Phase II studies of Gadobenate dimeglumine (MultiHance) for MR Angiography

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Introduction Gadobenate dimeglumine (MultiHance™, Gd-BOPTA; Bracco SpA, Milan, Italy) is a Gd-chelate with weak affinity for serum albumin which has been shown to exhibit preferential properties for MR Angiography (MRA). The Phase II studies were designed based on previous Phase I data and covered four different doses in order to find the most effective dose for subsequent trials. The study was designed as a double blinded, multicenter trial covering three different vascular territories (042- Carotid; 043- Abdomen; 044- Pelvis).

Methods Fourteen experienced European centers participated in this trial. All requirements of GCP and IRB approval were strictly adhered to. A total of 392 patients were included, with 161 carotid, 94 abdominal and 137 pelvic studies. Patients had to give informed consent to participate and needed to have a documented vascular pathology within the imaging region.

Imaging was performed on several different MRI systems, all operating at 1.5 T. A non-enhanced study was always performed for comparison with the enhanced MRA. Detailed safety assessments were concurrently performed including blood assay, vital signs and ECG.

Four different doses were administered in a double blinded fashion based on randomization tables (0.025; 0.05; 0.1; 0.2 mmol/kg BW). The contrast agent was administered at a constant rate by power injector at 2 ml/s followed by a 20 ml saline flush. A test bolus scheme (up to 2 ml) was used to determine the individual timing.

The carotid imaging volume had to include the aortic arch. Pre-contrast imaging was done using a 3D MOTSA sequence within 20 min. The 3D Gd-MRA had to fulfill the following requirements: TR <7 ms; TE <2.8 ms; α 40°; Ma 200x512; FOV 40x20; acq. time < 15 s.

The abdominal imaging included the aorta and the renal arteries. Pre-contrast imaging was specified to include a 3D TOF sequence acquired within 10 min. The 3D Gd-MRA had to fulfill the following requirements: TR <7 ms; TE <2.8 ms; α 40°; FOV <40; acq. time < 26 s.

The pelvic imaging included for pre-contrast imaging with a 2D TOF sequence acquired within 10 min. The 3D Gd-MRA had to fulfill the following requirements: TR <7 ms; TE <2.8 ms; α 40°; FOV <40; acq. time < 26 s.

Onsite reading by 1 reader as well as off site by two radiologists was performed.

Results The current data are still preliminary until the final report is approved. Overall image quality was determined to be excellent starting at doses of 0.05 mmol/kg BW (Fig.1).

Adverse event (AE) data are available for the 043 abdomen and 044 pelvis trials. Only one severe adverse event was reported but this was classified as being unrelated to the study drug. The overall incidence of AE was approx. 9 % with 6% being study drug related. Of these, the overwhelming majority were classified as mild. No relevant dose dependent association of AE were noted.

The assessment of quality by diagnostic scores revealed a saturation pattern at 0.1 mmol/kg BW for both blinded readers. A clear diagnostic gain was found compared to the unenhanced study. While the 0.05 mmol/kg dose was frequently considered to be diagnostic, a further improvement was detected at the next higher dose (0.1 mmol/kg) especially for the more peripheral arteries. No substantial improvement could be seen with further increases of dose. This pattern was determined for several criteria.

Conclusion Gd-BOPTA was demonstrated to be a safe and highly effective contrast agent for MRA in all three vascular territories. The dose response data indicate a saturation pattern around 0.1 mmol/kg BW. The diagnostic range seems to be within 0.05 to 0.15 mmol/kg BW. The safety assessment confirmed the previously reported excellent findings. Gd-BOPTA was shown to be a very capable, safe and effective MRA agent which warrants further phase III development.

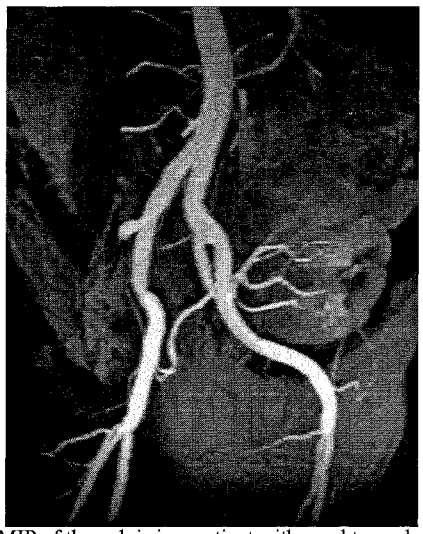

Fig. 1: MIP of the pelvis in a patient with renal transplant imaged at 0.1 mmol/kg BW. Note the homogeneous enhancement within the field of view as well as excellent delineation of small vessels

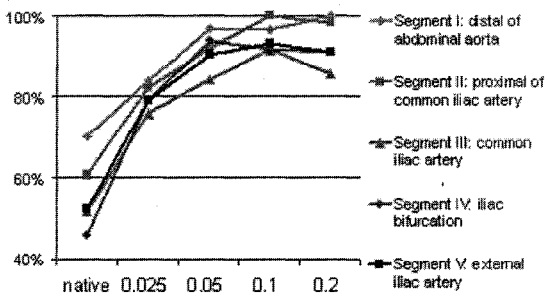

Fig. 2: Number of segments in the pelvis (044) with adequate diagnostic information for blinded reader #1. Note the substantial increase from unenhanced MRA and the saturation pattern at 0.1 mmol/kg BW of Gd-BOPTA

References:

Knopp MV et al. (1999) JMRI; 10:314-316
Knopp MV et al. Sydney: ISMRM, 1998; Vol. 1:174