RELATHIONSHIP BETWEEN SKIN METABOLISM AND SKIN ABSORPTION

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BACKGROUND

Skin metabolism is recognized as an important consideration in evaluating the exposure of topically applied pharmaceutical and cosmetic products. Potential impact of metabolism on skin absorption and the effect of metabolism inhibition on skin absorption and distribution are poorly documented. Moreover, the relationship between absorption and metabolism remains to be fully elucidated. Indeed, skin metabolism may have an effect on the percutaneous penetration and delivered dose of xenobiotics administered by the topical route. The objective of this work was to evaluate the in vitro skin metabolism of [4, ^{14}C]-Testosterone and the effect of the well-known cytochrome P450 inhibitor Ketoconazole on skin absorption and metabolism of testosterone.

METHODS

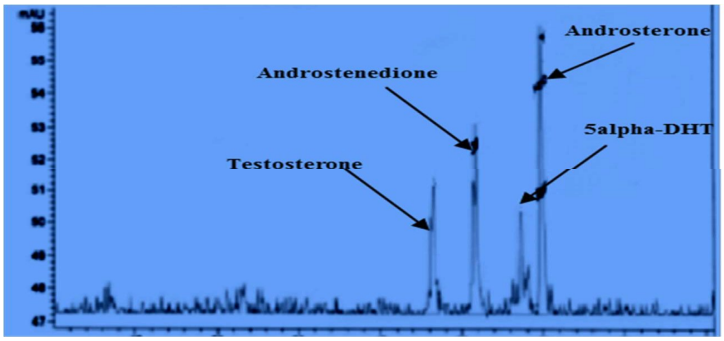
Freshly excised full-thickness minipig skin samples from 3 animals were placed in flow-through diffusion cells (Figure 1) perfused with HEPES-buffered Hank's balanced salt solution containing 0.5% bovine serum albumin and 1% penicilline-streptomycine. Skin samples were first dosed with 5 µg/cm² Ketoconazole for 30 minutes and then dosed with [4,^{14}C]-Testosterone (28 µg/cm²; 5 µCi/cm²) for 16 hours. Control skin samples were only dosed with Ketoconazole vehicle before applying testosterone. Receptor fluid fractions were collected at 2 h intervals over a 16 hours dosing period (flow rate 1.5 mL/h). High performance liquid chromatography was used to assess metabolism of [4, ^{14}C]-Testosterone. Skin penetration (stratum correum, epidermis, dermis, and receptor fluid) was determined by liquid scintillation counting and expressed as a percent of the applied dose.

Figure 1 **Flow-through diffusion cells**

RESULTS

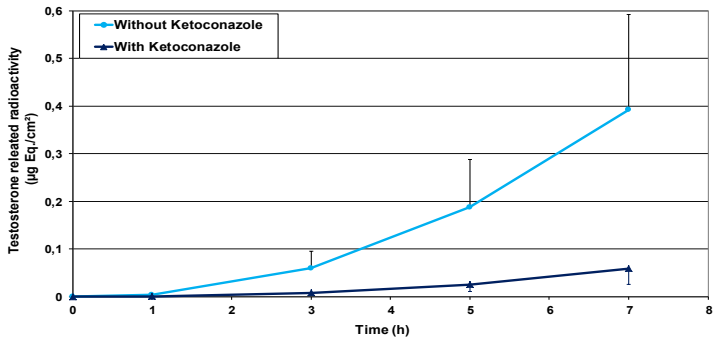
1. METABOLITE PROFILE OF [4, ^{14}C]-TESTOSTERONE

Figure 2 **[4, ^{14}C]-Testosterone metabolites profile in receptor fluid of minipig *skin***



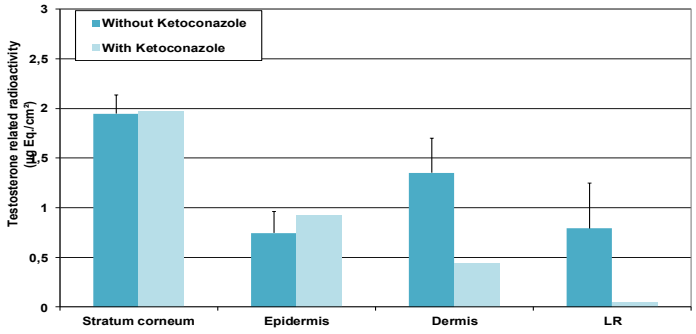
2. [4, ^{14}C]-TESTOSTERONE ABSORPTION

Figure 3 **Kinetic of [4, ^{14}C]-Testosterone absorption on fresh minipig skin (N=3) with and without ketoconazole**



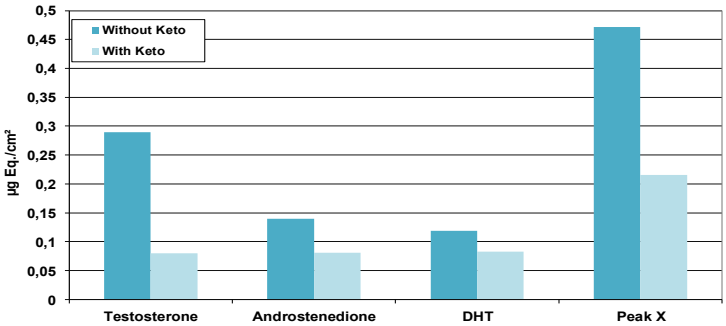
3. [4, ^{14}C]-TESTOSTERONE SKIN DISTRIBUTION

Figure 4 **Effect of Ketoconazole on the distribution of [4, ^{14}C]-Testosterone related metabolites in fresh minipig skin**



4. [4, ^{14}C]-TESTOSTERONE RELATED METABOLITES

Figure 5 **Metabolisme of [4, ^{14}C]-Testosterone in the dermis and receptor fluid with and without ketoconazole**



DISCUSSION

Metabolism of [4, ^{14}C]-Testosterone was clearly shown in minipig skin (Figure 2). Skin absorption of [4, ^{14}C]-Testosterone and metabolites in minipig skin was reduced by 23% with ketoconazole treatment (Figure 3). Pre-treatment of skin with ketoconazole considerably inhibited the metabolism of [4, ^{14}C]-Testosterone and modified skin distribution (Figures 4 & 5).

CONCLUSION

Pretreatment with Ketoconazole decreased both metabolism and absorption of testosterone in minipig skin. This further shed light on the relationship between skin absorption and metabolism. Indeed, inhibition of skin metabolism induced by ketoconazole may result in decrease of percutaneous absorption of chemicals.

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