

THE INFLUENCE OF CORRECTING ENDOGENOUS CONCENTRATIONS IN THE BIOEQUIVALENCE ASSESSMENT OF TESTOSTERONE

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Introduction

Circulating concentrations of endogenous compounds complicate the analysis of pharmacokinetic parameters and the determination of bioequivalence (BE) when these compounds are administered exogenously. Current BE guidelines both documented by FDA [1] and CPMP [2] do not cover endogenous compounds, although BE studies of levothyroxine sodium [3] and potassium chloride [4] have recently been documented by the FDA. To determine the true bioavailability of exogenous testosterone, plasma concentration values have to be corrected in order to remove its influence on the endogenous concentrations. This study examines the influence of three correction methods of accounting for endogenous concentrations on the determination of bioequivalence between two transdermal testosterone formulations.

Study Method

Twelve healthy males received 50mg TDS[®]-Testosterone (Transdermal Technologies Inc, Florida, USA), TDS[®]-Placebo (Transdermal Technologies Inc, Florida, USA), and 50mg AndroGel[®] (Solvay Pharmaceuticals) in a randomised placebo controlled study with a minimum of one week washout period. Serum testosterone concentrations were obtained from -0.5, 0, and up to 24h post-dose [5]. The TDS[®] drug delivery system (Transdermal Technologies Inc, Florida, USA) is a proprietary technology, which has been developed for use in pharmaceutical, cosmetic and over-the-counter products. The system consists of a true solution of ethanol, propylene glycol, monolaurins, vitamins and pro-vitamins, and cAMP energy donors. Three correction methods to remove the influence of

endogenous testosterone from the exogenous blood concentrations data were used out before the calculation of the AUC and C_{\max} .

Endogenous Correction Methods

Correction 1

The mean pre-dose testosterone concentration (-0.5 and 0h) was subtracted from each testosterone concentration after dosing

Correction 2

The endogenous data (TDS[®]-Placebo) were modelled from the placebo data using a polynomial equation and subtracted from the measured treatment values.

Correction 3

The concentrations on the placebo day (TDS[®]-Placebo) were subtracted from the active treatment day concentrations.

Pharmacokinetic and Statistical Analysis

A non-compartmental method was used to determine the pharmacokinetic parameters of AUC and the C_{\max} . The analysis of variance (ANOVA) was carried out on AUC and C_{\max} data from 0-12 hours to compare the relative bioavailability between two treatments when the data were uncorrected and corrected. For formulations to be bioequivalent, the ratio (test/reference) must fall between 80 to 125% confidence interval (CI). All the statistical analyses were carried out using Kinetica version 4.2 Software.

Results

Table 1 Relative bioavailability (90% CI) for AUC and C_{max} for the comparison between AndroGel[®] and TDS[®]-Testosterone
Bioequivalence (90% CI)

Correction Methods	AUC ₀₋₁₂	C_{max}	Bioequivalent ?
Uncorrected	93-120	88-117	Yes
Correction 1	52-106	50-258	NO
Correction 2	71-655	87-286	NO
Correction 3	67-315	88-157	NO

Reference AndroGel[®]

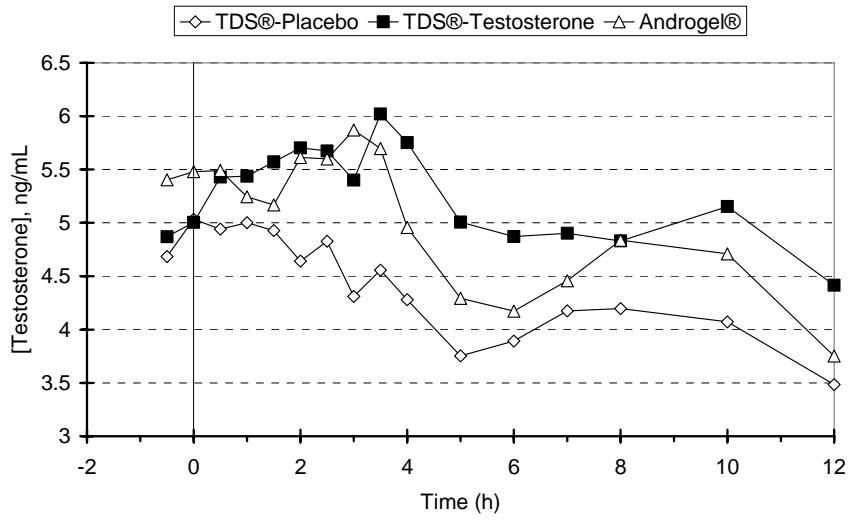


Figure 1 Plots of mean serum testosterone concentration (ng/mL) versus time (h) for each treatment based on uncorrected data.

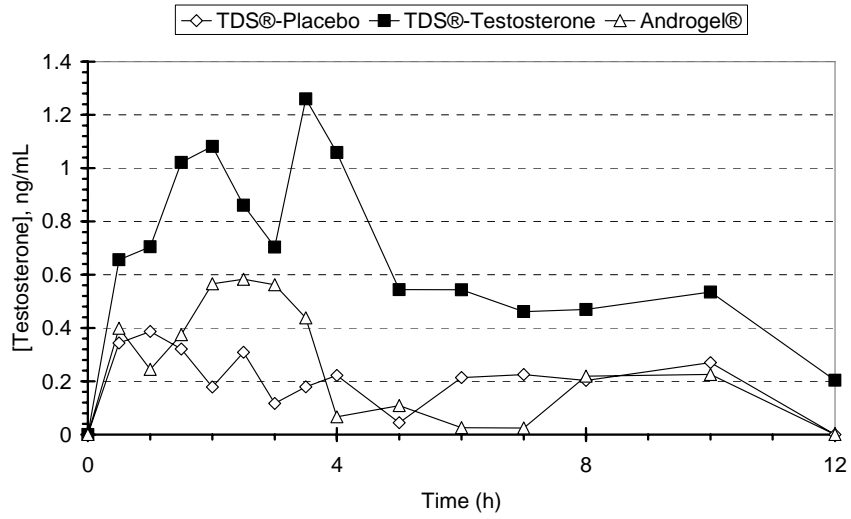


Figure 2 Plots of mean serum testosterone concentration (ng/mL) versus time (h) for each treatment based on Correction 1.

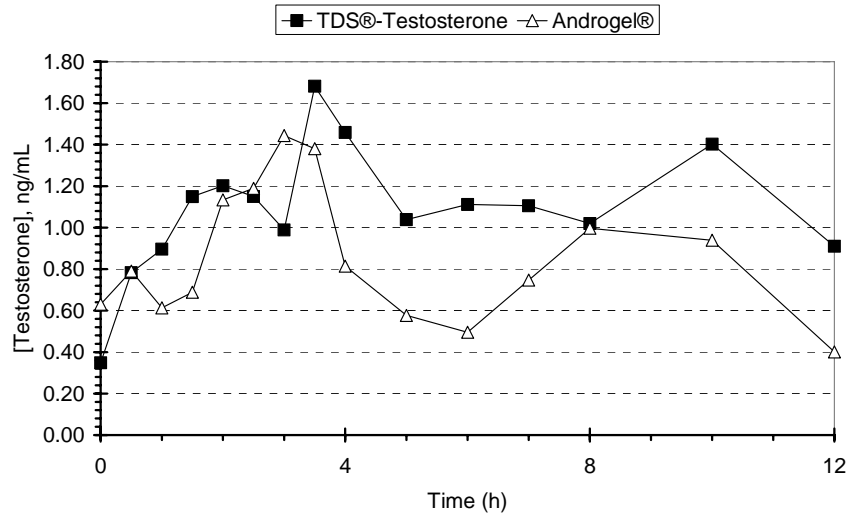


Figure 3 Plots of mean serum testosterone concentration (ng/mL) versus time (h) for TDS®-Testosterone and AndroGel® based on baseline Correction 2. Note: Is this truly a Baseline correction – seems from the description above to be an adjustment of all data.

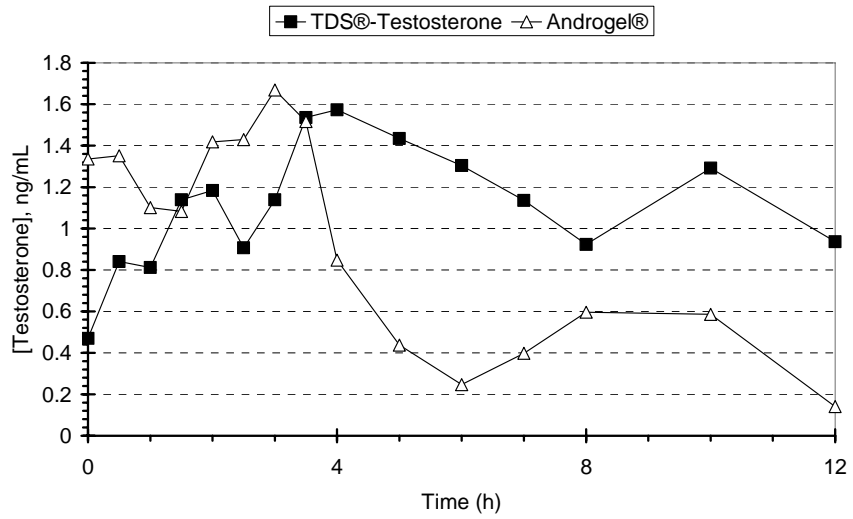


Figure 4 Plots of mean serum testosterone concentration (ng/mL) versus time (h) for TDS®-Testosterone and AndroGel® based on baseline Correction 3. Same comment

Discussion

All the correction methods performed were well correlated in the relative bioavailability results. The comparison between two products for the AUC and C_{\max} within all the correction methods resulted in a determination of bioequivalence. However, when the comparison is performed using uncorrected data, TDS[®] - Testosterone and AndroGel[®] were found to be bioequivalent. The AUC and C_{\max} results were higher for TDS[®] - Testosterone as compared to AndroGel[®] for both the uncorrected and the corrected data.

Conclusion

Different results obtained in the relative bioavailability between TDS[®] - Testosterone and AndroGel[®] for uncorrected data and corrected data, suggests that correcting endogenous concentrations is important for the proper determination of bioequivalence for endogenous compounds such as testosterone. Without endogenous data corrections, an incorrect conclusion about bioequivalence may result with products being declared bioequivalent when they were actually not bioequivalent or *vice versa*.

Reference List

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