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'Acute on chronic' effect of depot leuprolide in patients with stage D2 cancer of prostate

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During a phase III open study of depot leuprolide for stage D2 cancer of the prostate, we studied the effect of depot leuprolide on chronic leuprolide users. To determine whether there was a transient elevation of testosterone or luteinizing hormone (LH) 4–24 h and 3–5 days following the monthly injections, we monitored the changes of testosterone and LH before injection and 24 h post-injection in 10 patients who have been under depot leuprolide Rx for 24–36 weeks, and in 35 patients before injection and 3–5 days post-injection who have received depot leuprolide for 8–24 weeks prior to monitoring. Comparison of the data between pre-injection within 24 h and 3–5 days post-injection showed no significant changes of testosterone and LH values between these levels for either testosterone ($P = 0.31$) or LH ($P = 0.45$). We therefore conclude that there was no 'acute on chronic' effect of depot formulation in chronic users of depot leuprolide.

Key words: Leuprolide, prostate cancer.

Introduction

Since the initial observations of Russell S. Ferguson,[1] Alexander Randal[2] and Charles Huggins[3] and others five decades ago regarding the efficacy of different hormonal manipulations in relieving the symptoms of metastatic prostate carcinoma, investigators have looked for less toxic, less invasive methods of androgen deprivation to avoid adverse psychological impact of surgical castration and cardiovascular side effects of estrogen therapy. These methods were considered standard and first line therapy for progressive or symptomatic disseminated prostate cancer.

The discovery of molecular structure of natural GnRH by Shally[4] was soon followed by the synthesis of several other analogs. These analogs are called agonist analogs or super agonist because they release a greater amount of luteinizing hormone (LH) for longer periods due to increasing binding affinity for LH receptors in the pituitary. These agents have a paradoxical effect on pituitary which results in initial stimulation but subsequent inhibition of LH and follicle-stimulating hormone (FSH). The resultant decrease in serum testosterone is followed by a decline in the number of surgical castrations. Numerous studies have demonstrated this endocrine effect utilizing a variety of agonists.[5–9] Slow release depot formulation proves to be as effective as daily injection and has the advantage of better compliance and fewer possible side effects.[10]

It was important to determine whether or not an increase in testosterone or LH occurred after each injection of depot leuprolide and if it occurs when it happens. We therefore studied this effect for the first 24 h and 3–5 days post-injection of depot leuprolide.

Material and methods

We studied testosterone and LH values in two groups of patients.

Group I. Testosterone and LH levels were measured pre-injection and 4–8 and 24 h post-injection in patients. These patients had been receiving depot leuprolide for 24–36 weeks inclusive at the time these measurements were made.

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Group II. Testosterone and LH determination was made on 35 specimens of 32 patients pre-injection and 3–5 days post-injection. These patients had been on leuprolide therapy for 8–24 weeks.

The results were compared for statistical analyses.

Results

The testosterone data for the first group are presented in Table 1. The mean pre-injection testosterone volume was 9.2 ng/dl; mean levels at 4–8 and 24 h post-injection were 9.3, 9.9 and 12.4 ng/dl respectively. There were no statistically significant changes in mean values for pre- to post-injection of leuprolide.

In group II, the testosterone and LH levels immediately prior to injection and 3–5 days post-injection are compared. The mean (standard error) and range for testosterone and LH levels observed pre- and post-injection are shown in Table 2.

These data indicate that there was no statistically significant mean change from the injection day to 3–5 days post-injection for either testosterone ($P = 0.31$) or LH ($P = 0.45$). Testosterone levels were elevated above 50 ng/dl 4 days post-injection for two patients (65 and 72 ng/dl) following the fifth and sixth injections respectively. However by the next evaluation 2 and 4 weeks later, testosterone levels had fallen to 12 ng/dl for both patients. Thus increases in testosterone and LH levels at day 4 were only observed following the first injection of depot leuprolide, and no stimulation of testosterone and LH was observed following any of the subsequent injections.

Discussion

An increase in testosterone within the first week of therapy has been associated with a worsening of clinical symptoms in about 10% of patients with stage D2 prostate cancer being treated by injection of daily leuprolide acetate and other analogs.[11–13]

As previously shown, the mean testosterone level peaked on day 4 following the first depot injection[10] (Figure 1).

Table 1. Summary of testosterone values measured after 7–10 injections of leuprolide in 10 patients

Patient	Injection no.	No. of days since last injection	Testosterone values (ng/dl)			
			0 h	4 h	8 h	24 h
1	9	29	6	8	8	10
2	9	23	15	18	28	25
3	9	28	14	18	18	21
4	9	27	5	7	4	4
5	9	28	3	2	3	4
6	10	27	10	9	12	21
7	10	27	14	10	10	15
8	8	28	6	3	3	8
9	7	27	8	8	7	7
10	9	29	11	10	6	9
Mean			9.2	9.3	9.9	12.4
Standard error			1.3	1.7	2.5	2.4

Table 2. Testosterone and LH levels immediately prior to injection and 3–5 days post-injection in 35 samples from 32 patients who received depot leuprolide for 8–24 weeks

	Testosterone levels		LH levels	
	Pre-injection	Post-injection	Pre-injection	Post-injection
Mean	16.1 ng/dl	19.0 ng/dl	4.1 mIU/ml	4.4 mIU/ml
Range	(3–43) ng/dl	(2–72) ng/dl	(1–12) mIU/ml	(2–7) miU/ml
Standard error	1.6 ng/dl	2.5 ng/dl	0.3 mIU/ml	0.3 mIU/ml

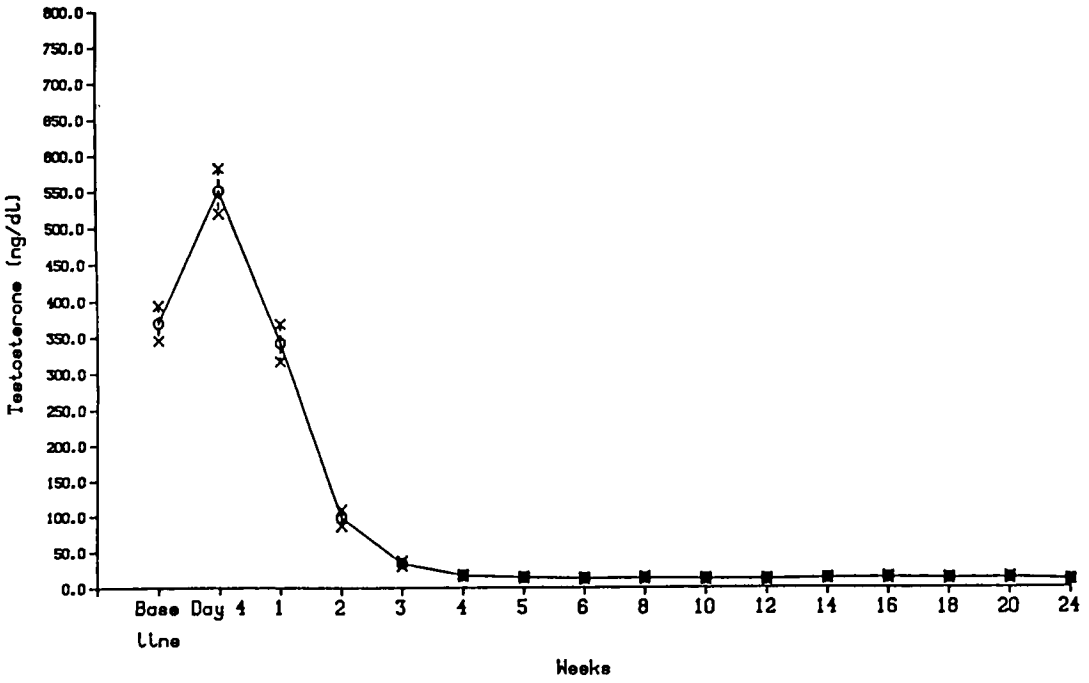

Figure 1. Mean testosterone levels at each visit (weeks) using evaluable data for 51 patients.

We wanted to determine if a similar increase would be observed following subsequent depot injections during the chronic treatment. We did not observe the development of any new symptoms or noticeable exaggeration of any present clinical symptoms during the course of study, especially during the first week after the injection of depot leuprolide. The data for testosterone value during the first 24 h and for testosterone and LH 3–5 days after injection in chronic users of leuprolide did not show any additional stimulation of testosterone or LH following any subsequent injections.

This result shows that there is no 'acute on chronic' effect in patients who have been treated with leuprolide depot formulation for at least 24 weeks.

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