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Pharmacokinetic of the New Testosterone Transdermal Delivery System, TDS® - Testosterone in Healthy Subject

Z Chik[1] - A Johnston[1] - A T Tucker[1,2] - L Michaels[3] - S L Chew[4] - C A S Alam[5]

[1]Clinical Pharmacology, [5]Experimental Pathology, Barts and The London Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK
[2]The Ernest Cooke Clinical Microvascular Unit, [3]Anaesthetics and [4]Endocrinology Departments, St. Bartholomew's Hospital, London EC1A 7BE

Introduction

Testosterone (17 α-hydroxyandrost-4-ene-3-one) is the most important androgen secreted into the blood. Its concentration declines with age [1] and testosterone replacement therapy may be indicated, especially for the hypogonadal (testosterone deficiency) men.

A number of testosterone preparations have been studied for replacement therapy. These include testosterone ester injections, subcutaneous implants, scrotal transdermal patches, transdermal patches, oral and sublingual dosage forms, and testosterone gel. With the exception of the transdermal preparations, most of the available preparations are not suitable for replacement therapy. Oral administration leads to absorption into hepatic circulation but rapid catabolism by the liver [2]. Methyl- testosterone may lead to hepatic toxicity and adversely affects cholesterol levels following long-term usage [3]. The scrotal patch causes less skin reactions compared to non-scrotal patches, however result in increased levels of dihydro-testosterone (DHT) after 3 months of treatment [4]. Testosterone gels are also being developed, these are effective in delivering the testosterone. However, care must be taken to prevent transfer of testosterone to another person. Patients must wash their hands after covering a substantial surface area of the body and they must cover this application site with clothing once the gel has dried [5]. We have developed a more convenient method to deliver testosterone through the skin via a metered pump dispenser using TDS® delivery system.

Objectives

To assess the ability of TDS®-Testosterone to deliver a therapeutically acceptable testosterone serum concentration in comparison with TDS®- Placebo and Androgel® 1% in healthy Volunteers.

Methods

A single dose, randomised, three-way crossover study (3 treatments, 3 periods, and 3 sequences) with a minimum of one week washout period between administrations was carried out in 12 healthy volunteers. The three treatments studied were TDS®-Testosterone 50 mg, TDS®-Placebo, and Androgel® 1% (50 mg). Twelve healthy male subjects successfully participated in this study. The mean (SD) age of the subjects was 29.0 (6.2) years old, and the mean (SD) BMI was 24.1 (3.2) kg/m^2. The dose applied to the left arm and gently rubbed into the skin. Blood sample was collected at -30 min., 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose. Blood serum was transferred to labelled tubes and stored at -20°C until analysis. Testosterone concentrations were measured in serum using an Enzyme Link Immunosorbent Assay (ELISA) method.

Result and Discussion

No serious or unexpected adverse events were reported or observed during the study. The applied dosages and protocol requirements were well tolerated by all subjects.

Figure 1 and 2 shows the plot of mean serum concentration and mean the change in serum concentration of testosterone from baseline (0 h) against the sampling time for 12 subjects. Table 1 shows the pharmacokinetic parameters AUC, Cmax, and tmax for all the treatments. The AUC and Cmax values were calculated for both 0-12 and 0-24 hours. The average AUC0-12 was higher following application of TDS®-Testosterone compared to Androgel® and TDS®-Placebo. However, the average AUC_{0-24} for Androgel® was higher than TDS®-Testosterone and TDS®-Placebo. The average Cmax (0-12 h) was similar for TDS®-Testosterone and Androgel® and higher than TDS®-Placebo. Due to the high concentrations of testosterone at 24 hour in a few subjects, the average Cmax (0 - 24h) value for Androgel® was high compared to TDS®-Testosterone and TDS®-Placebo.

The 90% confidence interval (CI) of the ratio TDS® to Androgel® for Cmax (0-12h) and AUC0-12 were contained within the bioequivalence limit (80 - 125%). The 90% CI of the ratio was 89.2 to 112.3% for Cmax and 93.5 to 120.5% for AUC. The serum testosterone concentrations were lower following TDS®-Placebo and were not bioequivalent with either formulation.

Result and Discussion continued

Figure 1 : Plot of mean serum testosterone concentration (ng/mL) versus time (h) for all the treatments.

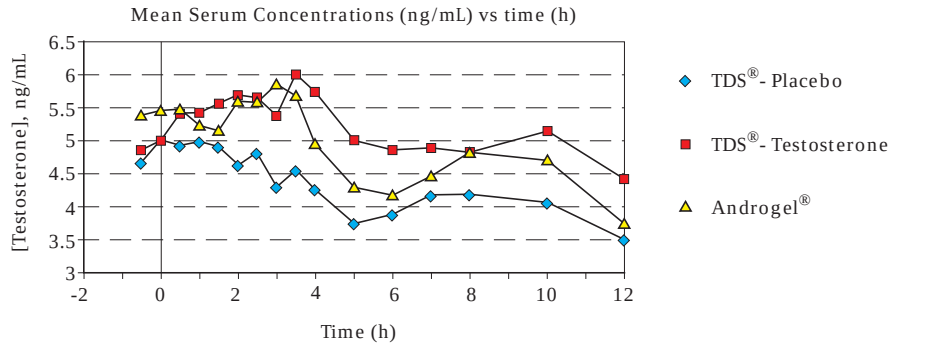

Figure 2 : Plot of mean serum testosterone concentration changed from baseline (ng/mL) versus time (h) for all the treatments.

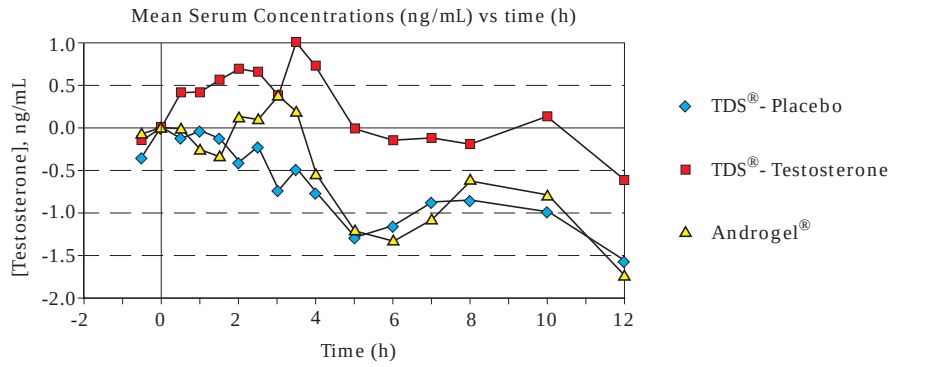

Table 1 : Geometric mean (CV %) for Cmax, tmax and AUC for all the treatments.

	Cmax (ng/mL)		tmax (h)		AUC (ng/mL.h)	
	0-12 h	0-24 h	0-12 h	0-24 h	0-12 h	0-24 h
TDS® - Testosterone	6.64 (22.4)	8.38 (49.7)	2.42 (58.4)	11.75 (92.3)	61.85 (24.7)	135.77 (34.1)
TDS® - Placebo	5.72 (21.1)	5.95 (22.2)	3.29 (111.5)	9.00 (107.4)	50.67 (23.6)	101.67 (25.5)
Androgel®	6.54 (24.1)	13.17 (99.2)	1.83 (52.4)	16.79 (63.5)	57.67 (19.3)	157.41 (57.7)

Conclusion

In conclusion, the TDS®-Testosterone preparation can deliver testosterone systemically in humans and the concentrations of hormone in the first 12 hours following TDS® administration are bioequivalent to an already marketed topical delivery gel. Compared to the gel formulation the TDS preparation provides a more convenient mode of application and results in less contamination of patients' hands and clothing.

Reference

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