# Preclinical evaluation of P846, a new high-relaxivity low diffusible Gadolinium-based contrast agent, for contrast-enhanced MR angiography in rabbits at 1.5T

**K. Peldschus[1], M. Hamdorf[1], P. Robert[2], G. Adam[1], and C. Herborn[3]**

[1]Diagnostic and Interventional Radiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Guerbet Group, Aulnay-sous-Bois, France, [3]Medical Prevention Center Hamburg, University Medical Center Hamburg-Eppendorf, Germany

## Introduction

Contrast-enhanced three-dimensional (3D) magnetic resonance angiography (MRA) has become a standard procedure for the non-invasive diagnostic evaluation of the arterial vasculature. Image quality and diagnostic accuracy permit the safe evaluation of thoracic and abdominal vessels [1]. However, the detection of subtle vascular abnormalities which might influence both diagnosis finding and clinical treatment is frequently restricted due to insufficient contrast enhancement in small vessels [2] or requires a higher Gadolinium (Gd) dose [3]. Clinically approved paramagnetic contrast agents have been reported with relaxivities (r1) of 3 - 4 $mM^{-1}s^{-1}$ which is vastly differing from theoretically achievable values up to 40 $mM^{-1}s^{-1}$ at 1.5T [4]. New Gd contrast agents with higher relaxivities are very likely to improve the performance of contrast-enhanced 3D MRA. In turn, an increased contrast enhancement offers potential reduction of the dose of Gd necessary for MRA. The purpose of this animal study was to compare the high-relaxivity low diffusable Gd-contrast agent P846 (Guerbet Research, France) with the clinically approved Gadoterate Meglumine Gd-DOTA (Dotarem®, Guerbet, France) for contrast-enhanced MR angiography at a magnetic field strength of 1.5T.

## Material & Methods

P846 is a moderate molecular weight (MW=3.5 kDa) and high relaxivity (r1/r2=32/41 $s^{-1}.mM^{-1}$ at 37°C in 4% HSA) contrast agent, containing one gadolinium atom per molecule. This molecule belongs to the Low Diffusion contrast Agent (LDA) class [5]. Five female New Zealand rabbits (aged 5 - 6 months; 2.8-3.3 kg) underwent MR-angiography of the abdominal arteries with both contrast agents in random order and separated by 72 hours. All rabbits were examined on a clinical 1.5T MR scanner (Magnetom Symphony, Siemens Medical Solutions, Erlangen, Germany) using a conventional knee coil for signal detection. A 3D gradient recall echo (fast low angle shot, FLASH) sequence with TR = 4.3 ms, TE=1.6 ms, FA = 30°, and a spatial resolution of 0.52 x 0.69 x 0.8 mm was used for data acquisition. Contrast media was applied at doses of 0.025 mmol Gd/kg for P846 and 0.1 mmol Gd/kg for Gd-DOTA, respectively. A 2 mL bolus of diluted contrast agent was intravenously injected at a rate of 0.2 mL/sec followed by 5 mL of saline with the same flow rate (Spectris, MEDRAD, Pittsburgh, PA). Data acquisition was performed up to 10 minutes after contrast administration. Data analysis included determination of values for CNR (abdominal aorta/lumbar muscle) and assessment of image quality regarding the visualization of the abdominal aorta and its branches on a 5-point scale. For statistical analysis the level of significance was set at $p<0.05$.

## Results

MR-angiography with both contrast agents visualized the abdominal aorta, renal arteries, and large mesenteric vessels in all rabbits. Determination of CNR revealed statistically significantly higher values for P846 (arterial phase: 42.6±4.0; after 10 min: 6.8±0.8) as compared to Gd-DOTA (arterial phase: 24.2±3.7; 10 min after injection: 3.2±0.7) at all time points. Decrease of image contrast 10 min after injection compared to the arterial phase was similar for both contrast agents with a lowering of CNR of 83.7 % for P846 and 86.2 % for Gd-DOTA, respectively (Figure 1). In the arterial phase, image quality was judged statistically significantly better for P846 (4.8±0.5) than for Gd-DOTA (3.8±0.4) (Figure 2).

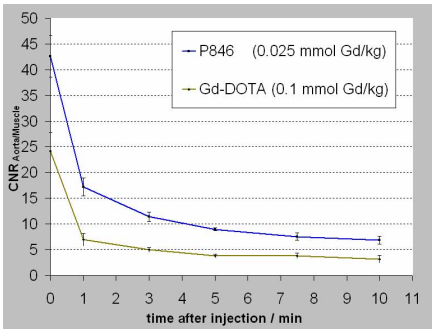


**Figure 1.** CNR evaluation of both contrast agents in the abdominal aorta and lumbar muscle observed within 10 minutes after injection of contrast agents.

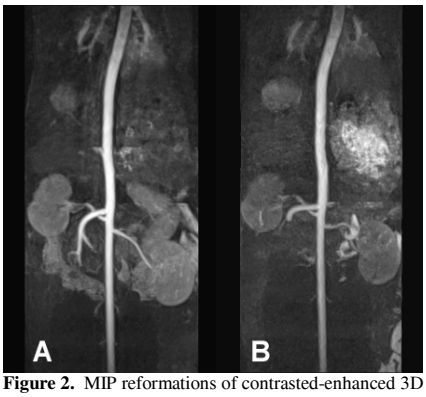


**Figure 2.** MIP reformations of contrasted-enhanced 3D MRA in arterial phase with P846 (A) and Gd-DOTA (B)

## Discussion

P846 demonstrated excellent image contrast for contrasted-enhanced 3D MRA by using a lower Gd dose compared to Gd-DOTA. Image quality was rated superior for P846 with special regard to small vessels, thus prospecting to improve diagnostic performance of first-pass arterial phase MRA. Despite of differences in molecular weight, P846 presented with a rapid blood clearance and extra-vascular contrast enhancement comparable to Gd-DOTA. In conclusion, preclinical evaluation of P846 in rabbits demonstrated the ability of a high relaxivity low diffusible contrast agent to provide a higher quality of first-pass arterial MR angiography at a lower Gd dose compared to Gd-DOTA.

## References

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