Contrast-enhanced MRA of the abdominal and peripheral vessels: is there a need for blood pool agents?

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Introduction. Contrast-enhanced MR angiography (CE-MRA) is an increasingly important diagnostic tool for the assessment of abdominal and peripheral vascular pathology. The traditional approach has been to use a conventional extracellular gadolinium agent in conjunction with fast or ultrafast image acquisition within one breath-hold. The availability of higher T1 relaxivity agents such as gadobenate dimeglumine (MultiHance; Bracco) allowed greater vascular signal intensity (SI) enhancement to be obtained and hence greater diagnostic efficacy at an equivalent dose, or similar SI enhancement and diagnostic efficacy at doses lower than the dose required for conventional gadolinium agents. The recent approval of the first blood pool agent (gadofosveset, Vasovist; Schering) in Europe [1] raises the question as to whether blood pool agents offer significant advantages over currently available extracellular agents for MRA of the abdominal and peripheral vasculature. This analysis was conducted using all the data available in the Regulatory dossiers for gadofosveset [1–3] and gadobenate dimeglumine that were used to pursue the MRA indication in Europe.

Materials and Methods. This was a prospective study aimed at comparing gadobenate dimeglumine at 0.1 mmol/kg bodyweight and gadofosveset at 0.03 mmol/kg bodyweight for CE-MRA of the abdominal and peripheral arteries. Diagnostic performance was assessed in terms of sensitivity, specificity, accuracy, and predictive values (PVs) for detecting significant steno-occlusive disease (50%-99% stenosis or occlusion) using DSA as reference standard. Patients with suspected abnormalities of the renal, aorto-iliac or peripheral arteries were assessed in five studies overall. Two studies were performed using gadobenate dimeglumine and three using gadofosveset (Table 1).

Table 1. Distribution of patients in the 5 studies conducted for regulatory approval

Contrast agent	Renal artery		Peripheral		Total	
	Dosed	ITT *	Dosed	ITT *	Dosed	ITT *
Vasovist	145	136	452 **	443 **	597	579
MultiHance	293	268	287	272	580	540

* ITT population = patients with MRA and DSA performed
** Two studies with 274 + 178 and 268 + 175 patients dosed and ITT, respectively

All patients underwent CE-MRA with 3D-spoiled gradient-echo sequences on 1.5 T systems operating with gradient strengths of ≥20mT/m. MRA images were assessed independently by three off-site board-certified radiologists per study, who had no involvement with the patients and investigators and were blinded to all patient clinical and radiological information. Assessments of reference DSA images were conducted by one (gadobenate dimeglumine) or two (gadofosveset) further independent fully blinded radiologists per study. Grading of stenoses was classified as non-significant (<50%), significant (50-99%) or occlusion (100%). All uninterpreptable images were considered inaccurate for determinations of diagnostic performance. Sensitivity, specificity, accuracy, and PVs for the detection of clinically significant stenosis were determined against findings at DSA and were compared between the two contrast agents. The point estimates and 95% confidence intervals of average diagnostic performance indicators across multiple readers were calculated and compared. Inter-reader agreement in each study was estimated using generalized Kappa statistics. Safety was assessed by comparing incidences of adverse reactions, i.e. adverse events with definite, possible or unknown relationship to the test agent, in the overall MRA clinical development populations (all doses combined) comprising 1321 and 1463 patients receiving gadofosveset and gadobenate dimeglumine, respectively. Data were compared using the Chi-square test.

Results. The sensitivity, specificity, accuracy and positive and negative PVs (PPV and NPV) for detection of clinically significant steno-occlusive disease of the abdominal and peripheral arteries on CE-MRA with gadofosveset and gadobenate dimeglumine are shown in Table 2.

Table 2. Sensitivity, specificity, accuracy, and positive and negative predictive values

Vascular territory	Contrast agent	Number of segments assessed	Sensitivity	Specificity	Accuracy	PPV	NPV
Renal vasculature	Vasovist	282	62.3%	80.5%	77.1%	42.5%	90.2%
	MultiHance	518	69.5%	92.4%	83.6%	85.0%	82.9%
Peripheral vasculature	Vasovist	1405	74.3%	88.2%	86.3%	49.9%	95.6%
	MultiHance	3910	67.4%	93.0%	86.6%	76.2%	89.6%

Whereas similar overall accuracy was obtained for peripheral MRA, gadobenate dimeglumine showed better sensitivity, specificity and accuracy for CE-MRA of the renal arteries. Gadobenate dimeglumine-enhanced MRA showed significantly higher average PPV (76% to 85%) compared to gadofosveset-enhanced MRA (42% to 45%), while the NPV were consistently high and comparable across readers and vascular territories for both agents. Inter-reader agreement analysis determined that gadobenate dimeglumine-enhanced MRA is a diagnostic test with "substantial" reproducibility (Kappa between 0.66 and 0.69) while gadofosveset-enhanced MRA shows only "fair" reproducibility (Kappa between 0.32 and 0.42) according to the ranking described by Landis and Koch [4].

Comparison of safety data revealed a significantly ($p<0.0001$) higher incidence of adverse reactions for gadofosveset (31.4%, 415/1321 patients) compared to gadobenate dimeglumine (7.2%, 106/1463 subjects). Moreover, while no dose dependence was shown in the incidence of adverse reactions with gadobenate dimeglumine, an increased occurrence of related adverse events was reported with increasing doses of gadofosveset, ranging from 22.9% at the approved dose of 0.03 mmol/kg to 67.6% at doses >0.05 mmol/kg. Additionally, exposure of patients to doses of gadofosveset greater than 0.05 mmol/kg may increase the possibility of QT prolongation (see Summary of Product Characteristics).

Conclusions. Although blood pool agents have theoretical advantages for CE-MRA including prolonged blood residence time, enhanced T1 relaxation effect and decreased dose and injection volume requirements, a clear benefit for gadofosveset over gadobenate dimeglumine for CE-MRA of the renal and peripheral arteries could not be demonstrated. Moreover, the safety profile of gadofosveset appears significantly worse, determining a risk-benefit ratio that does not justify the replacement of currently used gadolinium agents for most MR angiographic procedures.

References.

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