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## Are gadolinium-based contrast media really safer than iodinated media for digital subtraction angiography in patients with azotemia?

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**Abbreviation:**

DSA = digital subtraction  
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<sup>2</sup> 9\*: Vascular system, location unspecified.

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See also the Viewpoint and Commentary by Spinosa et al in this issue.

# Are Gadolinium-based Contrast Media Really Safer than Iodinated Media for Digital Subtraction Angiography in Patients with Azotemia?<sup>1</sup>

Gadolinium chelates, intended as intravenous contrast media for magnetic resonance imaging, have been regarded as nonnephrotoxic and recommended to replace iodinated contrast media in patients with azotemia who are undergoing digital subtraction angiography (DSA). High intraarterial doses (up to 220 mmol of gadodiamide) have been used, with a 40% incidence of nephropathy. The authors discourage the use of gadolinium for DSA for several reasons. (a) There exist no randomized studies comparing the nephrotoxic effects of gadolinium-based and iodinated media at equal-attenuating concentrations and doses. (b) Gadolinium-based media are hypertonic, a pathogenetic factor in contrast medium-induced nephropathy after renal angiography, with an osmolality two to seven times that of plasma. Iodinated media in concentrations that are equally attenuating with gadolinium-based media can be made isotonic. (c) In vitro measurements indicate that 0.5 mol/L gadolinium chelates are equally attenuating with 60–80 mg iodine per milliliter at the commonly used 70–90-kV range used for DSA. Thus, 50 mL of 0.5 mol/L gadolinium chelate ( $\approx 0.3$  mmol/kg in an 80-kg person) would be equally attenuating with a dose of 3–4 g of iodine in an iodinated medium (eg, 50 mL iohexol at 60–80 mg I/mL or 10–13 mL at 300 mg I/mL). (d) By combining these data on attenuation and results of toxicity studies in mice, the general toxicity of gadolinium chelates may be six to 25 times higher than that of equal-attenuating doses of iodinated media at 70-kV DSA. Thus, the authors believe that at equal-attenuating doses for DSA, modern iodinated contrast media should result in a lower toxic load on the body than with presently available gadolinium chelates.

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It is well known that intravascular administration of iodinated contrast medium may induce a transient or irreversible decline in renal function in patients with preexisting renal insufficiency, especially in those with diabetes mellitus (1). On the other hand, gadolinium-based contrast media are regarded as nonnephrotoxic in clinically recommended doses for magnetic resonance (MR) imaging and MR angiography (2). Gadolinium chelates have thus been advocated (3–14) as safer than iodinated media in patients with azotemia who are undergoing x-ray angiography with digital subtraction technique (ie, digital subtraction angiography [DSA]) for endovascular diagnostic and therapeutic purposes.

Since the sole purpose of contrast media for conventional angiography is to attenuate x rays, any comparison regarding toxicity between different contrast medium solutions should be made in equal-attenuating concentrations or doses. To our knowledge, neither the renal nor the general toxicity of gadolinium chelates and iodinated contrast media have been compared in such a way in experimental or clinical studies. We have, therefore, reviewed the literature with the purpose of finding (a) the concentration of iodinated contrast medium that will attenuate x rays to the same degree as commercially available

**TABLE 1**  
**Characteristics of Four Commonly Used Contrast Media**

Contrast Medium	Attenuating Atom*	Weight of Attenuating Atoms (mg/mL)	Example of Use	No. of Attenuating Atoms (mmol/mL)	No. of Contrast Medium Molecules (mmol/mL)	Osmolality at 37°C (mosm/kg) <sup>†</sup>
<b>High osmolality</b>						
Gadopentetate dimeglumine (Magnevist; Berlex Laboratories)	Gadolinium	79	MR imaging	0.5	0.5	1,960
Diatrizoate (Urografin 76%; Schering, Berlin, Germany)	Iodine	370	Coronary arteriography	2.9	0.97	2,100
<b>Low osmolality</b>						
Gadodiamide (Omniscan; Amersham Health)	Gadolinium	79	MR imaging	0.5	0.5	780
Diluted iohexol (Omnipaque; Amersham Health) <sup>‡</sup>	Iodine	63 <sup>§</sup>	...	0.5	0.17	285
Iohexol	Iodine	140	DSA	1.1	0.37	285
Iohexol	Iodine	200	DSA	1.58	0.52	410
Iohexol	Iodine	300	Cut-film angiography	2.36	0.79	643
Iohexol	Iodine	350	Coronary arteriography	2.76	0.92	783

Note.—Atomic masses of iodine and gadolinium are 126.9 and 157.3 amu, respectively.

\* Gadolinium chelates contain one gadolinium atom per chelate molecule; iodinated media, three iodine molecules per contrast medium molecule.

<sup>†</sup> Osmolality data are according to manufacturers.

<sup>‡</sup> Iohexol data would be similar for any other nonionic monomer (eg, iopromide). Iohexol is isotonic with plasma at 63 and 140 mg iodine per milliliter.

<sup>§</sup> Iohexol 140 mg iodine per milliliter diluted with saline.

gadolinium chelates at different levels of photon energies and (*b*) some data on general and renal toxicity of iodinated contrast media and gadolinium chelates. On the basis of these findings, we will try to predict whether iodinated or gadolinium-based contrast media would show the higher toxicity if the two types of media were compared at equal-attenuating concentrations or doses. From such a prediction, we challenge the concept that gadolinium chelates provide a safer alternative than iodinated media for x-ray angiography. The issue will be further discussed in connection with some statements commonly made to motivate the use of gadolinium chelates for DSA in patients with azotemia.

#### CONTRAST MEDIUM CONCENTRATIONS, ATOMIC MASSES, AND MOLES

A comparison of toxic properties between gadolinium chelates and iodinated contrast media at equal-attenuating concentrations is complicated by the fact that the concentration is given in the number (in millimoles) of contrast medium molecules per milliliter on vials containing gadolinium and in the weight (in milligrams) of the attenuating atom, iodine, per milliliter on vials containing iodinated contrast medium.

The SI definition of a mole is the amount of substance containing the same number

of chemical units (atoms, molecules, or other specified entity) as the number of atoms in exactly 12 g of the carbon isotope <sup>12</sup>C. The number of entities in 1 mol is approximately  $6.022 \times 10^{23}$  (ie, Avogadro's number).

The mass of atoms and molecules is often measured in atomic mass units (amu). The atomic mass unit is defined so that the mass of the <sup>12</sup>C atom is exactly 12 amu ( $1 \text{ amu} = 1.660 \times 10^{-24} \text{ g}$ ). The masses of an iodine atom, a gadolinium atom, an iohexol molecule (Omnipaque; Amersham Health, Princeton, NJ), and a gadopentetate dimeglumine molecule (Magnevist; Berlex Laboratories, Montville, NJ) are 126.9, 157.3, 821.1, and 938 amu, respectively. So, 12 g of <sup>12</sup>C, 126.9 g of iodine, and 157.3 g of gadolinium atoms all contain  $6.022 \times 10^{23}$ , or 1 mol, of atoms. Similarly, 938 g of gadopentetate dimeglumine and 821.1 g of iohexol molecules correspond to  $6.022 \times 10^{23}$ , or 1 mol, of contrast medium molecules. In summary, the number of moles of a substance are its weight in grams divided by the mass of its constituent atoms expressed in atomic mass units.

Gadolinium chelates such as gadopentetate dimeglumine, gadoterate meglumine (Dotarem; Guerbet, Roissy, France), gadodiamide (Omniscan; Amersham Health), and gadoteridol (ProHance; Bracco, Princeton, NJ) are commercially available at a concentration of 0.5 mmol/mL (ie, 0.5 mol/L). The molar concentration refers both

to the number of complete contrast medium molecules and to the number of attenuating gadolinium atoms, since there is only one gadolinium atom in each gadolinium chelate molecule.

The mass of an iodine atom is 126.9 amu. Consequently, 1 mmol of iodine corresponds to 126.9 mg, and a 0.5 mmol/mL solution corresponds to 63 mg of iodine per milliliter (mg I/mL) ( $0.5 \times 126.9$ ). Thus, a solution of iodinated contrast medium with a concentration of 63 mg I/mL contains the same number of attenuating atoms as do all commercially available 0.5 mol/L solutions of gadolinium-based contrast media. Sixty-three milligrams of iodine per milliliter is only 17%–21% of the iodine concentration used for conventional cut-film angiography and coronary arteriography; that is, 300–370 mg I/mL. The molar and weight content of some gadolinium chelates and iodinated contrast media discussed in this article, as well as their osmolality, are given in Table 1.

Iodinated ionic monomers (eg, diatrizoate [Urografin; Schering]) and nonionic monomers (eg, iopromide [Ultravist; Berlex Laboratories], iohexol), contain three iodine atoms per contrast medium molecule. Hence, the number of contrast medium molecules per milliliter will be only one-third the number of iodine atoms (Table 1). If, for the sake of simplicity, we assume that iodine and gadolinium atoms attenuate x rays to the same extent, then 63 mg

**TABLE 2**  
Total Attenuation by Iodine and Gadolinium at Different Photon Energies of Monochromatic Radiation

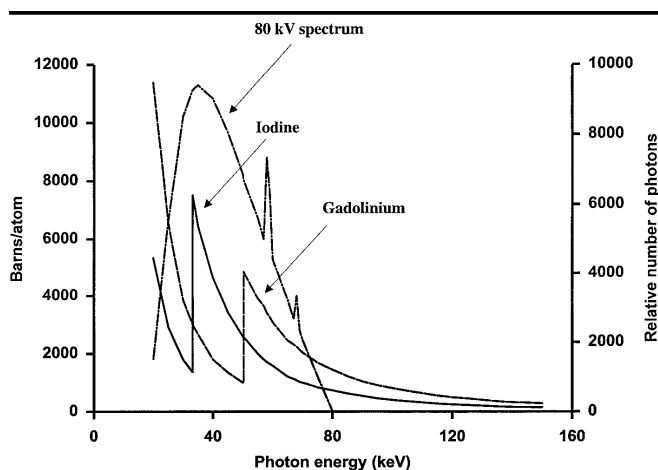
Atom	Photon Energy (keV)										
	20	30	35	40	50	60	70	80	90	100	150
Iodine	5,300	1,800	1,400, 7,600*	4,600	2,600	1,600	1,200	730	570	400	150
Gadolinium	11,000	3,800	2,800	1,800	1,000, 4,800†	3,100	2,300	1,500	1,100	800	290

Source.—Reference 15. Data at 35, 70, and 90 keV were interpolated.

Note.—Data are barns per atom (1 barn =  $10^{-28}$  m<sup>2</sup>, which is the cross-sectional area of a hydrogen atom nucleus. Total attenuation is photoelectric absorption and incoherent and coherent scattering.

\* Change in attenuation at k edge of iodine (33.2 keV).

† Change in attenuation at k edge of gadolinium (50.2 keV).



Graph shows the relative number of photons in an 80-kV polychromatic x-ray spectrum in relation to the attenuation of iodine and gadolinium measured in barns per atom at different photon energies.

l/mL would be equally attenuating with a 0.5 mol/L gadolinium chelate solution.

In summary, if iodine and gadolinium atoms attenuate x rays to the same extent, then an iodinated solution with an iodine concentration as low as 63 mg l/mL would be equally attenuating with all presently available gadolinium chelate solutions, and the number of potentially nephrotoxic monomeric iodinated contrast medium molecules would be only one-third the number of gadolinium chelate molecules.

#### ATTENUATION OF X-RAY PHOTONS BY GADOLINIUM AND IODINE ATOMS

Table 2 shows the ability of gadolinium and iodine atoms to attenuate a mono-

chromatic beam of x-ray photons at different energies (15). Attenuation increases with the atomic number, *Z*, of the atom (for iodine, *Z* = 53; for gadolinium, *Z* = 64) but decreases with the energy (kilo-electron volts) of the x-ray photons, except at the k edges. At photon energies between the k edge of iodine (33.2 keV) and that of gadolinium (50.2 keV), iodine attenuates roughly twice as many photons as does gadolinium. At all other photon energies, the opposite prevails.

A rule of thumb states that in a spectrum of photon energies exiting a filtered x-ray tube, the most common energies are at a level about one-half of their maximum. When the maximal photon energy is about 120–140 keV, as for computed tomography (CT), the most common photon energies in the spectrum are about

60–70 keV. This is above the k edge for gadolinium, where attenuation by gadolinium is about twice that by iodine (Table 2). So, a rough estimate for the complete spectrum of photon energies exiting an x-ray tube used for CT suggests that gadolinium attenuates twice as much radiation as does iodine. An iodinated contrast medium molecule containing three iodine atoms would then still attenuate 1.5 times the amount of radiation as a gadolinium chelate molecule with one gadolinium atom.

For conventional x-ray angiography, the voltage applied commonly varies between 70 and 90 kV (16). Therefore, a large part of the x-ray spectrum is found between the k edges of iodine (33.2 keV) and gadolinium (50.2 keV), where the attenuation by iodine is more than twice that by gadolinium (Figure, Table 2). Another part of the spectrum is above 50.2 keV, where the attenuation by gadolinium is twice that by iodine. The third part, below 33.2 keV, has such low energies that very few photons will pass through the human body and reach the detector. A rough integration of the data in the Figure and Table 2 over the spectrum of photon energies when a tube setting of 80 kV is used for conventional angiography would then indicate that the attenuation would be approximately the same for iodine and gadolinium atoms; namely, 0.5 mmol/mL of a gadolinium chelate would be equally attenuating with 63 mg l/mL.

In summary, an iodinated contrast medium molecule containing three iodine atoms would theoretically attenuate 1.5 times the number of x-ray photons as a gadolinium chelate molecule at 120 kV and three times the number of photons at 80 kV.

#### IN VITRO X-RAY ATTENUATION MEASURED WITH CT

Quinn et al (17) have been cited (3,13) for their conclusion that “[a]t equi-molar

concentrations, Gd-DTPA caused 2.5 times the attenuation by a solution of iopromide" measured with CT at 120 kV. This is the opposite of our theoretical assumption, stated earlier, that at CT a triiodinated molecule such as iopromide should attenuate 1.5 times more than a gadolinium chelate molecule. However, in the next sentence they state that "it was calculated that 90 mL Magnevist (47 mmol Gd-DTPA) would give similar attenuation to our usual dose of 50 mL iopromide 300 (117 mmol iodine) in cranial CT." This sentence shows that they have compared a gadolinium chelate with an equimolar concentration of iodine atoms and not iopromide molecules. Thus, according to the measurements presented by Quinn et al, an iopromide molecule, which contains three iodine atoms, actually attenuates 1.2 times the radiation attenuated by a gadolinium chelate molecule at 120 kV.

CT measurements at 120 kV performed by Schmitz et al (18), Gierada and Bae (19), and ourselves (unpublished data, 2000) demonstrated that triiodinated monomers cause 1.6–1.7 times the attenuation caused by an equimolar solution of gadolinium chelate; that is, 106–117 mg I/mL is equally attenuating with 0.5 mol/L of gadolinium chelate (Tables 3, 4). The reported differences among various authors with regard to the attenuation relationship between gadolinium-based and iodinated contrast media might, at least in part, be explained by differences in detector systems, x-ray tube filtration, and age of CT equipment. However, these in vitro CT measurements are in accordance with our previous theoretical assumptions.

CT measurements performed at 80 kV by Kaufmann et al (3) demonstrated that 0.5 mol/L gadopentetate dimeglumine was equally attenuating with 80 mg I/mL. Schmitz et al (18) and ourselves (unpublished data, 2000) found that the attenuation of a 0.5 mol/L gadolinium chelate corresponded to about 95–97 mg I/mL (Table 3). Since x-ray tubes in DSA equipment generally have less filtration than those used in CT equipment, one may expect that the iodine concentration that is equally attenuating with 0.5 mol/L gadolinium chelate at an 80-kV DSA study will be lower than that found for an 80-kV CT study.

**TABLE 3**  
Concentrations of Iodinated Contrast Media Equally Attenuating with Gadolinium-based Contrast Media

Study	X-ray Tube Current			
	72 kV	80 kV	90 kV	120 kV
CT				
Kaufmann et al (3)	ND	80	ND	ND
Quinn et al (17)	ND	ND	ND	160
Schmitz et al (18)	ND	95	ND	110
Gierada and Bae (19)	ND	ND	ND	106
Unpublished data (Elmstahl et al)	ND	97	ND	117
X-ray angiography				
Cardinal et al (16)	63	ND	ND	ND
Unpublished data (Elmstahl et al)	63	73	75	ND
Bittner et al (20)	37.5–75.0*	ND	ND	ND

Note.—Data are milligrams of iodine per milliliter in relation to a 0.5 mol/L solution of gadolinium chelate. Data are calculated or directly quoted from in vitro and in vivo experiments performed with different x-ray equipment. ND = not determined.

\* Actual tube current not reported.

### IN VITRO AND IN VIVO ATTENUATION AT X-RAY ANGIOGRAPHY

Using an image intensifier with a cesium iodide input screen in "an experimental and theoretical x-ray imaging performance" study, Cardinal et al (16) found that for x-ray spectra above 72 kV  $\pm$  6, the "radiographic contrast" obtained with gadolinium atoms generally exceeded that obtained with iodine atoms, while the opposite was true for spectra below that value.

Our own preliminary in vitro measurements with a DSA unit (unpublished data, 2000) also demonstrated that syringes placed in a phantom equivalent to 20 cm of water and filled with 0.5 mol/L solutions of iodine (63 mg I/mL) and gadolinium atoms were equally attenuating at 72 kV. At 85–90 kV, 0.5 mol/L gadodiamide demonstrated approximately the same radiopacity as 75 mg I/mL (Table 3). Bittner et al (20) found the overall quality of swine hepatic angiograms when 37.5–75.0 mg I/mL was used to be similar to that when 0.5 mol/L gadopentetate dimeglumine was used, although they did not mention the tube current used.

In summary, both our previous theoretical estimation and the in vitro measurements and in vivo results from animal experiments indicate that gadolinium and iodine atoms provide roughly equal attenuation in the commonly used 70–90-kV range for DSA. Thus, a solution of 60–80 mg I/mL should produce the same radiopacity as a 0.5 mol/L solution of gadolinium chelate. This range of iodine concentrations can be achieved by diluting vials containing commonly used con-

centrations for DSA; for example, 140–150 mg I/mL diluted 1:1 or 300 mg I/mL diluted 1:3 with saline.

### CONTRAST MEDIUM-INDUCED NEPHROPATHY

Vehmas and Markkola (6) stated that "gadolinium has been assessed as less nephrotoxic than iodinated contrast agents," referring to the clinical work of Prince et al (2), who had concluded that "high-dose gadolinium chelates are significantly less nephrotoxic than iodinated contrast." This statement may be true when comparing equivalent "clinical" doses of gadolinium chelates for MR angiography with those of iodinated media for x-ray angiography to achieve a similar diagnostic result.

Prince et al (2) investigated a cohort of 64 patients who received a gadolinium chelate for MR angiography and an iodinated contrast medium for x-ray angiography and CT on different occasions. After administration of the gadolinium chelate, no patient experienced an increase in serum creatinine level of 0.5 mg/dL (0.44  $\mu$ mol/L) or more, while 11 patients (17%) did experience such an increase after injection of iodinated medium. The gadolinium chelate was injected at a dose of 0.2–0.4 mmol per kilogram of body weight, resulting in a total dose of 15–30 mmol gadolinium chelate molecules in a 75-kg person. For the iodinated medium, a total dose of 30–60 g of iodine was administered, resulting in a molecular dose ranging from about 80 to 160 mmol (30,000–60,000 mg of iodine divided by 126.9  $\times$  3); in

**TABLE 4**  
Attenuation by Gadolinium and Iodine as Measured at CT

Study	CT Equipment	80 kV		120 kV	
		Gadolinium	Iodine	Gadolinium	Iodine
Kaufmann et al (3)	GE 9800*	6,840	5,533	ND	ND
Quinn et al (17)	SCT-3000TX†	ND	ND	6,600	2,455
Schmitz et al (18)‡	Somatom Plus S§	7,560	5,031	5,840	3,375
Gierada and Bae (19)	Somatom Plus S§	ND	ND	6,138	3,554
Unpublished data (Elmstahl et al)	Somatom Plus 4§	7,582	4,949	5,788	3,130

Note.—Data are Hounsfield units per millimole per milliliter of attenuating atoms. ND = not determined.

\* GE Medical Systems, Milwaukee, Wis.

† Shimadzu Medical Systems, Tokyo, Japan.

‡ Calculations are based on data in table 2 in reference 18.

§ Siemens Medical Systems, Erlangen, Germany.

**TABLE 5**  
Number of Attenuating Atoms per Contrast Medium Molecule, Molecular Mass, and Median Lethal Dose in Mice of Iodinated and Gadolinium-based Contrast Media

Contrast Medium*	No. of Attenuating Atoms per Molecule	Molecular Mass (amu)	Acute Intravenous Median Lethal Dose in Mice	
			Grams of Contrast Medium per Kilogram	Millimoles of Attenuating Atoms per Kilogram
Iodomethamate (31)	2	493‡	4.5	18.3‡
Iodopyracet (31)	2	510§	6.4	25.1‡
Diatrizoate (31)	3	636†	14.0	66.0‡
Diatrizoate (29)	3	Not reported	ND	51‡
Iopromide (29)	3	791	ND	153‡
Gadopentetate dimeglumine (29)	1	938	ND	6
Gadoterate (29)	1	754	ND	18
Gadoteridol (29)	1	559	ND	7.5
Gadodiamide (30)	1	574	ND	25

Note.—ND = not determined.

\* Number in parentheses is the reference number.

† Sodium salt.

‡ Calculated from original values.

§ Diethanolamine salt.

other words, up to 10 times more iodinated medium molecules than gadolinium chelate molecules were used. In addition, the gadolinium chelates were injected intravenously, while the iodinated compounds were used for both intravenous and intraarterial injections, with direct exposure to the renal arteries in a number of patients. Thus, the differences in injected dose and injection site may explain the reported higher nephrotoxicity of iodinated media as compared with that of gadolinium chelates.

Prince et al (2) actually used 240–480 mmol of iodine atoms (30,000–60,000 mg of iodine divided by 126.9) for x-ray angiography (eg, 100–200 mL of 300 mg I/mL). As previously discussed, gadolinium and iodine atoms appear to be roughly equally attenuating at the kilo-

voltage settings commonly used for DSA. Thus, an equal-attenuating dose of 480 mmol of gadolinium atoms is equivalent to almost 1 L of a 0.5 mmol/mL gadolinium chelate solution. If 1 L of gadopentetate dimeglumine were to be given to an 80-kg person, it would be equal to the median lethal dose, or LD<sub>50</sub>, in mice (6 mmol/kg) (Table 5). One can only speculate about any possible renal and other toxic effects of such a gadolinium dose in those surviving the LD<sub>50</sub> dose. As a comparison, a dose of 480 mmol of iodine in an 80-kg person (6 mmol/kg) is equal to only 4% of the LD<sub>50</sub> of nonionic iopromide in mice (153 mmol of iodine per kilogram) (Table 5).

In some animal experiments (21–23), the degree of albuminuria and increased excretion of brush-border and cytoplas-

matic enzymes have been in the same range in comparisons between equimolar concentrations of ionic iodinated and gadolinium-based contrast media, as well as for comparisons between nonionic iodinated media and gadolinium chelates, in both normal and diseased kidneys.

In an ischemic rat model (24), intraaortic injections of 1.5 mL of gadopentetate dimeglumine and 2.6 mL of diatrizoate caused a decrease of similar magnitude in creatinine clearance: 50% and 67%, respectively. However, the dose of iodine atoms appears to have been 10 times that of gadolinium atoms, according to the following: The osmolality of the gadopentetate dimeglumine solution used was reported to be 1,900 mosm/kg and “very close to diatrizoate.” These statements, as well as a previous report from the same research group (25), indicate that a 0.5 mol/L gadopentetate dimeglumine solution and a 76% diatrizoate solution (0.97 mmol/mL diatrizoate molecules; Table 1) were used. Thus, only 0.75 mmol (1.5 mL × 0.5 mmol/mL) of gadopentetate dimeglumine molecules (0.75 mmol of gadolinium atoms) seems to have been injected, compared with 2.5 mmol (2.6 mL × 0.97 mmol/mL) of diatrizoate molecules (3 × 2.5 = 7.5 mmol of iodine atoms). If the two contrast media had been compared at equal-attenuating doses at the kilovoltage used for DSA, the dose of diatrizoate would have been on the order of one-tenth of that actually used. One would then expect the decrease in creatinine clearance caused by diatrizoate to be much lower than that caused by gadopentetate dimeglumine.

In a recent experimental study (26) in pigs after left-sided nephrectomy, 3 mL/kg (20 mL/min) of various contrast media solutions or saline was injected in to the right renal artery during a 10-minute balloon occlusion. The half-life



elimination of contrast medium from plasma 60–180 minutes after injection was calculated as a measure of glomerular filtration. In the saline groups, 0.15 mL/kg of iohexol was injected for evaluation of glomerular filtration. The plasma half-life of gadopentetate dimeglumine was 25 times longer than that of the small iohexol dose in the saline group. In practical terms, this means that gadopentetate dimeglumine eliminated glomerular filtration. Gadodiamide and iohexol at 190 mg I/mL (equimolar to 0.5 mol/L gadolinium chelates) increased the plasma half-life 92% and 34%, respectively. All differences between the contrast media were statistically significant. Most noteworthy was that iohexol at 70 mg I/mL (equally attenuating as 0.5 mol/L gadolinium-based media) had effects on glomerular filtration that were not different from the effects of saline, with or without ischemia.

Acute renal failure was described after lower extremity arteriography with 80 mL of 0.5 mmol/mL (0.44 mmol per kilogram body weight) of nonionic gadoteridol (Prohance; Bracco Diagnostics) in an insulin-dependent diabetic patient with nephropathy (27). A transient increase in serum creatinine level, from about 350 to 820  $\mu$ mol/L, occurred.

Spinosa et al (14) reported one case of deteriorating renal function after administration of 70 mL of gadodiamide (0.3 mmol/kg) in 18 patients (6%) with azotemia who were undergoing carbon dioxide-enhanced angiography supplemented with 0.5 mol/L gadodiamide (20–100 mL; mean volume, 55 mL; 0.13–0.40 mmol/kg). When “small” volumes (33–100 mL; mean, 53 mL) of iohexol were used as supplement, as many as six of 15 patients (40%) had an increase in serum creatinine level of more than 0.5 mg/dL (44  $\mu$ mol/L). However, no true randomization was used, and iohexol was injected at a concentration of 300 mg I/mL (Spinosa DJ, written communication, 2000); that is, approximately four to five times the concentration (60–80 mg I/mL) necessary to achieve the same attenuation as a 0.5 mol/L gadolinium chelate during a DSA examination.

Injections of 80–440 mL of gadodiamide during arteriography have recently been reported (28). A serum creatinine level increase of 0.6 mg/dL (53  $\mu$ mol/L) or higher occurred in eight of 20 patients (40%) with a preprocedural serum creatinine level of 1.3–6.2 mg/dL (115–548  $\mu$ mol/L). In three of the eight patients, the creatinine values did not return to baseline values. Nevertheless, the conclu-

sion was that “intraarterial gadolinium in high volumes is a relative safe contrast agent with a low rate of postprocedural renal failure in patients with elevated creatinine level.” The intraarterial dose used by Gemmete et al (28) would, in a 75-kg person, range from 0.5 to 2.9 mmol per kilogram. Note that an intravenous injection of 0.4 mmol of gadolinium chelate per kilogram of body weight for MR imaging or MR angiography is considered to be a high dose (2). Thus, it seems that the intraarterial doses of gadolinium chelates for DSA are used uncritically. Another example of an uncritical attitude toward acceptable doses of gadolinium-based contrast media was presented by “experts” on the renal effects of contrast media and members of the European Society of Urogenital Radiology (29). They were of the opinion that “intravascular administration of gadolinium-based contrast media was not considered a risk factor for the development of nephrotoxicity even at the very high dose of 0.9 mmol/kg body weight.” No statement was made as to whether they meant an intravenous injection or a selective intrarenal injection of a high-osmolar gadolinium solution.

In summary, the general concept that gadolinium chelates are nonnephrotoxic may not hold true, especially when injected in relatively high doses resulting in a substantial osmotic load to the kidneys (1) or when the renal arteries are directly exposed to these hypertonic solutions. There are also results from one experimental study (24) that indicate that intraarterial injections of iodinated contrast medium may be less nephrotoxic than gadolinium chelates, when compared in equal-attenuating doses.

#### GENERAL TOXICITY

Murphy et al (7) stated that “gadolinium has proved to be safer than non-ionic contrast media,” and Fobbe et al (4) reported that “the rate of adverse side effects is lower than with iodine-containing contrast agents.” Again, the statements do not make any reference to the large differences in the number of contrast medium molecules administered for MR and x-ray imaging. Acute toxicity after intravenous administration in experimental animals has been evaluated (30,31), and differences in general toxicity between the two types of contrast media have been demonstrated.

The acute intravenous median lethal doses of contrast media in mice have been reported by Weinmann et al (30,31), who

compared gadopentetate dimeglumine, gadoterate, gadoteridol, and gadodiamide with the iodinated agents diatrizoate and iopromide; also, Hoppe et al (32), during the 1950s, compared diatrizoate, iodopyracet, and iodomethamate. The latter two iodinated contrast media were introduced during the early 1930s. From the results of these studies, we calculated the number of attenuating atoms (millimoles of iodine or gadolinium) per kilogram of body weight that was necessary to kill 50% of the animals (Table 5). Providing that iodine and gadolinium atoms are equally attenuating at about 72 kV during a DSA study, the general toxicities of the three media gadopentetate dimeglumine, gadoterate, and gadodiamide were about 25, eight, and six times, respectively, that of an equal-attenuating dose of iopromide. For the same radiopacity, gadopentetate dimeglumine may have an acute intravenous toxicity in mice three to four times worse than that of iodinated agents introduced 70 years ago.

In summary, gadolinium chelates have a higher general toxicity, according to the results of experimental median lethal dose studies, than do iodinated media when equal-attenuating doses for DSA at about 70 kV are compared.

#### EQUAL-ATTENUATING DSA CONTRAST MEDIUM DOSES IN AZOTEMIA

The maximum dose of gadolinium compounds, according to manufacturers' recommendations, is 0.2 mmol/kg for gadopentetate dimeglumine and 0.3 mmol/kg for gadoterate and gadodiamide. Gadolinium-based agents have generally not been injected in doses higher than 0.4 mmol/kg for DSA examinations (14). In a 75-kg person, this would correspond to 30–60 mL of a commercially available 0.5 mol/L solution. Accepting that iodinated contrast medium with 60–80 mg I/mL is equally attenuating with a 0.5 mol/L gadolinium chelate, then the same radiopacity would be achieved by using 30–60 mL of a concentration of 60–80 mg I/mL; that is, a total dose of only about 2–5 g of iodine. This dose corresponds to about 7–15 mL of a commonly used solution of 300 mg I/mL (Table 6). Frennby et al (33) used a similar dose of iohexol (10 mL of 300 mg I/mL [3 g of iodine]) to determine the glomerular filtration rate, or GFR, in 53 patients with severe chronic renal failure (overall, GFR  $\leq$  30 mL/min per 1.73 m<sup>2</sup>; in 40 patients, GFR  $\leq$  20 mL/min per 1.73 m<sup>2</sup>)



**TABLE 6**  
Volume of Iodinated Contrast Medium at Different Concentrations Resulting in Same Iodine Dose

Contrast Medium Volume (mL)	Iodine Concentration (mg/mL)	Iodine Dose (g)
60	70	4.2
30	140	4.2
21	200	4.2
14	300	4.2
11	370	4.2

Note.—In a 75-kg person, 60 mL of 0.5 mol/L gadolinium chelate (0.4 mmol/kg) for DSA at 60–80 kV may result in same attenuation as 60 mL of iodinated medium at concentration of about 70 mg I/mL. This table gives volumes of some commercially available iodine concentrations resulting in the same low iodine dose.

and did not notice any decline in renal function.

In summary, 2–5 g of iodine, equally attenuating with a relatively high dose of a gadolinium chelate, is a low iodine dose and could hardly have any important nephrotoxic effects. When using a mean iodine dose that was 10–25 times higher (140 mL of 350 mg I/mL [49 g of iodine]) in the Iohexol Cooperative Study, Rudnick et al (34) found only a 2.4% rate of severe contrast medium–induced renal failure after coronary angiography with iohexol in patients with preexisting renal insufficiency (serum creatinine level,  $\geq 1.5$  mg/dL [133  $\mu$ mol/L]).

#### OSMOLALITY AND OSMOTICITY OF CONTRAST MEDIA

The osmolality of a solution depends on the number of independently mobile moieties (ions, molecules, aggregates of molecules) per kilogram of water. It is given as osmoles or milliosmoles per kilogram of water. It is well recognized that many side effects of contrast media have been abolished with the introduction of “low-osmolality” agents, or those isotonic relative to human serum and other body fluids (35). On the basis of results from experimental studies, it is well known that hypertonicity plays an important role in contrast medium–induced nephropathy (1).

Gadopentetate dimeglumine is an ionic compound and contains one attenuating atom per three ions in solution—that is, a ratio of 1:3 (one gadolinium-containing

anion and two cations [meglumine]). The nonionic medium gadodiamide has a ratio of 1:1 (Table 4). The osmolalities of 0.5 mol/L solutions of gadopentetate dimeglumine and gadodiamide are 1,960 and 780 mosm per kilogram of water, respectively—three to seven times that of human serum ( $\approx 290$  mosm/kg; Table 1). Thus, the osmolality of gadopentetate dimeglumine is close to that of the previous generation of iodinated contrast media; namely, “high-osmolality” agents such as metrizoate (Isopaque Coronar, 370 mg I/mL; Nyegaard, Oslo, Norway) and diatrizoate (Urografin 76%; Schering). In comparison, a modern iodinated nonionic monomeric agent such as iohexol has a ratio of 3:1 and is isotonic at a concentration of 140 mg I/mL and will stay isotonic at lower concentrations if diluted with isotonic saline (Table 1).

In summary, the use of high-osmolality gadolinium chelates in patients with azotemia, especially when renal arteries are directly exposed to the hyperosmotic solution during renal arteriography, angioplasty, or stent placement (8,9), cannot be recommended when there is an isotonic equal-attenuating alternative (eg, proper dilution of iopromide) readily available at a low iodine dose.

#### VISCOSITY

The low viscosity of 0.5 mol/L gadopentetate dimeglumine—2.9 mPa at 37°C compared with 10.6 mPa for iohexol at a concentration of 350 mg I/mL—has been advocated as an advantage during hand injection (12). However, both iohexol and iopromide have a viscosity of 1.5 mPa at 37°C at a concentration of 140–150 mg I/mL. The ease of manual injection of contrast media should, therefore, be an even greater advantage with iodinated nonionic monomeric compounds at 60–80 mg I/mL.

#### COST

It has generally been claimed that gadolinium-based media are about four to five times more expensive per milliliter than are iodinated nonionic compounds. With equal-attenuating doses of iodinated nonionic monomers and depending on the size and number of vials that have to be opened, gadolinium-containing compounds may cost up to 20 times more than iodinated agents: Two 40-mL bottles of a gadolinium chelate cost approximately \$280, while a 50-mL vial of 140 mg I/mL iodinated nonionic mono-

mer for dilution with saline costs about \$11. (Our calculations were based on conversion from Swedish kronors at the April 15, 2001, rate of \$1  $\approx$  10 kronors.)

#### CONCLUSIONS

The performance of lumbar aortography with 40 mL of hyperosmolar 0.5 mol/L solutions of, for example, gadopentetate dimeglumine (osmolality, 1,960 mosm/kg) or gadodiamide (osmolality, 780 mosm/kg) will result in radiopacity similar to that achieved with a dilution (with 20 mL of saline) of, for example, 20 mL iohexol (140 mg I/mL) or a dilution (with 10 mL of sterile water and 20 mL of saline) of 10 mL iohexol (300 mg I/mL). These will result in isotonic contrast medium solutions with a total iodine dose of only about 3 g.

We have found no experimental or clinical evidence indicating that the general or renal toxicities of gadolinium chelates are lower than those of iodinated media in the small total doses of 2–5 g of iodine used to achieve the same degree of x-ray attenuation. On the contrary, gadolinium chelates have a substantially higher acute intravenous toxicity in experimental animals, and for some of the gadolinium compounds the toxicity may be even higher than that of iodinated media introduced 70 years ago. The nephrotoxicity of iso-osmolar iodinated media should be expected to be far less than that of hyperosmolar gadolinium solutions when equal-attenuating doses are used, especially during renal artery interventions. In addition, iodinated media are approved for intraarterial use, while gadolinium chelates are not. Finally, iodinated media are much less expensive than gadolinium-based media in equal-attenuating doses.

Therefore, it is our opinion that the clinical use of gadolinium chelates for diagnostic and therapeutic endovascular procedures guided with DSA in patients with azotemia should not be applied until their safety relative to equal-attenuating doses of iodinated media has been proved on the basis of systematic experimental and clinical study results, as is the case for any new experimental contrast medium.

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