Are there differences between macrocyclic gadolinium contrast agents for brain tumor imaging? Results of a Multicenter Intra-individual Crossover Comparison of Gadobutrol with Gadoteridol (The TRUTH study)

Martin P Smith[1], Kenneth R Maravilla[2], Stefano Bastianello[3], Eva Bueltmann[4], Toshinori Hirai[5], Tiziano Frattini[6], Cesare Colosimo[7], and Gianpaolo Pirovano[8]
[1]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, United States, [2]University of Washington, WA, United States, [3]Neuroradiology Department, University of Pavia, Pavia, Italy, [4]Oberartzin Institut fur Diagnostiche und Interventionelle Neuroradiologie, Hannover, Germany, [5]Kumamoto University, Kumamoto, Japan, [6]Ospedale Valduce, Como, Italy, [7]Policlinico "Agostino Gemelli", Rome, Italy, [8]Bracco Diagnostics Inc., Monroe, NJ, United States

Target Audience: Radiologists performing contrast-enhanced MR examinations of the brain.

Purpose: Gadobutrol (Gadovist®/Gadavist®; Gd-BT-DO3A) and gadoteridol (ProHance®; Gd-HP-DO3A) differ only in that a hydroxypropyl (HP) group on the gadoteridol molecule is replaced by a trihydroxybutyl (BT) group on the gadobutrol molecule and that gadobutrol is formulated at a 1M concentration compared to 0.5M for gadoteridol. We sought to determine whether these differences impact morphologic contrast-enhanced MRI of brain tumors using a multicenter intra-individual crossover study design.

Materials and Methods: 229 adult patients with suspected or known brain tumors underwent two identical MRI exams at 1.5T, one with gadoteridol and the other with gadobutrol, both at a dose of 0.1 mmol/kg body weight. The agents were injected in randomized order separated by 2-14 days. Imaging sequences and post-injection acquisition timing were identical for the two exams (T1wSE and high-resolution T1wGRE sequences at 3–7 min post-injection). Three blinded readers evaluated images qualitatively for diagnostic information (lesion extent, delineation, morphology, enhancement, global preference) and quantitatively in terms of pre- to post-injection changes in % lesion enhancement and lesion-to-background ratio (LBR). Accuracy for the MR diagnosis of brain lesions was assessed using the final clinical diagnosis as reference standard. Data were analyzed using the Wilcoxon signed rank test, McNemar test and Mixed model.

Results: 209 patients successfully completed both examinations. None of the readers noted a significant qualitative or quantitative difference in lesion enhancement, lesion extent, lesion delineation, or lesion internal morphology (p-values: 0.69-1.00). 139 patients had at least one histologically-confirmed brain lesion. Two readers found no difference in the detection of patients with lesions (133/139 vs. 135/139, p=0.317; 137/139 vs. 136/139, p=0.564) while one reader found minimal differences in favor of gadoteridol (136/139 vs. 132/139, p=0.046). Similar findings were noted for the numbers of lesions detected, for characterization of tumors (malignant vs.benign) and for reader confidence in diagnosis. Three-reader agreement for characterization was similar (66.4% [κ=0.43] for gadobutrol; 70.3% [κ=0.45] for gadoteridol). No significant differences in the incidence of adverse events were noted (p=0.199).

Conclusions: Our findings indicate that gadoteridol and gadobutrol at 0.1 mmol/kg bodyweight provide similar qualitative and quantitative diagnostic information for the visualization and diagnosis of brain lesions. Assessment by three blinded neuroradiologists revealed no significant differences between the agents. There is no clinical benefit to the two-fold higher concentration of gadobutrol in the detection or characterization of brain lesions. Our results confirm findings from a previous Phase III clinical trial designed to prove non-inferiority of gadobutrol compared to gadoteridol for brain tumor imaging (1, 2).

Fig. 1. Global diagnostic preference expressed by three blinded readers

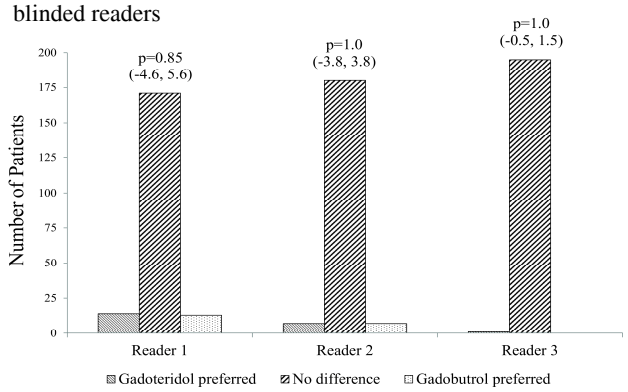
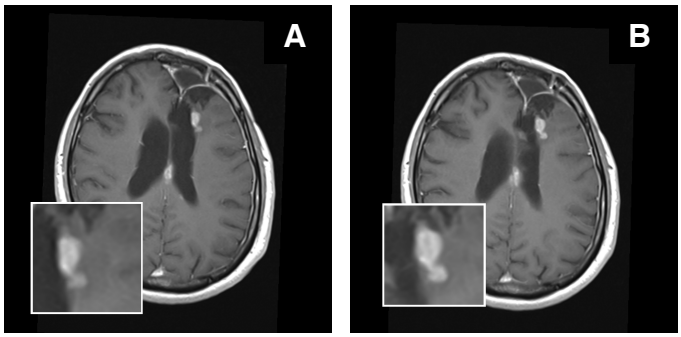


Fig. 2. 39-year old male with anaplastic astrocytoma, grade IV.
A: Gadavist 0.1 mmol/kg. B: ProHance 0.1 mmol/kg.
No differences in contrast enhancement or lesion size are apparent.



References

1. Center for Drug Evaluation and Research. FDA Advisory Committee Briefing Document. New Drug Application 201-277. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240354.pdf. Accessed November 4, 2014.
2. Center for Drug Evaluation and Research. FDA Advisory Committee Briefing Document. New Drug Application 201-277. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM255169.pdf. Accessed November 4, 2014