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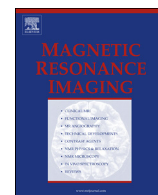

Original contribution

The stability of gadolinium-based contrast agents in human serum: A reanalysis of literature data and association with clinical outcomes

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ABSTRACT

Purpose: To reanalyze literature data of gadolinium (Gd)-based contrast agents (GBCAs) in plasma with a kinetic model of dissociation to provide a comprehensive assessment of equilibrium conditions for linear GBCAs.
Methods: Data for the release of Gd from GBCAs in human serum was extracted from a previous report in the literature and fit to a kinetic dissociation/association model. The conditional stabilities ($logK_{cond}$) and percent intact over time were calculated using the model rate constants. The correlations between clinical outcomes and $logK_{cond}$ or other stability indices were determined.
Results: The release curves for Omniscan®, gadodiamide, OptiMARK®, gadoversetamide Magnevist® and Multihance® were extracted and all fit well to the kinetic model. The $logK_{cond}$s calculated from the rate constants were on the order of ~4–6, and were not significantly altered by excess ligand or phosphate. The stability constant based on the amount intact by the initial elimination half-life of GBCAs in plasma provided good correlation with outcomes observed in patients.
Conclusions: Estimation of the kinetic constants for GBCA dissociation/association revealed that their stability in physiological fluid is much lower than previous approaches would suggest, which correlates well with deposition and pharmacokinetic observations of GBCAs in human patients.

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1. Introduction

Questions about the stability of gadolinium (Gd)-based contrast agents (GBCAs) *in vivo* have recently received renewed attention following reports of Gd deposition in the brains [1,2], skin [3] and bones [4] of patients with normal renal function. While much of the original work in developing these agents for human use was appropriately dedicated to confirming that the toxic Gd metal was not released [5], the conclusion of acceptable stability was determined to be clearance of not significantly < 100% of injected Gd. The statistics allowed a point average retention of anywhere from 1 to 5% of total dose [6], which we are now finding may have been clinically significant, despite not being statistically significant.

At this time, no unconfounded neurological symptoms have been reported in patients with autopsy-confirmed Gd deposition in the brain [7], and a recent animal model failed to find any histological evidence of toxicity from deposition [8]. However, in a case with biopsy-confirmed soft-tissue deposition of Gd, the patient also reported severe joint pain for which the authors did not provide an alternative explanation [9]. There is also a growing number of patients with purported Gd toxicity who have experienced elevated urine Gd months after undergoing a contrast-enhanced MRI, with a collection of symptoms including joint pain and an alarming "brain fog," which can otherwise be described as slowed cognition or perception [10]. There is no strong evidence of causality between GBCA exposure, retention and any of the reported symptoms, nor is there any evidence of a specific patient population that may be at greater risk of Gd retention or negative outcomes. However, a conservative approach would consider methods to identify and mitigate risks to patients as we attempt to determine causation; rather than attempting to elucidate patient-specific risk factors, it may be more rational to address gaps in the extensive body of evidence around GBCAs themselves.

Attempts to predict or approximate GBCA stability *in vivo* have ranged from comparison with Gd salt pharmacokinetics [11], correlation with dissociation in acid [5], stability in simulated plasma [12,13] and direct measurement of dissociation in plasma [14]. While each approach has some methodological limitations, direct measurement has the most potential value because it allows adequate control over a physiologically relevant system and it will not be confounded by distribution and elimination kinetics (computer simulated plasma would allow complete control over a system without confounding pharmacokinetics, but requires *in vitro* data to verify the assumptions of the model are valid). A major work assessing the stability of GBCAs in human serum

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(plasma without clotting factors) was reported by Frenzel et al. in 2008 [14]. This analysis assigned GBCAs into three categories based on their stability, in descending order: macrocyclic, ionic linear and nonionic linear. A strength of this study was the duration of measurement (15 days), which was not physiologically relevant but presented several dissociation curves reaching an apparent equilibrium, signifying a balance produced by the reverse reaction, *i.e.*, association. The equilibrium was not addressed by the original report, which was mainly focused on dissociation rates and less on the more complete kinetic picture that could be provided by the data. As such, the present analysis attempts to determine the kinetic constants from the Frenzel et al. report and use them to approximate GBCA stability *in vivo*.

2. Methods and methods

2.1. Data collection

Data for dissociation of Gd from GBCAs in human serum at physiological temperatures was acquired from a previous report which measured released Gd in human serum at 37° C using a chelating HPLC column with ICP/MS [14]. Individual data points for the dissociations of gadodiamide, gadoversetamide, Omniscan® (gadodiamide with 5 mol% caldiamide), Optimark® (gadoversetamide with 10 mol% calversetamide), Magnevist® (gadopentetate with 0.2 mol% DTPA) and Multihance® (gadobenate) were digitized from published plots using WebPlotDigitizer (v 3.10; Austin, Texas). These agents were chosen because they showed observable dissociation within the measurement period (15 days), and because their package inserts state they do not bind plasma proteins [15–18], which would complicate the kinetic model. Although gadobenate relaxivity *in vitro* is influenced by protein concentration [19,20], Multihance® data was included in the present analysis because it does not measurably bind proteins in human, rat or rabbit plasma during equilibrium dialysis (indicating the protein binding constant logK was <2.3 and thus <9% bound at equilibrium when the total gadobenate concentration is 1 mM) [21]; by comparison, Primovist® (gadoxetate) was not included because it is known to be 10% bound to proteins in plasma when the GBCA concentration is 1 mM [22]. While the original report presented Gd released as a function of time, the data were transformed to express intact GBCA concentration remaining by subtracting each point from 100% and multiplying by the initial concentration used in each assay (1 mM).

2.2. Data analysis

Dissociation of a GBCA can be modeled by the differential equation:

$$\frac{d[\mathrm{GBCA}]}{dt} = -k_d[\mathrm{GBCA}] + k_a[\mathrm{Gd}][\mathrm{Ligand}] \tag{1}$$

where k_a and k_d are the conditional association and dissociation rate constants, respectively. While Eq. (1) may appear to oversimplify the dissociation kinetics of GBCAs in plasma (even *in vitro*) based on potential competing reactions for Gd or ligand, those factors are relevant only to the equations for [Gd] and [Ligand] change over time (*i.e.*, d[Gd]/dt and d[Ligand]/dt); by not considering d[Gd]/dt and d[Ligand]/dt, competing reactions are incorporated into the empirical, conditional rate constants. Assuming there is no unchelated Gd in plasma initially, and ligand concentration at time zero is controlled by the formulation, Eq. (1) can be rewritten as

$$\frac{d[\mathrm{GBCA}]}{dt} = -k_d[\mathrm{GBCA}] + k_a([\mathrm{GBCA}]_0 - [\mathrm{GBCA}]) \times ([\mathrm{GBCA}]_0 + X - [\mathrm{GBCA}]) \tag{2}$$

where $[\mathrm{GBCA}]_0$ is the initial concentration of GBCA and X is the initial molar concentration of excess ligand. There is an analytical solution for Eq. (2), but it is unwieldy for the purposes of this analysis. Thus, regressions to determine k_d and k_a from the dissociation data used the numerical solution (*i.e.*, computational determination of [GBCA] based on Eq. (2) by integration at a given time point provided $[\mathrm{GBCA}]_0$) and iteration over estimates to determine the optimal rate constants that minimize least square error; this analysis was performed with the packages deSolve [23] and minpack.lm [24] in the R programming language (R Foundation for Statistical Computing; Vienna, Austria). The percent of GBCA intact at equilibrium was found by solving for θ in the expression

$$K_{cond}[\mathrm{GBCA}]_0 = \frac{\theta}{(1-\theta)\left(\frac{X}{[\mathrm{GBCA}]_0} + 1 - \theta\right)} \tag{3}$$

where K_{cond} is the conditional stability constant, calculated by division of the conditional rate constants (k_a/k_d). Correlation and concordance between the best-fit regression estimates and the actual data were determined, and the residuals (difference between the predicted value and the observed value of the dependent variable) were analyzed.

2.3. Associations with clinical data

Data from brain deposition studies [25–27] and a meta-analysis of GBCA pharmacokinetics [28] in humans and animals were collected and fit to stability constants that could be calculated using the association and dissociation rate constants, and the traditional thermodynamic constant, $\log K_{therm}$ and pH-based conditional stability constant, $\log K_{cond,pH}$. The rate-constant-derived stability constants were $\log K_{cond}$ (calculated as the logarithm of the association and dissociation rate constant ratio) and a proposed constant which considers the amount dissociated at any time point in plasma. The proposed constant is a reaction quotient, $\log Q_t$, calculated based on the percent of GBCA intact at time t, θ_t:

$$\log Q_t = \log \frac{\theta_t}{(1-\theta_t)\left(\frac{X}{[\mathrm{GBCA}]_0} + 1 - \theta_t\right)} \tag{4}$$

Eq. (4) is similar to Eq. (3), except a $[\mathrm{GBCA}]_0$ term has been eliminated to facilitate comparisons across different initial GBCA concentrations, as it can be seen that the magnitude of Q_t can be arbitrarily altered by selection of the magnitude of $[\mathrm{GBCA}]_0$. The variable θ_t was calculated from the analytical solution for Eq. (2), which used an initial GBCA concentration of 1 mM.

The specific outcomes of interest were deposition ratio in the dentate nucleus and globus pallidus (concentration of Gd in these regions normalized by total GBCA dose) [25,26], terminal elimination constant observed in healthy patients and animals [28] and cerebellar concentration of Gd after prolonged repeated doses of Gd in rats [27]. In the latter two cases, outcome data were all generated by the same investigators, but deposition ratios were calculated from multiple sources. All data used are detailed in Supplementary material. Correlations between the stability constants and the outcomes were determined by simple linear regression, with significance determined by the *F*-test.

3. Results

The extracted points from the previous report are plotted in Fig. 1 with an overlay of the regression lines. It is clear that the regression overestimates the stability of the GBCAs analyzed, since they tend to plateau while the data points continue to descend. The best fit lines appeared to match the earlier time points better than the later time points. Overall, the curves fit the data with good correlation (r^2) and concordance (r_c), with both values >0.75 under normal and high phosphate conditions for all GBCAs (Table 1). Analysis of the residuals suggested competing reactions may be confounding the dissociation kinetics of

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