# Application Site Affects the Pharmacokinetics of Topical Testosterone Applied to the Axilla Compared With the Inner Arm

Susan R. Davis, MBBS, PhD[1]; Allan M. Evans, PhD[2]; and Andrew Humberstone, PhD[3,*]

*[1]Women's Health Research Program, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, Melbourne, Victoria, Australia; [2]Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia, Australia; and [3]Acrux DDS Pty Ltd., West Melbourne, Victoria, Australia*

## ABSTRACT

**Purpose:** This study compared the pharmacokinetics of a single dose of 1% testosterone solution after application to the inner arm or the axilla as application sites for transdermal testosterone therapy.

**Methods:** Healthy, not pregnant, premenopausal women, 18 to 45 years of age with a body mass index of 20 to 28 kg/m$^2$ were enrolled into a single-center, open-label, randomized, 2-way crossover study. Serum total testosterone (TT), free testosterone (fT), and sex hormone binding globulin concentrations were measured. Pharmacokinetic parameters determined from serum TT and fT included area under the serum concentration versus time curve from time zero (predose) until 72 hours post-dose ($AUC_{0–72}$), $C_{max}$, and $T_{max}$. Descriptive statistics were performed on serum concentrations of TT and fT for each site. ANOVA was performed on $AUC_{0–72}$ and $C_{max}$.

**Findings:** A single-dose application of 1% testosterone solution to the inner arm and the axilla produced clear increases in TT and fT. Slower and lower increases in TT and fT were observed after treatment to the inner arm. Based on baseline-corrected AUC versus time curves, the bioavailability of 1% testosterone solution was increased 2-fold for the axilla compared with the inner arm.

**Implications:** The absorption of a 1% testosterone solution was significantly greater after application to the axilla than to the inner arm. Study number DDS16; Australian Therapeutic Goods Administration, CTN 2005/158. (*Clin Ther*. 2014;36:1395–1401) 

**Key Words:** axilla, hypogonadism, testosterone, transdermal therapy.

## INTRODUCTION

Transdermal delivery systems for testosterone replacement in hypogonadal men include patches, hydroalcoholic gels, and hydroalcoholic solutions. Studies of Long-term use demonstrated these transdermal systems are suitable for the treatment of hypoandrogenic men, providing relatively stable serum testosterone levels and showing enhanced libido, enhanced erectile frequency and satisfaction, improved mood, increased muscle strength, and improved body composition.[1–3] Gels offer a convenient mode of transdermal testosterone therapy and have been shown to restore eugonadal serum concentrations of testosterone (300–1000 ng/dL).[2,4] A drawback of patches is the high rate of skin irritation,[1–3,5] and for gels, it is a large application area and the potential for interpersonal transfer via skin contact.[6] Typical application sites for gels have included the shoulders, abdomen, thighs, and upper arms. Application to the axilla could potentially address these issues.

The objective of this study was to compare the pharmacokinetics of transdermal absorption when testosterone solution was applied in identical volumes to the inner arm and the axilla. The study used testosterone prepared as a 1% topical solution, which

*Current affiliation: ObsEva SA, Obstetrics and Beyond, Chemin des Aulx, 12, CH-1228 Plan-Les-Ouates, Geneva, Switzerland.

*Accepted for publication June 26, 2014.*
http://dx.doi.org/10.1016/j.clinthera.2014.06.037
0149-2918/$ - see front matter

was a formulation used in early research for testosterone topical solution.

Testosterone therapy has been traditionally studied in healthy male volunteers depleted of testosterone by gonadotropin suppression or in hypogonadal men in whom their usual testosterone therapy has been withdrawn. However, studies of testosterone delivery in women and men have shown similar magnitudes of absorption, and female testosterone levels have been briefly raised to male levels with no reported adverse events[7]; therefore, this study was conducted in healthy premenopausal female volunteers.

## PATIENTS AND METHODS

This was a single-center, open-label, randomized, 2-way crossover study conducted at the Centre for Clinical Studies, Melbourne, Victoria, Australia. It was undertaken with the approval of the Alfred Hospital Human Research Ethics Committee, and all participants provided written informed consent. The study met the Clinical Trial Notification requirement of the Therapeutic Goods Administration of Australia and the requirements for an Investigational New Drug Application for the US Food and Drug Administration.

### Study Subjects

Healthy, premenopausal, female volunteers 18 to 45 years of age with body mass index of 20 to 28 kg/m$^2$ and a negative result on a serum pregnancy test at screening were recruited. Subjects were required to have used an estrogen-containing contraceptive pill for $\geq$2 consecutive menstrual cycles and were willing to remain on the medication to study end. Women were excluded if they had a chronic skin disorder such as eczema or psoriasis, which was likely to interfere with transdermal drug absorption. Subjects were excluded if they had a history of treatment with testosterone, tibolone, or dehydroepiandrosterone or had taken concomitant medications known to be cytochrome P-450 3A4 inducers or inhibitors or known to interact with testosterone metabolism or reproductive hormone levels. Use of prescribed, over-the-counter, or complementary medication for 7 days before, as well as throughout the course of the study, was not permitted.

### Study Design

The study involved a screening period of up to 4 weeks followed, in succession, by a 4-day treatment period, a minimum 4-day washout, another 4-day treatment period, and a minimum 1-week follow-up. Each participant was randomized to receive a single transdermal application of testosterone solution to the inner arm in 1 period and the axilla (in the contralateral arm) in the other period. For each period, the participants were admitted to the study center and had blood samples drawn at baseline (the evening before dosing and the following morning pre-dose) and at 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours after each single-dose application. Postdose blood samples were also collected at 36, 48, and 72 hours. Subjects returned to the study center 1 to 4 weeks after the end of period 2 for poststudy evaluation.

### Study Treatment

The 1% testosterone solution* was packaged in a 50-mL bottle fitted with a 1-mL metered dose pump. The solution contained 1.0% testosterone, 8.0% octisalate, and 0.6% hydroxypropylcellulose in a volatile solvent mix (ethanol 95%:isopropanol 50:50). In order to directly compare the 2 administration sites in question, the same dose of 1 mL was administered to the inner arm and axilla. The 1-mL dose was applied to the inner arm or axilla contralateral to the blood sampling arm by the principal investigator or her designated trained nominee, and the application area was allowed to dry for at least 3 minutes. Participants were then able to wear loose clothing and instructed to refrain from washing the area for 8 hours. Participants were instructed to shave their axilla 24 to 48 hours before dosing and to refrain from shaving and using deodorant for 24 hours before dosing as well as throughout the pharmacokinetic (PK) sampling period. Participants were advised to refrain from skin-to-skin contact for 2 days after dose administration.

### Determination of Serum Hormone Levels

Serum total testosterone (TT), free testosterone (fT) and sex hormone binding globulin concentrations were measured by Esoterix Inc Laboratory Services (Calabasas Hills, California). TT was determined by HPLC mass spectrometry with a validated range of 2.5 to 5000 ng/dL. fT was determined by equilibrium dialysis with a minimal reportable free fraction of

*Trademark: Testosterone MD Lotion™ (Acrux DDS Pty Ltd., West Melbouorne, Victoria, Australia).