Dissertations

In Vivo Microdialysis for the Investigation of Drug Levels in the Dermis and the Effect of Barrier Perturbation on Cutaneous Drug Penetration

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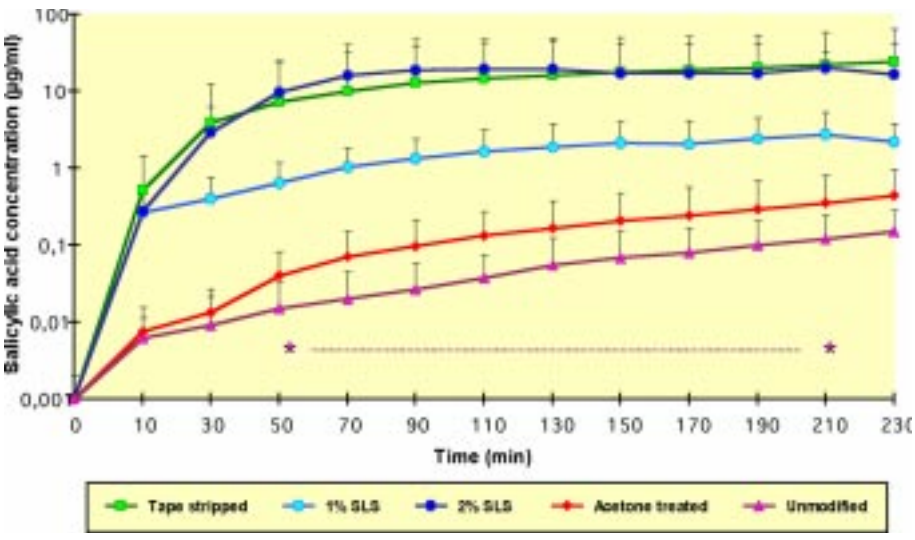
Eva Benfeldt defended her thesis on December 10th, 1999 at Gentofte Hospital. Chairman was Professor Hans Christian Wulf, Department of Dermatology at Bispebjerg Hospital, University of Copenhagen, and Faculty Opponents were Scientific Director Hans Schaefer, Division of Dermatological Research, L'Oreal, Clichy, France and Associate Professor Markus Müller, Department of Clinical Pharmacology, Allgemeines Krankenhaus, Vienna, Austria.

The focus of the thesis is on the development and employment of microdialysis technique for in vivo sampling of pharmacokinetics in the skin. The technique offers unique possibilities for investigations of drug contents in the skin as a target organ, based on the sampling of extracellular fluid by insertion of semi-permeable hollow microdialysis fibres (so-called probes) in the living tissue. The theoretical and practical aspects of microdialysis are reviewed, and the advantages and limitations of the method are discussed. In particular, the difficulties of sampling very lipophilic or highly protein-bound drugs by microdialysis are shown (I).

The technique can be used for measurement of cutaneous penetration of topically applied drugs, and the factors influencing the barrier function of the normal human skin are described, as are the changes in skin barrier function found in diseased and experimentally barrier perturbed skin.

Topical drug administration was investigated in 2 studies of the cutaneous penetration of a model drug, salicylic acid, initially in hairless rats (II) and subsequently in human volunteers (III). In both studies, barrier perturbation of the skin was undertaken by physical (stratum corneum removal by repeated tape stripping) or chemical (acetone treatment) methods or by induction of irritant dermatitis (by application of sodium lauryl sulphate). The barrier damage

Pharmacokinetic differences in salicylic acid penetration in barrier perturbed skin.



Note the logarithmic y-axis scale. The curves show the mean SA concentration sampled by microdialysis probes, inserted in each of the 4 barrier perturbed skin areas, during the 4 h experiment (n = 16). Error bars are SD. In the interval from 50-210 min, there is a statistically significant difference between the mean SA concentration levels ($p < 0.05$) of all treatment groups, except between tape stripped and 2% SLS pre-treated skin.

inflicted was quantified by non-invasive measurements of trans-epidermal water loss and erythema. Salicylic acid in an ethanol solution was applied to the skin surface, and the drug penetration was measured by microdialysis sampling in the underlying dermis.

In both humans and hairless rats the cutaneous drug penetration was highly increased in tape stripped skin (157- and 170-fold increased, respectively) and in skin with irritant dermatitis (46- and 80-fold increased). Delipidization by acetone led to a doubling of the drug penetration in humans (Fig. 1).

In both studies a close correlation between the measured barrier perturbation and the cutaneous drug penetration in the same area was found. In the human study, a dose-response relationship between the concentration of detergent used for the induction of irritant dermatitis and the increase in drug penetration across the skin could be demonstrated. From a dermatological point of view, the very large increase in drug penetration in barrier perturbed skin shown is relevant to the treatment of patients with extensively barrier deficient skin (e.g. eczematous or exfoliative disorders). Conversely, when observed over time the healing of the diseased skin will lead to a restitution of the skin barrier function with a subsequent decrease in drug penetration and thus also reduced efficacy of topical treatment.

Systemic drug distribution was studied in healthy volunteers following oral administration of 2 g acetylsalicylic acid (IV). Drug levels in the dermis were investigated by simultaneous microdialysis and suction blister fluid sampling. A comparison of the 2 methods showed a very good correlation between the free drug concentration in plasma, suction blister fluid and microdialysate, and an even closer correlation between results obtained by the 2 methods for sampling in the peripheral compartment.

List of original publications

I Benfeldt E, Groth L. Feasibility of measuring lipophilic or protein-bound drugs in the dermis by in vivo microdialysis after topical or systemic drug administration. Acta Derm Venereol 1998; 78: 274-279.

II Benfeldt E, Serup J. Effect of barrier perturbation on cutaneous penetration of salicylic acid in hairless rats: In vivo pharmacokinetics using microdialysis and non-invasive quantification of barrier function. Arch Dermatol Res 1999; 291: 517-526.

III Benfeldt E, Serup J, Menné T. Effect of barrier perturbation on cutaneous salicylic acid penetration in human skin: in vivo pharmacokinetics using microdialysis and non-invasive quantification of barrier function. Br J Dermatol 1999; 140: 739-748.

IV Benfeldt E, Serup J, Menné T. Microdialysis vs. Suction Blister Technique for In Vivo Sampling of Pharmacokinetics in the Human Dermis. Acta Derm Venereol 1999; 79: 338-342.

Cutaneous Microdialysis Club

Are you aware of the small society for people working with microdialysis in the skin? The Cutaneous Microdialysis Club is a non-profit interest group with members from all over the world. Members receive newsletters with information about upcoming meetings and recent publications, and the first scientific meeting was held in connection with the 2nd International Symposium on Microdialysis in Drug Research in Stockholm, June 14-17 2000. If you would like more information about the Cutaneous Microdialysis Club, contact the chairman (EB, above) or the secretary Lotte Groth by e-mail: CMC@leo-pharma.com, or visit the CMC home page at www.physiologie1.uni-erlangen.de/Schmelz/cmc_home/CMC_frame.htm.