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Gadolinium-based contrast media compared with iodinated media for digital subtraction angiography in azotaemic patients

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Abstract

Background. To determine whether gadolinium-based contrast media (CM) could be used safely for angiographies in patients with renal dysfunction we investigated renal function after gadobutrol exposure and compared the results with standard iodinated CM (iohexol) in a randomized clinical study.

Methods. Twenty-one patients (aged 67 ± 11 years, nine female and 12 male) with severely impaired renal function [mean serum creatinine 3.2 ± 1.3 mg/dl, mean glomerular filtration rate (GFR) 31 ± 16 ml/min/1.73 m^2] who needed to have angiography because of severe peripheral vascular disease, renal artery stenosis or aortic aneurysms were randomized to receive in a blinded manner either gadobutrol (Gadovist® 1.0 mmol/ml) or iohexol (Omnipaque® 350) as contrast agents. GFR was measured by CM clearance (Renalyzer®) at baseline and 48 h after CM administration. The primary end point was the mean change of GFR from baseline at 48 h, the secondary one the incidence of CM-induced acute renal failure, defined as a decrease in GFR of >50% from baseline within 48 h of CM administration.

Results. In the gadobutrol group ($n = 10$) we observed a statistically significant decrease in GFR of 10.6 ± 13.8 ml/min/1.73 m^2 within 48 h after CM administration ($P < 0.05$, paired t test). The incidence of CM-induced ARF amounted to 50%. In comparison, the iohexol group ($n = 11$) also showed a statistically significant GFR reduction of 8.7 ± 8.8 ml/min/1.73 m^2 ($P < 0.05$, paired t test), and of ARF by 45%. The percentile of differences of GFR decreases between the two groups was not significant ($P = 0.70$). No patient demonstrated other adverse effects of gadobutrol or iohexol administration, apart from GFR reduction. Despite the decline in GFR, no patient required haemodialysis in the 10 following days.

Conclusions. In our study, gadolinium-based angiography showed no benefit over iohexol angiography with respect to preventing GFR reduction in patients with severely impaired renal function.

Keywords: angiography; contrast media-induced nephropathy; contrast media plasma clearance; gadolinium; glomerular filtration rate; iohexol

Introduction

Administration of contrast media (CM) is a frequent cause of hospital-acquired acute renal failure [1] associated with increases in in-hospital mortality [2] and in costs [3]. The pathogenesis of this so-called CM-induced nephropathy (CMIN) consists of a haemodynamic response to CM and direct tubulotoxicity. The biochemical and physico-chemical properties of the CM, which are responsible for this reaction have not yet been defined clearly. Several published studies have attempted, and partly succeeded, to prevent CMIN employing hydration strategies, the administration of theophylline or acetylcysteine and the use of new ionic contrast agents or negative CM, such as carbon dioxide.

Gadolinium chelates, intended as i.v. CM for magnetic resonance imaging, have been regarded as non-nephrotoxic [4], even when administered intra-arterially in doses of <0.3–0.4 mmol/kg body weight to patients with renal insufficiency [5]. Gadopentetate dimeglumine has sufficient radio-density to allow visualization using digital subtraction techniques [6] and has been described as an alternative CM for the digital subtraction angiography of several vascular territories. However, there is little data on the intra-arterial use of gadolinium in patients with renal

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insufficiency, particularly at doses that exceed those routinely used in magnetic resonance angiography [7].

We conducted a prospective, randomized controlled pilot-study to compare the renal effects of gadolinium-based media (gadobutrol) and iodinated media (iohexol) when used for digital subtraction angiography in patients with severe renal insufficiency.

Subjects and methods

Patients

Patients with known renal insufficiency [baseline serum creatinine >1.5 mg /dl (132 μmol/l) or glomerular filtration rate (GFR) <50 ml/min/1.73 m^2, or both, and with either symptoms of advanced peripheral vascular disease (any or all of severe claudication, rest pain, tissue loss) or signs of organ impairment due to vascular occlusion, and who had been referred for digital subtraction angiography (DSA), were included in the study. Only patients with stable serum concentrations of creatinine were included. Initially 70 patients were assessed for eligibility. Most of them were excluded for several reasons (Figure 1). Out of those 70 patients, primarily assessed for eligibility, only 25 patients were randomized (see Figure 1). The large number of exclusions were related to the following factors: (i) subjects were gathered from different departments of the hospital, and sometimes were participants in other studies; (ii) the informed consent was very detailed concerning the adverse effects of either drug to be used, therefore, some patients declined to participate; (iii) a relatively high number of patients showed BMIs >30, therefore, the amount of gadobutrol needed for good visualization would have been too high; (iv) the duration of the study (72 h) was too long for some patients who had been hospitalized only for diagnostic reasons or to undergo surgery.

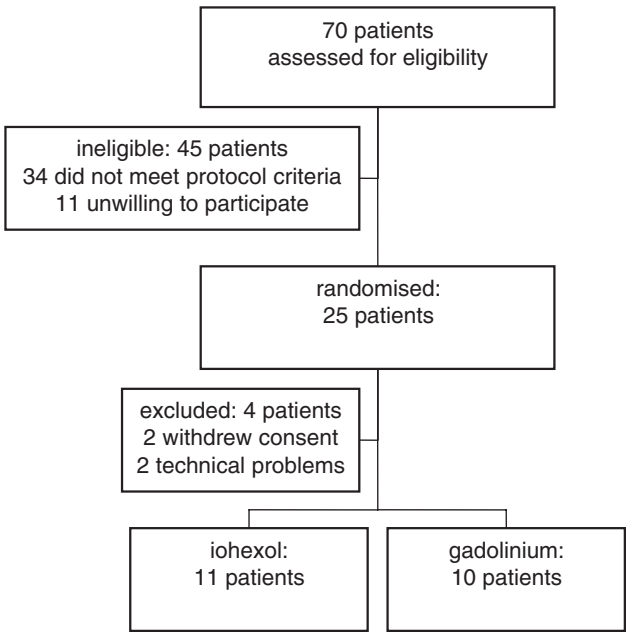

Fig. 1. Progress of patients throughout the trial.

Table 1. Patients' characteristics at baseline

Characteristics	Iohexol	Gadobutrol
Number	11	10
Age (years)	66 ± 14	68 ± 6
Sex (M/F)	6/5	6/4
Serum creatinine (mg/dl)	3.0 ± 1.2	3.4 ± 1.4
GFR (ml/min × 1.73 m^2)	29 ± 11	34 ± 21
Dose of CM (ml)	49 ± 25	44 ± 18
Dose of CM (mmol/kg body weight)	0.60 ± 0.271	0.57 ± 0.17
Diabetes mellitus (no. [%])	4 [36]	6 [60]
Diuretics (no. [%])	6 [55]	6 [60]
ACE-inhibitors (no. [%])	5 [45]	4 [40]

No significant differences ($P > 0.05$) were observed between the two groups except in the numbers of diabetic patients.

In all, we prospectively studied 21 patients with severe renal impairment and serum creatinine levels between 1.8 and 5.9 mg/dl (159–522 μmol/l).

Patients were eligible if they needed DSA for clinical reasons. The need for DSA was determined by independent physicians on clinical bases, and patients were informed about the study only after being scheduled for the procedure in the radiology department. None of the patients had a history of allergic reactions to CM and had not received NSAID. Pregnancy, uncontrolled arterial hypertension, severe heart failure (NYHA III-IV) and liver failure were exclusion criteria. Table 1 shows the patients' characteristics at baseline.

The study protocol was approved by the local ethics committee. Written informed consents were obtained from all participants.

It was planned to examine 40 patients (20 patients in each group). Because of the lack of data relevant to the intra-arterial use of gadolinium-based CM for DSA and the potential toxicity of gadolinium in high doses [7], an interim analysis was conducted after half of the planned number of patients had been studied. Based on the results of this interim analysis, showing no significant benefit of gadobutrol regarding renal protection, the investigators decided to terminate the study.

Study protocol

Patients were randomly assigned to receive either iohexol (Omnipaque® 350) or gadobutrol (Gadovist® 1.0) as CM during DSA. Randomization was performed by the statistical institute of the University of Tuebingen in blocks of four with a centralized masked-draw system that combined coded numbers with drug allocation. The characteristics of the CM we used are given in Table 2. The amount of CM used in each patient was calculated by the investigator to provide the same diagnostic information in both groups and to optimally visualize the vessels. All patients were hydrated intravenously with 1000 ml fluid 12 h before and 12 h after CM administration. Additionally, patients were allowed to drink mineral water before and after the angiography (~1000 ml in 24 h). The underlying medications were not changed over the study period. None of the patients received theophylline, acetylcysteine, dopamine or mannitol during the study. The subjects underwent radiographic procedures due to the following diseases: peripheral arterial disease (eight in the gadobutrol group and nine in the iohexol group); aortic aneurysm (two in

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Table 2. Characteristics of the CM

Characteristics	Iohexol	Gadobutrol
Trade name	Omnipaque® 350	Gadovist® 1.0
Manufacturer	Schering, Germany	Schering, Germany
Generic name	Iohexol	Gadobutrol
Concentration	755 mg/ml 0.92 mmol/ml Iodine 350 mg/ml	604.72 mg/ml 1 mmol/ml Gadolinium 157.25 mg/ml
Osmolality at 37°C	820 mosm/kg H_2O	1603 mosm/kg H_2O
Viscosity at 37°C	10.5 mPa·s	4.96 mPa·s
Elimination	Renal	Renal
Costs	About € 11.44/10 ml	About € 118.82/10 ml

the gadobutrol group and one in the iohexol group) and renal artery stenosis (none in the gadobutrol group and one in the iohexol group).

Serum creatinine, blood urea nitrogen, plasma renin activity (PRA), angiotensin II, endothelin and urinary sodium excretion were measured before CM administration and 48 h ± 2 afterwards.

GFR was determined by CM clearance. We used X-ray fluorescence analysis in our study (Renalyzer PRX90, Provalid AB, Lund, Sweden) to measure iodine. The calculation of GFR by determining the plasma clearance of iohexol/iopromide is a simple and rapid method that allows a reasonable estimation of GFR [8]. The method was designed specifically for the purpose of measuring CM clearance. The principle and the technique are described in detail elsewhere [9]. In brief, two ^{241}Am sources are used for the emission of 60 keV photons to excite the iodine in the sample. The iodine then emits characteristic X-ray radiation, which is detected and analysed by a NaI detector and a multichannel analyser. The amount of characteristic X-ray radiation emitted is proportional to the concentration of iodine in the sample and can be quantified after calibration. Clearance was determined either by the multiple-point method, based on the plasma iodine concentrations of the blood samples obtained 2.5, 3.25 and 4 h after injection of the CM, or it was derived from a double-iodine determination in blood obtained between 2.5 and 4 h after injection (two-point technique).

Patients randomized to the iohexol group did not receive any additional CM for determining CM clearance on the day of the angiographic procedures, patients in the gadobutrol group received 10 ml iohexol at the end of the examination—an amount of iodine CM known not to affect renal function. Two days after the actual angiography, the participants of both groups received a further 10 ml of iohexol i.v. to determine CM clearance once more. To exclude false values of the CM clearance resulting from the residual iodine from the first administration, we performed casual iodine measurements before the second administration of CM.

PRA and angiotensin II and endothelin levels were measured by radioimmunoassays (renin: Renin MAIA, Biochem Immunsystems; ATII: RIA Nichols Institute, San Juan Capistrano, USA; endothelin: Peninsula Labaratories Inc., Belmont, USA).

The primary end point was the mean change of GFR from baseline at 48 h, the secondary one the incidence of CM-induced acute renal failure, defined as a decrease in GFR of >50% from baseline within 48 h of CM administration.

After the first 21 patients had been studied, an editorial was published by Nyman *et al.* [7] dealing with the potential toxic effects of gadobutrol. This paper was discussed in detail in our study group and with the physicians who cared for the patients, and we decided to perform an interim analysis. The decision was pushed by a cost/benefit analysis—as the study was financially independent and without any support from the industry. Once our results indicated a more pronounced decline in GFR in nearly every patient investigated with gadobutrol, we decided to terminate the study.

Statistical analysis

After performing an interim analysis, we terminated the study due to the adverse outcome in the patients in the gadobutrol group.

The final analysis was conducted on an intention-to-treat basis (no power analysis was done because of the small number of patients). Categorical variables (e.g. the incidence of CM-induced acute renal failure) were analysed by Fisher's exact test. Differences in GFR within and between the groups were analysed by the paired *t* test for intra-group analysis and unpaired *t* test for inter-group analysis after testing for Gaussian distribution by the Kolmogorov–Smirnov test. Analyses were performed with the GraphPad Prism software (version 3.00, GraphPad Software, San Diego, CA). All statistical tests were two-sided.

Plus-minus values in the text and tables are means ± standard deviation.

Results

A summary of the results is shown in Table 3. The mean GFR for all patients was 31 ± 16 ml/min/1.73 m^2 at baseline and the mean serum creatinine 3.21 ± 1.31 mg/dl (283.76 ± 115.8 μmol/l) at baseline. In the iohexol group ($n = 11$), the mean GFR decreased from 29 ± 11 initially to 19 ± 11 ml/min/1.73 m^2 48 h after the administration of the contrast agent ($P = 0.0080$) (Table 3). In the gadobutrol group ($n = 10$), the GFR decreased from 31 ± 21 to 21 ± 21 ml/min/1.73 m^2 48 h after CM administration ($P = 0.0393$) (Table 3). There was no statistical difference between the two groups (Table 3).

The incidence of CM-induced acute renal failure—defined as a decrease in GFR of >50% of the baseline GFR within 48 h of CM administration—was equal in both groups (Table 3). Of the iohexol group, five patients (45%) presented with ARF as did five patients (50%) of the gadobutrol group ($P = 1.0$; relative risk, 0.91; 95% interval, 0.37–2.23; odds ratio 0.83). Despite the decline in GFR, no patient required acute, temporary or chronic haemodialysis treatment within the following 10 days.

The patients who received gadobutrol as contrast agent for the angiographies showed a higher decline in GFR (ΔGFR 10.0 ± 13.1 ml/min/1.73 m^2) compared with patients receiving iohexol (ΔGFR 8.7 ± 8.8 ml/min/1.73 m^2). The difference between the two groups in the percent of GFR decrease was not

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Table 3. Baseline GFR, serum creatinine, PRA, angiotensin II, endothelin and urinary NAG excretion and absolute changes in GFR, serum, creatinine, PRA, angiotensin II and urinary sodium excretion 48 h after exposure to CM, and incidence of CM-induced acute renal failure[a]

Variable ($n=11$)	Iohexol ($n=10$)	Gadobutrol	P-value
GFR (ml/min/1.73 m^2)			
Baseline	29 ± 11	31 ± 21	0.7807
After 48 h	19 ± 11*	21 ± 21*	0.8210
Change 48 h after	−8.7 ± 8.8	−10.0 ± 13.1	0.7910
CM exposure			
DGFR (%)	−39 ± 50	−32 ± 36	0.6997
Serum creatinine (mg/dl)			
Baseline	3.04 ± 1.19	3.40 ± 1.45	0.5274
After 48 h	3.20 ± 1.58	3.98 ± 1.94	0.3226
Change 48 h after	0.16 ± 0.92	0.58 ± 0.88	0.3156
CM exposure PRA (ng/ml/h)			
Baseline	12.12 ± 10.20	7.46 ± 11.12	0.3292
After 48 h	10.97 ± 12.31	5.79 ± 6.00	0.2467
Change 48 h after	−1.67 ± 8.15	1.09 ± 7.65	0.4440
CM exposure Angiotensin II (pmol/l)			
Baseline	40.55 ± 38.96	29.23 ± 30.61	0.4793
After 48 h	28.50 ± 23.15	34.75 ± 29.84	0.6071
Change 48 h after	−12.05 ± 35.02	5.52 ± 15.57	0.1643
CM exposure endothelin (pg/ml)			
Baseline	17.60 ± 5.46	20.15 ± 8.97	0.4523
After 48 h	18.31 ± 4.67	21.03 ± 7.24	0.3491
Change 48 h after	0.71 ± 4.50	−0.41 ± 10.99	0.7716
CM exposure NAG excretion (U/l)			
Baseline	8.01 ± 6.93	12.50 ± 9.88	0.3106
After 48 h	18.52 ± 17.27	20.33 ± 14.93	0.8292
Change 48 h after	12.09 ± 12.84	6.13 ± 9.59	0.3330
CM exposure			
Incidence of CM-induced acute renal failure (no. [%])	5 [45]	5 [50]	1.0

[a]Conversion of creatinine to SI unit multiply by 88.4.
* = $P<0.05$ compared with baseline

statistically significant ($P=0.70$). Diabetic patients in the gadobutrol group ($n=6$) showed a higher decrease ($P=0.0451$) in GFR than ones in the iohexol group ($n=4$) (ΔGFR −17.3 ± 7.0 ml/min/1.73 m^2 in the gadobutrol group *vs* ΔGFR −4.3 ± 10.6 ml/min/1.73 m^2 in the iohexol group).

A distinct, but statistically insignificant increase in serum creatinine was observed in both groups. Baseline serum creatinine was 3.04 ± 1.19 mg/dl (268.7 ± 105.2 μmol/l) in the iohexol group and 3.40 ± 1.45 mg/dl (300.6 ± 128.2 μmol/l) in the gadobutrol group. In the gadobutrol group, the serum creatinine rose higher than in the iohexol group (iohexol group Δcreatinine 0.16 ± 0.92 mg/dl, $P=0.5688$; gadobutrol group Δ creatinine 0.58 ± 0.88 mg/dl, $P=0.0679$). But the difference between the two groups was not statistically significant ($P=0.3050$).

Values for PRA, angiotensin II, endothelin and urinary *N*-acetyl-β-D-glucosaminidase (NAG) excretion did not change significantly during the study (Table 3).

No other significant side effects were observed in either group.

Discussion

Our data suggest that gadolinium-based CM used in the setting of DSA seem unable to prevent a decline in GFR in patients with severe renal insufficiency. The use of from 0.34 up to 0.90 mmol/kg body weight of gadobutrol in this small number of patients resulted in a significant decline in GFR, which seems to exceed even the decline observed in patients who received iodinated CM (Figure 2). These data may confirm a recently published editorial by Nyman *et al.* (17), where the authors concluded that, due to their physico-chemical properties, gadolinium chelates given in amounts necessary for satisfactory angiograms (generally >0.3–0.4 mmol/kg body weight) are highly (nephro)toxic.

Nevertheless, our results should be interpreted with caution as one has to take into account various limitations of this study, which include the heterogeneity of the two groups, i.e. significantly more diabetics in the gadobutrol group. Furthermore, the sample size of the study was probably too small to reach meaningful conclusions, at least from a statistical point of view, as there were no trends evident in the two groups of 21 patients in total to suggest the benefit of one compound over the other. Furthermore, all patients in the gadobutrol group received an additional 10 ml of iohexol for GFR measurement. Radiocontrast media-induced renal failure has been very rarely described after dosages as low as 20 ml. It may be that the additional nephrotoxic potential of gadobutrol is enhanced by the concomitant iohexol administration under this protocol—despite the fact that the clinical

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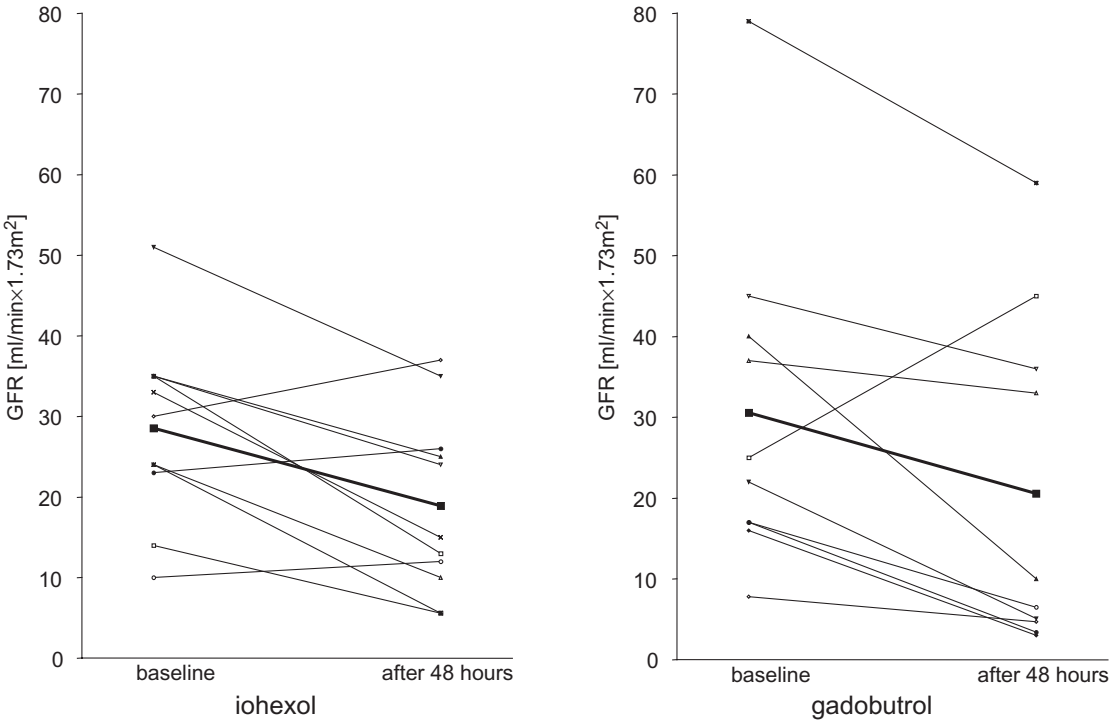

Fig. 2. Individual GFRs at baseline and 48 h after administration of either iohexol or gadobutrol.

practice of adding small amounts of iohexol during a study with gadobutrol (in order to visualize small vessels) is very common (personal communications Prof. Dr Stephan Duda).

Gadolinium-based CM are hypertonic, with an osmolality 2–7 times that of plasma, which seems to be a pathogenetic factor in CMIN following renal angiography. Iodinated media in concentrations that are equally attenuating as gadolinium-based media can be made isotonic. *In vitro* measurements indicate that 0.5 mol/l of gadolinium chelates are equally attenuating as 60–80 mg iodine/ml at the 70–90 kV range commonly used for DSA. Thus, 50 ml of 0.5 mol/l gadolinium chelate (~0.3 mmol/kg in an 80 kg person) would attenuate as well as a dose of 3–4 g of iodine in an iodinated medium (e.g. 50 ml iohexol at 60–80 mg iodine/ml or 10–13 ml at 300 mg iodine/ml). By combining these data on attenuation and the results of toxicity studies in mice [10] the general toxicity of gadolinium chelates may be estimated to be 6–25 times higher than that of equally attenuating doses of iodinated media at 70-kV DSA.

To date there are only few clinical data available on the administration of gadolinium for DSA in patients with renal insufficiency. In several case reports [11] and retrospective [12] or non-randomized prospective studies [13–15], acute renal failure following CM administration did not occur routinely when gadolinium was given in doses <0.50 mmol/kg body weight. Gadolinium chelates have been shown to absorb sufficient energy to be visualized with DSA. Despite theoretically favourable X-ray imaging properties, the image quality and the vascular enhancement observed during DSA using gadolinium are poorer than those obtained with iodinated contrast agents. To overcome this drawback, gadolinium must be administered in higher concentrations. So far, the only data published in abstract form have been on the use of higher doses of gadolinium (0.5 up to 2.9 mmol/kg body weight) in 20 patients with renal impairment [16]. The investigators observed acute renal failure in eight patients. In animals, intra-arterial injections of iodinated CM seem to be less nephrotoxic than gadolinium chelates, when equi-attenuating doses are compared [17].

Our protocol led to the comparison of a relatively low dose of iohexol (0.6 mmol/kg, Table 1) *vs* a somewhat high dose of gadobutrol (0.57 mmol/kg)—compared with the doses used in MR tomography. The amount given each patient was determined by the investigating radiologist, and depended on the ability to visualize during the examination. Whether or not a high image quality could also be obtained by using lower amounts of gadobutrol (with less toxicity) could not be answered.

This first randomized and prospective pilot study seems to indicate, in a preliminary fashion, that gadobutrol and iodinated CM have similar nephrotoxic effects when administered in equi-attenuating doses adequate for good visualization of vessels in patients with chronic renal failure. To definitively answer the question would require a larger, randomized trial. Our limited data only show that there is no trend in the two groups of at least 10 patients to suggest an advantage of gadobutrol over iodinated CM. Based on the results of this small pilot study, gadolinium chelates must be used with caution as alternative CM in digital subtraction

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arteriography in patients with severe renal insufficiency, especially when a cost/benefit analysis is taken into consideration.

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Conflict of interest statement. None declared.

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