The influences of albumin binding and field strength on the relaxivity of gadofosveset (Ablavar), and its potential beyond angiography as clinical field strengths increase

O. C. Richardson[1], S. F. Tanner[1], M. Scott[2], and D. L. Buckley[1]
[1]Division of Medical Physics, University of Leeds, Leeds, West Yorkshire, United Kingdom, [2]AstraZeneca, Alderley Park, Cheshire, United Kingdom

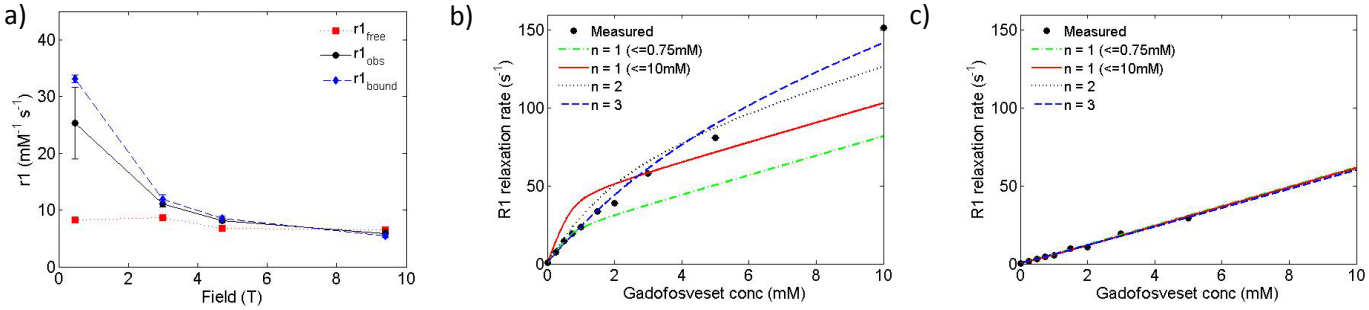
Introduction: Gadofosveset trisodium (Ablavar, Lantheus Medical Imaging) is a small molecule gadolinium-based contrast agent, which binds reversibly with albumin in the blood. At high concentrations, up to 20 gadofosveset molecules may bind to a single albumin molecule [1]. This binding process enables: a) significantly higher longitudinal relaxivity than in the unbound form [2], facilitating equivalent contrast enhancement at lower contrast agent doses; and, b) limited extravasation and a slower body excretion rate, which makes gadofosveset well suited to angiography [3]. The observed relaxivity ($r1_{obs}$) of gadofosveset peaks at around 0.5 T, with a substantial decrease at higher fields [4, 5]. The relaxivity of unbound gadofosveset ($r1_{free}$) may be derived from relaxation measurement in the absence of albumin; bound relaxivity ($r1_{bound}$) may be derived using the following model [6]:

$$R1_{obs} = R1_{HSA} + r1_{free}.C_{total} + (r1_{bound} - r1_{free}).\left(\frac{(n.HSA.K_a + C_{total}.K_a + 1) - \sqrt{(n.HSA.K_a + C_{total}.K_a + 1)^2 - 4.K_a^2.n.HSA.C_{total}}}{2.K_a}\right)$$

$R1_{obs}$ = observed relaxation rate; $R1_{HSA}$ = relaxation rate of serum albumin solution; C_{total} = total gadofosveset concentration; HSA = serum albumin concentration; n = number of gadofosveset molecules bound per serum albumin molecule; K_a = binding affinity.

Previous gadofosveset relaxivity studies assuming one albumin binding site [4, 7] are likely to underestimate relaxivity at higher gadofosveset concentrations. It may be necessary to consider additional binding sites when analysing peak concentration levels, such as during the first pass of a bolus in the blood. This study has calculated $r1_{obs}$, $r1_{bound}$ and $r1_{free}$ for gadofosveset at field strengths up to 9.4 T and concentrations up to 10 mM, and investigated the validity of model fitting for single and multiple bound gadofosveset molecules per albumin molecule. Characterising gadofosveset in this way may aid assessment of its potential value, beyond its established application in angiography, as clinical field strengths increase.

Methods and Results: T1 relaxation times were measured for gadofosveset in phosphate-buffered saline (PBS) and in 4.5% bovine serum albumin (BSA) at 0.47, 3.0, 4.7 and 9.4 T, and linear fits of relaxation rate (1/T1) used to determine $r1_{free}$ and $r1_{obs}$. Using the above equation, with a fixed K_a value and n = 1, $r1_{bound}$ was calculated for low gadofosveset concentrations (≤ 0.75 mM). $r1_{bound}$ and 95% confidence intervals were additionally calculated for gadofosveset concentrations ≤ 10 mM and n ≤ 3, using published K_a values [K_a (n=1): 11.0 mM^{-1}; K_a (n = 2): 0.84 mM^{-1}; K_a (n = 3): 0.26 mM^{-1}] [5].



***a)** Calculated relaxivity values (with 95% confidence intervals) assuming a single binding site (for gadofosveset concentrations ≤ 0.75 mM). **b)** Model fitting to 0.47 T data for n = 1 (using data for gadofosveset concentrations ≤ 0.75 mM and for concentrations ≤10 mM) and n = 2-3 (for concentrations ≤10 mM). **c)** Equivalent model fitting to 9.4 T data. Graphs show room temperature values (18-22°C); body temperature values (not plotted) display a similar trend.*

Discussion: At high fields, $r1_{free}$ and $r1_{bound}$ converge and $r1_{obs}$ declines to levels comparable to established small-molecule contrast agents. Although the influence of multiple binding at high gadofosveset concentrations is important at low fields, it may be acceptable to assume one binding site at high fields. Despite the reduced relaxivity at high fields, the kinetic characteristics of gadofosveset remain a differentiating feature. In particular, its limited extravasation through leaky angiogenic vessels, in comparison to small molecule contrast agents, may provide an improved quantitative biomarker of tumour response to treatment [8]. It is possible that tracer kinetic modelling may unlock the potential of gadofosveset at high field strengths, where the convergence of $r1_{free}$ and $r1_{bound}$ reduces contrast enhancement but moderates the complexity of relaxivity modelling.

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