

## Effect of Intravenous Iron on Nephrogenic Systemic Fibrosis in Rats

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**Purpose:** Nephrogenic Systemic Fibrosis (NSF) is a debilitating disease associated with the administration of gadolinium-based contrast agents (GBCAs) in patients who have severe renal disease (1). High serum iron levels have been associated with an increased patient specific risk for developing NSF (2). More recently, increased deposition of metals, including iron, has been associated with worse cardiac and vascular complications in patients who have NSF (3). Patients with on dialysis frequently are administered intravenous (IV) iron to help treat anemia. This study intends to determine if the administration of IV iron increases the deposition of gadolinium in the dermis and worsens skin findings in rats that have been administered high dose GBCAs.

**Materials and Methods:** 12 healthy Hannover-Wistar rats were administered 2.5 mmol / kg of gadodiamide (Omniscan, GE Healthcare) via tail vein injections for 20 days over a four week period based on previous methodologies (4). 6 of these animals were also given 2 mg / kg of iron dextrose (Dexferrum, American Regent Inc, Shirley, NY) via intravenous injection, five doses per week for two weeks starting the first day of gadodiamide injections. Each animal was examined for skin changes daily. All animals were sacrificed 7 days after the final injection of gadodiamide. Skin biopsies were taken, and gadolinium deposition was measured using ICP-AES (inductively coupled plasma atomic emission spectroscopy) (5). The biopsies were also stained with hematoxylin and eosin (H&E) and CD-34 antibodies. Review by a board-certified dermatopathologist is pending at this time.

**Results:** On visual examination necropsy two rats from each group had skin findings (Figure 1). There was no clear indication that lesions were more severe in either group. Levels of gadolinium deposition between both groups did not differ significantly (1109 ppm for gadolinium animals vs 1191 ppm for gadolinium + IV iron, p value = 0.52). Review of H&E and CD34 stained slides is pending.

**Conclusions:** Understanding the relationship between IV iron and gadolinium in the development of NSF is an important clinical question especially for dialysis patients. Visual inspection of skin and analysis of gadolinium deposition did not show any differences between rats receiving IV iron and those that did not. Histopathology analysis is still pending, including CD34 staining.

**References:** 1. Cowper SE et al. Lancet, 2000. 2. Swaminathan S et al. The New England journal of medicine, 2008. 3. Swaminathan S, et al. Kidney Int. 2008. 4. Sieber MA. Investigative radiology, 2008. 5. High WA et al. Journal of the American Academy of Dermatology, 2007.



**Figure 1:** Left – representative animal treated with gadodiamide. Top row shows the back of the entire animal and bottom row depicts a close up of two flank lesions in each animal. Right – representative animal treated with gadodiamide and IV iron.