphatases								Testosterone					
		Acid total (2.17–10.52)[a] (U/l)		Acid prostatic (0.0–2.5)[a] (U/l)		Alkaline (52–70)[a] (U/l)		PSA (0.3–1.9)[a] (ng/ml)		Total (10.4–34.6)[a] (n mol/l)		Free (41.6–138.6)[a] (p mol/l)		24-hr urinary frequency (diurnal/ nocturnal)	
Case	Age	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
							STAGE C								
1	77	24.1	11.1	3.8	1.0	90	48	7.8	0.2	16.6	0.69	55	1.04	11 (5/6)[b]	6 (5/1)[b]
2	55	24.9	0.9	3.7	0.3	76	52	3.4	0.4	20.8	0.69	72.8	0.86	16 (8/8)[b]	8 (6/2)[b]
							STAGE D2								
3	73	27.34	14.3	13.67	7.1	225	65	>150	45.2	20.8	0.69	65.1	4.50	24 (12/12)[b]	6 (5/1)[b]
4	89	20.34	14.3	7.34	4.2	332	262	>150	78.0	18.2	10.40	44.2	30.33	11 (5/6)[b]	5 (4/1)[b]
5	65	15.51	12.6	2.01	2.03	339	297	>150	75.6	16.9	0.69	51.6	6.41	15 (10/5)[b]	7 (6/1)[b]
6	55	17.16	12.3	2.66	1.50	159	93	73	2.1	22.5	0.34	45.5	2.60	9 (6/3)[b]	6 (4/2)‡
Mean±SEM		21.55±1.9	10.9±2.0*	5.35±1.79	2.68±1.03**	203.5±47.2	136±46.1**			19.3±0.9	2.2±1.6*	55.2±4.8	7.6±4.6*	14.3±2.2 (7.6/6.6)[b]	6.3±0.4** (5/1.3)[b]

[a]normal
[b]ratio diurnal/nocturnal.
*$P < 0.01$.
**$P < 0.05$.

tained with a single dose of an LH-RH antagonist [1,2,3,9,12,13]. Originally, antagonistic analogs of LH-RH were developed for contraception. More than 10 years ago, in collaborative studies in Mexico, it was shown that the administration of an early antagonist (N-Ac-D-p-Cl-Phe^{1,2},D-Trp^{3},D-Phe^{6},D-Ala^{10}) LH-RH, inhibited the midcycle surge of LH and FSH and ovulation in normally cycling women [21,22]. During the past few years, several modern LH-RH antagonists possessing various structural modifications have

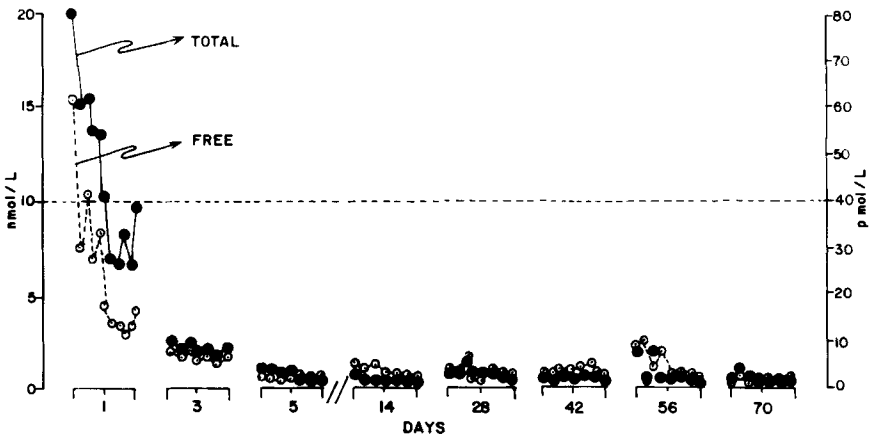

Fig. 6. Inhibition of serum total and free testosterone levels in a 73-year-old patient with prostatic cancer stage D2 after sc administration of 500 μg every 12 hr of antagonist SB-75. (Dashed line represents the low normal levels.)

been synthesized and evaluated in vitro and in vivo in animals [12–16].

Studies with sustained delivery systems of the antagonistic analog SB-75 in intact normal male rats revealed inhibition of serum testosterone to castration levels and decreases in testicular, ventral prostate, and seminal vesicle weights [23]. In female rats, treatment with SB-75 disrupted normal estrous cycles, lowered serum estradiol, and decreased ovarian and uterine weights [23]. However, 60–90 days after cessation of treatment, there was a complete recovery of pituitary and gonadal function in male and female rats [23]. Experimental oncological studies have shown that SB-75 causes a marked inhibition of tumor growth in mice bearing hormone-sensitive MXT mammary cancers [24], in rats with Dunning R 3327 prostate cancer [25], in nude mice bearing PC-82 human prostate carcinoma [26], and in hamsters with BOP-induced pancreatic cancer [27].

Clinical studies have demonstrated that some of these LH-RH antagonists, including Detirelix Nal-Glu antagonist and SB-75 (Cetrorelix), are potent inhibitors of gonadotropins and sex-steroid secretion in men and women [17,28–31]. The experimental studies with SB-75 did not reveal any edematogenic effects in rats [12,23,24]. However, since it has been reported previously that related basic antagonistic analogs caused anaphylactic reactions, we performed intradermal skin tests in our patients on the first day and extreme precautions were taken each time that the analog was injected. None of the patients who were treated for 2 months with 500 μg every 12 hr complained of any allergic reaction or side effects.

Nearly all patients treated with SB-75 showed reduction of serum testosterone during the treatment. Androgens, specifically dihydrotestosterone, play a role in the pathogenesis of BPH and prostatic cancer [32]. In order to obtain a powerful suppression of the pituitary-gonadal axis, it may be necessary to use higher doses of the antagonistic analog SB-75 during the first week. Then the doses of Cetrorelix can be reduced to 500 μg b.i.d. or less for chronic therapy. The clinical improvement in prostate cancer and BPH patients and the decrease of PSA observed in our study must be due to the blockade of the pituitary-gonadal axis induced by the continuous administration of the antagonistic analog. However, the antagonist could also have some direct effect on the prostate [25]. Experimental studies in athymic nude male mice bearing the PC-82 human prostatic carcinoma showed that chronic administration of antagonist SB-75 causes a marked inhibition of pituitary and gonadal function, a down regulation of pituitary LH-RH receptors, and a marked decline in sex hormone levels [26]. SB-75 inhibited the growth of the transplanted PC-82 tumor by decreasing cellular proliferation and enhancing cellular death via apoptosis [26]. The persistent clinical improvement and reduction in the prostatic volume observed in the BPH patients after discontinuation of the LH-RH antagonist may be due to the induction of those phenomena. It has been indicated that the morbidity and mortality from transurethral prostatectomy in BPH patients may be higher than previously suspected [33–35]. In addition, Roos et al. [33] found that transurethral prostatectomy is less effective in overcoming urinary obstruction than the open operation. Fowler et al. [34] reported that after prostate surgery for BPH, 24% of the men had short-term complications, 4% had persistent incontinence, and 5% became impotent. Previous studies, using long-acting agonistic analogs of LH-RH, have reported a reduction of prostate size

and improvement in symptoms of prostatism in men with BPH [32–35]. Our findings indicate that LH-RH antagonist SB-75 decreases prostatic volume and induces improvement in urinary flow from the first week of administration. The rapid shrinkage of the prostate gland and reversal of the signs of prostatism suggest that Cetrorelix may offer an alternative therapy in men with BPH who are poor surgical risks. This approach may also be considered for those patients with symptomatic BPH who may wish to delay surgery.

Although long-term studies are still necessary, the clinical improvement seen in patients with prostate cancer treated with antagonist SB-75 is comparable to that produced by LH-RH super agonist D-Trp-6-LH-RH [1,3,4,19,20]. In addition to clinical improvement, SB-75 induced a persistent blockade of the pituitary-gonadal axis, and caused a progressive fall of the serum tumor markers in patients with prostate cancer.

In conclusion, our results show that this antagonistic analog SB-75 is completely devoid of anaphylactoid reactions, extremely active in small doses in humans beings, and can be safely administered for prolonged periods of time. Antagonist SB-75 and related antagonists should be useful for the treatment of prostate cancer, other sex hormone-dependent tumors, as well as other conditions and diseases in which the inhibition of sex steroids and/or gonadotropins is desirable. The advantage of the antagonists is based on the fact that they inhibit LH, FSH, and thus, sex steroids, from the start of administration. The use of antagonists would prevent the temporary clinical "flareup" of disease, which may occur with the agonists. The development of sustained delivery systems for SB-75 based on microcapsules or microgranules, which would be convenient to use and which would ensure the compliance of patients, is in progress [2,23–27].

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REFERENCES

1. Schally AV, Bajusz S, Redding TW, Zalatnai A, Comaru-Schally AM: Analogs of LH-RH: The present and the future. In Vickery BH, Lunenfeld V (eds): "GnRh Analogues in Cancer and in Human Reproduction. Basic Aspects." Dordrecht Boston/London: Kluwer Academic Publishers, 1989, pp. 5–31.
2. Schally AV: The use of LH-RH analogs in gynecology and tumor therapy. In Belfort P, Pinotti JA, Eskes TKAB (eds): "Advances in Gynecology and Obstetrics. General Gynecology," Vol 6. Carnforth, England: Parthenon Publishing, 1989, pp. 3–20.
3. Vickery BH: Comparison of the potential for therapeutic utilities with gonadotrophin-releasing hormone agonists and antagonists. Endocr Rev 7:115–124, 1986.
4. Tolis G, Ackman D, Stellos A, Labrie F, Metha A, Fazekas ATA, Comaru-Schally AM, Schally AV: Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone releasing agonists. Proc Natl Acad Sci USA 79:1662–1685, 1982.
5. Parmar H, Lightman SL, Allen L, Phillips RH, Edwards L, Schally AV: Randomized controlled study of orchidectomy vs. long-acting D-Trp-6-LH-RH microcapsules in advanced prostatic carcinoma. Lancet 2:1202–1205, 1985.
6. Zorn JR, Tanger CH, Roger M, Grenier J, Comaru-Schally AM, Schally AV: Therapeutic hypogonadism induced by a delayed-release preparation of microcapsules of D-Trp-6-luteinizing-hormone-releasing hormone: A preliminary study in eight women with endometriosis. Int J Fertil 31:11–27, 1986.
7. George M, Lhomme C, Lefort J, Gras C, Comaru-Schally AM, Schally AV: Long term use of an LH-RH agonist in the management of uterine leiomyomas. A study of 17 cases. Int J Fertil 34:19–24, 1989.
8. Parmar H, Nicoll J, Stockdale A, Cassoni F, Phillips RH, Lightman S, Schally AV: Advanced ovarian carcinoma. Response to the agonist D-Trp-6-LH-RH. Cancer Treat Rep 69:1341, 1985.
9. Dutta AS: LH-RH antagonists. Drugs Future 13:761–787, 1988.
10. Gonzalez-Barcena D, Kastin AJ, Coy DH, Nikolics K, Schally AV: Suppression of gonadotropin release in man by an inhibitory analogue of luteinizing hormone-releasing hormone. Lancet 2:997–998, 1977.
11. Schmidt F, Sundaram K, Thau RB, Bardin CW: (Ac-D-Dal(2)^1, 4FD-Phe^2, D-Trp^3, D-Arg^6)-LH-RH, a potent antagonist of LHRH, produces transient edema and behavioral changes in rats. Contraception 29:283–289, 1984.
12. Bajusz S, Csernus VJ, Janaky T, Bokser L, Fekete M, Schally AV: New antagonists of LH-RH: II. Inhibition and potentiation of LH-RH by closely related analogues. Int J Pept Protein Res 32:425–435, 1988.
13. Bajusz S, Kovacs M, Gazdag M, Bokser L, Karashima T, Csernus V, Janaky T, Gouth J, Schally AV: Highly potent antagonists of luteinizing hormone-releasing hormone free of edematogenic effects. Proc Natl Acad Sci USA 85:1637–1641, 1986.
14. Ljungqvist A, Feng DM, Hook W, Shen ZX, Bowers C, Folkers K: Antide and related antagonists of luteinizing hormone release with long action and oral activity. Proc Natl Acad Sci USA 85:8236–8240, 1988.
15. Rivier JE, Porter J, Rivier CL, Perrin M, Corrigan A, Hook WA, Siraganian RP, Vale WW: New effective gonadotropin releasing hormone antagonists with minimal potency for histamine in vitro. J Med Chem 29: 1846–1851, 1986.
16. Nestor JJ Jr, Tahilramani R, Ho TL, McRae GI, Vickery BH: Potent, long-acting luteinizing hormone-releasing hormone antagonists containing new synthetic amino acids: N,N^1-Dialkyl-D-homoarginines. J Med Chem 31: 65–72, 1988.
17. Gonzalez-Barcena D, Vadillo-Buenfil M, Guerra-Arguero L, Carreno J, Comaru-Schally AM, Schally AV:

Potent antagonistic analog of LH-RH (SB-75) inhibits LH, FSH, and testosterone levels in human beings. Program 72nd Annual Meeting of Endocrine Society. Atlanta. (Abstract 1318) p. 354, 1990.
18. Hendrikx AJM, Doesburg WH, Reintjes ABM, Strijk SP, Debruyne FMJ: Effectiveness of ultrasound in the preoperative evaluation of patients with prostatism. Prostate 13:199–208, 1988.
19. Gonzalez-Barcena D, Perez-Sanchez P, Berea-Dominguez H, Graef-Sanchez A, Becerril-Morales M, Comaru-Schally AM, Schally AV: Persistent blockade of the pituitary-gonadal axis in patients with prostatic carcinoma during chronic administration of D-Trp-6-LH-RH. Prostate 9:207–215, 1986.
20. Gonzalez-Barcena D, Rangel-Garcia NE, Perez-Sanchez P, Gutierrez-Samperio C, Garcia-Carrasco F: Response to D-Trp-6-LH-RH in advanced adenocarcinoma of pancreas. Lancet 2:154, 1986.
21. Canales ES, Montvelinsky H, Zarate A, Kastin AJ, Coy DH, Schally AV: Suppressive effect of an inhibitory LH-RH analog on the gonadotropin response to LH-RH in normal women. Int J Fertil 25:190–192, 1980.
22. Zarate A, Canales ES, Sthory I, Coy DH, Comaru-Schally AM, Schally AV: Anovulatory effect of a LH-RH antagonist in women. Contraception 24:315–320, 1981.
23. Bokser L, Srkalovic G, Szepeshazi K, Schally AV: Recovery of pituitary gonadal function in male and female rats after prolonged administration of a potent antagonists of luteinizing hormone-releasing hormone. Neuroendocrinology 54:136–145, 1991.
24. Szende B, Srkalovic G, Groot K, Lapis K, Schally AV: Growth inhibition of mouse MXT mammary tumor by the luteinizing hormone-releasing hormone antagonists SB-75. J Natl Cancer Inst 82:513–517, 1990.
25. Korkut E, Bokser L, Groot K, Schally AV: Inhibition of growth of experimental prostate cancer with sustained delivery systems (microcapsules and microgranules) of an antagonist of luteinizing hormone-releasing hormone SB-75. Proc Natl Acad Sci USA 88:844–848, 1991.
26. Redding TW, Schally AV, Radulovic S, Milovanovic S, Szepeshazi K, Isaacs J: Sustained release formulations of LH-RH antagonist SB-75 inhibit proliferation and enhance the apoptotix cell death of human prostate carcinoma (PC-82) in male nude mice. Cancer Res 52: 2538–2544, 1982.
27. Szende S, Srkalovic G, Groot K, Lapis K, Schally AV: Regression of Nitrosamine-induced pancreatic cancers in hamsters treated with luteinizing hormone-releasing hormone antagonists and agonists. Cancer Res 50: 3716–3721, 1990.
28. Andreyko JL, Monroe SE, Marshall LA, Fluker MR, Nerenberg CA, Jaffe RB: Concordant suppression of serum immunoreactive luteinizing hormone (LH), follicle-stimulating hormone, α subunit, bioactive LH, and testosterone in postmenopausal women by a potent gonadotropin releasing hormone antagonist (Detirelix). J Clin Endocrinol Metab 74:399–405, 1992.
29. Pavlou SN, Wakefield G, Schlechter NL, Lindner J, Souza KH, Kamilaris TC, Konidaris S, Rivier JE, Vale WW, Toglia M: Mode of suppression of pituitary and gonadal function after acute or prolonged administration of a luteinizing hormone-releasing hormone antagonist in normal men. J Clin Endocrinol Metab 68:446–454, 1989.
30. Pavlou SN, Wakefield GB, Island DP, Hoffman PG, LePage ME, Chan RL, Nerenberg CA, Kovacs WJ: Suppression of pituitary-gonadal function by a potent new luteinizing hormone-releasing hormone antagonist in normal men. J Clin Endocrinol Metab 64:931–936, 1987.
31. Jockenhovel F, Bhasin S, Steiner BS, Rivier JE, Vale WW, Swerdloff RS: Hormonal effects of single gonadotropin-releasing hormone antagonist doses in men. J Clin Endocrinol Metab 66:1065–1070, 1988.
32. Peters CA, Walsh PC: The effect of Nafarelin acetate, a luteinizing hormone-releasing hormone agonist, on benign prostatic hyperplasia. N Engl J Med 317:599–604, 1987.
33. Roos NP, Wennberg JE, Malenka DJ, Fisher ES, McPherson K, Andersen TF, Cohen MM, Ramsey E: Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. N Engl J Med 320:1120–1124, 1989.
34. Fowler Jr JF, Wennberg JE, Timothy RP, Barry MJ, Mullery Jr AG, Hanley D: Symptoms status and quality of life following prostatectomy. J Am Med Assoc 259: 3018–3022, 1988.
35. Gabrilove JL, Levine AC, Kirschenbaum A, Droller M: Effect of long-acting gonadotropin-releasing hormone analog (Leuprolide) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. J Clin Endocrinol Metab 69:629–632, 1989.