Gadolinium contrast agents as a possible trigger for the development of Nephrogenic Fibrosing Dermopathy (NFD)

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Purpose: Several recent publications suggested a high likelihood of association between the administration of a Gd – contrast agent – reported as with Omniscan- and the occurrence of nephrogenic fibrosing dermopathy (NFD), which is an acquired, idiopathic disorder in patients with severe renal dysfunction.
NFD is characterized clinically by thickening, indurations and hardening of the skin. The objective of this study was to investigate a possible causative influence of released Gd^{3+} or reactions of the chelate with endogenous metal ions as a possible trigger for NFD.
Methods and Materials: A 28- day subchronic toxicity study was performed in 40 male Han Wistar rats. Four groups of 10 rats each received one of four different treatments administered intravenously 5 times a week: Magnevist, Omniscan or gadodiamide (the active Gd - chelate in Omniscan without caldiamide sodium), at a dose of 2.5 mmol Gd/kg body weight or a corresponding volume of 0.9 % w/v saline as the control treatment. Animals were examined at the time of each injection, regarding clinical observations, body weight and pathologic findings. At the end of the treatment period animals were sacrificed to assess histopathological changes. Furthermore the Gadolinium concentrations in different organs were measured.
Results: The daily injection of high Gd-dosages resulted in a long exposure of the organism to the contrast agents, similar to the situation in patients after intravenous injection and before hemodialysis. No rat in the Magnevist or placebo group showed any kind of pathologic reactions at the end of the study, neither macroscopic nor histo-pathological changes. In the gadodiamide group all animals developed skin changes, namely epidermal ulceration and acanthosis, dermo-epidermal clefts and minimal to slight dermal fibrosis starting on day 6. In this group treatment had to be terminated on day 10. Corresponding skin changes to a lesser degree were observed from day 16 on in the majority of animals after administration of Omniscan. In both groups significantly higher Gadolinium concentrations were found, especially in the skin.
Conclusion: The application of high doses of gadodiamide and to a lesser degree also of Omniscan leads to marked epidermal lesions and to fibrosing skin alterations comparable to the phenotype of NFD. This also correlates with a high gadolinium concentration in the skin, which was more pronounced in the gadodiamide group. Further studies are needed to demonstrate that these findings correlate with the already known lower stability of the complex.