Subcutaneous administration of testosterone

A pilot study report

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ABSTRACT

Objective: To investigate the effect of low doses of subcutaneous testosterone in hypogonadal men since the intramuscular route, which is the most widely used form of testosterone replacement therapy, is inconvenient to many patients.

Methods: All men with primary and secondary hypogonadism attending the reproductive endocrine clinic at Royal Victoria Hospital, Monteral, Quebec, Canada, were invited to participate in the study. Subjects were enrolled from January 2002 till December 2002. Patients were asked to self-administer weekly low doses of testosterone enanthate using 0.5 ml insulin syringe.

Results: A total of 22 patients were enrolled in the study. The mean trough was 14.48 ± 3.14 nmol/L and peak total testosterone was 21.65 ± 7.32 nmol/L. For the free testosterone the average trough was 59.94±20.60 pmol/L and the peak was 85.17 ± 32.88 pmol/L. All of the patients delivered testosterone with ease and no local reactions were reported.

Conclusion: Therapy with weekly subcutaneous testosterone produced serum levels that were within the normal range in 100% of patients for both peak and trough levels. This is the first report, which demonstrated the efficacy of delivering weekly testosterone using this cheap, safe, and less painful subcutaneous route.

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Androgen replacement therapy has evolved as a result of many years of modifying the testosterone molecule. Changes in the method of testosterone delivery have included implantable pallets, intramuscular injections, and oral formulations. Recently transdermal patches and gels have also been introduced, but these are costly. Choosing between the different testosterone preparations depends upon efficacy, safety, cost, as well as patient acceptability. The most widely used form of testosterone replacement therapy is the intramuscular injection of mixed testosterone esters. This depot formulation relies on retarded release of the testosterone esters from the oil vehicle injection depot as following release; esters undergo rapid hydrolysis by ubiquitous esterases to liberate free testosterone into the circulation. The pharmacokinetics and pharmacodynamics of androgen esters are therefore primarily determined by ester side chain length, volume of oil vehicle, and site of injection via hydrophobic physiochemical partitioning of the androgen ester between the hydrophobic oil vehicle and the aqueous extracellular fluid.[1] The advantage of testosterone esters over other testosterone preparations is that they are biologically

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effective in initiating and maintaining normal virilization in all hypogonadal men. The disadvantage is that the need for deep intramuscular administration of an oily solution causes pain at the injection site. In addition, it is also associated with breast tenderness and fluctuations in the serum testosterone concentration.[2] The latter can result in variability of energy, mood, and libido in many patients.[3] Furthermore, the parenteral route is also to be avoided in those with bleeding disorders or those taking anticoagulants.[4] However, few comparative studies have been performed to differentiate between the different techniques. The activity of oral testosterone undecenoate has been proposed to be low and erratic.[5,6] The oral testosterone undecenoate preparation has also been associated with a short duration of action as well as elevation of estrogen levels causing raised enzymes level.[7-9] The use of implantable testosterone pellets is one of the older form of testosterone administration. However, the pellets are not widely used because of cumbersome surgical implantation procedures and the associated complications (extension, 5%; bleeding or infection 1%).[10,11] Since testosterone injection is safe, reliable, and cheap. We investigated the effect of regular, low doses of subcutaneous testosterone. These could be self-administered using modern insulin syringes, which are non-traumatic and allow easier flow of viscous fluids.

Methods. Twenty-two patients with hypogonadism (primary and secondary) were enrolled from the reproductive endocrine clinic in the Royal Victoria Hospital, Montreal, Quebec, Canada. Subjects were selected from January 2002 to December 2002. Prior to starting testosterone therapy an initial blood was taken for baseline total testosterone and free testosterone. Total testosterone was measured using Advia Centaur assay (Bayer Corporation). This assay is a competitive immunoassay using direct chemiluminescent technology. The total percent coefficient of variation (CV) for this test is 5%. Coat-A-Count (Diagnostic Products Corporation, Los Angeles, CA) was used to measure free testosterone. This assay uses a solid-phase 125I radioimmunoassay designed for the quantitative measurement of free testosterone in serum with a coefficient of variation of 8%. Each patient was then educated on how to prepare testosterone injections. Testosterone enanthate in oil was used (Delatestryl, X Corp; 200mg/ml). The oily liquid was made less viscous by warming the bottle in the axilla for at least 5 minutes before injection. A microfine 0.5 ml insulin syringe (Becton-Dickensen, Chicago, IL, USA) was also warmed in the opposite axilla. The patient was then shown how to give testosterone injections subcutaneously into the abdomen. One week later a peak and a trough levels for both free and total testosterone were taken a day before and a day after the injection. The starting dose of testosterone enanthate was 25-50 mg each week and then we adjusted according to the peak and trough levels and patient symptoms. The Hospital Ethics Committee granted institutional review board approval.

Results. A total of 22 hypogonadal men were enrolled in the study. The mean age was 33 ± 13 years with an age range of between 15 and 55 years. The mean subcutaneous weekly testosterone dose was 55 ± 27 mg with a minimum of 25 mg and a maximum of 100 mg. Age, hypogonadal diagnostic category, prior treatment regimen, and sex hormone levels are summarized in **Table 1**. Following initiation of treatment, the peak total and free testosterone levels were within the normal range both before (trough) and following injection (peak). The results are shown in **Table 1 and Figures 1a and 1b**. The mean total testosterone prior to injection was 14.5 ± 3.14 nmol/L and 21.7 ± 7.32 nmol/L the day following the injection. For the free testosterone, the mean trough level was 59.9 ± 20.6 pmol/L and the peak one day later was 85.2 ± 32.9 pmol/L. These results were within the normal male range for our laboratory (total testosterone10-38.5 nmol/L, and free testosterone 31.2-162.9 pmol/L). All the patients stated that, subcutaneous injections were easy to use, and well tolerated. None of them reported any local reactions due to subcutaneous injections such as bruising, erythema, pain, swelling, and nodules. None discontinued using it.

Discussion. In the current study, we demonstrated the efficacy of delivering subcutaneous testosterone using fine needle insulin syringes. Therapy with weekly subcutaneous testosterone produced levels that were within the normal range in 100% of patients for both peak and trough levels. Weekly testosterone injections thus resulted in much-reduced fluctuations in steroid hormone level and achieved normal circulating hormone levels. An earlier study reported using 100 mg of intramuscular testosterone once a week for 12 weeks in 12 men with primary hypogonadism.[12] The mean serum testosterone concentration increased to slightly higher than upper limit of normal 1-2 days after the injection and gradually decreased to the mid-normal range by the time of the next injection.[12] In contrast, biweekly intramuscular treatment with 200 mg testosterone enanthate produced fluctuation in testosterone levels between the supraphysiological

Table 1 - Demographic, hypogonadal diagnostic category, previous route of testosterone therapy, weekly subcutaneous dose, peak and trough total and free testosterone levels.

No.	Age (years)	Diagnosis	Previous route of testosterone therapy (if any)	Weakly SC Dose (mg)	Trough (nmol/L)		Peak (pmol/L)	
					TT	FT	TT	FT
1	25	Kallmann's syndrome	IM	50	22.1	33.6	28.8	34.0
2	44	Testicular hypogonadism	IM	100	13.8	91.7	26.6	134.0
3	25	Kallmann's syndrome	IM	25	11.6	39.0	13.9	57.7
4	50	Panhypopituitarism	IM	50	14.8	44.0	30.2	64.0
5	44	Panhypopituitarism	IM	50	13.3	33.0	20.9	46.3
6	44	Testicular hypogonadism	IM	25	10.9	23.5	12.7	45.5
7	33	Kallmann's syndrome	none	50	12.3	36.3	11.2	61.2
8	36	Panhypopituitarism	none	100	20.1	90.2	14.2	61.3
9	16	Congenital adrenal hypoplasia with hypogonadism	none	25	15.2	60.2	15.7	102.3
10	50	Panhypopituitarism	none	50	13.6	70.7	29.2	70.5
11	17	Congenital adrenal hypoplasia with hypogonadism	none	25	11.6	66.2	28.2	90.8
12	40	Testicular hypogonadism	none	100	17.2	78.2	18.2	130.0
13	15	X-linked congenital adrenal hypoplasia	IM	50	14.3	60.4	18.1	72.5
14	28	Kallmann's syndrome	IM	50	13.7	70.5	16.2	130.2
15	55	Panhypopituitarism	IM	50	12.8	44.7	24.2	63.0
16	17	Hypogonadotrophic hypogonadism	none	50	17.2	90.5	30.7	112.5
17	19	Hypogonadotrophic hypogonadism	none	50	17.2	67.4	21.6	100.5
18	40	Testicular hypogonadism	IM	100	11.8	65.1	36.6	128.1
19	16	Hypogonadotrophic hypogonadism	none	25	13.9	90.3	29.2	112.9
20	51	Testicular hypogonadism	IM	100	10.8	60.1	15.3	132.8
21	39	Testicular hypogonadism	none	50	19.2	45.2	21.6	55.2
22	25	Kallmann's syndrome	none	25	11.2	57.9	13.1	68.5

SC - subcutaneous route of administration; IM - intramuscular route of administration, TT - total testosterone; FT - free testosterone

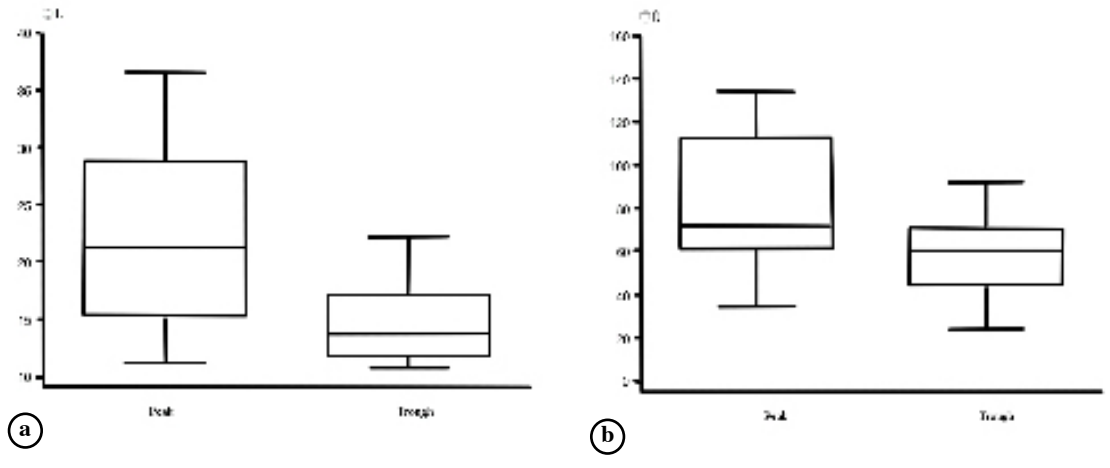

Figure 1 - A box plot of peak and trough **a)** total testosterone following the subcutaneous administration of 25 to 100 mg of testosterone enanthate in oil and **b)** free testosterone following the subcutaneous administration of 25 to 100 mg of testosterone enanthate in oil.

and low-normal range.[12-14] Regimens of 300 mg every 3 weeks and 400 mg every 4 weeks increased the peaks and decreased the nadir further.[12] Subcutaneous testosterone injection was well tolerated by most patients and no local side effects were reported by any of the 22 patients. This eliminates the frequently reported local side effects caused by intramuscular injection such as local pain (7.4%), bleeding or bruising (15.2%), and coughing-fits or fainting possibly due to oil microembolization (1.5%).[15]

In conclusion, this is the first report on the use of subcutaneous testosterone administration, which with new syringe technology appeared to be a safe, inexpensive, and an effective form of treatment for hypogonadal men. Although the number of patients using subcutaneous testosterone was small, the overall clinical response was satisfactory. A large-scale study is needed to confirm these results. We foresee the production of a testosterone "pen" delivery system in the future.

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