Hyperphosphataemia Reveals Skin Lesions in Gadodiamide-Treated Rats with Low Renal Function

J-M. Idée¹, N. Fretellier¹, S. Guerret², M-C. De Goltstein¹, A. Dencausse¹, N. Poveda¹, C. Hollenbeck¹, W. Gonzalez¹, C. Factor¹, and C. Corot¹

¹Research, Guerbet, Roissy-Charles de Gaulle cedex, France, ²Novotec, Lyon, France

Introduction

Elevated serum phosphate levels have been shown to accelerate the release of free Gd³⁺ from linear, nonionic gadolinium chelates (GC) such as gadodiamide whereas macrocyclic GC remained stable in human serum at both normal and high phosphate levels (1). As higher serum phosphate levels have been reported in patients with nephrogenic systemic fibrosis (NSF) compared to control patients (2), the purpose of this study was to investigate the clinical, pathological and bioanalytical consequences of hyperphosphataemia in rats with subtotal nephrectomy following administration of gadodiamide.

Methods

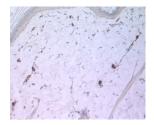
Male Wistar rats with subtotal $(5/6^{th})$ nephrectomy (n = 7 to 8/group) received a normal (0.6%) or high-phosphate (1%) diet and were allocated to single daily intravenous injections of 2.5 mmol/kg (5 mL/kg) of gadodiamide (Omniscan®) or saline (5 mL/kg) for 5 consecutive days. The gadolinium concentration was measured by ICP-MS in skin, cortical bone (femur) and plasma at sacrifice (Day 11) and free Gd³⁺ measured in the plasma at sacrifice by liquid chromatography coupled to ICP-MS. Daily clinical examinations and histopathological study (blinded) were performed. Data are given as mean \pm SD.

Results

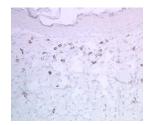
On Day 0, the plasma phosphate level was higher in the high phosphate diet group $(2.4 \pm 0.4 \text{ mmol/L vs.}_1.9 \pm 0.2 \text{ mmol/L})$, p < 0.01). No skin lesions were observed in the normal diet, gadodiamide-treated group while 4 out of 7 hyperphosphataemic rats showed macroscopic skin lesions. Histologically, epidermal necrosis, increase in dermal cellularity, more abnormalities in dermal collagen fibres and higher TGF β -1 immunostaining were observed in the gadodiamide + high phosphate diet group vs. the gadodiamide + normal diet and control groups. A slight increase in CD34+ cells expression was also noticed.



Control



Gadodiamide (normal diet)



Gadodiamide (high-phosphate diet)

Figure 1

There was no significant difference between the gadodiamide alone and the gadodiamide + high phosphate diet as regards the non-chelated/total gadolinium ratio in plasma ($62 \pm 15\%$ vs. $52 \pm 8.6\%$ respectively), the gadolinium concentration in skin at Day 11 (490.5 ± 223.2 nmol/g vs. 613.5 ± 195.5 nmol/g respectively) or the gadolinium concentration in the femur at Day 11 (353.1 ± 81.4 nmol/g vs. 357.3 ± 49.9 nmol/g respectively).

 $TGF\beta$ -1 immunostaining (gadodiamide/high phosphate diet > gadodiamide/normal diet > control)

In the gadodiamide + high phosphate diet group, the total plasma gadolinium concentration was higher in the rats with skin lesions than in the rats without lesions (2.4 ± 0.2 vs. 1.4 ± 0.06 mmol/L respectively, p < 0.01) as well as the free Gd³⁺ concentration at Day 11 (1.1 ± 0.08 mmol/L vs. 0.9 ± 0.07 mmol/L respectively, p < 0.05).

Discussion

In addition to low renal function, hyperphosphataemia seems to sensitize rats to macroscopic and histopathological lesions associated with the nonionic linear GC gadodiamide. Further studies are required to compare the various categories of GC on this model.

Conclusion

Hyperphosphataemia enhances skin histological and macroscopic lesions in renally-impaired rats receiving gadodiamide.

References

- 1. Frenzel T et al. Invest Radiol 2008; 43:817-828
- 2. Marckmann P et al. Nephrol Dial Transplant 2007; 22: 3174-3178