In vitro skin penetration measurement with contrast-enhanced MRI at 7 Tesla

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Hypothesis:

The penetration of MRI contrast agents into the skin can be measured directly by MRI. With a submicron emulsion as carrier system the efficiency and the dynamics of a Drug Carrier System on the penetration of a topically applied contrast agent can be assessed.

Methods:

Penetration studies according to OECD guidelines [1] were performed using skin samples taken from porcine ear. For enhancing the transport of the contrast agent into the skin a submicron emulsion containing 1mmol/ml Gadolinium (Gadobutrol, Gadovist, Schering, Germany) was used. The experiments were performed using the Franz-Diffusion-Cell setup, a standard device for in vitro penetration studies. The penetration was done for 6h respectively 24h followed by deep-freezing of the skin samples.

In vitro MRI was performed on a 7T small animal scanner (Clinscan, Bruker, Ettlingen, Germany). A Bruker mouse head phased array coil (2x2) was used for imaging the skin samples. High resolution (55 x 55 x 400µm) T1-weighted TSE-sequences (TR: 600ms, TE: 11ms, FA: 120°) were used for imaging the skin and assessing contrast agent penetration with and without background inversion. TIR-sequences (TR: 5000ms, TE: 14ms, 200 x 200 x 500µm) with 5 Inversion times (100, 250, 500, 750 and 1000ms) were used for measuring T1-Relaxation and contrast media quantification. T1-Relaxivity and concentration of Gadobutrol were measured with TIR-Sequences as well. Measurement setup additionally consists of one untreated skin sample and one measurement phantom containing 0.01mmol/ml Gadobutrol as references. T1 was calculated ROI-based in the different skin layers. One ROI was drawn for each of epidermis (0.1–0.2 mm deep), outer dermis (0.6 – 0.7 mm deep) and inner dermis (0.9 – 1.0 mm deep).

Results:

On T1- TSE- images the different skin layers can be distinguished easily (Fig.1). Contrast enhancement due to Gadobutrol application is depicted in every layer of epidermis and dermis after 6 and 24 hours of penetration. The distribution of the contrast agent is more homogenous after 24h. The uptake of Gadobutrol after 24h is between 120% in the outer skin layers and 150% in the deeper skin layers higher compared to the 6h sample (Table 1).

	Epidermis	Outer Dermis	Inner Dermis
T1 ± SD /ms	712 ± 13	631± 16	545,6 ± 26
T1 /ms 6 h	170	200	229
T1 /ms 24 h	63	65	69

Table 1: T1- measurements

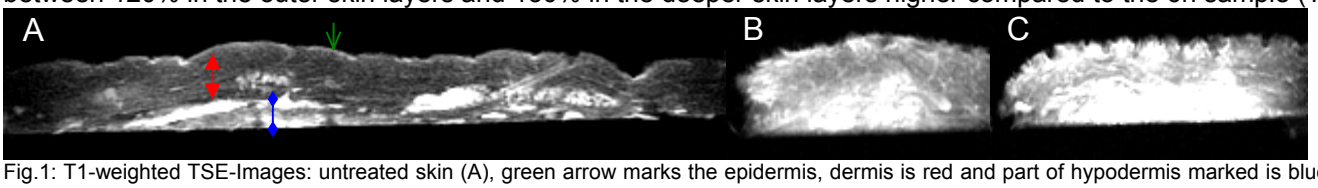

Fig.1: T1-weighted TSE-Images: untreated skin (A), green arrow marks the epidermis, dermis is red and part of hypodermis marked is blue; Gadobutrol treated skin (6 hours = B, 24 hours = C) show high contrast media uptake

Discussion:

The submicron emulsion is a suitable carrier system for facilitating the Gadobutrol transport into the skin. The influence of other drug carrier systems on the penetration performance of contrast agents and potential penetration enhancers, such as DMSO [2], should also be compared to the submicron emulsion.

Skin penetrating contrast agents could be a new diagnostic tool for the staging of skin tumours like Maurer et al. [3] did by intravenous injected contrast agents in mice or can also be useful as a marker for topically applied drugs. Further measurements are required to quantify the penetration of MRI contrast media into the skin and determine optimal concentration [4].

References:

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