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Abbreviation:

β -NAG = *N*-acetyl- β -*D*-
glucosaminidase

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Renal Tolerance of a Neutral Gadolinium Chelate (gadobutrol) in Patients with Chronic Renal Failure: Results of a Randomized Study¹

PURPOSE: To assess the renal tolerance of 1.0 mol/L gadobutrol as an electrically neutral contrast agent at magnetic resonance (MR) imaging in patients with impaired renal function.

MATERIALS AND METHODS: Twenty-one patients with impaired renal function were enrolled in this prospective randomized study and classified into two subgroups according to their creatinine clearance: group 1 ($n = 12$), less than 80 mL/min (<1.33 mL/sec) and greater than 30 mL/min (>0.50 mL/sec); group 2 ($n = 9$), less than 30 mL/min (<0.50 mL/sec) and not requiring dialysis. Gadobutrol (1.0 mol/L) was injected intravenously at randomly assigned doses of either 0.1 or 0.3 mmol per kilogram of body weight. Changes in vital signs, clinical chemistry, and urinalysis results, including creatinine clearance, were monitored before, at 6 hours, and then every 24 hours until 72 hours (group 1) or 120 hours (group 2) after intravenous injection of gadobutrol. Hematologic results were checked every other day.

RESULTS: No serious adverse event occurred, and no clinically relevant changes in vital signs, hematologic results, clinical chemistry, or urinalysis results were detected in the observation period. Markers for glomerular filtration (creatinine, cystatin C, β 2-microglobulin, creatinine clearance) and tubular function (*N*-acetyl- β -*D*-glucosaminidase, α 1-microglobulin) were unaffected by gadobutrol in both groups.

CONCLUSION: Gadobutrol did not affect renal function and, therefore, proved to be a safe MR contrast agent in patients with impaired renal function. Even in patients with marginal excretory function (creatinine clearance, <30 mL/min [<0.50 mL/sec]), prehydration or treatment with diuretics or hemodialysis are not required after the administration of gadobutrol.

Gadolinium-enhanced magnetic resonance (MR) imaging increasingly replaces examinations with iodinated contrast agents in patients at risk for contrast material-induced nephrotoxicity (1). Frequent findings in these patients include preexisting elevated serum creatinine levels (>1.5 mg/dL [$133 \mu\text{mol/L}$]), diabetic nephropathy, severe albuminuria, advanced age, hypertension, hyperuricemia, and dehydration; the contribution of each of these factors to total risk is unknown (2–16). Findings in several clinical studies with extracellular MR contrast agents (0.5 mol/L) document no observable nephrotoxic effects in this patient population (1,17–26). The assumption that higher doses of concentrated extracellular MR contrast agents are diagnostically useful for MR angiography, MR perfusion studies, and MR imaging necessitates the injection of high doses or multiple injections of smaller doses up to the safety limit (27–32). Therefore, an increased renal load of contrast agent may result in increased renal toxicity according to the higher intravascular concentration during the first pass.

TABLE 1
Physicochemical Characteristics of Gadobutrol Compared with Other MR Imaging Contrast Agents

Physicochemical Characteristic	Gadobutrol (1.0 mol/L)	Gadoteridol (0.5 mol/L)	Gadopentetate Dimeglumine (0.5 mol/L)	Gadodiamide (0.5 mol/L)	Gadobenate Dimeglumine (0.5 mol/L)
Thermodynamic complex stability (log K_{eq})	21.80	23.80	22.10	16.90	22.60
Osmolality (osm/kg)	1.60	0.63	1.96	0.65	1.97
Viscosity (mPa)	4.96	1.30	2.90	1.40	5.40
T1 relaxivity (L/mmol · sec ⁻¹), 0.47 T, plasma	5.60	4.90	4.80	4.40	9.70

We found only a few clinical data for patients with preexisting renal insufficiency who received high doses (>0.3 mmol/kg) of extracellular MR contrast agents (0.5 mol/L) (1,33). In a retrospective analysis of 31 patients with preexisting renal insufficiency (serum creatinine, >1.5 mg/dL [$>133 \mu\text{mol/L}$]), the frequency of contrast material-induced renal failure with iodinated contrast material ($n = 9$) was 29% compared with 0% for that with gadolinium chelates, including gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), gadodiamide (Omniscan; Nycomed, Oslo, Norway), or gadoteridol (ProHance; Bracco, Milan, Italy) at doses of 0.2–0.4 mmol per kilogram of body weight (1). In four patients with renal insufficiency, the high dose of 0.5 mmol/kg of gadoversetamide (Optimarck; Mallinckrodt, St Louis, Mo) resulted in no adverse effect on renal function (33).

Gadobutrol (gadolinium-DO3A-butriol, Gadovist; Schering) is approved for use in Germany, Australia, and Switzerland as an electrically neutral gadolinium chelate for MR imaging. Specific physicochemical properties of gadobutrol allow the preparation of a highly concentrated MR contrast agent for intravenous injection with a gadolinium concentration of 1.0 mol/L, whereas approved commercially available gadolinium chelates are prepared with a gadolinium concentration of 0.5 mol/L (34,35). The 1.0 mol/L concentration provides increased gadolinium concentrations with a sharper bolus peak because of the reduced injection volume, which may be advantageous for first-pass investigations such as perfusion imaging and contrast material-enhanced MR angiography (31,36–38). With regard to renal toxicity, highly concentrated gadolinium chelates (1.0 mol/L) may also result in an increased renal concentration and thus increased renal toxicity during the first pass; however, data in patients with preexisting renal failure are not available, to our knowledge.

The purpose of our study was to determine the renal tolerance of 1.0 mol/L

gadobutrol in patients with chronically impaired renal function after intravenous injection of randomly assigned doses of 0.1 and 0.3 mmol/kg.

MATERIALS AND METHODS

Contrast Agent

Gadobutrol (1.0 mol/L) is a gadolinium-based hydrophilic neutral macrocyclic MR contrast agent with a molecular mass of 604.72 daltons (34). The mode of relaxation enhancement is primarily based on shortening of the T1 of protons. The physicochemical characteristics (thermodynamic complex stability, osmolality, viscosity, T1) of gadobutrol compared with those of gadoteridol, gadopentetate dimeglumine, gadodiamide, and gadobenate dimeglumine (MultiHance; Bracco) are presented in Table 1 (34–36,39).

The steady-state distribution volume indicates a predominantly extracellular distribution of gadobutrol, which is excreted by means of glomerular filtration via the kidneys, with a half-life of approximately 1½ hours (35). The median lethal dose of gadobutrol in mice, rats, and dogs is greater than 25, 20, and 6 mmol, respectively. Exact values or ranges could not be determined, because no lethal effects were observed in either mice or rats at maximum administration volume. In healthy volunteers, gadobutrol is safe over a dose range from 0.04 to 0.5 mmol/kg, with urinary excretion rates of 92.5%, 98.0%, and 96.6% for doses of 0.04, 0.1, and 0.4 mmol/kg, respectively, 12 hours after injection. The average renal clearance of gadobutrol is 121 mL/min, close to the normal level of creatinine clearance in humans (35).

Study Design

The objective of this randomized open-label study was to evaluate the safety of gadobutrol administered intravenously at randomly assigned doses of either 0.1 or 0.3 mmol/kg in patients with impaired renal function who under-

went MR imaging for any indication. The primary variable was the change in creatinine clearance after contrast material injection. Physical examination findings, vital signs, adverse events, serious adverse events, and extensive clinical laboratory test results were defined as secondary variables. To detect minimal changes in renal function, sensitive indicators of renal injury for both glomerular and tubular damage were determined at several time points.

Adverse events were defined as any illness, sign, symptom, or unfavorable change (eg, headache, nausea, dizziness) in the clinical status that appeared or worsened after the start of the study. Adverse events during the clinical study that were fatal, life threatening, resulted in serious or permanent damage to health, required intervention to prevent permanent impairment or damage, or necessitated or extended the hospital stay were classified as serious adverse events (eg, myocardial infarction, life-threatening bleeding). A causal relationship with the trial medication had to be assessed and documented for both adverse events and serious adverse events.

Patients

This study was approved by our institutional review board and ethics committee. Informed consent was obtained from each patient at least 24 hours before the study. Between October 1996 and February 1998, 21 patients (16 men, five women; age range, 20–76 years; mean age, 59.6 years) with a creatinine clearance of less than 80 mL/min (<1.33 mL/sec) who did not require chronic hemodialysis treatment, were willing and able to continue study participation, and had any indication for contrast-enhanced MR imaging were enrolled.

The 21 patients were classified into two subgroups according to their creatinine clearance: group 1, $n = 12$, less than 80 and greater than 30 mL/min (>0.50 mL/

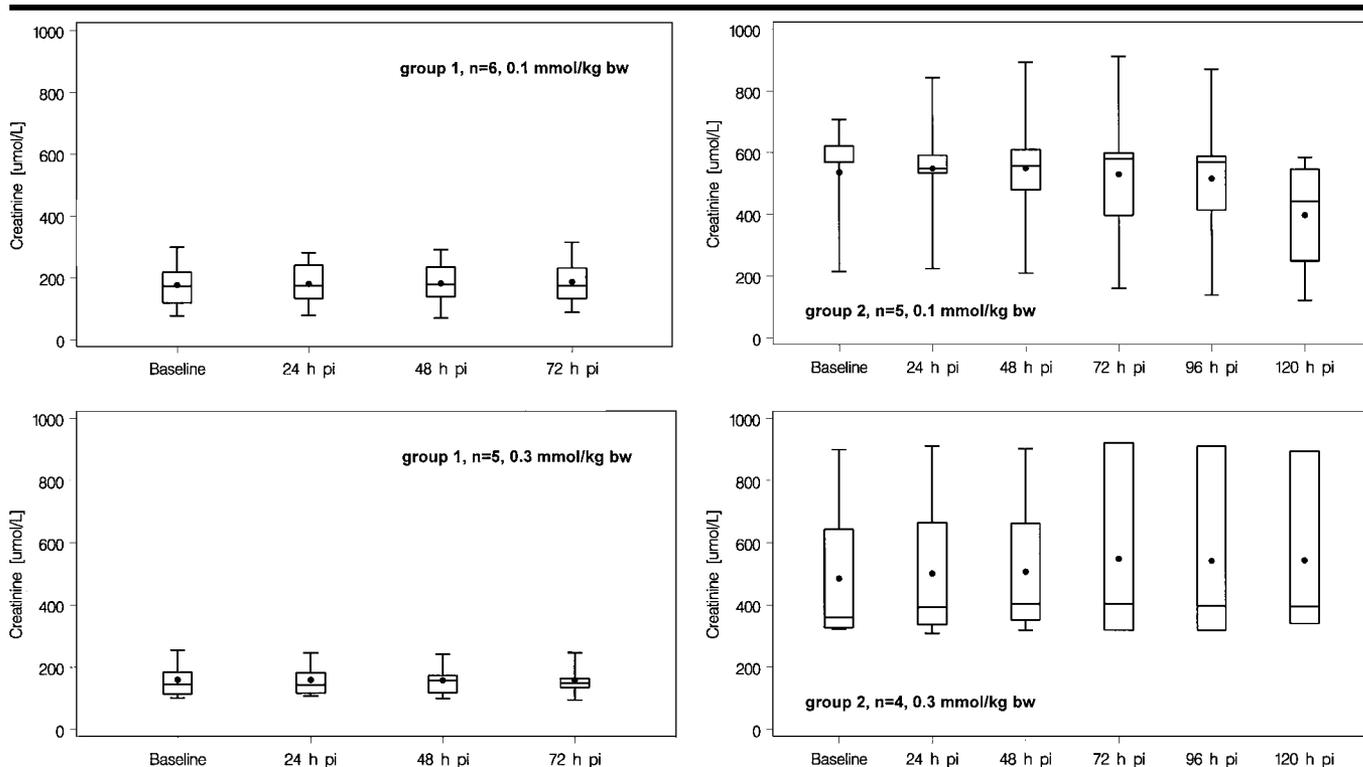


Figure 1. Box plots present follow-up data for serum creatinine concentration. Left: Within 72 hours after injection of gadobutrol (group 1, baseline creatinine clearance, <80 mL/min [<1.33 mL/sec] and >30 mL/min [>0.50 mL/sec]). Right: Within 120 hours after injection of gadobutrol (group 2, baseline creatinine clearance, <30 mL/min [<0.50 mL/sec]). Top: Gadobutrol dose of 0.1 mmol/kg. Bottom: Gadobutrol dose of 0.3 mmol/kg. *bw* = body weight, *pi* = postinjection.

sec); group 2, $n = 9$, less than 30 mL/min (<0.50 mL/sec) and did not require dialysis. According to the experience of nephrologists (R.M.S., K.K.), the estimated serum creatinine levels for creatinine clearance values of 80 mL/min (1.33 mL/sec) and 30 mL/min (0.50 mL/sec) are 1.0 mg/dL (88 μ mol/L) and 2.9–3.2 mg/dL (256–283 μ mol/L), respectively, depending on age, sex, and body weight. Eleven patients were randomly assigned to receive the lower dose of gadobutrol of 0.1 mmol/kg (group 1, $n = 6$; group 2, $n = 5$), and 10 patients were assigned to receive the higher dose of 0.3 mmol/kg (group 1, $n = 6$; group 2, $n = 4$).

Overall ($n = 21$), renal impairment was associated with respiratory abnormalities in 29% of patients (chronic bronchitis, chronic obstructive lung disease), cardiovascular abnormalities in 91% (hypertension, coronary heart disease), and endocrine dysfunction in 48% (adrenal gland insufficiency, hyperparathyroidism, hypo- and hyperthyroidism, diabetes). These findings reflected a patient population with severe disease. Four patients had diabetes treated with insulin. All patients received concomitant medication. No restriction of medication or

fluid was required before the study, and all patients appeared well hydrated according to clinical signs.

MR imaging was performed with a 1.5-T imager (Magnetom Vision; Siemens, Iselin, NJ) to exclude abdominal emphyema ($n = 1$), renal tumor ($n = 2$), abdominal tumor ($n = 12$), metastases ($n = 5$), or aortic aneurysm ($n = 1$).

Inclusion and exclusion criteria.—Only patients with a creatinine clearance value of less than 80 mL/min (<1.33 mL/sec) were enrolled in the study. Exclusion criteria were the following: age less than 18 years, pregnancy or lactation in women, treatment with any investigational drug within 30 days before the study, treatment with any contrast material within 5 days before the study or in the observation period, substantial fluctuation of laboratory parameters (eg, as a result of chemotherapy or radiation therapy), clinical instability with unpredictable clinical course during the observation time, organ transplantation, acute renal failure, a history of severe adverse reaction to drugs or contrast agents, a history of severe anaphylactoid allergy to any other allergen, surgery scheduled in the observation period, and any contraindication to MR imaging.

Monitoring.—Results of physical examinations, vital signs, and clinical laboratory tests were recorded at baseline and at 6, 24, 48, and 72 hours after the intravenous injection of gadobutrol. For group 2 patients, additional sampling was performed at 96 and 120 hours. Blood samples were analyzed for hematologic results (leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, thrombocytes) and clinical chemistry (urea nitrogen, total protein, albumin, sodium, potassium, calcium, iron, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, amylase, cyclic adenosine monophosphate receptor protein), including the markers for glomerular filtration (creatinine, cystatin C, β 2-microglobulin).

Cystatin C and β 2-microglobulin in serum were measured as additional parameters of excretory renal function, which allowed differentiation between laboratory variations and real changes in glomerular filtration rate in cases of fluctuating creatinine values. The serum creatinine level was determined on the basis of the Jaffe reaction, and the creatinine clearance value was calculated as the product of urine creatinine concen-

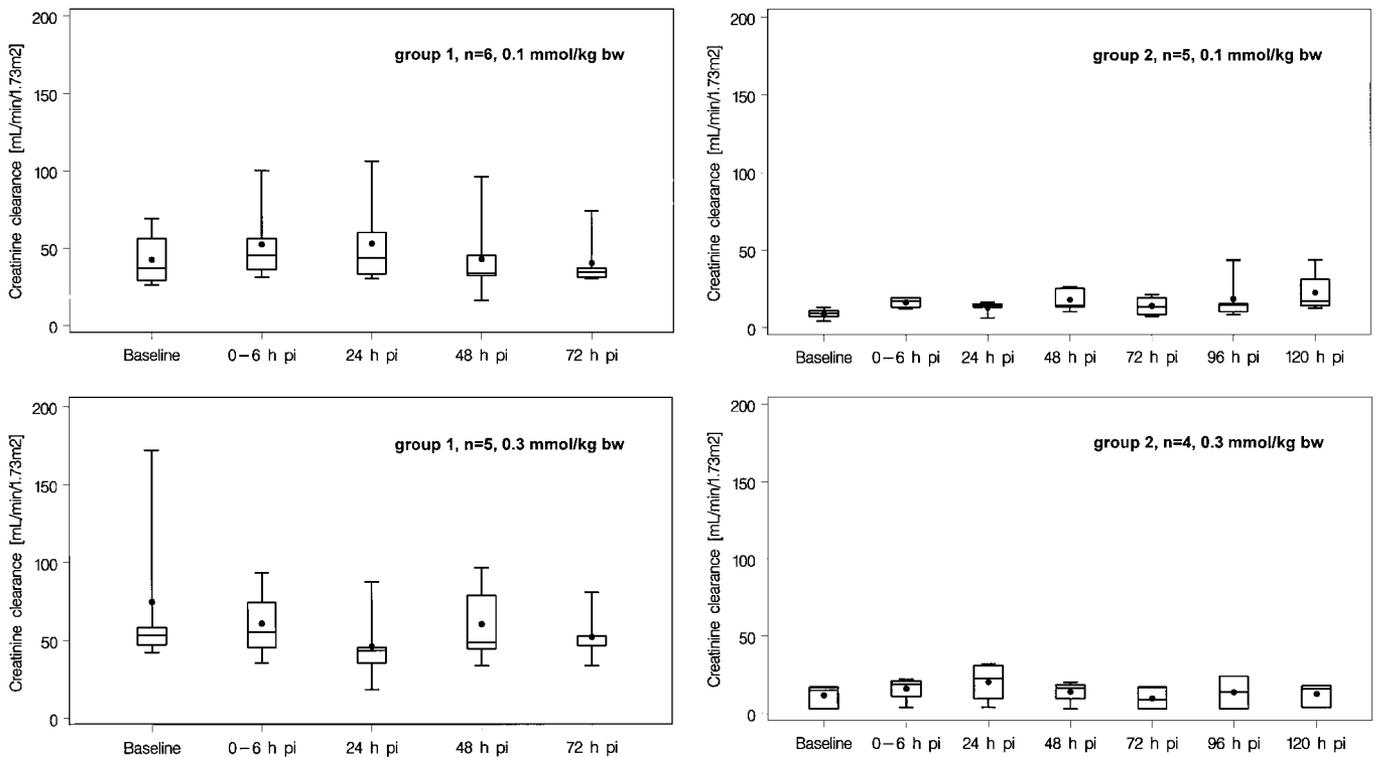


Figure 2. Box plots present follow-up data for creatinine clearance. Left: Within 72 hours after injection of gadobutrol (group 1). Right: Within 120 hours after injection of gadobutrol (group 2). Top: Gadobutrol dose of 0.1 mmol/kg. Bottom: Gadobutrol dose of 0.3 mmol/kg. *bw* = body weight, *pi* = postinjection.

TABLE 2
Follow-up of Serum Creatinine Concentration and Calculated Serum Creatinine Clearance Regardless of Dose

Data	Baseline Value	Collection Period (h)				
		24	48	72	96	120
Serum creatinine concentration ($\mu\text{mol/L}$)						
Group 1						
Mean \pm SD	167.7 \pm 69.0	169.5 \pm 64.5	169.5 \pm 67.7	171.5 \pm 69.5	ND	ND
95% CI	121.4, 214.1	126.2, 212.8	124.0, 215.0	124.8, 218.2		
Group 2						
Mean \pm SD	512.7 \pm 217.7	526.4 \pm 231.7	529.9 \pm 240.1	535.3 \pm 273.1	524.8 \pm 266.4	458.7 \pm 240.6
95% CI	345.4, 680.1	348.3, 704.5	345.4, 714.4	306.9, 763.6	302.0, 747.5	236.1, 681.2
Creatinine clearance (mL/min)*						
Group 1						
Mean \pm SD	56.9 \pm 40.4	49.5 \pm 26.3	50.5 \pm 27.2	45.3 \pm 17.2	ND	ND
95% CI	29.7, 84.1	31.8, 67.1	32.2, 68.7	33.7, 56.9		
Group 2						
Mean \pm SD	9.9 \pm 5.1	16.1 \pm 9.4	16.0 \pm 7.2	12.1 \pm 6.4	16.4 \pm 12.4	18.0 \pm 12.0
95% CI	5.6, 14.1	8.9, 23.4	10.5, 21.5	6.8, 17.5	6.0, 26.7	6.9, 29.1

Note.—Group 1: baseline creatinine clearance, <80 and >30 mL/min. Group 2: Baseline creatinine clearance, ≤ 30 mL/min. ND = no data acquired.
* SI unit, mL/sec; conversion factor, $\times 0.01667$.

tration and urine volume divided by the serum creatinine concentration and the collection period (40). Urinalysis was performed to determine total protein, albumin, and the markers for tubular function (*N*-acetyl- β -D-glucosaminidase [β -NAG], α 1-microglobulin). The level of α 1-microglobulin was measured to assess global tubular damage (proximal and dis-

tal); increased β -NAG excretion indicated proximal tubular damage.

Data Analysis

An increase in serum creatinine level greater than 1.0 mg/dL (>88.4 $\mu\text{mol/L}$) within 48 hours after intravenous injection of the contrast agent is considered

diagnostic of acute renal failure, according to Katzberg (3). For descriptive analysis of serum and urinary clinical chemistry parameters, the following data were calculated: mean, SD, median, range, and 95% CIs. Individual differences between baseline and postinjection values were also calculated: mean, SD, median, and 95% CIs.

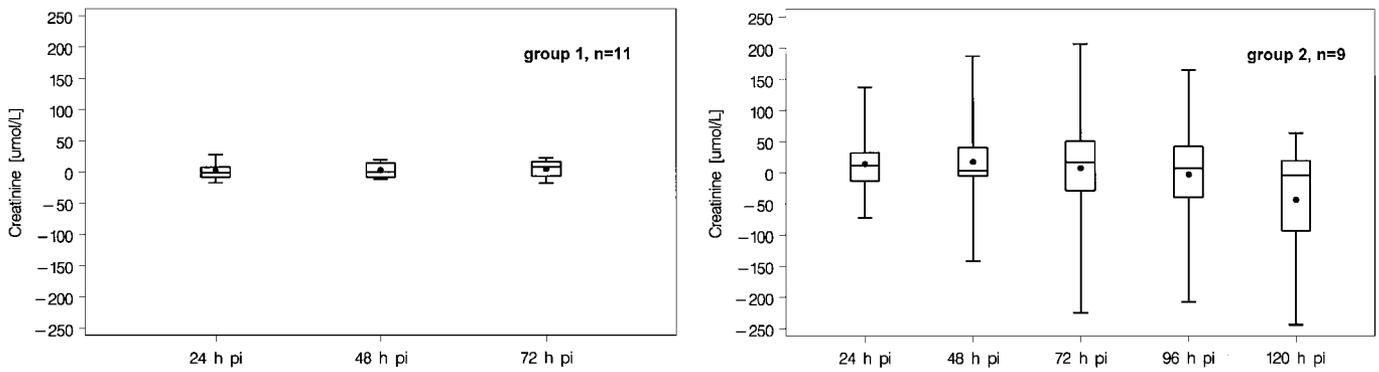


Figure 3. Box plots present follow-up data for differences in serum creatinine concentrations from baseline to postinjection, regardless of the assigned dose. Left: Within 72 hours after injection of gadobutrol (group 1). Right: Within 120 hours after injection of gadobutrol (group 2). *pi* = postinjection.

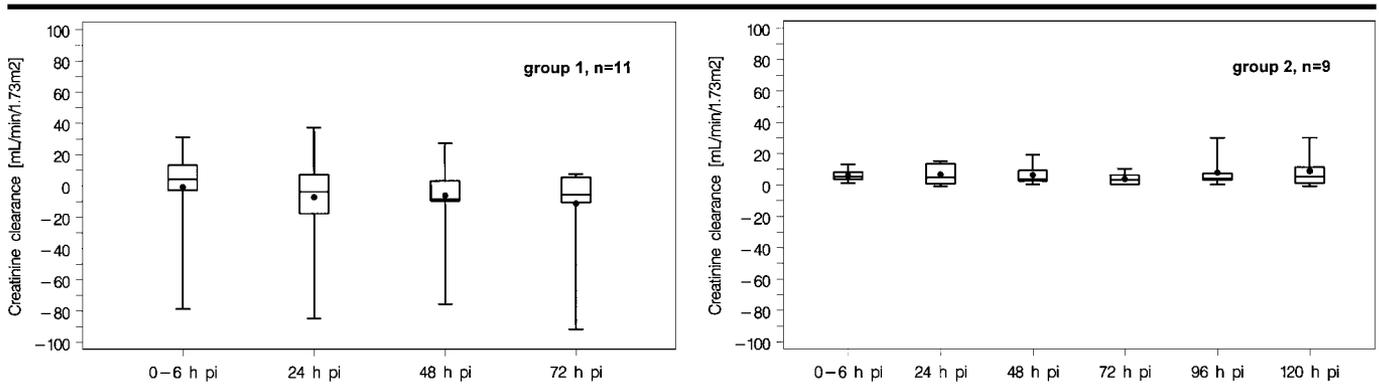


Figure 4. Box plots present follow-up data for differences in calculated creatinine clearance from baseline to postinjection values, regardless of the assigned dose. Left: Within 72 hours after injection of gadobutrol (group 1). Right: Within 120 hours after injection of gadobutrol (group 2). *pi* = postinjection.

The clinical course of each patient was analyzed by the two nephrologists, who were blinded regarding the injected dose of gadobutrol. Therefore, consensus evaluation of results of physical examination, medical and surgical history including current anamnesis, vital signs, and clinical laboratory tests in the observation period was performed individually for each patient by analyzing all available parameters. No inferential statistical analysis was performed owing to the small number of patients in each group ($n = 6$).

RESULTS

No gadobutrol-related adverse events, serious adverse events, or clinically important changes in vital signs occurred after intravenous injection of the contrast agent at either dose. No patient developed acute renal failure or anuria, and no patient required hemodialysis treatment during the observation period. As analyzed by the two nephrologists, varia-

tions in hematologic results and clinical chemistry values in the observation period were a result of the clinical course and individual disease process and were not related to the intravenous injection of gadobutrol.

One group 1 patient (0.3 mmol/kg), who had a 1-year history of urinary retention caused by benign prostatic hyperplasia associated with chronic urinary tract infection and chronic pyelonephritis, was excluded from assessment of the primary variable. A suprapubic urinary catheter caused an inflammation and was removed before the MR investigation. Subsequently, urinary retention, fever, leukocyturia, and bacteriuria occurred within 24 hours after the administration of gadobutrol and persisted for 1 week. The serum creatinine level increased from 1.6 mg/dL (141 μ mol/L) at baseline to 1.6 mg/dL (141 μ mol/L) at 24 hours, 1.7 mg/dL (150 μ mol/L) at 48 hours, 1.87 mg/dL (165 μ mol/L) at 72 hours, 2.33 mg/dL (206 μ mol/L) at 96 hours, and 2.85 mg/dL (252 μ mol/L) at 120 hours.

The level returned to baseline within 8 days after high-dose antibiotic therapy.

For all other patients ($n = 20$), no clinically relevant changes in the glomerular filtration markers of serum creatinine, creatinine clearance, cystatin C, and β 2-microglobulin occurred in the observation period after the injection of gadobutrol. For group 1, the mean serum creatinine concentration was 175.0 μ mol/L (low dose) and 158.9 μ mol/L (high dose) before administration of gadobutrol and was 183.4 μ mol/L (low dose) and 157.2 μ mol/L (high dose) at the end of the observation period (72 hours). For group 2, the mean serum creatinine concentration changed from 535.4 to 395.8 μ mol/L (low dose) and from 484.4 to 542.5 μ mol/L (high dose) during the 120-hour observation period (Fig 1). Furthermore, creatinine clearance values did not decrease in either group at either dose during the observation period (Fig 2). Table 2 presents the follow-up data for both groups for serum creatinine levels and creatinine clearance values in 24-hour intervals of the observation pe-

TABLE 3
Markers for Tubular Function Regardless of Dose

Parameter	Baseline Value	Collection Period (h)					
		0-6	6-24	24-48	48-72	72-96	96-120
β-NAG (U/g of creatinine)							
Group 1							
Mean ± SD	14.7 ± 18.1	18.1 ± 15.7	12.4 ± 9.2	20.3 ± 19.9	11.7 ± 7.7	ND	ND
95% CI	4.0, 25.4	8.8, 27.4	7.0, 17.8	8.6, 32.1	7.1, 16.2		
Group 2							
Mean ± SD	25.2 ± 26.3	24.4 ± 32.2	20.6 ± 30.6	22.8 ± 23.2	28.5 ± 39.0	20.1 ± 23.2	19.6 ± 25.1
95% CI	7.0, 43.5	3.3, 45.4	0.6, 40.5	7.7, 38.0	1.5, 55.5	4.1, 36.2	1.0, 38.2
α1-microglobulin (mg/g of creatinine)							
Group 1							
Mean ± SD	4.6 ± 3.5	4.5 ± 3.9	4.0 ± 4.0	4.8 ± 5.4	3.6 ± 4.3	ND	ND
95% CI	2.6, 6.7	2.2, 6.8	1.6, 6.4	1.6, 7.9	1.1, 6.2		
Group 2							
Mean ± SD	24.0 ± 21.2	22.5 ± 20.8	20.7 ± 17.0	19.9 ± 17.0	21.0 ± 17.6	21.9 ± 18.8	16.9 ± 15.5
95% CI	9.3, 38.7	8.9, 36.0	9.6, 31.8	8.8, 31.0	8.8, 33.2	8.9, 34.9	5.4, 28.3

Note.—Group 1: baseline creatinine clearance, <80 and >30 mL/min, respectively. Group 2: baseline creatinine clearance, ≤30 mL/min. ND = no data acquired.

riod, regardless of the assigned dose of 0.1 or 0.3 mmol/kg. Figures 3 and 4 present the differences in serum creatinine and creatinine clearance from baseline to postinjection values, regardless of the assigned dose. Urinary parameters, including markers for tubular function (β-NAG, α1-microglobulin), were unaffected by gadobutrol in both groups (Table 3).

DISCUSSION

In patients at risk for contrast material-induced nephrotoxicity, imaging examinations with iodinated contrast agents are increasingly replaced with gadolinium-enhanced MR imaging with larger doses of gadolinium chelates (0.5 mol/L) and highly concentrated agents (1.0 mol/L) (1,27-32). Prospective evaluation in this patient population (1,33) is relevant, because clinical experiences with high-dose injections (>0.3 mmol/kg) of extracellular MR contrast agents (0.5 mol/L) are very limited and, to our knowledge, data for highly concentrated gadolinium chelates (1.0 mol/L) are not available.

Findings in animal studies with gadopentetate dimeglumine (0.5 mmol/kg) and ex vivo experimental models with high doses of gadopentetate dimeglumine (0.6 mL/kg) suggest a correlation between the excretory function and the dose of MR contrast agent (41,42). Systemic influences and direct nephrotoxicity are discussed, but all effects are transient, reflecting a nonspecific osmotically induced alteration by the contrast agent (41-44). However, the extrapolation of animal data to humans can be misleading. Clinical experience after the injection

of 0.5 mol/L extracellular MR contrast agents in patients with chronically impaired renal function is limited (18-26). Data for the renal tolerance of doses as high as 0.5 mmol/kg are available in two prospective studies and one retrospective analysis (1,24,25,33). To our knowledge, however, the renal tolerance of 1.0 mol/L gadolinium chelates as MR contrast agents has not been investigated previously.

The reported stable courses of renal function in patients with preexisting renal impairment document the safety of 1.0 mol/L gadobutrol at randomly assigned doses of 0.1 or 0.3 mmol/kg. Besides some minor fluctuations in individual patients in this study, hematologic results and clinical chemistry, including serum creatinine levels, were unchanged in both groups in the observation period. To improve sensitivity for the detection of glomerular intolerance on the basis of serum creatinine level, which is a less sensitive indicator of renal injury, we monitored additional markers of glomerular filtration (cystatin C, β2-microglobulin) and calculated creatinine clearance values. No clinically relevant change indicated a gadobutrol-induced impairment of glomerular function.

The glomerular tolerance of gadobutrol at doses of either 0.1 or 0.3 mmol/kg is comparable to that of the clinically approved reference agents gadopentetate dimeglumine, gadodiamide, gadoteridol, and gadoversetamide (19-25,33). Data from the most comprehensive experience with gadopentetate dimeglumine, however, are based on the follow-up of only serum creatinine levels as an indicator of renal impairment, and no creati-

nine clearance values were calculated (19). On the basis of the definition of acute renal failure according to Katzberg et al (an increase in serum creatinine greater than 1 mg/dL [88.4 μmol/L] in 48 hours), we did not observe any increase in the level of serum creatinine that is diagnostic for acute renal failure (3). Furthermore, tubular function (β-NAG, α1-microglobulin) was unaffected by gadobutrol in both dose groups. β-NAG, a lysosomal enzyme located in the proximal tubular cells, is considered a highly sensitive but nonspecific enzyme for detection of renal tubular damage (45). A statistically significant but transient increase due to hyperosmolality was reported after intravenous injection of gadopentetate dimeglumine (19-21).

A limitation of the current study is the small number of patients in each subgroup; therefore, we performed a descriptive data analysis on the basis of calculated measures and could not calculate statistical significance. Nevertheless, findings in this prospective study support reports on the absence of observable nephrotoxicity after the intravenous injection of 0.5 mol/L gadolinium chelates.

In conclusion, gadobutrol did not affect renal function in patients with impaired renal function; therefore, it is a safe MR contrast agent at doses of either 0.1 or 0.3 mmol/kg. After intravenous injection, highly concentrated gadolinium chelates (1.0 mol/L) are well tolerated even in patients with severely reduced renal function (creatinine clearance, <30 mL/min [<0.50 mL/sec]). Prehydration or treatment with hemodialysis or diuretics is not required. Even in patients

with marginal excretory function (creatinine clearance, <30 mL/min [<0.50 mL/sec]), hemodialysis treatment did not have to be performed after the injection of gadobutrol. Intraindividual studies are required in the future to compare clinical aspects of the highly concentrated gadobutrol with high doses of 0.5 mol/L gadolinium chelates.

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References

- Prince M, Arnoldus C, Frisoli J. Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. *J Magn Reson Imaging* 1996; 1:162-166.
- Byrd L, Sherman RL. Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review. *Medicine* 1979; 58:270-279.
- Katzberg R. New and old contrast agents: physiology and nephrotoxicity. *Urol Radiol* 1988; 10:6-11.
- Berns AS. Nephrotoxicity of contrast media. *Kidney Int* 1989; 36:730-740.
- Hou SH, Bushinski DA, Wish JB, Cohann JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; 74:243-248.
- Dorph S. The effect of contrast agents on renal function. *Eur Radiol* 1995; 5:74-78.
- Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. *N Engl J Med* 1989; 320:143-149.
- Schwab SJ, Hlatky MA, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of non-ionic and ionic radiographic contrast agent. *N Engl J Med* 1989; 320:149-153.
- Teruel JL, Marcen R, Onaindia JM, Serrano A, Quereda C, Ortuno J. Renal function impairment caused by intravenous urography: a prospective study. *Arch Intern Med* 1981; 141:1271-1274.
- Kumar S, Hull JD, Lathi S, Cohen AJ, Pletka PG. Low incidence of renal failure after angiography. *Arch Intern Med* 1981; 141:1268-1270.
- D'Elia JA, Gleason RE, Alday M, et al. Nephrotoxicity from angiographic contrast material: a prospective study. *Am J Med* 1982; 72:719-725.
- Port KF, Wagoner RD, Fulter RE. Acute renal failure after angiography. *Am J Radiol* 1974; 121:544-550.
- Weinrauch LA, Healy RW, Leland OS, et al. Coronary angiography and acute renal failure in azotemic diabetic nephropathy. *Ann Intern Med* 1977; 86:56-59.
- Harkonen S, Kjellstrand CM. Exacerbation of diabetic renal failure following intravenous pyelography. *Am J Med* 1977; 63:939-946.
- Van Zee BE, Hoy WE, Talley TE, Jaenicke JR. Renal injury associated with intravenous pyelography in non diabetic and diabetic patients. *Ann Intern Med* 1978; 89:51-54.
- Diaz-Buxo JA, Wagoner RD, Hattery RR, Palumbo PJ. Acute renal failure after excretory urography in diabetic patients. *Ann Intern Med* 1975; 83:155-158.
- Rofsky N, Weinreb J, Bosniak M, Libes R, Birnbaum B. Renal lesion characterization with gadolinium-enhanced MR imaging: efficacy and safety in patients with renal insufficiency. *Radiology* 1991; 180:85-89.
- Niendorf HP, Hausteiner J, Cornelius I, Alhassan A, Clauss W. Safety of gadolinium-DTPA: extended clinical experience. *Magn Reson Med* 1991; 22:222-228.
- Hausteiner J, Niendorf HP, Krestin G, et al. Renal tolerance of gadolinium-DTPA/dimeglumine in patients with chronic renal failure. *Invest Radiol* 1992; 27:153-156.
- Schuhmann-Giampieri G, Krestin G. Pharmacokinetics of Gd-DTPA in patients with chronic renal failure. *Invest Radiol* 1991; 26:975-979.
- Krestin GP, Schuhmann-Giampieri G, Hausteiner J, et al. Functional dynamic MR imaging, pharmacokinetics and safety of Gd-DTPA in patients with impaired renal function. *Eur Radiol* 1992; 2:16-23.
- Berg KJ, Lundby B, Reinton V, Nordal KP, Rootwelt K, Smith HJ. Gadodiamide in renal transplant patients: effects on renal function and usefulness as a glomerular filtration rate marker. *Nephron* 1996; 72:212-217.
- Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol* 1998; 5:491-502.
- Yoshikawa K, Davies A. Safety of ProHance in special populations. *Eur Radiol* 1997; 7(suppl 5):246-250.
- La France ND, Parker JR, Lucas TR, et al. Clinical investigation of the safety and pharmacokinetics of gadoteridol injection in renally impaired patients requiring hemodialysis (abstr). In: Proceedings of the Third Meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 1995; 287.
- Arsenault TM, King BF, Wallis MJ, et al. Systemic gadolinium toxicity in patients with renal insufficiency and renal failure: retrospective analysis of an initial experience. *Mayo Clin Proc* 1996; 71:1150-1154.
- Runge V, Kirsch J, Thomas G. High-dose applications of gadolinium chelates in magnetic resonance imaging. *Magn Reson Med* 1991; 22:358-363.
- Yuh WTC, Engelken JD, Muhonen MG, et al. Experience with high dose gadolinium MR imaging in the evaluation of brain tumors. *AJNR Am J Neuroradiol* 1992; 13:335-345.
- Knauth M, Forsting M, Hartmann M, Heiland S, Balzer T, Sartor K. MR enhancement of brain lesions: increased contrast dose compared with magnetization transfer. *AJNR Am J Neuroradiol* 1996; 17:1853-1859.
- Lemke AJ, Sander B, Balzer T, Geens V, Hosten N, Felix R. Sicherheit und nutzen von gadobutrol bei patienten mit zerebralen tumoren (phase-III-studie). *Rofo* Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1997; 167:591-598.
- Heiland S, Benner T, Reith W, Forsting M, Sartor K. Perfusion-weighted MR imaging using gadobutrol as a contrast agent in a rat stroke model. *J Magn Reson Imaging* 1997; 7:1109-1115.
- Kawai J, Takahashi M, Kato N, Takashima K, Miyazawa T. Comparison of a 1.0 molar and a 0.5 molar formulation of gadobutrol in dynamic MR imaging of the liver in rats with hepatocellular carcinoma. *Magn Reson Imaging* 1999; 17:91-97.
- Swan SK, Baker JF, Free R, et al. Pharmacokinetics, safety, and tolerability of gadoversetamide injection (OptiMark) in subjects with central nervous system or liver pathology and varying degrees of renal function. *J Magn Reson Imaging* 1999; 9:317-321.
- Vogler H, Platzek J, Schuhmann-Giampieri G, et al. Pre-clinical evaluation of gadobutrol: a new, neutral, extracellular contrast agent for magnetic resonance imaging. *Eur J Radiol* 1995; 21:1-10.
- Staks T, Schumann-Giampieri G, Frenzel T, Weinmann HJ, Lange L, Platzek J. Pharmacokinetics, dose proportionality, and tolerability of gadobutrol after single intravenous injection in healthy volunteers. *Invest Radiol* 1994; 29:709-715.
- Mühler A. Assessment of myocardial perfusion using contrast-enhanced MR imaging: current status and future developments. *MAGMA* 1995; 3:21-33.
- Mühler A, Weinmann HJ. Arterial concentrations following intravenous bolus injection of gadobutrol: comparison of 0.5 and 1.0 molar stock solutions (abstr). In: Proceedings of the Third Meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 1995; 1128.
- Benner T, Tombach B, Synnott JP, et al. Human cerebral blood flow maps improve with higher concentration of contrast agent (abstr). In: Proceedings of the Eighth Meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 2000; 2024.
- Weinmann HJ, Platzek J, Radüchel B, Schumann-Giampieri G, Vogler H. A new macrocyclic gadolinium chelate as a contrast agent for MR imaging (abstr). *Eur Radiol* 1993; 3(suppl 3):126.
- Chasson AL, Grady HJ, Stanley MA. Determination of creatinine by means of automatic chemical analysis. *Am J Clin Pathol* 1961; 35:83-88.
- Brown PWG, Haylor JL, Morcos SK, Meguid El Nahas A. The functional effects of gadolinium-DTPA on the isolated perfused rat kidney. *Eur J Radiol* 1993; 16:85-89.
- Katzberg RW, Sahler LG, Duda SW, et al. Renal handling and physiologic effects of the paramagnetic contrast medium Gd-DOTA. *Invest Radiol* 1990; 25:714-719.
- Dawson P, Trehwella M. Intravascular contrast agents and renal failure. *Clin Radiol* 1990; 41:373-375.
- Dawson P. Contrast agent nephrotoxicity: an appraisal. *Br J Radiol* 1985; 58:121-124.
- Guder W. Enzyme distribution along the nephron. *Kidney Int* 1984; 26:101-111.