Extravascular Enhancement with a blood-pool contrast agent - a new class of contrast in Magnetic Resonance Imaging

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Introduction

Gadofosveset (Vasovist®, Schering, Berlin, Germany) is a new blood-pool-agent based on Gd-complex recently approved for MRA. The chelate binds non covalent to albumin, thus changing the relaxivity and half-life of the complex [1-2]. Binding affinity leads to a significant increase of T1- and T2 relaxivities. The increase in T1 relaxivity causes a rise in enhancement with direct influence on the MR signal. The longer half-life of the blood-pool-agent prolongs the dwell time in the vascular system. So far no experience exist about the use of Vasovist® as an "extracellular"contrast agents in cases which allow the complex to extravasate, e.g. in tumors. The non binded fraction, 15% of the Gadofosveset molecules [3], is able to extravasate and bind at proteins in the extracellular space. This increases the T1 relaxivity substantially with direct effect on the contrast properties. But even if the agent is bound to serum-albumin it might be speculated that the compley is able to extravasate into pathologic tissue if the gap between the vesselwall cells are large enough.In respect to the brain the situation is even easier. Because of the presence of the BBB, represented mainly by endothelial tight junctions, all current available MR contrast media does not leake into the brain tissue. The BBB blocks all molecules except those that cross cell membranes by means of lipid solubility (such as oxygen, carbon dioxide, ethanol, and steroid hormones) and those that are allowed in by specific transport systems (such as sugars and some amino acids). Substances with a molecular weight higher than 180 daltons (Da), which include all available imaging contrast media, generally cannot cross the blood-brain barrier.Therefore all MR contrast media are intravascular agents in the presence of an intact BBB. However, if the BBB is altered by circumstances which increase the permeabilty, contrast media can leak into the tissue. This is also true for the extracellular agents, as well as for blood-pool agents like Vasovist®.There have been a huge number of reports about the role of Vasovist® in MR angiography [1-4], however, no reports exist about the extravascular behaviour of the agent and the potential in imaging tissue pathologies. In this report we present our first experience with the blood-pool agent Vasovist® for contrast enhanced MR imaging of brain tumors.

Methods

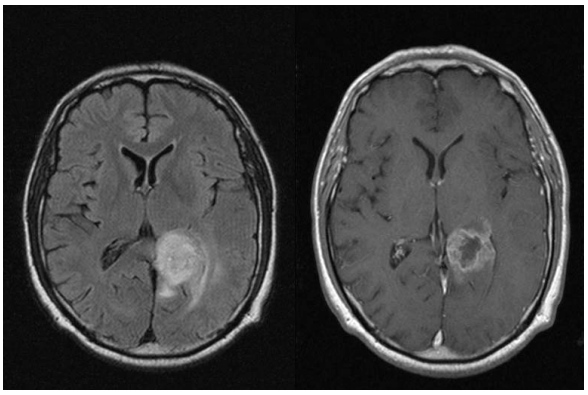
In a pilot study 10 consecutive patients with different intracerebral tumors were examined with a standard dose (0,03mmol/kg BW) of Vasovist®. Three patients with malignant glioma, one patient with cerebral metastases, one patient with acoustic schwannoma and 5 patients with meningeomas have been scanned using the same sequence parameters as for an examination with standard contrast media. The imaging protocol included a T1-SE, T2-FSE and FLAIR prior contrast and contrast enhanced T1-SE in axial and coronal orientation. In patients with skull base tumors, an additional fat suppression T1-SE was performed. The time between contrast media application and imaging was about the same for all patients at 3 min after application.

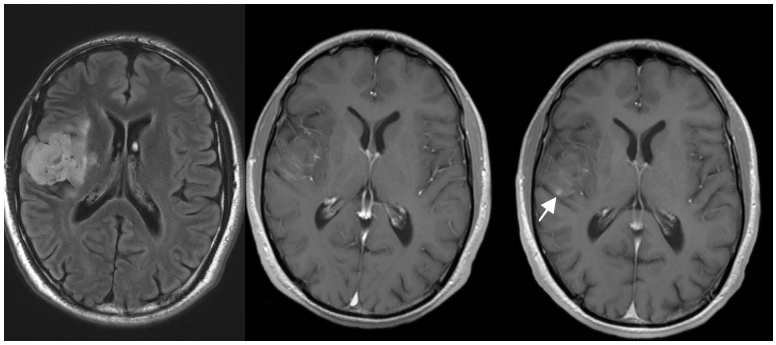
All MR examinations were performed on standard clinical 1.5T systems (Magnetom Avanto and Magneton Symphony, Siemens, Erlangen, Germany) using a circular polarized head coil or an 8 channel head coil. Eight patients were referred for follow-up MRI after radiotherapy, two patients in the pretherapeutic work-up. In all patients previous MR examinations with a standard extracellular contrast agent (1,5 years to 2 weeks prior the Vasovist® examination) are available and served as a reference.

Results

With Vasovist® a sufficient and with the previous exams comparable contrast enhancement could be achieved in all lesions, even in small extraaxial lesions like a 5mm neurinoma or enhancing primary tumors like the glioblastoma multiforme in Case 1. The detection and delineation of more complex lesions was also not different from the examinations with a standard Gd-chelate. Over time we observed an increase in the enhancement intensity for at least 8 hours with a maximum after 6-7 hours. The enhancement did last for more than 24 hours. Even in lesions that did not enhanced at the 5 min post contrast MRI showed enhancing nodules at the 5 hour exam (Case 2).

Case 1: 68 year old patient with malignant glioma. The patient presented with seizures and minor neurologic deficits. FLAIR imaging presents a large mass lesion in the left temporal, parietal and occipital lobe with strong enhancement of the central tumor parts. The enhancement pattern and intensity was rated equal to the previous exam only one week before. In cases like this, the agent is able to achieve a strong tumor enhancement with clear delineation of the enhancing tumor parts allowing a treatment planning both for Neurosurgery and Radiotherapy.





Case 2: 52 year old patient with suspected low grade astrocytome, referred for follow-up after combined radio-chemotherapy. The tumor was stable in size with no enhancement on the last control 8 month ago. T2 and FLAIR present a heterogeneous high intensity tumor with infiltration of frontal and temporal lobe. After Vasovist application no obvious contrast enhancing lesion was obvious (b), consitent with the previous exam. The patient was asked to return 5 hours later for an additional T1 imaging (c). The late scan presented a mild enhancing nodular lesion in projection to the insular cortex (arrow) which was not detectable on the early 5 min scan. The presence of a contrast enhancing lesion is suspicious for malignization of the tumor and therefore of great impact on the furhter management of the patient. Malignization has to be proved using a biopsy sampling.

Discussion and Conclusion

As shown in this intial report also intravascular agents like the protein binding blood-pool-agent Vasovist® are able to pass a disrupted BBB and to allows a sufficient contrast enhancement. Even if there is a smaller amount of contrast media leaking into the extracellular space, the high relaxivity of the complex might compensate for the smaller dosage of Gd which gives a great potential also outside the brain. Due to its long lasting contrast, the agent has a high potential to detect even subtible enhancing lesions and to allow a robust contrast at a later time point after administration. However, since Vasovist® is very different than conventional contrast agents due to its properties, optimized acquisition patterns, and especially optimized reconstruction strategies, must be developed and verified clinically in a large number of cases.

References: 1: Shamsi K, Yucel EK, Chamberlin P. A summery of gadofosveset (MS-325) at 0.03mmol/kg body weight dose: Phase II and Phase III clinical trials data. Invest Radiol 2006; 41:822-830; **2:** Hartman M, Wiethoff AJ, Hentrich HR, Rohrer M. Initial imaging recommendations for Vasovist angiography. Eur Radiolg 2006; 16:Suppl 2:B15-23. **3:** Steger-Hartmann T, Graham PB, Muller S, Schweinfurth H. Preclinical sefety assessment of Vasovist, a new MRI contrast agent for angiography. Invest Radiol 2006; 41:449-459. 4: Jerosch-Herold M, HuX, Murthy NS, Rickers C, Stillman AE. Magnetic resonance imaging of myocardial enhancement with MS-325 and its relation to myocardial blood flow and the perfusion reserve. J Magn Reson Imaging 2003; 18:544-554