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Monthly triple-dose gadolinium administration: potential associations with leukopenia, hypophosphatemia, and bone marrow T1 hyperintensity

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Abstract

Objective: Monthly scanning with triple-dose gadopentetate dimeglumine has been shown to be associated with progressive increases in bone T1 hyperintensity, hypophosphatemia, and leukopenia. This study was performed to retrospectively investigate the potential associations among these phenomena.

Methods: This retrospective analysis involved patients who had received monthly triple-dose gadopentetate dimeglumine for up to 2 years as part of treatment for multiple sclerosis. Monthly magnetic resonance imaging scans of the brain (n = 67) were segmented to evaluate the signal intensity in the cranial marrow. Potential associations among the marrow T1 hyperintensity, serum phosphate concentration, and white blood cell count were examined.

Results: Patients in the no leukopenia group showed a statistically significant mean monthly increase in the bone marrow signal-to-noise ratio of 0.0430/month. Patients in the leukopenia group showed a mean monthly increase in the bone marrow signal-to-noise ratio of 0.0398/month, but this was not statistically significant. Patients in the hypophosphatemia group were significantly less likely to develop leukopenia than patients who had never developed hypophosphatemia.

Conclusions: Although monthly administration of triple-dose gadopentetate dimeglumine over 13 months has been associated with progressive increases in leukopenia, hypophosphatemia, and

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T1 signal intensity of bone, this study showed an inverse relationship between leukopenia and hypophosphatemia.

Keywords
Gadolinium deposition, hypophosphatemia, leukopenia, multiple sclerosis, toxicity, magnetic resonance imaging

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Background

Recent studies have revealed deposition of gadolinium (Gd) within the tissues of patients who have undergone Gd-based contrast-enhanced magnetic resonance imaging (MRI).[1–3] Most notably, deposition of Gd within the gray matter has been demonstrated.[1–6] Evidence of retention has been seen as late as 10 years after administration of repeat doses.[7] Recent studies have demonstrated Gd deposition in bone using emission spectroscopy in ex vivo studies[8] and in live patients using MRI.[9] The question that remains unanswered from these preliminary studies is whether the deposition of Gd results in immediate or long-term cellular or physiologic effects of clinical significance in patients with normal renal function.

Perhaps the largest currently available clinical and imaging data sets of patients who have undergone serial Gd-based contrast examinations are from the randomized controlled trial "Betaseron vs Copaxone in Multiple Sclerosis with Triple-Dose Gadolinium and 3-Tesla MRI Endpoints" (BECOME trial).[10] This study included 75 patients with multiple sclerosis who underwent monthly contrast-enhanced MRI scans of the brain using off-label triple-dose (0.3 mmol/kg) gadopentetate dimeglumine contrast for up to 2 years. The purpose of that study was to compare the clinical efficacy of the immunomodulating therapeutic agents interferon beta-1b (Betaseron®; Bayer, Leverkusen, Germany) and glatiramer acetate (Copaxone®; Teva Neuroscience, Kansas City, MO, USA). A retrospective analysis of the data from that trial, which included serial bloodwork, showed that patients receiving serial triple-dose Gd-based contrast demonstrated a higher frequency of hypophosphatemia[9] and leukopenia when compared with pre-study levels.[11] This was true of both treatment arms. Furthermore, the frequency of hypophosphatemia was found to progressively increase with repeat triple doses over 12 months (only 4% of patients developed episodes of hypophosphatemia in the first 3 months of the study, but 26% developed hypophosphatemia over the last 3 months).[12] In addition, a retrospective analysis of the bone marrow signal intensity over 13 months of monthly triple-dose Gd contrast administration demonstrated a progressive increase in the mean T1 signal-to-noise ratio (S/N) in the medullary cavity (0.039/month, $p < 0.0001$), suggesting bone marrow Gd deposition.[9] The purpose of the present study was to investigate the potential associations among leukopenia, hypophosphatemia, and bone marrow T1 hyperintensity secondary to serial Gd administration.

Methods

De-identified data from the first 13 months of the BECOME trial (cohort study) were

retrospectively analyzed. Because the current study was a retrospective analysis of de-identified patients, the IRB office issued a waiver of IRB approval and patient consent. Analysis of Gd bone deposition has been described in a separate report.[9] Patients from the original BECOME trial were consecutively enrolled at New Jersey Medical School from 16 February 2003 to 26 February 2005. Scans from 67 patients from the BECOME multiple sclerosis trial cohort (original cohort, n = 75) were available for analysis. Eight patients were excluded from the analysis because of corrupted imaging data. The demographic characteristics of the patients are listed in Table 1.

Data included monthly contrast-enhanced brain MRI scans obtained using triple-dose gadopentetate dimeglumine contrast. Monthly blood specimens were collected immediately prior to contrast injection to identify any potential effects from prior months. The monthly brain MRI scans were segmented to evaluate the signal intensity within the marrow compartment, and signal intensity changes were compared with the serum phosphate concentration and white blood cell count measured at the same time points to identify a potential relationship.

T1-weighted fat-suppressed MRI scans of each patient at 14 time points spanning 13 months were used (screening, baseline, and months 1–12). ITK-SNAP software[13] (https://www.itksnap.org) was used to manually segment regions of interest (ROIs) centered on the medullary cavity of the skull base, which served as a mask for subsequent automated analysis of co-registered T1-weighted fat-suppressed images. The internal occipital protuberance or the clivus was chosen to optimize the size of the ROI. In any given patient, the same medullary cavity was used at all time points. The S/N was defined as the ratio between the signal intensity of the bone ROI and the signal intensity of the air ROI.

Table 1. Demographic characteristics of the 75 patients randomized in the BECOME study.

Demographic characteristics	Number of patients
Age, mean (range) years	36 (18–55)
Female	52
Male	23
Ethnicity	
White	39
Black	21
Hispanic	14
Indian-Asian	1

Linear mixed regression modeling with a random intercept using the monthly data was performed. The patients were divided into groups based on whether their bloodwork revealed an episode of hypophosphatemia (defined as a phosphate concentration of <2.5 mg/dL). These groups of patients were defined as the hypophosphatemia group (≥ 1 episode) and no hypophosphatemia group (0 episodes). Similarly, the patients were divided into groups based on the number of episodes of leukopenia (defined as a leukocyte count of $<4000/\mu L$). These groups of patients were defined as the leukopenia group (≥ 1 episode) and no leukopenia group (0 episodes). The relationship between leukopenia and the phosphate concentration was analyzed using the chi-square test. The relationship between leukopenia groups was analyzed using analysis of variance. All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) and R Version 3.6.1. (R Core Team, Vienna, Austria). The reporting of this study conforms to the Equator STROBE guidelines.[14]

Results

Patients in the hypophosphatemia group were significantly less likely to develop leukopenia than patients in the no

hypophosphatemia group ($p = 0.038$) (Table 2). Patients in the no leukopenia group showed a mean monthly increase in the bone marrow S/N of 0.0430/month ($p = 0.013$) (Figure 1). Patients in the leukopenia group showed a mean monthly increase in the bone marrow S/N of 0.0398/month, but this finding was not statistically significant (Figure 2). There was no statistically significant difference between the slopes of these two groups.

Discussion

It has been proposed that the mechanism underlying episodes of hypophosphatemia is Gd activation of the calcium-sensing receptor of the parathyroid gland.[9] Gd is a lanthanide, an ion family sometimes referred to as "super calcium" that can act as a calcium-sensing receptor agonist.[15] Hypothetically, this activation could cause downregulation of the release of parathyroid hormone, resulting in transient hypocalcemia.[9] This hypocalcemia may then trigger a rebound increase in parathyroid hormone secretion, causing bone resorption by osteoclast activation. Under this hypothesis, individuals exposed to high doses of Gd could develop hypophosphatemia and changes in bone signals.

Previous research on patients receiving monthly triple-dose gadopentetate dimeglumine showed that patients who experienced at least one episode of hypophosphatemia developed bone marrow T1 hyperintensity,

Table 2. Relationship between hypophosphatemia and leukopenia.

	No hypophosphatemia	Hypophosphatemia	Total
No leukopenia	17 (33%)	34 (67%)	51
Leukopenia	10 (63%)	6 (37%)	16
Total	27	40	67

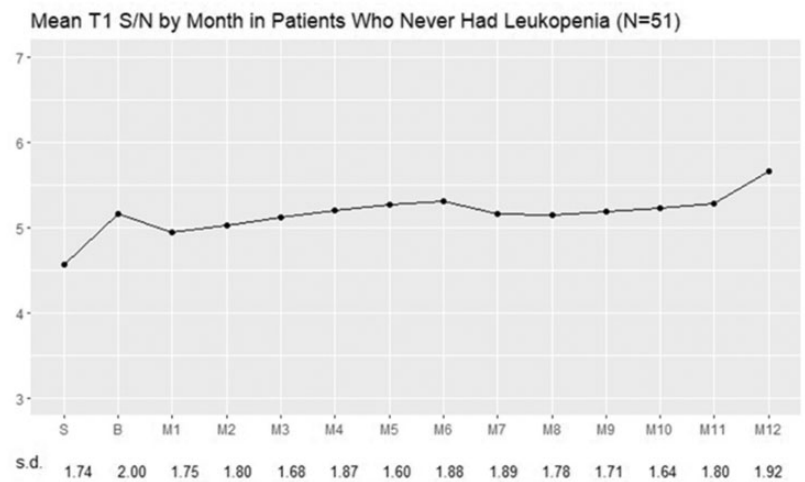

Figure 1. Signal-to-noise ratio by month of triple-dose gadopentetate dimeglumine administration in patients without leukopenia.
S, screening; B, baseline; M, month; s.d., standard deviation.

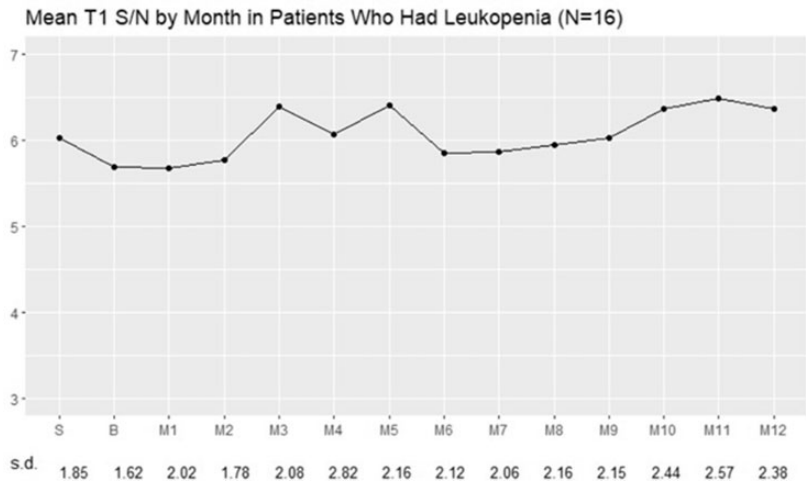

Figure 2. Signal-to-noise ratio by month of triple-dose gadopentetate dimeglumine administration in patients with leukopenia.
S, screening; B, baseline; M, month; s.d., standard deviation.

but at a slower rate than patients who were consistently normophosphatemic.[9] The reason for this is unclear.

An unanswered question is whether Gd deposited in bone can cause both leukopenia and hypophosphatemia. Macrophages (a subtype of white blood cell) and osteoclasts (which resorb bone, releasing free serum phosphorus) reportedly share a common macrophage/osteoclast progenitor cell.[16] Therefore, any marrow cytotoxic effect specific to this common progenitor cell (e.g., Gd released from bony trabeculae) could conceivably result in both leukopenia and hypophosphatemia.

Dissociation of free Gd ions (Gd^{3+}) from chelated complexes allows for transmetalation and deposition within the bone reservoir, which could explain the progressive increase in the MRI signal upon serial administration. Osseous release of Gd ions could conceivably cause selective cytotoxic, antagonistic, or inhibitory effects on leukocyte precursors within the marrow cavity. One study showed that leukocytes can internalize an amount of Gd that is two orders of magnitude higher than that internalized by red blood cells.[17]

If the T1 hyperintensity seen in the medullary cavity of bone represents Gd deposition, it is unclear whether the deposition is in the trabecular bone or the red marrow itself. Bony trabeculae have a paucity of mobile protons and therefore seem to be unable to facilitate Gd-induced proton–electron dipole–dipole relaxation enhancement, central to the T1-shortening effect of Gd. Despite the lack of mobile protons within the trabeculae, water hydration layers along the large surface areas at the "red marrow–trabecular bone interfaces" could allow for the necessary T1 shortening. This is akin to the mechanism that has been theorized as the cause of fluid-attenuated inversion recovery-related cerebrospinal fluid suppression failure in the sulci between closely spaced gyri.[9] Alternatively, the development of T1 hyperintensity may be an indirect rather than direct effect of Gd. A multitude of factors can influence signal intensity on T1-weighted images even when no Gd is

present. Fat was not a contributor in our study because fat suppression was used.

Although serial triple-dose Gd administration has been associated with all three phenomena (T1 shortening of bone marrow, hypophosphatemia, and leukopenia),[9,11] that patients with hypophosphatemia in our study were less likely to have leukopenia (and vice versa) argues against the "single-hit" model of toxicity of the macrophage/osteoclast progenitor cell. It is possible that Gd toxicity may selectively affect either osteoclasts or macrophages, but not both, based on some unknown biologic polymorphism.

In addition, confounding factors may have influenced the measured leukopenia. Patients in the present trial were receiving interferon beta-1b (for which leukopenia is a common adverse effect) or glatiramer acetate (for which leukopenia is an extremely rare adverse effect).[18] Both groups of patients demonstrated higher frequencies of leukopenia than expected ($p = 0.003$ for interferon beta-1b, $p = 0.001$ for glatiramer acetate), suggesting that additional episodes of leukopenia may be attributable to Gd effects.[11]

Because the absence of leukopenia was significantly associated with a progressive increase in the marrow signal ($p = 0.013$) but the presence of leukopenia was not may have occurred because the latter was underpowered by the small sample size, a limitation of this study. The actual slopes of the curves in the two groups were comparable (Figures 1 and 2), but the leukopenia group contained a smaller number of patients (n = 16 vs. n = 50).

One consideration for future analysis is the practical implications of our findings for patient care because the amount and dosage of Gd used in this study well exceed the amount and dosage used in the clinical evaluation of patients with multiple sclerosis. Further research is needed to determine whether progressive increases in T1 bone hyperintensity, leukopenia, and hypophosphatemia may be detected at standard-of-care doses when reviewing large populations or if this is an isolated phenomenon with monthly triple-dose Gd.

Conclusion

Although monthly administration of triple-dose gadopentetate dimeglumine over 13 months has been associated with progressive increases in leukopenia, hypophosphatemia, and the T1 signal intensity of bone, we found a paradoxical inverse relationship between leukopenia and hypophosphatemia. The cause of these phenomena warrants further investigation.

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Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Each author made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; and the drafting or substantial revision of the work. Additionally, each author approved the submitted version and agreed to be personally accountable for their own contributions. Each author has ensured that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and that the resolution is documented in the literature.

Ethics approval and consent to participate

Because the current study was a retrospective analysis of de-identified patients, the IRB office

issued a waiver of IRB approval and patient consent.

Consent for publication

Not applicable.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: LW received salary support from Bayer during the BECOME study and from Guerbet during the present retrospective study. The other authors have no competing interests relevant to this work.

Disclosure

At the time of patient participation in the randomized trial, the use of gadopentetate dimeglumine was approved by the Food and Drug Administration but not at the 0.3 mmol/kg dose utilized.

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