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Development of an *In Vitro* secondary transfer model for testosterone gel to elucidate protocols of safe contact.

Jedidiah Kellaway[a]*, William McAuley[a], Robert P Chilcott[a], Mubinah Beebeejaun[a]

[a]University of Hertfordshire, Hatfield, AL10 9AB, United Kingdom

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*Jedidiah Kellaway.
Tel.: +44 7752163075
E-mail: jk21abj@herts.ac.uk

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SUMMARY

Testosterone gels applied to skin carry a risk of secondary transfer to non-patients , leading to development of symptoms such as precocious purberty. Currently, there is a lack of *in vitro* data available to inform guidance over safe contact parameters. A secondary transfer model using porcine skin to model primary (patient) skin and secondary (contact) skin was employed, with testosterone permeation and distribution analysis after 24 hours. Primary skin saw increasing amounts of unabsorbed testosterone and a reduction in delivery to the skin during at later contact times. Secondary skin saw a reduction in unabsorbed testosterone and delivery with later contact times. Permeation data mirrored the distribution data. These differences could be explained by changes in the formulation on the skin surface after application.

INTRODUCTION

Testosterone gels are predominantly prescribed in men to alleviate low testosterone symptoms. Testosterone gels are applied to low hair areas such as the abdomen, shoulders, upper arms, and are volatile in nature progressing through dynamic formulation changes leaving dried films on the application site soon after application (Kamal, 2020). There are potential safety concerns raised by the FDA and UKMHRA over inadvertent secondary transfer of testosterone gel to other individuals. To date, clinical studies have been conducted to investigate the degree of transfer from timed skin to skin contact (Stahlman, 2012). However, no *in vitro* model exists to evaluate transfer loss (De Ronde, 2009). This project will seek to develop an *in vitro* model to characterise the impact of application protocols on the transfer loss of Testogel (a testosterone gel product), with a view to develop a body of evidence on understanding secondary transfer.

MATERIALS AND METHODS

Secondary transfer was modelled with primary skin (modelling patient skin) or secondary skin (contact skin) using 500 µm dermatomed porcine skin. Primary skin was dosed with a finite amount of the formulation and standardised contact between the two skin samples was initiated at 4 different time points: immediate contact or 1/5/10-minute(s) post-dose, including a non-contact primary condition. Primary and secondary skin samples were mounted onto Franz cells (n=6) and testosterone permeation and distribution (unabsorbed, stratum corneum, epidermis, dermis and receptor fluid) after 24 hours was determined. Testosterone concentrations were determined by reverse-phase HPLC-UV.

RESULTS AND DISCUSSION

For primary skin, two trends were observed (Figure 1). The total recovery of testosterone increased with a longer time interval between dosing and contact, due

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to more drug being retained in the unabsorbed domain of primary skin. This observation could be explained by the rapid evaporation of the alcoholic vehicle in Testogel once applied to the skin leaving a dried residual film on the skin at later time points, reducing the potential for drug to be transferred via the formulation onto secondary skin.

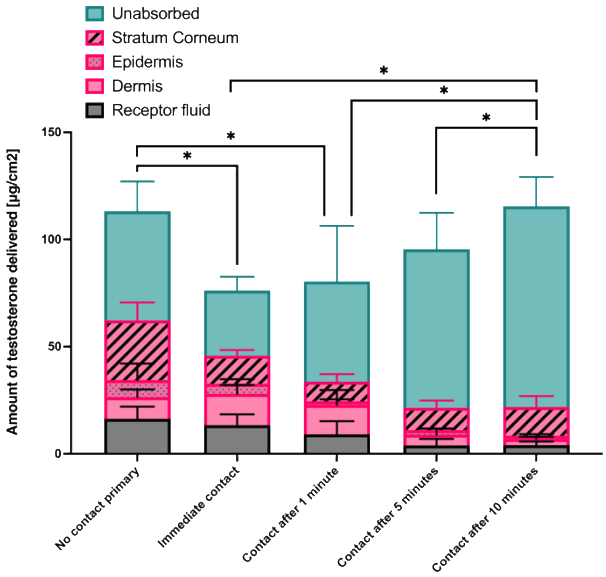

***Fig. 1. Total testosterone distribution across primary skin models**. Statistical comparison (* = p<0.05) was made between total testosterone across all contact times.*

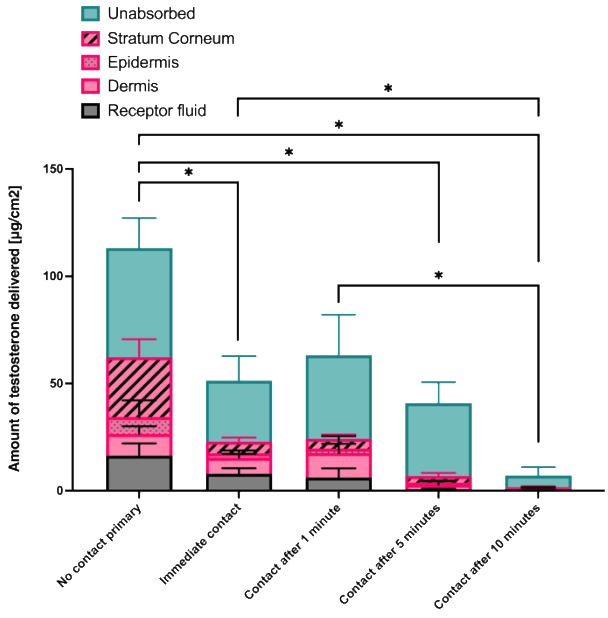

***Fig. 2. Total testosterone distribution across secondary skin models**. Statistical comparison (* = p<0.05) was made between total testosterone across all contact times.*

Although the total drug recovered for primary skin increased with later contact times, the amount of testosterone delivered to the skin (stratum corneum to receptor fluid) was lower compared to earlier primary skin contact times or primary skin receiving no contact ($p<0.05$). This may be due to disruption of contact between the residual dried formulation and the skin surface caused by the contact event, reducing drug partitioning from the formulation into the skin.

For secondary skin, contact occurring at longer time intervals post-dose resulted in significantly less amounts of testosterone delivered to the skin when compared to the no contact condition (Figure 2) and ranged from 1.5 % to 35.2 % of the applied dose.

Drug permeation into the receiver fluid mirrored the trends observed in the drug delivery to the skin. For primary and secondary skin, total drug delivered at 24 hours decreased with longer time intervals between contact, matching observations from the skin distribution data.

CONCLUSIONS

For primary skin, unabsorbed testosterone increased with longer time intervals pre-contact whilst testosterone delivered to the skin decreased. For secondary skin, longer time intervals resulted in decreased testosterone delivery to the skin. Further microscopy work evaluating drug deposition patterns will help understand the observations in primary skin distribution.

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