

Safety assessment of gadolinium-based contrast agents (GBCAs) requires consideration of long-term adverse effects in all human tissues

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Publication of Schlemm et al.: Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients Mult Scler 2016, accepted 29 August 2016

Determination of the clinical importance of gadolinium (Gd) deposition must include the entire body. The benefit/risk assessment of only cerebral Gd deposition is not sufficient. The conclusion from the study of Schlemm et al.,¹ 'Dentate nucleus T1 hyperintensity is not associated with gadobutrol', suggests the authors' confidence in administration of the macrocyclic agent gadobutrol. The statement 'since long-term clinical effects of cerebral Gadolinium (Gd) deposition are still unknown, the indication for GBCA administration should be strict' is incomplete, and in reality, far from clinical practice. The focus after administration of GBCAs must be on patients with frequent applications, particularly patients with multiple sclerosis (MS). The detection of disease activity in MS, defined as new/enlarging T2 lesions on brain magnetic resonance imaging (MRI), has been proposed as a biomarker in MS and is also possible in principle without GBCA. The number of GBCA administrations is crucial, since each can result in Gd deposition. Participants in this study received no more than three doses of gadobutrol, but in daily practice, in 1 year alone, a single control MRI study in MS patients means two to three GBCA doses (one for brain, one to two for spinal cord (cervical spine and thoracic spine on 2 days)), and this can occur for many years. It is important to recognize, however, that Gd is not only being retained in the brain. There seem to be three cases of nephrogenic systemic fibrosis (NSF) following the prior unconfounded administration of gadobutrol. Although this number is exceedingly small, the fact remains that since it is a macrocyclic

agent, it is not clear why the incidence is not zero.² In a rat study by Robert et al., although the Gd concentration in the brain after repeat linear GBCA administration was 14 times greater than after repeat macrocyclic GBCA administration, Gd from the macrocyclic was not zero.³ With lower levels of Gd deposition from macrocyclic agents such as gadobutrol, it is unlikely that all side effects will be detected and published by physicians; there are probably a number of undetected cases.

The focus of the radiological community is the assessment of the difference in the signal change between patients repeatedly administered linear and macrocyclic GBCA. A change in the signal intensity of the dentate nucleus was observed in the former, but not in the latter.^{4,5} MRI alone is not a reliable analytical tool for the detection of Gd of unknown composition and environment (free Gd ion or intact Gd chelate form). The observation of long-term, multi-year residual Gd in the organism and lasting deleterious effects must be included in the evaluation of Gd retention.⁶ The presence of Gd in resected femoral head specimens has been described. Newer reports have emerged regarding the accumulation of Gd in various tissues, including brain, bone, skin and possibly also liver or lung, and increasing serum levels of inflammatory cytokines.⁷ Gd deposited in the bone can persist long term. Murata et al. found that bone Gd levels measured as much as 23 times higher than brain Gd levels. Bone might serve as a surrogate to estimate brain deposition if brain Gd were to become a useful clinical or research marker.⁸ It remains possible that bone matrix may rapidly take up a small fraction of intravenously administered GBCA and act as a reservoir, slowly releasing Gd with subsequent uptake in other tissues.^{9,10} Hence, brain deposition of Gd as

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determined by dentate nucleus T1 hyperintensity may be the tip of the iceberg when trying to determine the total amount of Gd a patient has retained.

Children and adolescents with MS are an extremely vulnerable group of patients. The monitoring of therapy using MRI with multiple doses of GBCA can lead to high cumulative Gd concentrations throughout the patient's life. The exposure to high cumulative doses of GBCAs during skeletal ossification and periods of rapid bone growth carries an unknown risk. Brain development begins during foetal life and continues throughout adolescence.¹¹ During this critical period of development ('maturational changes in the human brain'), the brain is particularly vulnerable to toxin exposure.^{11,12} Caution is called for when monitoring MS therapy with GBCAs in young women with MS who may become pregnant. Pregnancy can lead to mobilization of Gd induced by transmetallation from the bone.^{9,10,13} Because Gd penetrates through the placenta, released Gd can cause health issues in the mother and foetus.¹⁴ Gd is released again and again through the kidneys of the foetus into the amniotic fluid, which the foetus regularly swallows during gestation. A retrospective study by Ray et al. found that GBCA-enhanced MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory or infiltrative skin conditions, and for stillbirth or neonatal death.¹³

There are reports of Gd toxicity in patients with normal renal function. Semelka et al. report that Gd in humans can cause health issues, described as a family of disorders.¹⁵ They report typical clinical features as central and peripheral pain, headache and bone pain. Patients with distal leg and arm distribution described skin thickening. Clouded mentation and headache were the symptoms described as persistent beyond 3 months. The term gadolinium deposition disease (GDD) is proposed for a disease process observed in patients with normal renal function who have laboratory evidence of the presence of Gd in their body more than 30 days after their last MRI with a GBCA.^{15,16} While these publications (Semelka et al.) are called into question, still applies 'from symptom to diagnosis' is a foundation of medical diagnostics. Since gadolinium retention is known to occur in patients with normal renal function, it is only logical to think that these patients might also develop toxic effects from retained Gd that are similar, but not identical, to those observed in NSF. Gathings et al. describe Gd-associated plaques as a new, distinct clinical entity.¹⁷ The potential clearly exists for biomolecular interferences with oxidative stress by the

deposition of Gd.¹⁸ Interestingly, one factor of the molecular mechanisms for underlying progression in MS is also chronic oxidative stress, which leads to mitochondrial injury. Remarkably, mitochondria and mitochondrial DNA are highly susceptible to oxidative damage. Prospective studies incorporating measurement of serum and urine Gd³⁺ and clinical symptoms can help correlate the Gd³⁺ body burden with MRI T1-weighted intensity data.

Conflict of interest

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