Acute phase reaction to gadolinium-DTPA in dialysis patients

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Abstract

Background. Several late sequelae of the administration of gadolinium (Gd)-containing MRI contrast agents have been described in patients with advanced renal failure. In an observational series, we found a remarkable frequency of peracute reactions after administration of Gd-DTPA used for cardiovascular evaluation before renal transplantation.

Methods. In a 26-month observational period, 13 of 136 haemodialyzed or CAPD patients exhibited onset of fever, chills and nausea within hours after administration of Gd-DTPA peracute. A minority showed persistent cessation of residual diuresis. We performed blood cultures in most patients and evaluated white blood cell (WBC) counts, eosinophils, CRP, heart rate and blood pressure.

Results. Within an average of 12 h (range 12–36 h) after Gd administration, the 13 patients (9 males, 4 females; median age 61 years, range 47–79) developed consistent symptoms with fever (median 39.0°C, range 37.5–39.5), chills, malaise, hypotension, vomiting, dyspnoea—initially raising suspicion of septicemia. Subsequent blood cultures on bacterial contamination of the injected product remained negative throughout; bacterial or endotoxin contamination of the reagent was excluded. Steroids were tried in the first two patients without a noticeable effect. In all subsequent patients, symptoms were attenuated during the first 5 h dialysis (F60HPS with 280 ml/min blood flow) and disappeared within 72 h. CRP levels remained markedly elevated up to 14 days. Lymphopenia was seen in all patients, and polymorphic neutrophils (PMN) remained normal. Two polyuric patients developed persistent anuria. After a median of 16 months, none of these patients developed nephrogenic systemic fibrosis.

Conclusion. This series with unusually severe acute phase reactions was caused by one specific preparation. Such peracute reactions may be relevant for the so-far largely unresolved pathogenesis of the skin reaction to some Gd products in end-stage renal disease (ESRD) patients. It remains unresolved whether the reaction observed with Gd-DTPA do in principle also occur with other Gd reagents.

Keywords: acute phase reaction; acute renal failure; dialysis; gadolinium; lymphopenia

Introduction

Since the first observation [1], there have been numerous reports on gadolinium (Gd)-induced nephrogenic systemic
fibrosis (NSF) [2–4], which is at least partially explained by an endothelial cell reaction [5]. In addition, in some polyuric patients acute renal failure was provoked by the administration of Gd [6]. In several recent reports, the authors mention that symptoms developed in the course of 3 weeks to 18 months after administration of Gd [7].

Here we report an acute phase reaction to at least one of the Gd compounds used for MRI investigation, i.e. diethylenetriamine penta-acetic acid (Gd-DTPA). It is currently unclear whether this complication is related to the late cutaneous sequelae of Gd.

**Patients and methods**

Gd-DTPA (Magnevist®, Schering, Berlin, Germany) was administered to 136 patients on haemodialysis or CAPD, 76 in Heidelberg and 60 in Würzburg. One hundred twenty-eight patients were on haemodialysis and 8 patients on CAPD. The indication for the administration of Gd-DTPA was cardiovascular evaluation before renal transplantation (cardio MRI in Heidelberg and cardio MRI or peripheral angiography in Würzburg). All patients received contrast enhancement MRI using Gd-DTPA at a dose between 0.28 and 0.34 ml/kg body weight (bw) of standard dose 0.5 mmol Gd-DTPA. Consecutive blood samples were drawn only from the 13 patients who developed symptoms.

**Results**

Of these 136 patients, the 13 patients (6/76 in Heidelberg, 7/60 in Würzburg, 9 males, 4 females; median age 61 years; range 47–79) developed a consistent symptomatology within an average of 12 h (range 12–36 h): without any skin reaction patients had fever (median 39.0°C, range 37.5–39.5), chills with shivering, malaise, hypotension, vomiting, and dyspnoea initially raising suspicion of septicaemia. Because of suspicion of bacterial contamination of the injected contrast agent, blood cultures were obtained in all but two patients and remained negative throughout; the producer excluded bacterial or endotoxin contamination of the reagent (personal communication). Owing to the alternative suspicion of an anaphylactic reaction, we administered steroids to the two initial patients. Because in all subsequent patients clinical signs and symptoms were attenuated
during the first 5 h dialysis (F60HPS with 280 ml/min blood flow) and disappeared completely within 72 h, subsequent steroid administration was halted. Two of the six polyuric patients in Heidelberg developed persistent anuria. One of the six Heidelberg patients (differential blood count was performed only in the Heidelberg patients), an increase of eosinophils up to 22% (1.8/nl) was observed. Immunoglobulin E (IgE), not available in all patients, rose up to 615 kU/l. All patients developed marked lymphopaenia (median 0.6/nl, range 0.6–1.3/nl, median relative cell count 10%, range 6–15%), and polymorphic neutrophils (PMN) remained within the normal range in all patients (median 5.3/nl, range 5.3–7.4, median relative cell count 72.3%, range 58–77.8%). Spleen size (by sonography) did not change.

None of the patients had a history of allergy or autoimmune disease, and specifically none had a history of adverse reactions to radiocontrast. The underlying renal diseases were glomerulonephritis 4/13; diabetic nephropathy 4/13; hypertension (n = 1); reflux nephropathy (n = 1); hepatorenal syndrome (n = 1) and unknown (n = 2). After a 16-month follow-up, none of the 13 (but 1 of the 123 patients) in 25 of 13219 patients receiving gadopentetate dimeglumine, but no reaction was considered to be serious and no fever was mentioned [8]. However, this severe systemic response to Gd administration seems to be specific, or at least aggravated in renal failure patients.

The present observation does not permit conclusions as to whether this acute reaction was triggered by Gd per se (potentially released by transmetallation), by the chelate or by contaminants. One has to consider that transmetallation is accentuated, when the half-life of Gd is prolonged [9]. Gd chelates are distributed in the extra-cellular space and eliminated almost exclusively by the kidneys through glomerular filtration [9]. Renal failure impairs but maintains renal Gd excretion without resorting to a non-renal route [10]. For example, the gadodiamide half-life in healthy volunteers is 1.3 h. In end-stage renal disease (ESRD) patients, it is 34.3 h and in peritoneal dialysis patients even 52.7 h [10].

One can only speculate about the pathogenesis of the Gd-induced acute reaction in dialysis patients. In this context, it is of interest that Gd chloride not only blocks phagocytosis by Kupffer cells but also disrupts Kupffer cells [11]. There is evidence that circulating lipopolysaccharides (LPS), which are an important stimulus of proinflammatory cytokine synthesis, are cleared primarily by the liver [11,12]. In the case of Kupffer cell destruction or blocked phagocytosis (which occurs after Gd exposition), LPS clearance might be impaired. In this regard, it is remarkable that treatment with Gd chloride and elimination of Kupffer cells cause a significant increase of liver TNF-α transcripts [13]. This consideration may be of particular importance in dialysis patients. Increased plasma concentrations of LPS have been demonstrated in patients with chronic heart failure and hypervolaemia [14]. The authors argued that oedema of the bowel wall permits translocation of bacterial LPS [15] and the same might well be true for hypervolaemic dialysis patients as well.

The present series with unusually severe acute reactions was caused by Gd-DTPA, but we cannot exclude that it represents only the tip of the iceberg. We are currently aware of a substantial number of uraemic patients who have left radiology departments after administration of Gd compounds and developed a similar symptomatology at home or in dialysis units. We suspect that a non-negligible number of unreported cases exist.

NSF did not develop in our 13 patients. However, we cannot definitely conclude that the two reactions are unrelated.

**Discussion**

The extensive literature on NSF deals extensively with the cutaneous and renal complications from the administration of Gd compounds in patients with advanced renal failure [2–4]. So far the majority of reported cases concerned Omniscan [2], and only a minority was reported after administration of Gd-DTPA, the compound used in the present series [2].

To the best of our knowledge, the above constellation of acute signs and symptoms has not been reported before. So far, there is no evidence that the observed symptomatology generally ensues after Gd administration. An early report mentioned rash and urticaria (which was not observed in our patients) in 25 of 13219 patients receiving gadopentetate dimeglumine, but no reaction was considered to be serious and no fever was mentioned [8]. However, this severe systemic response to Gd administration seems to be specific, or at least aggravated in renal failure patients.

Conflict of interest statement. None declared.

**References**

Role of medication in the level of aluminium in the blood of chronic haemodialysis patients

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Abstract

Background. Although dialysis facilities provide high-quality water, abnormal aluminium levels among patients on haemodialysis have still been reported. Since patients with chronic kidney disease are often on multiple medications, medicines may be an extra source of aluminium for them. The degree to which ingesting contaminated medication influenced the level of aluminium in the patients’ blood was investigated.

Methods. All medications consumed by a group of patients on regular dialysis treatment were analysed and the total aluminium ingested by each patient was calculated. At the same time, the patients’ blood was collected and aluminium was measured. The analyses were carried out by atomic absorption spectrometry.

Results. For all drugs consumed, the amount of aluminium ingested versus the blood aluminium level presented no correlation. Since a high level of contamination was presented by injectable iron, insulin and erythropoietin (EPO), another group of patients that received a reduced amount of oral medication was selected. Among them, eight did not receive any injectable drug, five received only EPO and seven injectable iron, EPO and insulin. With these restricted groups, it was possible to show that the injectable administration of contaminated medication increased the AI level in the patients’ blood, mainly in relation to iron formulations.

Conclusion. Among the medications investigated, the injectables are the most significant source of aluminium for patients with renal insufficiency. This extra aluminium intake is reflected in higher aluminium levels in the patients’ blood.

Key words: aluminium; elevated serum aluminium; erythropoietin; insulin; iron

Introduction

Patients with chronic kidney disease on regular haemodialysis treatment are theoretically exposed to Al mainly through the water used to prepare the dialysate. This assumption is due to the enormous volume of water to which the patients are usually exposed, ~360 l/week [1]. However, with the advent of the reverse osmosis for water purification, water contamination is no longer a problem. Since the previously used aluminium-based phosphate binder [2–4] has been replaced by calcium-based binders or Sevelamer, a polymeric amine that binds phosphate, no other significant Al sources for the patients are considered.

Nevertheless, patients on regular haemodialysis treatment present abnormal plasma/serum Al levels [5]. In the United Kingdom [6], plasma Al was audited over the period of January 2000–January 2004, resulting in a collection of