# Comparative Stability of Nonionic Linear and Ionic Macrocyclic Gadolinium Chelates in Renally-Impaired Rats

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**Introduction**

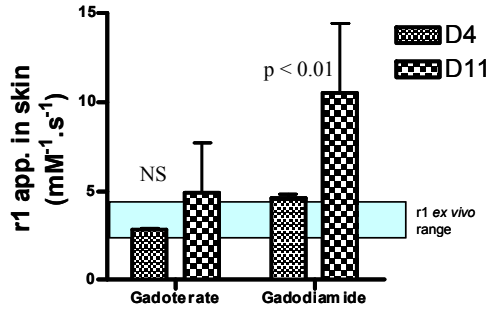
Several studies have demonstrated the presence of gadolinium in skin biopsies from patients who experienced nephrogenic systemic fibrosis (NSF) following administration of a gadolinium chelate (GC) (1,2). However, the techniques used in these studies are unable to formally discriminate between chelated and free $Gd^{3+}$ . The aim of our study was to characterize the free or chelated state of gadolinium in plasma, skin and cortical bone following administration of a marketed GC representative of two distinct categories with opposite physicochemical properties: a linear, nonionic GC (both low thermodynamic and kinetic stabilities) and an ionic, macrocyclic GC (both high thermodynamic and kinetic stabilities) (3) to rats with impaired renal function. For that purpose, we selected two techniques that allow discrimination between the free, chelated or insoluble states of gadolinium: relaxometry in skin and bone and LC-ICP-MS (liquid chromatography coupled to ICP-MS [inductively coupled plasma-mass spectrometer]) and ICP-MS techniques in plasma.

**Methods**

Wistar male rats with subtotal (5/6$^{th}$) nephrectomy were allocated to daily injections of 2.5 mmol/kg (5 mL/kg) of gadodiamide (Omniscan®) or meglumine gadoterate (Dotarem®) for 5 consecutive days. Control rats received saline (5 mL/kg) (n = 8 rats/group). The total gadolinium concentration was measured by ICP-MS in skin (Day 4 and sacrifice at Day 11), cortical bone (femur) and plasma at Day 11 and free $Gd^{3+}$ was measured in the plasma at Day 11 (LC-ICP-MS). Relaxometry was measured (Minispec, Bruker, 60 MHz) in skin (biopsy at Day 4 and 11) and bone. Data are given as mean ± SD.

**Results**

At Day 11, the total plasma gadolinium concentration was similar in both groups (gadoterate: 3.3 $\pm$ 3.1 µmol/L, gadodiamide: 2.3 $\pm$ 1.4 µmol/L, NS) while the free $Gd^{3+}$ concentration in plasma was below the limit of detection for gadoterate and 1.5 $\pm$ 0.7 µmol/L in the gadodiamide group, corresponding to 62 $\pm$15% of the total gadolinium concentration. An increase in the $r_1$ value over time was found in the skin of gadodiamide-treated rats but not of gadoterate-treated rats:




In the cortical femur, the $r_1$ value was higher in the gadodiamide group than in the *ex vivo* matrix (8.9 $\pm$ 2.1 vs. 4.5 $mM^{-1}.s^{-1}$ respectively). For gadoterate, the $1/T_1$ measured – $1/T_1$ diamagnetic difference was < 10% (limit of quantification) for 7 rats out of 8 (for the remaining rat: $r_1$ = 3.8 $mM^{-1}.s^{-1}$ ), because of low gadolinium concentration.

**Discussion**

Our study revealed the presence of free $Gd^{3+}$ in the plasma of rats treated with the nonionic linear GC gadodiamide at Day 11. Interestingly, most of the soluble gadolinium measured in the plasma was found to be non-chelated. The macrocyclic GC gadoterate released no free gadolinium at this time-point, a result consistent with *in vitro* (2) and *ex vivo* (4) studies. LC-ICP-MS allows the measurement of free $Gd^{3+}$ levels (4) but this technique can be used only in the plasma. Relaxometry allows an indirect approach of *in vivo* dechelation. An increase in the $r_1$ relaxivity value over the *ex vivo* value strongly suggests the presence of gadolinium under a non-chelated and soluble form while a decrease in $r_1$ is consistent with the presence of an insoluble form of gadolinium. The skin allows repeated measurements of the $r_1$ relaxivity value in the same animal. Our data, both in the cortical bone and the skin, are strongly suggestive of a progressive *in vivo* dechelation in the case of gadodiamide but not gadoterate.

**Conclusion**

Our data indicate gradual *in vivo* dechelation and release of free and soluble $Gd^{3+}$ in rats with subtotal nephrectomy receiving the nonionic and linear GC gadodiamide, while the ionic and macrocyclic GC gadoterate remained stable over the whole duration of the study.

**References**

[1]Boyd AS et al. *J Am Acad Dermatol* 2007 ; **56** : 27-30 ; [2] High WA et al. *J Am Acad Dermatol* 2007 ; **56** : 21-26 ; [3]Port M et al. *Biometals* 2008 ; **21** : 469-490 ; [4]Frenzel T et al. *Invest Radiol* 2008 ; **43** : 817-828