ORIGINAL RESEARCH

Accuracy of Testosterone Concentrations in Compounded Testosterone Products

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ABSTRACT

Objective: This study aims to evaluate the accuracy of the testosterone concentrations within testosterone gels and creams manufactured by compounding pharmacies.

Methods: Ten compounding pharmacies within Toronto area were included. Pharmacies were blinded as to the nature of the study. A standardized prescription for 50 mg of compounded testosterone gel/cream applied once daily was presented to each pharmacy. Two independently compounded batches were analyzed from each pharmacy 1 month apart. Testosterone concentrations in a 5-g sachet of Androgel® 1% (Abbott) and 5-g tube of Testim®1% (Auxilium) were evaluated as controls. Samples were analyzed independently and in a blinded fashion by the Laboratory Medicine Program at the University Health Network. Measurement of testosterone concentration was performed using a modified liquid chromatography tandem mass spectrometry validated for serum testosterone.

Results: Compounded formulations included seven gels and three creams with a volume/daily dose ranging from 0.2 mL to 1.25 mL. Product cost ranged from $57.32 to $160.71 for a 30-day supply. There was significant variability both within and between pharmacies with respect to the measured concentration of testosterone in the compounded products. In contrast, the concentration of testosterone within Androgel and Testim was consistent and accurate. Collectively, only 50% (batch 1) and 30% (batch 2) of the compounding pharmacies provided a product with a testosterone concentration within ±20% of the prescribed dose. Two pharmacies compounded products with >20% of the prescribed dose. One pharmacy compounded a product with essentially no testosterone.

Conclusions: Testosterone concentrations in compounded testosterone products can be variable and potentially compromise the efficacy and safety of treatment. **Grober ED, Garbens A, Božović A, Kulasingam V, Fanipour M, and Diamandis EP. Accuracy of testosterone concentrations in compounded testosterone products. J Sex Med 2015;12:1381–1388.**

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Introduction

Testosterone deficiency is common among North American men with contemporary crude prevalence rates that suggest approximately 25% of men between the ages of 40 and 62 years are biochemically testosterone deficient [1]. With the proportion of elderly males projected to increase globally over the next decades, the incidence of testosterone deficiency is expected to rise [2].

Signs and symptoms as a consequence of testosterone deficiency commonly include decreased energy levels and vitality, weakness and fatigue, diminished libido, erectile dysfunction, mood changes, and decreased overall quality of life [3,4].

Importantly, several prospective population-based studies have linked testosterone deficiency with significant comorbid conditions including type 2 diabetes, metabolic syndrome, obesity, hypertension, chronic obstructive pulmonary disease, and osteoporosis [5–10]. Moreover, a series of recent investigations have demonstrated an association between low testosterone and increased overall mortality [11,12]. The ability of testosterone replacement therapy to modify many of these comorbid conditions is currently being investigated [9,13,14].

The goals of testosterone therapy include symptomatic improvement through the achievement of physiologic testosterone levels [3,10]. A variety of safe and efficacious products are available for testosterone replacement for symptomatic, hypogonadal men and include injectable, oral, transdermal agents (patch, gel, axillary solution) and subcutaneous pellets [10].

On a global scale, the past decade has witnessed a progressive increase in testosterone prescribing with the most dramatic increases in per capita testosterone prescribing observed in Canada and the United States [15]. The utilization of compounded pharmaceutical products has evolved concurrently with the increase in prescriptions for testosterone from large-scale commercial pharmaceutical manufacturers. The compounding pharmacies industry experienced an annual revenue growth of 5.5% to $1.8 billion in the 5 years to 2012 [16].

The growth of the compounding market has been fueled by an aging population as well as an overall increased demand for pharmaceutical therapies. More specifically, compounding offers a potential solution to drug shortages and allows for customized preparations with respect to dosing, ingredients, delivery methods, flavoring, and modification for allergy and sensitivities. In some cases, compounded medicine may be more cost effective compared with brand name medications [17].

According to Health Canada's policy on Manufacturing and Compounding Drug Products (POL-0051, 2009), the compounding of drugs by healthcare professionals (pharmacists and doctors/veterinarians) is to be regulated by the respective regulatory authorities in each province/territory [18]. In contrast, drug manufacturing of commercial pharmaceuticals is regulated at a national level by Health Canada under the Federal Food and Drugs Act and Food and Drugs Regulations [18]. Similar to Canada, the federal U.S. FDA regulates commercial pharmaceutical manufacturing, whereas state law regulates standards and licensure of pharmacies (NCSL) [19].

Despite such regulation, concerns have been raised over the accuracy and safety of medications manufactured by compounding pharmacies. A report completed by the U.S. FDA in 2006 found that in 36 samples of medication from compounding pharmacies, 12 (33%) failed to meet standards for potency and uniformity. The U.S. FDA suggested that the route cause of such concerns relates directly to the compounding process itself [20]. Within Canada, following a national investigation of diluted chemotherapeutic medicines in 2012, the Ontario Ministry of Health and Long-Term Care made a series of recommendation designed to minimizing future compounding errors within Canadian hospitals [21].

Specific to testosterone, the safety and accuracy of the active ingredients within compounded products is not well established. As such, the primary objective of the current study was to evaluate the accuracy of the testosterone concentrations within testosterone gels and creams manufactured by compounding pharmacies.

Methods

This study was approved by the Research Ethics Board at Mount Sinai Hospital.

Compounding Pharmacies

Ten randomly selected compounding pharmacies within the greater Toronto area (GTA) were presented with a standardized prescription for compounded testosterone gel or cream. All pharmacies were active members of the Association of Compounding Pharmacies of Canada and were blinded to the nature of the study. Prior to inclusion, all pharmacies confirmed their experience and comfort in compounding testosterone products.

The standardized prescription was written for 50 mg of testosterone gel or cream to be applied once daily for 30 days.

To account for practice and product variability over time, each compounding pharmacy was presented with the standardized testosterone prescription on two occasions separated by approximately 30 days (batch 1—January 2012, batch 2—February 2012).

Sample Processing and Testosterone Concentration Determination

All testosterone samples were processed and analyzed in an independent and blinded manner by the Department of Pathology and Laboratory Medicine at the University Health Network and Mount Sinai Hospital. A detailed account of the methodology, materials used, sample preparation, and testosterone concentration determination is provided in Appendix 1. In brief, measurement of testosterone concentrations was carried out using a modified liquid chromatography tandem mass spectrometry (LC-MS/MS) method validated for serum testosterone [22]. An API 5000 (Applied Biosystems/Sciex, Concord, ON, Canada) tandem mass spectrometer was used for separation and detection of testosterone.

To account for the possibility of differences in the homogeneity or uniformity of testosterone concentrations within each supplied compounded preparation, two random samples (replicates) from each product in batch 1 and 3 replicates from each product in batch 2 were independently analyzed.

Manufactured Testosterone Products

Testosterone determinations in a 5-g sachet of Androgel® 1% (Abbott, Montreal, Quebec, Canada) and 5-g tube of Testim® 1% (Auxilium, Chesterbrook, PA, USA) were analyzed and included in the study as control or reference samples. According to the manufactures' product insert, each 5-g sample of Androgel and Testim contains 50 mg of testosterone [23,24].

Results

Characteristics of Compounded Testosterone Products

The testosterone products manufactured by the compounding pharmacies were supplied in a variety of containments systems (e.g., syringe, cups, and tubes) and were prepared using a various base preparations (gel and cream). The volume of product equivalent to the daily-prescribed testosterone dose (50 mg) ranged from 0.2 mL to 1.25 mL. The characteristics of the compounded testosterone products obtained from each of the ten compounding pharmacies are detailed in Table 1.

Table 1 Characteristics of the compounded testosterone products supplied by each pharmacy

Pharmacy no.	Type of container	Daily dose	Base
1	50 mL cup	1.25 mL (50 mg)	PLO gel
2	5 × 3 mL syringe	1 mL (50 mg)	VersaBase
3	1 × 20 mL syringe	1 mL (50 mg)	Alcohol gel
4	2 × 10 mL syringe	1 mL (50 mg)	Cream
5	Aluminum packet	5 g (50 mg)	Alcohol gel
6	5 × 3 mL syringe	1 mL (50 mg)	VersaBase gel
7	1 × 3 mL syringe	0.2 mL (50 mg)	Topical gel
8	Tube with a twist top	0.5 mL (50 mg)	PHLO gel
9	1 × 20 mL syringe	1 mL (50 mg)	CG transderm
10	3 × 3 mL syringe	0.5 mL (50 mg)	TM gel

The average cost of the compounded testosterone products was $104.74 with a range from $57.32 to $160.71 for a 30-day supply. The cost of a 30-day supply of Androgel and Testim was approximately $150.00 and $140.00, respectively.

Recovery of Testosterone in the Compounded Testosterone Products

The applied assay successfully indentified testosterone in all compounded samples. The percentage of testosterone recovered in each batch of the compounded testosterone products is summarized in Table 2. There was significant variability both within and between compounding pharmacies with respect to the measured concentration of testosterone. Collectively, only 50% (batch 1) and 30% (batch 2) of the compounding pharmacies supplied a product with a testosterone concentration within ±20% of the prescribed dose (Table 2). Two compounding pharmacies (#3 and #8) compounded testosterone products containing greater than 20% of the prescribed dose. One pharmacy (#6) compounded a product with virtually no testosterone at all (0.7%—batch 1, 3.6%—batch 2). Pharmacy #5 compounded products with the most accurate testosterone recovery concentrations (100%—batch 1, 93%—batch 2; Table 2).

Variability of the concentration of testosterone in the supplied products was observed *within* compounding pharmacies over time. For example, for pharmacy #1, the average testosterone recovery in batch 1 was 91% compared with 8% in batch 2 supplied only 30 days later. Similarly, the testosterone recovery rate in the products supplied by pharmacy #8 was 120% in batch 1 compared with 59% in batch 2.

In addition, significant *within batch* variability in the recovered testosterone rates was occasionally

Table 2 Percent testosterone recovery per batch in each of the compounded testosterone products

Pharmacy no.	Batch #1—Replicate 1	Batch #1—Replicate 2	Average—Batch #1	Batch #2—Replicate 1	Batch #2—Replicate 2	Batch #2—Replicate 3	Average—Batch #2
	Testosterone recovery (%)						
1	95.4	86.7	*91.0*	10.7	8.0	5.4	*8.0*
2	67.4	62.5	*64.9*	100.3	73.9	64.3	*79.5*
3	123.3	117.6	*120.5*	135.5	128.3	100.0	*121.3*
4	84.6	85.9	*85.2*	87.2	93.0	72.4	*84.2*
5	98.9	101.7	*100.3*	100.0	101.1	78.5	*93.2*
6	0.1	1.2	*0.7*	5.6	4.9	0.4	*3.6*
7	70.1	40.5	*55.3*	40.0	72.5	66.5	*59.7*
8	118.4	123.0	*120.7*	61.6	61.3	54.1	*59.0*
9	79.1	80.9	*80.0*	79.0	67.4	58.5	*68.3*
10	108.4	103.7	*106.1*	95.1	71.0	71.8	*79.3*

observed. This is best illustrated within batch 1 of pharmacy #7 where testosterone recovery percentages were 70% in replicate 1 and only 40% within replicate 2. Within-batch variability suggests of a lack of uniformity of testosterone within the compounded products.

Recovery of Testosterone in the Industry Manufactured Testosterone Products

Percent testosterone recovery within Androgel (100%—batch 1, 104%—batch 2) and Testim (113%—batch 1, 115%—batch 2) demonstrated both within and between batch consistency, with testosterone concentrations always demonstrated to be within ±20% of the prescribed dose (Figure 1).

Discussion

The primary objective of the current investigation was to evaluate the accuracy of testosterone concentrations in testosterone creams and gels prepared by compounding pharmacies throughout the greater Toronto area. We discovered significant variability, both within and between compounding pharmacies, with respect to the actual concentration of testosterone in the compounded products compared with the prescribed dose. Inconsistent testosterone preparations were observed over time, with only 50% (batch 1) and 30% (batch 2) of the compounding pharmacies providing a product within ±20% of the prescribed dose. Moreover, significant variability in testosterone concentrations from serial samples (replicates) within the same product identified with some pharmacies raises concerns regarding the homogeneity of the compounding products.

Collectively, these findings are in contrast to the results obtained from our analysis of industry-manufactured products (Androgel and Testim) that overall produced products with accurate, homogenous, and consistent testosterone concentrations over time.

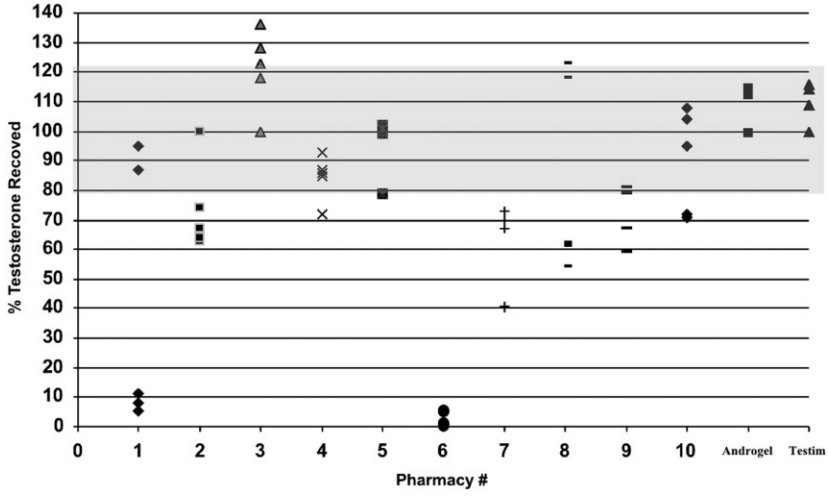

Figure 1 Within and between variability of % recovery of testosterone from products analyzed from each compounded pharmacy and drug manufacturer

Within Canada, testosterone is designated as a controlled substance under the Controlled Drugs and Substances Act (2012) [25]. This designation mandates stricter prescription practices by prescribing physicians and pharmacies as well as heightened requirements for patient identification. Such federal regulation highlights the desire for the responsible and safe administration of testosterone products to patients.

Our findings may have significant implications with respect to compounded medication efficacy and safety. Many of the compounded testosterone formulations fell well short of the prescribed dose, which may translate into inadequate symptomatic and biochemical response to treatment. Compounded formulations with higher than prescribed testosterone concentrations have the potential to produce supraphysiologic serum testosterone levels with associated adverse effects. Given that testosterone creams or gels are designed for daily application, inhomogeneous testosterone preparations may result in erratic clinical and biochemical responses to treatment over time.

On average, the costs of the compounded testosterone formulations were less than industry-manufactured products by about $40 to $45 for a 30-day supply. This may represent a meaningful savings to patients as testosterone replacement is typically regarded as long-term therapy. Any cost advantages offered by compounding formulations however needs to be balanced with the potential for uncertainty as to the product quality as highlighted in this report.

The results of the current investigation are supported by other published reports documenting concerns with medicines supplied by compounded pharmacies. Farid et al. studied the quality of 27 intrathecal baclofen samples obtained from a national compounding pharmacy and Novartis [26]. The baclofen obtained from Novartis had significantly greater accuracy and precision in concentration. All Novartis samples, compared with only 19% of the compounded products, were within 5% of expected concentration.

Rood et al. evaluated the degree in variation between compounded preparations of 147 oral liquid pediatric medications prepared by 244 pharmacies [27]. Wide variability in the prepared concentrations was identified, with up to nine different concentrations of the same medication and prescribed dose being prepared by the same compounding pharmacy. Of further concern was that awareness of compounding errors was low among the participating pharmacies.

Kadi et al. assessed accuracy of the compounding ability of pharmacy students [28]. Their data suggested that only 78% and 54% of pharmacy students could prepare a citrated caffeine syrup and potassium permanganate solution within 10% of the desired concentration, respectively. Although it is recognized that pharmacy students would not have the experience of fully trained compounding pharmacists, investigators highlighted a number of error sources that could easily occur within an experienced pharmacy setting including incomplete or improper dissolution of medication, measurement, and equipment error.

Legitimizing concerns to patient safety, scrutiny toward pharmacy compounding escalated in the United States in 2012 following a highly publicized investigation by the Centers for Disease Control and Prevention and the U.S. FDA of a multistate outbreak of fungal meningitis and other infections among patients who received contaminated steroid injections from the New England Compounding Center in Massachusetts [29]. With reference to the CDC investigation, Gudeman et al. argued that the regulatory oversight of pharmacy compounding in the United States is significantly less rigorous than that required for FDA-approved drugs, with no requirement of compounders to report adverse events to regulatory authorities [30]. As such, compounded medicines may pose additional risk to patients. The report suggests that unlike FDA-approved drugs, pharmacy-compounded products are not clinically evaluated for safety or efficacy and lack standard product labeling and prescription information with instructions for safe use.

Within Canada, a 2013 report to the Ontario Ministry of Health and Long-Term Care detailed a series of recommendations following a national investigation into the under-dosing of chemotherapeutic drugs administered at five Canadian hospitals to over 1200 pediatric and adult cancer patients [21]. As part of their report, investigators identified a "substantial risk to patient safety for extemporaneously prepared products that do not meet the highest quality standards, particularly those associated with sterile compounding." Based on this incident, the Ministry and Health Canada issued a series of recommendations to the Ontario College of Pharmacists and the National Association of Pharmacy Regulatory Authorities specific to the compounding of medicines which included education and curriculum reform, establishing standards for best practice, licensure, and credentialing and regular audit and review for quality control [21].

The authors of this report acknowledge the following limitations. Although our results raise concerns regarding the accuracy of compounded testosterone products, our findings do not necessarily generalize to other compounded medicines. Moreover, a limited sample products from 10 compounded pharmacies within the GTA were included in this analysis. As such, our results may not be reflective of the quality of compounded testosterone products throughout the country or internationally. Finally, the analytics of our investigation focused strictly on the concentration accuracy of compounded and industry-manufactured testosterone products. Consequently, actual patient clinical and biochemical responses to treatment and potential adverse effects with these medicines were not evaluated as part of this research. In addition, the potential influence of chemical permeators added to some products to facilitate transdermal absorption is unknown as it relates to this investigation.

In conclusion, the concentration of testosterone in testosterone creams and gels supplied by compounding pharmacies can be variable and potentially compromise the efficacy and safety of testosterone replacement therapy. Patients, physicians, and pharmacists need to be aware of such uncertainty. Testosterone concentrations in products supplied by Health Canada approved industry manufacturers were accurate and consistent over time. Our results highlight the need for further review of the current best-practice standards as they relate to training, credentialing, and licensure and ongoing quality control and feedback for compounding pharmacist.

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Appendix 1

Materials

Testosterone (1 g) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Testosterone-2,2,4,6,6-d5, 98% internal standard was from CDN Isotopes (Pointe Claire, QC, Canada). The Eclipse C8 HPLC column (50 × 3.0 mm, 1.8 μm) was purchased from Agilent Technologies (Fairlaw, NJ, USA). Anhydrous ethyl alcohol was obtained from Commercial Alcohols (Brampton, Ontario), while HPLC grade methanol was from Fisher Scientific (Wilmington, DE, USA). Ultra-pure water came from the in-house PURELAB Ultra purification system with a resistivity of 18.2 MΩ·cm at 25°C.

Sample Preparation

Testosterone cream or gel formulations were obtained from 10 randomly chosen compounding pharmacies. It was assumed that each formulation consisted of testosterone in non-esterified form. A prescribed dose (e.g., 1 mL, 1 scoop etc.) that corresponded to 50 mg of testosterone was dissolved in anhydrous ethyl alcohol. Total volume of the solution was 20 mL. The mixture was vigorously shaken until all of the soluble material was dissolved. This solution was then serially diluted 20,000 fold (1,000 fold in 20 mL ethanol; followed by 20 fold, 1 mL total volume) to fall in the nmol/L (nM) range. If the dose contained the claimed amount (50 mg) of testosterone, the final concentration of the working solution would have been 433.5 nM. 100 uL of the final solution was mixed with 25 uL of internal standard (1.5 μM, d5-testosterone) and analyzed. Each sample was injected three times. Internal standard was added to compensate for any losses that may occur during ionization and separation processes.

Liquid Chromatography Tandem Mass Spectrometry

Measurements were carried out using a modified liquid chromatography tandem mass spectrometry (LC-MS/MS) method for serum testosterone. Separation by liquid chromatography was carried out using an Agilent Technologies 1200 series system in linear gradient mode at a flow rate of 0.60 mL/min on an Eclipse C8 column (50 × 3.0 mm, 1.8 μm) employing a mobile phase consisting of methanol–water (60:40) increasing to 100% methanol over 3 min and maintained at 100% methanol for 1.5 min. The column was then re-equilibrated with methanol–water (60:40) for 2 min. The column temperature was kept at 50°C. An API 5000 (Applied Biosystems/Sciex, Concord, ON, Canada) tandem mass spectrometer was used for further separation and detection of testosterone. Protonated testosterone was created in an atmospheric pressure chemical ionization (APCI) source that

operated in the positive ion mode. The ion source temperature was maintained at 400°C, the corona current adjusted to 3.0 μA, collision gas, nebulizer gas and curtain gas pressures set to 5.0 U, 30.0 U, and 30.0 U, respectively, the collision energy set to 31 V and the declustering potential set to 120 V. The ion-transitions of m/z 289.3 > 97.1, 289.3 > 109.1, for testosterone and 294.3 > 100.2 for d5-testosterone were monitored in the multiple reaction monitoring (MRM) mode. The dwell time per transition was set to 200 ms. Quantitation of testosterone was based on the six-point calibration curve (0–500 nM).

Analyst software (version 1.4.2) controlled the hardware and was also used for data analysis.