Preclinical studies to investigate the development of NSF: experiments in renally impaired rats

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Purpose:

Nephrogenic Systemic Fibrosis (NSF) is only observed in patients with severe renal dysfunction and a role for Gadolinium-based contrast agents (GBCAs) as a possible trigger has been suggested. The objective of this study was to evaluate the impact of prolonged circulation time of GBCAs on the onset of NSF-like signs in rats.

Materials and Methods:

The Gadolinium (Gd) concentration in the skin of 5/6-nephrectomized rats (simulating renal impairment), and of healthy Han-Wistar rats, was determined after application of Gadodiamide (Omniscan®), Gadoversetamide (OptiMARK®), Gd-DTPA (Magnevist®), and Gadobutrol (Gadovist®). The animals received single injections of 2.5 mmol Gd/kg into the tail vein on five consecutive days and the Gd-concentration in skin samples was determined by ICP-MS at several time points post-injection. Animals were examined daily for clinical findings.

Results:

Prolonged circulation times for all GBCAs were observed in the 5/6 nephrectomized rats as compared to healthy rats. For non-ionic linear compounds, the prolonged circulation time led to a higher Gd-concentration in the skin over time, while for linear ionic compounds, the increase in Gd-concentration was less pronounced. For the macrocyclic compounds, no long-term Gd retention in the skin could be observed for any of the animals.

Conclusion:

In the study a prolonged circulation time for linear contrast agents due to reduced renal elimination correlated with an increased Gd retention in skin, in particular after administration of non-ionic linear GBCAs. For macro-cyclic compounds, no long-term retention of Gd in the skin could be observed.