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Testosterone therapy with Testopel® and the Esoterix Laboratory assay: A CASE study

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ABSTRACT

We present a patient receiving Testopel® implants whose serum testosterone levels, as measured by a CDC certified assay, were accurately predicted by a multi-compartmental model. This is the first time a model has predicted measured serum testosterone levels within 4% of values calculated. To our knowledge, it was also the first time a pharmacokinetic model allowed patient targeted serum levels (peak/trough/average) to be reached within three months.

Introduction

Managing testosterone replacement therapy is difficult because target serum levels are not universally agreed upon, wide peaks and troughs in the serum levels occur with treatment, and, until recently, assays were not standardized to yield uniform or consistent results. [1]

In addition, Testopel® therapy is not standardized, and clinicians loosely time the next dose and the number of implanted pellets by the serum levels weeks or months after the previous pellet implantation. At best, pellet management is a very imprecise process.

Case presentation

A 60 plus year old male with a partial pituitary hypophysectomy for Cushing's disease in 1981 and pelvic radiation with chemotherapy for recurrent rectal pouch cancer in 2005 was treated for both primary and secondary hypogonadism. He was symptomatic with diminished libido, low hematocrit, osteopenia, and reduced lower limb hair and his total serum testosterone levels measured less than 200 ng/dL on multiple lab determinations.

Therapy with topical AndroGel®, 1%-5 gm packets or 1.62% pump applied daily, produced unpredictable levels. Subsequent therapy of approximately biweekly injections of testosterone cyprionate and Depo®-Testosterone also resulted in unpredictable serum levels.

In preparation for Testopel® therapy, a new baseline serum testosterone (233 ng/dL) was obtained after terminating testosterone supplements for about two weeks (per insurance requirements).

Testopel® therapy was begun using the implantation procedure as recommended by Endo Pharmaceuticals.[2] The implantation site alternated between left and right buttocks. Using sterile technique, two intramuscular pockets were created using gentle soft-tissue dissection, and the pellets were inserted using the manufacturer's insertion tool. The incision was then closed with 3–0 chromic suture and a sterile dressing applied.

The patient avoided showering for 40 hours and the bandage was removed within a few weeks if it did not separate spontaneously. The indwelling stitch decomposed a few weeks later. There were no cases of wound infection or wound dehiscence.

Serum testosterone was measured using the Esoterix assay (Esoterix Laboratory, Inc., Calabasas Hills, CA). With few exceptions, samples were obtained between 9:30AM and 10:00AM local time (EST/DST). When circumstances prevented timely blood sampling, the data was not used for analysis.

Since NPO status was not required by the facility, non-fasting and fasting lab values were co-mingled.

The therapy (number of pellets and the interval between implantations) was initially adjusted by examining previous peak and trough values. Once a few measurements had been obtained, it was possible to

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determine the best fit parameters and to calculate the average ("area-under-the-curve") value from a modified two-compartment model.[3] The calculated average (>800ng/dL) was higher than desired (~600ng/dL), so the dose and the interval were adjusted from 9 pellets every 11 weeks to 8 pellets every 12 weeks. Target levels were reached by the next implantation.

Only a few serum samples were obtained during each cycle, and data was analyzed retrospectively or concurrent with treatment. Table 1 shows the injection dates, the serum measurements, and the model's predicted values. Five early measurements formed the basis of a "training set" to determine initial values for the model's parameters.[3] These initial values (absorption half-life = 14.3 days, elimination half-life = 39.3 days, and pellet constant = 5060 ng/dL/pellet) were used to test the accuracy of the next three measurements (the "test set") taken after the next implantation. The training set average deviation (average percent difference between the measured values and the predicted values) was 3.14% (SD = 6.11%, n = 5), and the test set average deviation was -2.91% (SD = 1.55%, n = 3).

Using all data obtained in Table 1, the average deviation was 3.77% (mean residual = −0.63%, SD = 4.83%, n = 10). Fig. 1 shows the data in graphic form.

Discussion

The model incorporates some significant assumptions. Since the measured data agrees closely with the model, we assert that both the model is valid and the assay is accurate and consistent. This supports the clinical usefulness of the CDC's HoSt (Hormone Standardization Program) program[1] and the importance of using only certified assays. Attempts to fit data from a non-CDC HoSt assay were not successful.

Our model assumes there is no endogenous production when the serum testosterone is above a suppression level, and that endogenous production decreases linearly from baseline to zero as the serum level

Table 1
Implant summary with measured & calculated serum testosterone levels (ng/dL). Model parameters: absorption half-life = 14.3 days, elimination half-life = 39.3 days, and pellet constant = 5060 ng/dL/pellet.

Date	# pellets implanted	Esoterix assay	Calculated level	Percent difference
Nov 8, 2016	10			
Feb 14, 2017	10			
May 23, 2017	9			
Jun 13, 2017		911	955	4.8%
Aug 8, 2017	9			
Oct 18, 2017		573	587	2.4%
Oct 24, 2017	9			
Nov 8, 2017		1030	1039	0.9%
Jan 9, 2018	9			
Mar 30, 2018		512	516	0.8%
Apr 3, 2018	9			
Apr 9, 2018		735	785	6.9%
Apr 19, 2018*		1038	1010	-2.7%
Jul 3, 2018*		458	437	-4.6%
Jul 11, 2018*		417	411	-1.5%
Jul 13, 2018	8			
Aug 3, 2018		937	864	-7.7%
Oct 11, 2018		433	409	-5.5%

*-"test set" dates.

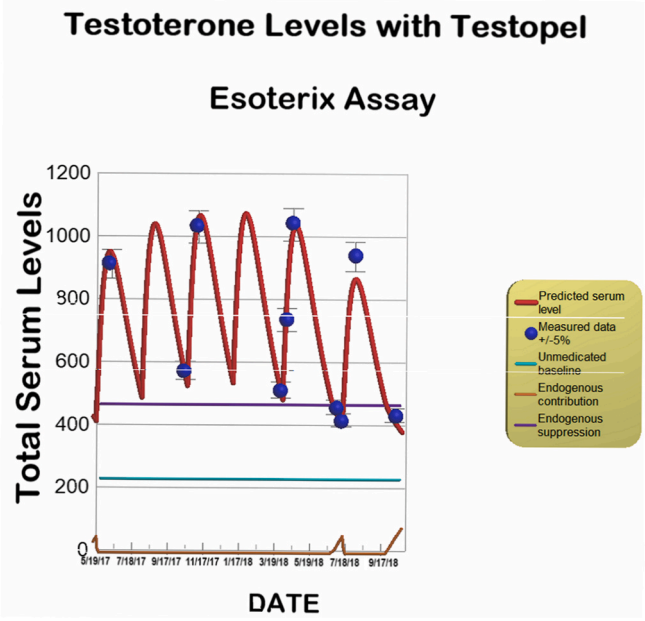

Fig. 1. Serum testosterone (ng/dL) measured using the Esoterix assay shown with values predicted by the model. Model parameters: absorption half-life = 12.6 days, elimination half-life = 42.0 days, and pellet constant = 4380 ng/dL/pellet.

increases above baseline to suppression level. Daily production is certainly more complicated as it includes diurnal and other rhythmic changes, which are ignored by the model.

While there is little clinical evidence showing how long it takes to stimulate testosterone production, the authors felt that a one day response time was reasonable and likely to yield clinically accurate results.

The model assumes that the suppression level (466 ng/dL) is twice the baseline level. Serum LH was measured at 0.1 (1.7–8.6) mIU/mL (Labcorp assay) when the serum testosterone level was 492 ng/dL. This supports our assumption.

The diurnal variation in testosterone production and changes in the androgen receptor caused by higher-than-baseline androgen levels were ignored. Also ignored were changes expected in testosterone production because of oral intake.[4]

Most blood work was collected between 9:30AM and 10:00AM. The pellet insertion time varied between 2:00PM and 4:30PM. Data entry reflected these times to assure maximum accuracy of the model's predictions.

After adequate testosterone supplementation, the patient's hemoglobin rose from 10 mg% to 15 mg%; his hair growth returned to his pre-50s levels; and his libido increased significantly. Months later, his bone density measured above the −2 SD level.

Conclusion

In current clinical practice, there is no pharmacokinetic model for the distribution and elimination of Testopel pellets, and clinicians qualitatively adjust treatment after checking testosterone levels from a recent blood sample.

A new pharmacokinetic model[3] for Testopel® absorption was verified by a "free" testosterone assay (Esoterix Laboratory, Inc., Calabasas Hills, CA) certified by the CDC's HoSt program. This is the first time a close correlation between predicted and measured serum testosterone has been shown using any testosterone assay. The assay's results were within 4% of predicted (average deviation = 3.77%, SD = 4.83%, n = 10), which is clinically insignificant. Instead of guessing at a pellet

dosage and an insertion interval, clinicians can now manipulate therapy quantitatively.

Furthermore, if treatment goals change, the model can be used to switch protocols so that the new goals are reached quickly. Less guesswork, predictable testosterone levels, and expedited clinical testosterone titration benefits are foreseeable results of this study.

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