Wissenschaftliches Hauptprogramm, Teil 1:
„Posterauszeichnungen“

Gesellschaft für
Dermopharmazie

Vorsitzende:
Prof. Dr. Dr. Jürgen Lademann, Berlin
Prof. Dr. Christel Müller-Goymann, Braunschweig

21. GD Jahrestagung am 20. - 22. März 2076

Hilton City Hotel, München

Hans Christian Korting-Nachwuchspreis für Dermopharmazie

Die anlässlich der 21. GD-Jahrestagung vom 20. bis 22. März 2017 in München im Rahmen einer Posterpräsentation vorgestellte Forschungsarbeit

„A novel strategy to assess drug delivery kinetics to epidermal targets *in vivo*"

von

Dr. Magdalena Hoppel und Mitarbeitern,
Bath/UK,

erzielte bei der Prämierung folgende Platzierung:

Platz 1

Der Vorstand der

GD Gesellschaft für Dermopharmazie e.V.

gratuliert den Autoren zu dieser Auszeichnung und verleiht ihnen dafür den „Hans Christian Korting-Nachwuchspreis für Dermopharmazie".

Für den Vorstand

Prof. Dr. Christel Müller-Goymann

Prof. Dr. Dr.-Ing. Jürgen Lademann

Professor Dr. Hans Christian Korting gehörte zu den herausragenden Persönlichkeiten der Dermatologie in Deutschland und Europa. Er war Gründungsmitglied und stellvertretender Vorsitzender der Gesellschaft für Dermopharmazie von 1995 bis zu seinem Tod im Jahr 2012.

A novel strategy to assess drug delivery kinetics to epidermal targets in vivo

Magdalena Hoppel (1), M. Begoña Delgado-Charro (1), Richard H. Guy (1)
(1)University of Bath, Department of Pharmacy & Pharmacology, Bath, UK

Introduction: It has proven difficult to quantify 'drug input' from a formulation to the viable skin because the epidermal and dermal targets of topically applied drugs are hard, if not impossible, to access in vivo. Defining the drug input function from a formulation to the viable skin with a straightforward and practical experimental approach would enable a key component of dermal pharmacokinetics to be characterised. Stratum corneum (SC) tape-stripping has been used to measure drug uptake from a formulation after a defined period of application; by delaying tape-stripping post-removal of the formulation, it is also possible to assess drug clearance from the SC. It is hypothesised that the difference between uptake and clearance measurements allows estimation of a topical drug's input function into the viable tissue [1]. This study aimed to test this idea by comparing the input of lidocaine into the viable skin, following application of commercialised patch and cream products, using SC tape-stripping in vivo with that determined more conventionally in vitro.

Methods: Twelve healthy human volunteers participated in the in vivo SC tape-stripping study, which was approved by the Research Ethics Approval Committee for Health of the University of Bath. On separate occasions, either a Versatis® 5 mg medicated plaster or LMX4 cream (lidocaine 4% w/w) was applied to both forearms. Drug uptake into, and clearance from, the SC were measured immediately following 12 hr of patch application, and 4 hr and 8 hr post-patch removal, respectively; for the cream, the uptake time was 1 hr, the clearance times were the same as those for the patch. In vitro experiments used dermatomed, abdominal pig skin (750 µm) and Franz diffusion cells ($n \geq 6$ for each formulation); the receptor solution was PBS buffered at pH 7.4.

Results and discussion: The in vivo SC uptake and clearance data provided estimates of the lidocaine input rate into the viable skin tissue of 11.5 ± 2.3 µg cm-2 h-1 and 5.3 ± 2.8 µg cm-2 h-1 from the cream and patch, respectively. The significantly higher delivery of the drug from the cream compared to the patch was confirmed qualitatively and quantitatively in vitro. From the estimated steady state flux of lidocaine from the patch in vivo, and the amount of drug cleared from the SC post-removal of the formulation, the total delivery was determined to be ~110 µg cm-2. This value agrees very well with the claimed [2] lidocaine absorption of 150 ± 100 µg cm-2. In conclusion, the results support the hypothesis that drug input into the viable skin from a topical formulation can be estimated using SC tape-stripping at judiciously selected uptake and clearance times.

References:

[1] N'Dri-Stempfer, B., et al. (2009). „Improved bioequivalence assessment of topical dermatological drug products using dermatopharmacokinetics." Pharmaceutical research 26(2): 316-328. [2] Electronic Medicines Compendium. Versatis 5% medicated plaster. Summary of Product Characteristics. Available at www.medicines.org.uk/emc/medicine/19291 [Last accessed 06/02/2017]

Acknowledgements:

M. Hoppel gratefully acknowledges the financial support of the Austrian Science Fund (FWF): J3754-B30 (Erwin-Schrödinger fellowship). This study forms part of a project funded by The Leo Foundation.

Hans Christian Korting-Nachwuchspreis für Dermopharmazie

Die anlässlich der 21. GD-Jahrestagung vom 20. bis 22. März 2017 in München im Rahmen einer Posterpräsentation vorgestellte Forschungsarbeit

„Fibroblasts from aged donors shape the morphology of reconstructed human skin towards an aged skin phenotype"

von

Christian Hausmann und Mitarbeitern,

Berlin/Sao Paulo/Teltow/Potsdam/Prag/Düsseldorf

erzielte bei der Prämierung folgende Platzierung:

Platz 2

Der Vorstand der

GD Gesellschaft für Dermopharmazie e.V.

gratuliert den Autoren zu dieser Auszeichnung und verleiht ihnen dafür den „Hans Christian Korting-Nachwuchspreis für Dermopharmazie".

Für den Vorstand

Prof. Dr. Christel Müller-Goymann	Prof. Dr. Dr.-Ing. Jürgen Lademann

Professor Dr. Hans Christian Korting gehörte zu den herausragenden Persönlichkeiten der Dermatologie in Deutschland und Europa. Er war Gründungsmitglied und stellvertretender Vorsitzender der Gesellschaft für Dermopharmazie von 1995 bis zu seinem Tod im Jahr 2012.

Fibroblasts from aged donors shape the morphology of reconstructed human skin towards an aged skin phenotype

*Christian Hausmann (1), Roberta Balansin Rigon (1, 2), Barbara Wanjiku (1), Christopher Wolff (1), Zijun Deng (3), Maxim Darvin (4), Fabian Schumacher (5), Michaela Sochorova (6), Andrej Kovacik (6), Julia Tigges (7), Jürgen Lademann (4), Ellen Fritsche (7), Burkhard Kleuser (5), Kateřina Vávrová (6), Nan Ma (3), Christian Zoschke (1), Monika Schäfer-Korting (1)**

(1) Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany
(2) School of Pharmaceutical Sciences, São Paulo State University, UNESP, São Paulo, Brazil
(3) Institute of Biomaterial Science, Helmholtz-Zentrum Geesthacht, Teltow, Germany
(4) Charité – University Medicine Berlin, Berlin, Germany
(5) Institute of Nutritional Science, Universität Potsdam, Potsdam, Germany
(6) Faculty of Pharmacy, Charles University Prague, Hradec Kralove, Czech Republic
(7) IUF - Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

** Corresponding Author:*
Prof. Dr. Monika Schäfer-Korting Freie Universität Berlin, Institute of Pharmacy (Pharmacology and Toxicology) Königin-Luise-Str. 2+4, 14195 Berlin, Germany Phone +49 30 838-53283; Fax+49 30 838-470871 E-mail monika.schaefer-korting@fu-berlin.de

Increasing numbers of multimorbid, elderly patients challenge translational pharmacology, which predominantly relies on young and healthy test subjects and animal models [1]. Several groups tried to model aged human skin in vitro, facing specific restrictions [2]. We studied the effects of normal human dermal fibroblasts (NHDF) from donors with varying age and sex on the morphology of reconstructed human skin (RHS). NHDF were either isolated from foreskin (medically-indicated circumcision of <9 year-old boys; juvenile RHS) or from breast skin (plastic surgery; 60 to 70 year-old women; aged RHS). Keratinocytes from the juvenile donors (<9 years) were used for the epidermal compartment of all RHS to investigate the influence of NHDF age and origin on epidermal development.

Microarray analysis revealed decreased collagen-1 and -3 expression only in RHS, but not in monolayer cultures. Sirtuin-1 and mitochondrial transcription factor-1 as well as apoptosis-related gene expression of E1A binding protein p300 declined with donor age. Dermal thickness, collagen content, and fibroblast count decreased markedly in aged RHS, whereas matrixmetalloproteinase-1 gene and protein expression increased. This is well in accordance to in vivo studies [3-6]. A thinner viable epidermis at the expense of a thickened stratum corneum and a decreased surface pH were observed in aged RHS, again being well in line to aged skin physiology [7]. Decreased free fatty acid content in the stratum corneum of aged RHS and increased amounts of cholesterol, cholesterol sulfate, and ceramide, in particular increased sphingosine- and dihydrosphingosine based ceramides, indicate an overall increase in barrier lipids. This might explain the slight decrease of caffeine permeation as well as the faster penetration of tacrolimus into aged RHS, given the very poorly penetrating high molecular and very lipophilic drug is entrapped in the stratum corneum. Taken together, fibroblasts do not only shape the dermal compartment, but also affect the epidermal differentiation and thus barrier function.

Understanding age-related changes in the barrier function will allow improving the dermatological treatment for the increasing number of aged patients – and might reduce animal testing as well.

References

[1] Arrowsmith, J. and P. Miller (2013). Nat Rev Drug Discov 12: 569.
[2] Nikolakis, G., et al. (2016). Hautarzt 67: 93-98.
[3] Branchet, M. C., et al. (1990). Gerontology 36: 28-35.
[4] Varani, J., et al. (2006). Am J Pathol 168: 1861-1868.
[5] Gunin, A. G., et al. (2011). Adv Gerontol 1: 43-47.
[6] Grondahl ML, et al. (2010). Hum Reprod 25: 957-68.
[7] Luebberding, S., et al. (2013). Int J Cosmet Sci 35: 477-483.

Hans Christian Korting-Nachwuchspreis für Dermopharmazie

Die anlässlich der 21. GD-Jahrestagung vom 20. bis 22. März 2017 in München im Rahmen einer Posterpräsentation vorgestellte Forschungsarbeit

„Micellar and non-micellar transport with various membranes"

von

Julia Puschmann und Mitarbeitern,

Braunschweig/Reinbek,

erzielte bei der Prämierung folgende Platzierung:

Platz 3

Der Vorstand der

GD Gesellschaft für Dermopharmazie e.V.

gratuliert den Autoren zu dieser Auszeichnung und verleiht ihnen dafür den „Hans Christian Korting-Nachwuchspreis für Dermopharmazie".

Für den Vorstand

Prof. Dr. Christel Müller-Goymann

Prof. Dr. Dr.-Ing. Jürgen Lademann

Professor Dr. Hans Christian Korting gehörte zu den herausragenden Persönlichkeiten der Dermatologie in Deutschland und Europa. Er war Gründungsmitglied und stellvertretender Vorsitzender der Gesellschaft für Dermopharmazie von 1995 bis zu seinem Tod im Jahr 2012.

Micellar and non-micellar transport with various membranes

Julia Puschmann (1,2), Michael Herbig (2), Christel C. Müller-Goymann (1)

(1) Institut für Pharmazeutische Technologie, TU Braunschweig
(2) Almirall Hermal GmbH

Introduction: The partition behaviour of various components of topical formulations within the different phases (oil, micelles, aqueous) is an important aspect. Distribution of API might have high impact on the stability regarding possible degradation mechanism in the aqueous phase. The Dianorm® Equilibrium Dialyser with its two-chamber-system shall be used for the determination of the micellar and free transport through membranes with various molecular weight cut offs (MWCO) to measure the amount of API in the aqueous phase. Whether micellar solubilisation in water prevents or supports API degradation has to be investigated [1,2]. Furthermore a non-micellar solubilised substance is used as a control substance to guarantee the permeability of the membranes. Polysorbate 80 (PS) in different concentrations was chosen as a surfactant with known CMC and micellar molecular weight to differentiate between micellar and free transport [3].

Methods: Various PS mixtures (0.15%, 1.5%, 5.0% (w/w)) in citric buffer pH 5 were prepared. Donor media contained betamethasone dipropionate (BDP) and phenoxyethanol in the PS mixtures. Additionally, emulsion gels containing 0.5% phenoxyethanol with varying PS-concentrations were tested. Donor and acceptor medium (citric buffer) were filled in PTFE-cells (n=5) separated by membranes and equilibrated at 25 °C for 24 h. Membranes made of hydrophilic cellulose ester (HCE) with various MWCO (0.5 - 100 kDa) were used and extracted in methanol. Samples were analysed via UPLC with PDA detector. Effective permeability coefficient (Peff) was calculated for BDP and phenoxyethanol [4]. An equivalence test was performed to control the equilibrium of donor and acceptor media (α=0.05).

Results: BDP-solubility increased linearly with increasing PS-concentration due to micellar solubilisation. The impact of the MWCO on the substance transport was measured with the 1.5% PS mixture. 0.5 kDa HCE membrane inhibited BDP transport as the molecular weight of BDP is 505 Da [5]. With increasing MWCO more BDP diffused into the acceptor phase. Only the 100 kDa membrane allowed equilibrium due to the enabled micellar transport. However, the recovery rate decreased (0.5 kDa: 89.5%, 100 kDa: 53.9%). It is assumed that BDP undergoes binding reactions with the membrane.

Three different PS mixtures comparing the 5 kDa and 100 kDa membranes were dialysed. Equilibrium for phenoxyethanol was reached within 0.15% and 1.5% PS mixtures ($p<0.05$). The PS-concentration and the varying MWCO of the membranes had no effect on the Peff of phenoxyethanol (Peff=0.6±0.07x102 cm/h). The Peff of phenoxyethanol of dialysed emulsion gels was 0.3±0.02x102 cm/h (n=44). The reduction of Peff between PS mixtures and emulsion gels is caused by the additional partition of phenoxyethanol in the oil phase of the emulsion. Around 4.3 times lower Peff-values of BDP were detected with increased PS-concentration. Reason for this is the enhanced micellar solubilisation of BDP. Due to enabled transport of micelles Peff increased with higher MWCO (5 kDa: Peff=1.9±0.17x102 cm/h; 100 kDa: Peff=2.6±0.09x102 cm/h).

Conclusion: Phenoxyethanol was detected as an indicator for the effective membrane permeability. As a non-micellar solubilised substance it supports the differentiation between free and micellar drug transport. The effect of varying oil and emulsifier systems on the partition behaviour regarding the degradation of BDP and the antimicrobial effect of phenoxyethanol has to be determined.

References:

[1] S. J. Choi et al., Food Chemistry. 122 (2010) 111–116.
[2] S. U. R. Khattak et al., Indian J Pharm Sci. 74(2) (2012) 133–140.
[3] A. C. Braun et al,. Eur J Pharm Biopharm. 94 (2015) 559-568.
[4] Yoon XA, Burgess DJ. J Pharm Pharmacol. 49(5) (1997) 478-84.
[5] Merck & Co. Inc. (ed.), (2006).