Japanese Journal of Radiology (2019) 37:458–465
https://doi.org/10.1007/s11604-019-00835-1

ORIGINAL ARTICLE

Changes in tissue gadolinium biodistribution measured in an animal model exposed to four chelating agents

Türker Acar[1,6] · Egemen Kaya[2] · Mustafa Deniz Yoruk[3] · Neslihan Duzenli[4] · Recep Selim Senturk[4] · Cenk Can[4] · Lokman Ozturk[3] · Canberk Tomruk[5] · Yigit Uyanikgil[5] · Frank J. Rybicki[6]

Received: 17 December 2018 / Accepted: 22 March 2019 / Published online: 30 March 2019

Abstract

Purpose This study investigated the potential to reduce gadolinium levels in rodents after repetitive IV Gadodiamide administration using several chelating agents.

Materials and methods The following six groups of rats were studied. Group 1: Control; Group 2: Gadodiamide only; Group 3: Meso-2,3-Dimercaptosuccinic acid (DMSA) + Gadodiamide; Group 4: *N*-Acetyl-L-cysteine (NAC) + Gadodiamide; Group 5: *Coriandrum sativum* extract + Gadodiamide; and Group 6: Deferoxamine + Gadodiamide. Brain, kidney, and blood samples were evaluated via inductively coupled plasma mass spectrometry. The brain was also evaluated histologically.

Results Kidney gadolinium levels in Groups 4 and 5 were approximately double that of Group 2 ($p = 0.033$ for each). There was almost no calcification in rat hippocampus for Group 4 rodents when compared with Groups 2, 3, 5 and 6.

Conclusion Our preliminary study shows that excretion to the kidney has a higher propensity in NAC and *Coriandrum sativum* groups. It may be possible to change the distribution of gadolinium by administrating several agents. NAC may lower Gadodiamide-induced mineralization in rat hippocampus.

Keywords Gadolinium deposition · Dimercaptosuccinic acid · *N*-Acetyl-L-cysteine · *Coriandrum sativum* · Deferoxamine

Introduction

Gadolinium-based contrast agents (GBCA) have been safely used in diagnostic radiology since the 1980s.

However, the safety profile of gadolinium-based agents [1] was questioned after the discovery of nephrogenic systemic fibrosis [2], a scleroderma-like disease characterized by hardening and thickening of the skin and joints of the extremities. Less commonly, visceral organs such as lungs, heart and liver may also be affected in NSF, leading to life-threatening conditions. In 2006, Grobner first noted the linkage between Gadodiamide and NSF in patients with end-stage renal disease, who underwent contrast-enhanced magnetic resonance angiography [3]. After realizing these potential harmful side effects, the United States Food and Drug Administration (FDA) released a warning in May 2007 [4] that highlighted the risk for NSF among patients with acute kidney injury or patients with acute/chronic kidney disease with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.

The 2014 report [5] that GBCAs accumulate in the brain (particularly in the cerebellar dentate nucleus and globus pallidus), despite normal renal function, again dramatically changed the attitude towards GBCA administration among radiologists. While no symptom or clinical scenario attributed to central nervous system (CNS) retention has

✉ Türker Acar
drtacar@hotmail.com

1 Department of Radiology, University of Health Sciences Bozyaka Education and Training Hospital, Saim Cikrici cd. No: 59 S.B.U. Bozyaka Egitim ve Arastirma Hastanesi Karabaglar, Izmir, Turkey

2 Department of Physiology, Ege University School of Medicine, Izmir, Turkey

3 Department of Anatomy, Ege University School of Medicine, Izmir, Turkey

4 Department of Pharmacology, Ege University School of Medicine, Izmir, Turkey

5 Department of Histology, Ege University School of Medicine, Izmir, Turkey

6 Department of Radiology, University of Ottawa Faculty of Medicine and The Ottawa Hospital Research Institute, 451 Smyth Road, Ottawa, ON, Canada

been identified to date, the European Medicines Agency's (EMA's) Pharmacovigilance and Risk Assessment Committee (PRAC) has recommended the suspension of marketing authorizations for the four linear GBCAs including Gadodiamide, Gadobenic acid, Gadopentetic acid and Gadoversetamide in March 2017 [6]; this was followed by the FDA issuing a new class warning for clinical application of GBCAs in December 2017 [7].

GBCAs are classified as ionic and non-ionic. Since free gadolinium is a toxic heavy metal, it must be tightly bound to a ligand to be safely used as a contrast agent. GBCAs can further be subdivided into two forms; the linear and the macrocyclic types. In the linear-type GBCA, cage-carrying Gd^{3+} is not totally closed giving it a supple structure, whereas in the macrocyclic Gd^{3+} is located in the central rigid core of the cage. The aforementioned structural differences, as well as chemical properties, determines the stability of GBCA. An in vitro study demonstrates that linear non-ionic GBCAs are more labile and release more Gd^{3+} when compared to macrocyclic ionic counterparts in human serum [8].

Several studies reveal that less stable linear GBCAs have greater propensity for retention in brain when compared to stable macrocyclic GBCAs [9–14]. Although there is no validated clinical manifestation of CNS retention of GBCA identified to date, negative sentiments regarding retained gadolinium have called the safety of gadolinium-enhanced MRI into question. To our knowledge, there are no proven methods to reduce gadolinium levels after GBCA administration. Since Gd^{3+} is a heavy metal in the lanthanide group of the periodic table, we hypothesized that agents already validated in the treatment of humans with heavy metal exposure could also be effective in an animal model, specifically for GBCA administered to rats. The purpose of this preclinical study is to test the hypothesis that different chelating agents or herbs could reduce brain gadolinium levels in rats, measured with Inductively Coupled Plasma–Mass Spectrometry (ICP–MS). We also investigated the histopathological alterations caused by these agents on different tissues with respect to gadolinium deposition in rat CNS.

Materials and methods

Features of the agents used in the preclinical study

The properties of the agents used in the current experimental study were as follows; (1) *Meso*-2,3-Dimercaptosuccinic acid (DMSA), a non-toxic agent with several metal-reducing properties, is a thiol group containing drug which can be administrated orally [15–17]. (2) cysteine (NAC) is a thiol-possessing antioxidant which can stimulate glutathione (GSH) synthesis. Several studies indicate that NAC has chelating activity against some heavy metals such as boron, chromium and it is also effective in lead-exposed rats [18, 19]. (3) *Coriandrum sativum* (*C. sativum*) common name: [Chinese parsley or Coriander] is a herb that belongs to Apiaceae (Umbelliferae) family. It was used as a protective-chelating agent on lead exposed mice [20] and on rats [21]. (4) Deferoxamine (Dfx) was used to chelate the excessive metals in their trivalent state [22]. Iron deposition in the brain is a consequence of aging process [23] and gadolinium in its trivalent state shows similarities to that of iron. In a case report, Dfx was used as a chelating agent in a patient diagnosed with NSF and increased urinary excretion of gadolinium [24]. We, therefore, hypothesized that Dfx may be used to mitigate gadolinium retention in brain.

Study design and animals

Following approval by the Animal Experiment Ethics Committee of our institution (ID: 2017-007), 36 healthy male Wistar albino rats (12–13 week old; 250–300 g) were housed three rats per cage, with water and food ad libitum under a 12:12 light–dark cycle. After completing a 1 week adaptation period, rats were randomly divided into six groups ($n = 6$ per group). All study groups excluding controls (Group 2, 3, 4, 5 and 6) were administrated intravenous (IV) Gadodiamide (Omniscan, GE Healthcare, Marlborough, MA, USA) from lateral tail vein with a high-dose protocol (2.5 mmol gadolinium per kilogram) as previously performed by McDonald et al. [14] twice a week. A total dosage of 15 mmol Gadodiamide was injected in each rat in Groups 2, 3, 4, 5 and 6. This supratherapeutic GBCA dosing was intentionally selected to maximize the possibility to detect gadolinium in the brains and kidneys. DMSA, NAC, and C. sativum liquid extract were given via oral gavage 15 times (one oral gavage per day for 5 days and 2 days with no gavages, repeated three times). Dfx was given twice a week in the first, three times per week in the second and five times per week in the third week of the study and a total of 10 Dfx injections were administrated to each rat in Group 6. Groups and specific dosages were indicated as follows.

Group 1 Control ($n = 6$) This group received IV saline volumetrically equivalent to that of 2.5 mmol gadolinium per kilogram.

Group 2 GBCA ($n = 6$) This group only received IV Gadodiamide without specific agent or herb.

Group 3 DMSA ($n = 6$) Administrated 100 mg/kg per day DMSA (Santa Cruz Biotechnology, Texas, USA; CAS 304-55-2) via oral gavage beginning with the first Gadodiamide injection. The dosage was determined according a study published by Saxena et al. [25] in which DMSA was used for the mobilization of lead and recovery of tissue oxidative injury in rats.

Group 4 NAC ($n = 6$) Treated with 150 mg/kg per day NAC (Santa Cruz Biotechnology, Texas, USA; CAS

616-91-1) via oral gavage stating with the first Gadodiamide injection. The dosage was selected from rat studies where NAC was used as an oxidative stress modulator in traumatic brain injury-induced rats [26] and as an alleviator in diazinon exposure-induced oxidative stressed rats [27].

Group 5 C. sativum (n = 6) This group was given 200 mg/kg per day whole-leaf *C. sativum* liquid extract (Cilantro, Herb Pharm, Oregon, USA) by means of oral gavage with the first Gadodiamide. The dosage was defined according an article published by Sreelatha et al. [28] where protective effects of *C. sativum* extracts on carbon tetrachloride-induced hepatotoxicity in rats were described.

Group 6 Dfx (n = 6) Administrated intraperitoneal (IP) deferoxamine mesylate (Desferal®, Novartis Pharmaceuticals Corp, East Hanover, NJ) 100 mg/kg per day. The rodent dosage was selected according to an animal study conducted by Lijun et al. [29] where Dfx was postulated to attenuate iron-induced long-term neurotoxicity in rats with traumatic brain injury.

Gadodiamide injections were administrated into the lateral tail vein via percutaneous access under a physical rodent restrainer (Plas-Labs, MI, USA) with 25G winged infusion set (Braun, Venofix®, Hessen, Germany) without application of anesthetic drug. Following IV GBCA injections, oral gavages and IP Dfx treatments, all groups were euthanized 7 days after the last IV dose of saline or GBCA. Killing procedure was performed under high-dose ketamine hydrochloride (Ketalar, Eczacibasi Parke-Davis, Istanbul, Turkey) and xylazine HCI (Alfazyne, Alfasan International Woerden, the Netherlands) anesthesia. The anesthetized animals were placed on a rack and fixed with pins. Lateral incision through the abdominal wall was made subsequently. At the bottom of the diaphragm, to access to rib cage, an incision was made using scissors. The lungs were displaced and on each side a cut toward the head across ribs was made. The heart was exposed and a perfusion needle was inserted into the left ventricle. At the same time blood samples were collected from each rat into dry anticoagulant tubes. An incision to the right atrium was made to supply fluid drainage. Blood was cleared from body by steady flow of phosphate-buffered saline. Four percent paraformaldehyde in 0.1 M phosphate buffer (RT, 200–250 ml) was used for fixing rat tissues. Following perfusion, rats were decapitated. Brains and both kidneys were dissected. Total body weights immediately before euthanasia, post-mortem fresh brain and right kidney weights were recorded. The fixed brains were isolated and bisected along the sagittal midline. Right hemispheres of cerebrum/cerebellum, right kidneys and blood samples were sent to ICP-MS to quantify elemental gadolinium levels whereas, left hemispheres were sent to histologic evaluation.

ICP–MS analysis

Before the procedure, 0.5 g of brain, blood, and kidney tissues was weighed out from each rats. Acquired samples were acidified with 65% HNO_3. According to the first step of the microwave digester temperature program, the temperature was raised to 120 °C in 10 min and held constant at 120 °C for 5 min. In the second step, the temperature was increased from 120 to 200 °C in 10 min and stabilized at 200 °C for 5 min. Complete digestion was achieved at 200 °C after 35 min. At the end of the digestion procedure, the samples were transferred to a 100 ml cylindrical graduates and a total volume of 30 ml was completed with ultrapure water for each sample. Quantitative gadolinium measurements examined with ICP-MS unit (Agilent 7500, Agilent Technologies, CA, USA) and gadolinium levels were expressed in nanogram per gram of tissue.

Histopathological analysis

After serial dehydration of dissected left cerebral and cerebellar hemispheres in 80–100% ethanol, the tissues were embedded in paraffin and sliced in coronal plane for cerebrum and sagittal plane for cerebellum, respectively, with a slice thickness of 5 µ. Tissue sections were stained with hematoxylin and eosin (H&E), subsequently. All sections were photographed with digital camera (DP72; Olympus, Tokyo, Japan) mounted on light microscope (BX51; Olympus) and evaluated via dedicated software (cellSens; Olympus). An experienced histologist who was blinded to study groups analyzed tissue samples.

Statistical analysis

The total body, whole brain, right kidney weights and quantitative gadolinium levels from blood, right hemisphere and right kidney of all groups were expressed as mean and range (minimum and maximum) values. A Kruskal–Wallis test was utilized to determine statistical difference in total rat, brain and right kidney weights among groups.

Binary comparisons of gadolinium levels between Group 2 and the treatment Groups 3, 4, 5 and 6 were examined with Mann–Whitney *U* test. The level of the significance was taken as $p < 0.05$. Statistical analyses were performed using statistical software (Statistical Package for Social Sciences, Version 18.0, SPSS Inc., Chicago, Illinois, USA).

Table 1 Mean, and range values (minimum–maximum) of whole body, brain and right kidney weights in grams for each of the six groups

	Whole body		Brain		Right kidney	
	Mean	(Min–Max)	Mean	(Min–Max)	Mean	(Min–Max)
Group 1 ($n=6$)	340	(300–390)	2.2	(2.0–2.3)	2.0	(1.8–2.4)
Group 2 ($n=6$)	350	(350–360)	2.2	(2.0–2.4)	2.1	(1.7–2.5)
Group 3 ($n=5$)	340	(300–370)	2.3	(2.1–2.5)	2.3	(2.1–2.4)
Group 4 ($n=4$)	340	(300–400)	2.1	(1.9–2.4)	2.1	(1.7–2.3)
Group 5 ($n=4$)	320	(300–340)	2.3	(2.1–2.5)	2.0	(1.4–2.6)
Group 6 ($n=6$)	330	(320–360)	2.2	(2.0–2.6)	2.4	(2.1–2.6)

Table 2 Median, range values (minimum–maximum) of gadolinium levels measured in the right hemisphere, blood, and right kidney for each of the six groups

	Brain (ng/g)		Kidney (ng/g)		Blood (ng/g)	
	Mean	(Min–Max)	Mean	(Min–Max)	Mean	(Min–Max)
Group 1 ($n=6$)	Trace	Trace	Trace	Trace	Trace	Trace
Group 2 ($n=6$)	450	(340–630)	1.2×10^5	(0.9×10^5–1.5×10^5)	480	(430–560)
Group 3 ($n=5$)	430	(340–540)	1.1×10^5	(0.9×10^5–1.3×10^5)	500	(430–640)
Group 4 ($n=4$)	400	(350–460)	2.6×10^5	(1.4×10^5–3.9×10^5)	570	(400–660)
Group 5 ($n=4$)	540	(460–650)	2.6×10^5	(1.4×10^5–5.1×10^5)	630	(450–860)
Group 6 ($n=6$)	540	(460–700)	1.2×10^5	(0.9×10^5–1.7×10^5)	460	(410–510)

Results

Animals

One rat in Group 3 was excluded due to soft tissue infection and subsequent abscess in the second week of the experiment. Two rats from Group 4 and Group 5 were also removed from the study after developing aspiration symptoms during the second week of oral gavage. Thus, 31 rats were included in the statistical evaluation. There was no significant difference between whole body mass (p = 0.218), whole brain mass ($p=0.742$), and right kidney mass (p = 0.262) for any of the six groups (Table 1).

Determination of brain, blood and kidney gadolinium levels with ICP–MS

Trace levels of brain, kidney, and blood gadolinium levels were detected in Group 1 (no Gadodiamide administration), most likely due to earth metal groundwater contamination [14, 30, 31]. All other groups (Table 2) had significantly higher levels of gadolinium in the brain, kidney, and blood when compared to Group 1.

Regarding brain gadolinium levels, there was no significant difference for Groups 3, 4, 5, or 6 when compared to Group 2 (Table 2, Fig. 1). The lowest level of gadolinium in brain tissue was noted in Group 4; however, it was statistically insignificant ($p=0.831$) when compared with Group 2. Regarding kidney gadolinium levels, both Group 4 and Group 5 (Table 2, Fig. 2) had higher values when compared with Group 2 ($p=0.033$ for each group). Regarding blood gadolinium levels, there was no difference in values when Groups 3, 4, 5, and 6 were compared with Group 2 (Table 2, Fig. 3).

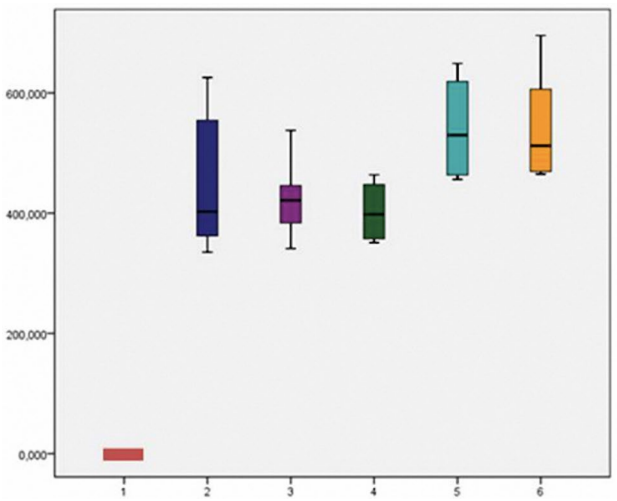

Fig. 1 Graphic demonstrates Gadolinium levels of brain in whole study group. Group 1: Control. Group 2: IV Gadodiamide 2.5 mmol/kg. Group 3: IV Gadodiamide 2.5 mmol/kg + oral Dimercaptosuccinic acid 100 mg/kg. Group 4: IV Gadodiamide 2.5 mmol/kg + oral NAC 150 mg/kg. Group 5: IV Gadodiamide 2.5 mmol/kg + oral Coriandrum sativum 200 mg/kg. Group 6: IV Gadodiamide 2.5 mmol/kg + IP Deferoxamine 100 mg/kg

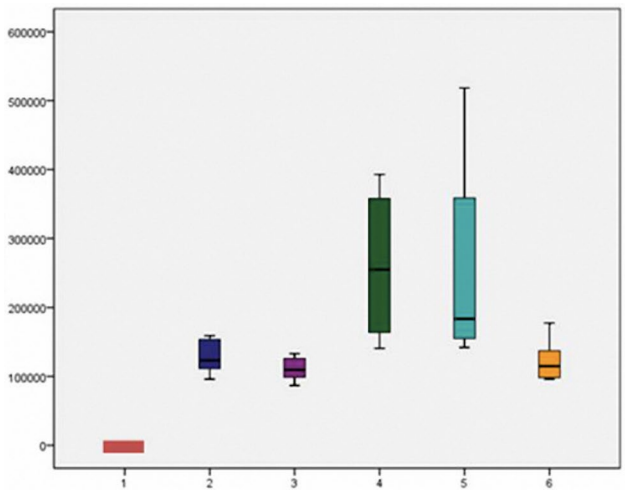

Fig. 2 Kidney Gadolinium levels of whole study group. Group 1: Control. Group 2: IV Gadodiamide 2.5 mmol/kg. Group 3: IV Gadodiamide 2.5 mmol/kg + oral Dimercaptosuccinic acid 100 mg/kg. Group 4: IV Gadodiamide 2.5 mmol/kg + oral NAC 150 mg/kg. Group 5: IV Gadodiamide 2.5 mmol/kg + oral Coriandrum sativum 200 mg/kg. Group 6: IV Gadodiamide 2.5 mmol/kg + IP Deferoxamine 100 mg/kg

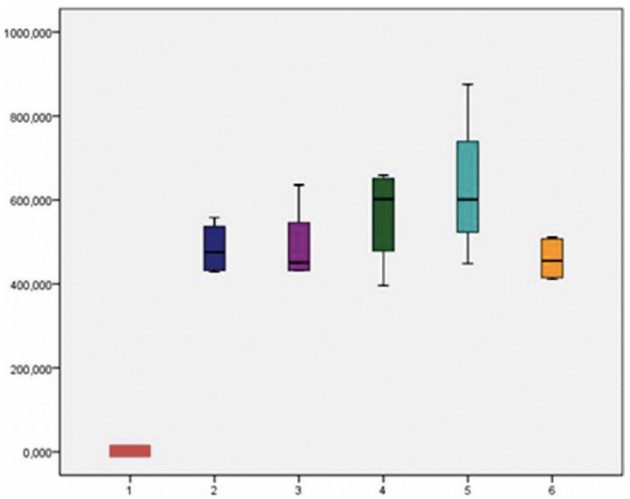

Fig. 3 Blood gadolinium levels of study groups. Group 1: Control. Group 2: IV Gadodiamide 2.5 mmol/kg. Group 3: IV Gadodiamide 2.5 mmol/kg + oral Dimercaptosuccinic acid 100 mg/kg. Group 4: IV Gadodiamide 2.5 mmol/kg + oral NAC 150 mg/kg. Group 5: IV Gadodiamide 2.5 mmol/kg + oral Coriandrum sativum 200 mg/kg. Group 6: IV Gadodiamide 2.5 mmol/kg + IP Deferoxamine 100 mg/kg

Histopathologic evaluation of left hemisphere of cerebral/cerebellar tissue

There was no visual histologic difference in cerebellar folia as well as deep nucleus in rodents exposed either Gadodiamide or chelating agents. Findings were more pronounced in hippocampal tissue sections obtained from the cerebrum. For Group 1 animals, the lamina zonalis (LZ), lamina pyramidalis (LP) and lamina multiformis (LM) layers of the hippocampus had normal histology. However, variable degree of vasogenic/perivascular edema adjacent to vessels of LZ and LM, vasodilatation and calcified bodies were observed in Groups 2, 3, 4, 5 and 6. Detailed analysis revealed some degree of edema in Group 4; however, there was almost no calcification (Fig. 4).

Discussion

The most important distinction of this study when compared to similar preclinical work is our attempt to test the hypothesis that known agents can be effective in the reduction of gadolinium tissue retention. Almost all peer-review reports to date have focused on gadolinium tissue retention and have proven some degree of gadolinium accumulation after divergent types of GBCA administration. The main results of this paper are (1) kidney accumulation of gadolinium may be modified with NAC and C. sativum extract, and (2) there is reduced mineralization in hippocampal histology sections of rats that received concomitant administration of NAC. Use of these agents to modify the effect of gadolinium distribution in animal models warrants further study.

Although not statistically significant, the lowest brain gadolinium levels were found among Group 4 (NAC plus Gadodiamide) animals. Two caveats may explain how a significant difference in brain gadolinium levels could be achieved in a follow-up study. First, our animal protocol delivered 2.5 mmol GBCA/kg, compared to 0.6 mmol GBCA per kilogram used by other preclinical studies [32–34]. Our rationale for the supra-physiological Gadolinium dose was an attempt to maximize the probability of detect gadolinium deposition (14) with only six lateral tail interventions. More injections would have increased animal stress, particularly given the concomitant oral or IP treatments to the animals in Groups 3, 4, 5 and 6. Second, a higher dose of NAC may have, in theory, resulted in lower brain gadolinium levels.

Rats in Group 4 and Group 5 demonstrated a significant increase in kidney gadolinium levels when compared to Group 2. These two agents are commercially available as nutritional supplements, and both have to our knowledge, a high safety profile. Further evaluation to test related hypotheses regarding urine gadolinium and renal excretion after supplemental NAC and C. sativum are warranted.

Brain, kidney, and blood gadolinium levels in Group 3 and in Group 6 animals did not differ from those of Group 2. DMSA (Group 3), a non-toxic agent that can reduce the body burden of several toxic metals [16], did not alter gadolinium levels, nor did Dfx (Group 6), the agent primarily

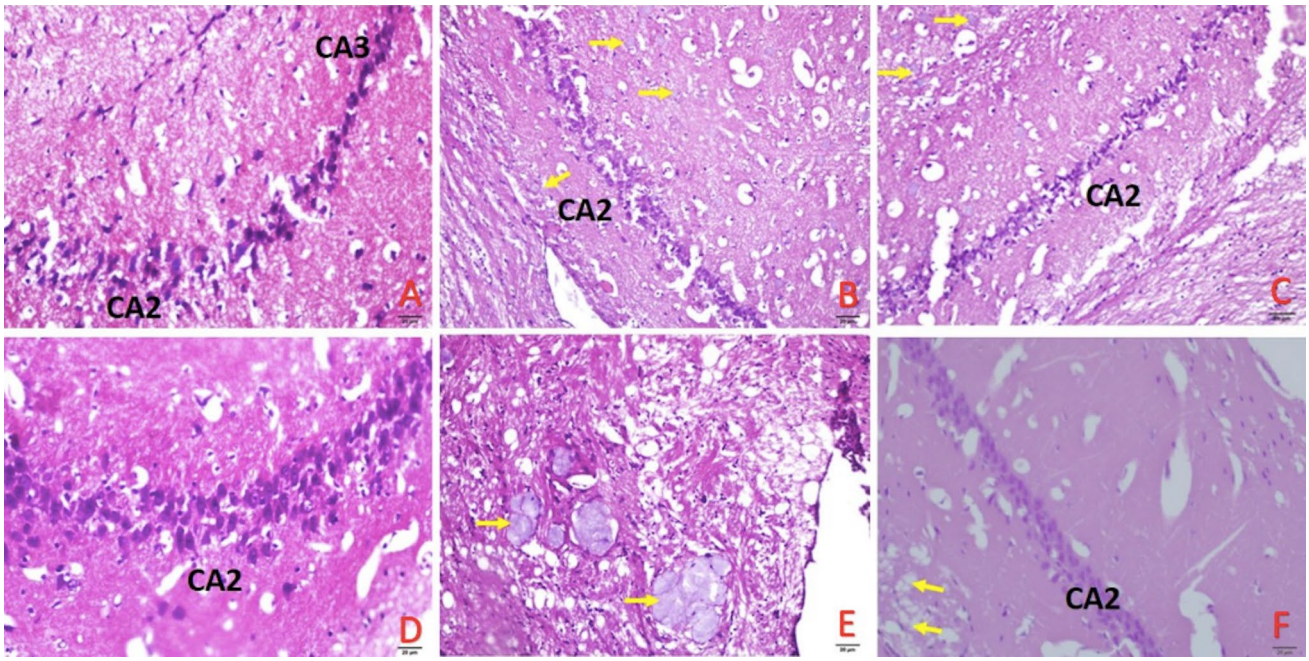

Fig. 4 Histologic depiction from hippocampus CA2 level of different rodent groups at 40× magnification. **a** Normal pyramidal neurons of hippocampus in seen in Group 1. **b** Group 2 shows mild vasodilatation, edema in the vessels adjacent to LZ and LM and calcified bodies. **c** Group 3 demonstrates minimal edema and vasodilation compared to that of Group 2 with comparable degree of calcification. **d** Group 4 reveals comparable edema with regard to Group 2 and 3 with almost no calcification. **e** Group 5 shows moderate to severe vasodilatation/edema with large islets of calcifications close to third ventricle. **f** Group 6 demonstrates edema/vasodilatation and smaller calcified bodies. (*CA2* Regio II Cornus ammonis, *CA3* Regio III Cornus ammonis, *LZ* Lamina zonalis, *LM* Lamina multiformis). Group 1: Control. Group 2: IV Gadodiamide 2.5 mmol/kg. Group 3: IV Gadodiamide 2.5 mmol/kg + oral Dimercaptosuccinic acid 100 mg/kg. Group 4: IV Gadodiamide 2.5 mmol/kg + oral NAC 150 mg/kg. Group 5: IV Gadodiamide 2.5 mmol/kg + oral Coriandrum sativum 200 mg/kg. Group 6: IV Gadodiamide 2.5 mmol/kg + IP Deferoxamine 100 mg/kg

used to decrease iron levels among chronic blood transfusion patients [35]. One case report demonstrated an increase in dose-dependent urine gadolinium excretion in a NSF patient treated with Dfx [24]. However, as in our study, there was no proportional decrease in serum gadolinium levels.

A histology study [36] demonstrated vascular mineralization after administration of Gadodiamide in naïve rats, using a NSF model. This work showed blood vessel mineralization in the great vessels of the heart, mesenteric vessels, renal vein, and intrapulmonary blood vessels. The mechanism of calcification is still unknown. However, the hypotheses include elevation of Ca/Phosphate or activity of transforming growth factor-β1 (TGF-β1) [36, 37]. Our light microscopic examination of the hippocampus showed varying degree of edema and calcifications adjacent to vessels in Groups 2, 3, 5, and 6. Almost no calcification was detected in hippocampus of Group 4. Given the high dose, short temporal protocol of Gadodiamide administration, we speculate that the calcifications may be induced by Gadodiamide.

We report three limitations. First, we had to exclude five rats either due to aspiration or soft tissue infection during the experiment. We were unable to substitute these rodents since they became symptomatic after completing two-thirds of Gadodiamide and/or oral gavage applications. Future studies with larger number of rodents may provide better interpretation about the potential chelator-redistributor effect of the NAC and C. sativum extract in gadolinium retention. Second, we did not assess potential variability in gadolinium retention induced by agents administered at different doses; only a single dose of each agent was given. Third, we did not quantitatively measure gadolinium levels within the hippocampus separately. Therefore, our findings regarding calcium deposits remains preliminary.

In conclusion, the administration of NAC and *C. sativum* significantly increased kidney gadolinium levels in our animal model. Simultaneous application of NAC with Gadodiamide lowered mineralization of rat hippocampus as determined by histology.

Acknowledgements This study is dedicated to pharmacist Ozler Kiris who provided inspiration for this preclinical study passed away unexpectedly during preparation phase of this work. Additionally, our special appreciation extends to Elif Tetik Acar who continuously assisted us during manipulation of lateral tail vein of rodents.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement Animal Experiment Ethics Committee of Ege University (ID: 2017-007).

References

1. Ersoy H, Rybicki FJ. Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. J Magn Reson Imaging [Internet]. 2007;26(5):1190–7. https://doi.wiley.com/10.1002/jmri.21135. Accessed 6 Mar 2019
2. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet (London, England) [Internet]. 2000;356(9234):1000–1. https://linkinghub.elsevier.com/retrieve/pii/S0140673600026945. Accessed 4 Apr 2018
3. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transpl [Internet]. 2006;21(4):1104–8. https://academic.oup.com/ndt/article/21/4/1104/1932577/Gadolinium-a-specific-trigger-for-the-development. Accessed 4 Apr 2018
4. Cite https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022066s007,020123s043lbl.pdf with a Browser Plugin—Mendeley Web Importer [Internet]. https://www.mendeley.com/reference-management/web-importer/#id_3. Accessed 4 Apr 2018
5. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology [Internet]. 2014;270(3):834–41. https://pubs.rsna.org/doi/10.1148/radiol.13131669. Accessed 4 Apr 2018
6. Medicines Agency E. PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations. 2017. https://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/03/WC500223209.pdf. Accessed 5 Apr 2018
7. Commissioner O of the. Safety Alerts for Human Medical Products-Gadolinium-based Contrast Agents (GBCAs): drug safety communication—retained in body; new class warnings. https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm589580.htm. Accessed 5 Apr 2018
8. Frenzel T, Lengsfeld P, Schirmer H, Hütter J, Weinmann H-J. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 °C. Invest Radiol [Internet]. 2008. 43(12):817–2. https://www.ncbi.nlm.nih.gov/pubmed/19002053. Accessed 4 Apr 2018
9. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology [Internet]. 2015;276(1):228–32. https://pubs.rsna.org/doi/10.1148/radiol.2015142690. Accessed 4 Apr 2018
10. Radbruch A, Weberling LD, Kieslich PJ, Hepp J, Kickingereder P, Wick W, et al. High-signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images. Invest Radiol [Internet]. 2015;50(12):805–10. https://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004424-201512000-00001. Accessed 4 Apr 2018
11. Cao Y, Huang DQ, Shih G, Prince MR. Signal change in the dentate nucleus on T1-weighted mr images after multiple administrations of gadopentetate dimeglumine versus gadobutrol. AJR Am J Roentgenol [Internet]. 2016;206(2):414–9. https://www.ajronline.org/doi/10.2214/AJR.15.15327. Accessed 5 Apr 2018
12. Radbruch A, Weberling LD, Kieslich PJ, Eidel O, Burth S, Kickingereder P, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology [Internet]. 2015;275(3):783–91. https://pubs.rsna.org/doi/10.1148/radiol.2015150337. Accessed 5 Apr 2018
13. Radbruch A. Are some agents less likely to deposit gadolinium in the brain? Magn Reson Imaging [Internet]. 2016;34(10):1351–4. https://linkinghub.elsevier.com/retrieve/pii/S0730725X16301412. Accessed 5 Apr 2018
14. McDonald RJ, McDonald JS, Dai D, Schroeder D, Jentoft ME, Murray DL, et al. Comparison of gadolinium concentrations within multiple rat organs after intravenous administration of linear versus macrocyclic gadolinium chelates. Radiology [Internet]. 2017;285(2):536–45. https://pubs.rsna.org/doi/10.1148/radiol.2017161594. Accessed 5 Apr 2018
15. Aposhian H V, Aposhian MM. meso-2,3-Dimercaptosuccinic acid: chemical, pharmacological and toxicological properties of an orally effective metal chelating agent. Annu Rev Pharmacol Toxicol [Internet]. 1990;30(1):279–306. https://www.annualreviews.org/doi/10.1146/annurev.pa.30.040190.001431. Accessed 5 Apr 2018
16. Jones MM. New developments in therapeutic chelating agents as antidotes for metal poisoning. Crit Rev Toxicol [Internet]. 1991;21(3):209–33. https://www.ncbi.nlm.nih.gov/pubmed/2039595. Accessed 5 Apr 2018
17. Saxena G, Pathak U, Flora SJS. Beneficial role of monoesters of meso-2,3-dimercaptosuccinic acid in the mobilization of lead and recovery of tissue oxidative injury in rats. Toxicology [Internet]. 2005;214(1–2):39–56. https://linkinghub.elsevier.com/retrieve/pii/S0300483X05002714. Accessed 5 Apr 2018
18. Gürer H, Ozgünes H, Neal R, Spitz DR, Erçal N. Antioxidant effects of *N*-acetylcysteine and succimer in red blood cells from lead-exposed rats. Toxicology [Internet]. 1998;128(3):181–9. https://www.ncbi.nlm.nih.gov/pubmed/9750041. Accessed 5 Apr 2018
19. Guo M-Y, Wang H, Chen Y-H, Xia M-Z, Zhang C, Xu D-X. N-acetylcysteine alleviates cadmium-induced placental endoplasmic reticulum stress and fetal growth restriction in mice. PLoS One [Internet]. 2018;13(1):e0191667. https://www.ncbi.nlm.nih.gov/pubmed/29373603. Accessed 5 Apr 2018
20. Aga M, Iwaki K, Ueda Y, Ushio S, Masaki N, Fukuda S, et al. Preventive effect of *Coriandrum sativum* (Chinese parsley) on localized lead deposition in ICR mice. J Ethnopharmacol [Internet]. 2001;77(2–3):203–8. https://www.ncbi.nlm.nih.gov/pubmed/11535365. Accessed 5 Apr 2018
21. Velaga MK, Yallapragada PR, Williams D, Rajanna S, Bettaiya R. Hydroalcoholic seed extract of *Coriandrum sativum* (Coriander) alleviates lead-induced oxidative stress in different regions of rat brain. Biol Trace Elem Res [Internet]. 2014;159(1–3):351–63. https://link.springer.com/10.1007/s12011-014-9989-4. Accessed 5 Apr 2018
22. Verpooten GA, D'Haese PC, Boelaert JR, Becaus I, Lamberts L V, De Broe ME. Pharmacokinetics of aluminoxamine and ferrioxamine and dose finding of desferrioxamine in haemodialysis patients. Nephrol Dial Transpl [Internet]. 1992;7(9):931–8. https://www.ncbi.nlm.nih.gov/pubmed/1328941. Accessed 5 Apr 2018
23. Aquino D, Bizzi A, Grisoli M, Garavaglia B, Bruzzone MG, Nardocci N, et al. Age-related iron deposition in the basal ganglia: quantitative analysis in healthy subjects. Radiology [Internet].

2009;252(1):165–72. https://pubs.rsna.org/doi/10.1148/radiol.2522081399. Accessed 5 Apr 2018
24. Leung N, Pittelkow MR, Lee CU, Good JA, Hanley MM, Moyer TP. Chelation of gadolinium with deferoxamine in a patient with nephrogenic systemic fibrosis. NDT Plus [Internet]. 2009;2(4):309–11. https://academic.oup.com/ckj/article-lookup/doi/10.1093/ndtplus/sfp042. Accessed 5 Apr 2018
25. Saxena G, Pathak U, Flora SJS. Beneficial role of monoesters of meso-2,3-dimercaptosuccinic acid in the mobilization of lead and recovery of tissue oxidative injury in rats. Toxicology [Internet]. 2005;214(1–2):39–56. https://linkinghub.elsevier.com/retrieve/pii/S0300483X05002714. Accessed 7 Apr 2018
26. Senol N, Nazıroğlu M, Yürüker V. N-acetylcysteine and selenium modulate oxidative stress, antioxidant vitamin and cytokine values in traumatic brain injury-induced rats. Neurochem Res [Internet]. 2014;39(4):685–92. https://link.springer.com/10.1007/s11064-014-1255-9. Accessed 7 Apr 2018
27. Oksay T, Nazıroğlu M, Ergün O, Doğan S, Özatik O, Armağan A, et al. *N*-Acetyl cysteine attenuates diazinon exposure-induced oxidative stress in rat testis. Andrologia [Internet]. 2013;45(3):171–7. https://doi.wiley.com/10.1111/j.1439-0272.2012.01329.x. Accessed 7 Apr 2018
28. Sreelatha S, Padma PR, Umadevi M. Protective effects of *Coriandrum sativum* extracts on carbon tetrachloride-induced hepatotoxicity in rats. Food Chem Toxicol [Internet]. 2009;47(4):702–8. https://linkinghub.elsevier.com/retrieve/pii/S0278691508007242. Accessed 7 Apr 2018
29. Zhang L, Hu R, Li M, Li F, Meng H, Zhu G, et al. Deferoxamine attenuates iron-induced long-term neurotoxicity in rats with traumatic brain injury. Neurol Sci [Internet]. 2013;34(5):639–45. https://link.springer.com/10.1007/s10072-012-1090-1. Accessed 10 Apr 2018
30. Birka M, Wehe CA, Hachmöller O, Sperling M, Karst U. Tracing gadolinium-based contrast agents from surface water to drinking water by means of speciation analysis. J Chromatogr A [Internet]. 2016;1440:105–11. https://linkinghub.elsevier.com/retrieve/pii/S0021967316301662. Accessed 17 Apr 2018
31. Telgmann L, Sperling M, Karst U. Determination of gadolinium-based MRI contrast agents in biological and environmental samples: a review. Anal Chim Acta [Internet]. 2013;764:1–16. https://linkinghub.elsevier.com/retrieve/pii/S0003267012017722. Accessed 17 Apr 2018
32. Smith APL, Marino M, Roberts J, Crowder JM, Castle J, Lowery L, et al. Clearance of gadolinium from the brain with no pathologic effect after repeated administration of gadodiamide in healthy rats: an analytical and histologic study. Radiology [Internet]. 2017;282(3):743–51. https://pubs.rsna.org/doi/10.1148/radiol.2016160905. Accessed 17 Apr 2018
33. Robert P, Violas X, Grand S, Lehericy S, Idée J-M, Ballet S, et al. Linear gadolinium-based contrast agents are associated with brain gadolinium retention in healthy rats. Invest Radiol [Internet]. 2016;51(2):73–82. https://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004424-201602000-00001. Accessed 17 Apr 2018
34. Robert P, Lehericy S, Grand S, Violas X, Fretellier N, Idée J-M, et al. T1-weighted hypersignal in the deep cerebellar nuclei after repeated administrations of gadolinium-based contrast agents in healthy rats. Invest Radiol [Internet]. 2015;50(8):473–80. https://www.ncbi.nlm.nih.gov/pubmed/26107651. Accessed 17 Apr 2018
35. Kontoghiorghe CN, Kontoghiorghes GJ. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. Drug Des Devel Ther [Internet]. 2016;10:465–81. https://www.ncbi.nlm.nih.gov/pubmed/26893541. Accessed 19 Apr 2018
36. Grant D, Johnsen H, Juelsrud A, Løvhaug D. Effects of gadolinium contrast agents in naïve and nephrectomized rats: relevance to nephrogenic systemic fibrosis. Acta Radiol [Internet]. 2009;50(2):156–69. https://journals.sagepub.com/doi/10.1080/02841850802637808. Accessed 11 Jan 2019
37. Thakral C, Abraham JL. Nephrogenic systemic fibrosis: histology and gadolinium detection. Radiol Clin North Am [Internet]. 2009;47(5):841–53. https://www.ncbi.nlm.nih.gov/pubmed/19744599. Accessed 12 Jan 2019