Are gadolinium contrast media really less nephrotoxic than iodine agents in radiographic examinations? A comparison in relation to their ability to attenuate x-rays in a pig model

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A comparison in relation to their ability to attenuate x-rays in a pig model

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To my father

"I will never give up"

Table of contents

Abbreviations

ARF	acute renal failure
b.w.	body weight
CM	contrast medium/media
CIN	contrast medium induced nephropathy
CT	computed tomography
DX	direct digital system
Gd	gadolinium
GFR	glomerular filtration rate
g	gram
HOCM	high-osmolal contrast media
H&E	haematoxylin and eosin
IOCM	iso-osmolal contrast media
I	iodine
i.a.	intra-arterial
i.v.	intravenous
keV	kiloelectronvolt
kVp	kilovolt peak
LOCM	low-osmolal contrast media
M	mole/L
mg	milligram
mL	millilitre
Mmol	millimole
MOsm	milliosmole
mPa·s	millipascal-second
Pa·s	pascal-second
RF	radiofluoroscopy
ROI	region of interest
SI	Système International d'Unités
T1/2	plasma half-life elimination time
u	(atomic mass) unit
XRA	x-ray angiography

List of papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I Nyman U, Elmståhl B, Leander P, Nilsson M, Golman K, Almén T. Are gadolinium-based contrast media really safer than iodinated media for digital subtraction angiography in patients with azotemia? Radiology 2002; 223:311-318.

II Nilsson M, Elmståhl B, Geijer H, Leander P, Almén T, Nyman U. Determination of equal attenuating concentrations of iodine and gadolinium contrast agents for CT, RF, XA and DX systems. Manuscript.

III Elmståhl B, Nyman U, Leander P, Chai C-M, Frennby B, Almén T. Gadolinium contrast media are more nephrotoxic than a low osmolar iodine medium employing doses with equal x-ray attenuation in renal arteriography. An experimental study in pigs. Academic Radiology 2004; 11:1219-1228.

IV Elmståhl B, Nyman U, Leander P, Chai C-M, Golman K, Almén T. Gadolinium contrast media are more nephrotoxic than iodine media. A comparison with iso-osmotic mannitol solutions after renal artery injections in ischemic porcine kidneys. Accepted for publication in European Radiology.

V Elmståhl B, Nyman U, Leander P, Golman K, Pehrson R, Chai C-M, Almén T. 0.5-1.0M gadolinium contrast media are more nephrotoxic and less radiodense than equal volumes of iodixanol 320 mg iodine/mL after renal arteriography in an ischemic porcine model. Submitted for publication to Radiology.

VI Elmståhl B, Leander P, Grant D, Doughty R, Nyman U, Chai C-M, Almén T. Histomorphological changes after renal x-ray arteriography using iodine and gadolinium contrast media in an ischaemic porcine model. Manuscript.

Introduction

Intravascular iodine contrast media (I-CM) for x-ray examinations may cause deterioration of the renal function (i.e. they may be nephrotoxic) in patients with pre-existing renal insuffiency, especially in combination with other risk factors such as diabetes mellitus (1). Modern "low- and iso-osmolality" I-CM are without doubt less nephrotoxic than the older "high-osmolality" I-CM, but they may still have a negative effect on the renal function (2-4).

Gadolinium-based contrast media (Gd-CM), developed for magnetic resonance imaging (MRI), do also attenuate (block) x-rays (5-7) and are regarded by many authors as non-nephrotoxic or considerably less nephrotoxic than I-CM (8-14). These circumstances has contributed to that Gd-CM came into use as a substitute for I-CM in patients with renal insufficiency in a variety of x-ray angiographic examinations (XRA), intravascular interventions and computed tomographic (CT) examinations (9,13,15-28). This alleged low nephrotoxicity of Gd-CM is mainly based on the result of one investigation using low doses of Gd-CM for MRI (8) and comparing them with noticeably higher molecular doses of I-CM in XRA and CT. Since the sole purpose of radiographic CM is to attenuate the x-ray photons, their nephrotoxicity must therefore be compared in equal attenuating concentrations and equal volumes resulting in the same diagnostic information. To this date there is only one randomized study comparing the nephrotoxicity of I-CM with Gd-CM (26). Equi-molar doses of the I-CM iohexol 350 mg I/mL (0.92M) and the Gd-CM 1.0M gadobutrol both caused a 50% incidence of contrast media induced nephropathy (CIN) during XRA (26). However, the x-ray attenuation of iohexol 350 should be more than twice the attenuation of 1.0M gadobutrol at 70-90 peak kilovoltage (kV_p) XRA (29). The existing conviction that "Gd-CM are less nephrotoxic than I-CM" still seems to lack a scientific background.

In summary the present thesis is based on the concept that the sole purpose of using I- and Gd-CM in diagnostic radiology is their ability to attenuate x-rays and thereby create image contrast. The nephrotoxicity of CM must therefore be related to its usefulness, i.e. its ability to attenuate x-rays.

The main question is: What type of CM has the lowest nephrotoxicity when I- and Gd-CM are compared in equal volumes of concentrations with equal ability to attenuate x-rays?

In the present thesis renal toxicity caused by I-CM is compared with that caused by Gd-CM after selective renal artery injections in a pig model.

The nomenclature of contrast media

All conventional I-CM are derivatives of tri-iodinated benzoic acid, *Figure 1*. They are named **monomeric** when they contain only one benzene ring, *Figure 2*, and **dimeric** when they contain two benzene rings, *Figure 3*. I-CM are water-soluble and may be characterized as **ionic** or **non-ionic**. Ionic media dissociate into ions in water or when they enter blood. The CM molecule carrying the iodine atoms constitutes the negative anion. The positive cation (usually sodium or

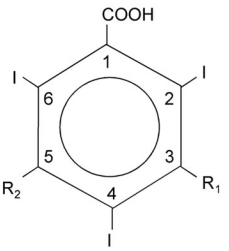

Figure 1. Structure of tri-iodinated benzoic acid

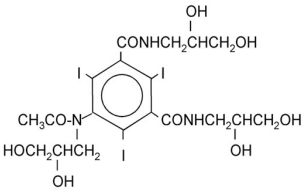

Figure 2. Non-ionic monomeric I-CM (iohexol- Omnipaque™)

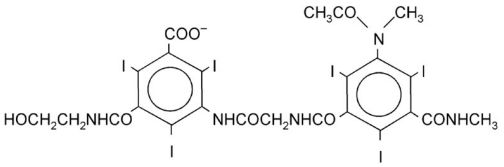

Figure 3. Ionic dimeric I- CM (ioxaglate - Hexabrix®)

meglumine ions) does not carry any iodine atoms and therefore does not yield any radiographic information. However, the cation is not biologically inert, since it (30) contributes to at least half the **osmolality** of the CM solution (31).

The ionic monomeric I-CM are referred to as the **"high osmolal" contrast media (HOCM)** because the osmolality at high concentrations (e.g. 370 mg I/mL) is approximately 7-8 times that of plasma. In 1969 Torsten Almén (31) considered that the osmolality of HOCM was responsible for much of their toxicity. He suggested the synthesis of a monomeric I-CM, which does not dissociate into ions, i.e. a non-ionic compound. His idea resulted in the first non-ionic I-CM, metrizamide (Amipaque), with an osmolality only one third that of ionic monomeric compounds at equal iodine concentration. Later non-ionic monomers including iohexol, iopamidol, iopromide, ioversol, iomeprol and iobitridol were developed. An ionic dimeric monoacidic I-CM (ioxaglate) was also synthesized with the same low osmolality as the non-ionic monomers. Both non-ionic monomeric and ionic dimeric monoacidic compounds are referred to as the **"low osmolal" contrast media (LOCM)**. It is important to realize that the osmolality of commercially available LOCM roughly ranges between one to approximately three times that of plasma depending on their concentration, i.e. they may be both iso-osmotic and hyper-osmotic relative to plasma. In order to reduce the hyper-osmolality at the higher concentrations of LOCM, two molecules of non-ionic monomers have been linked to produce a molecule containing six atoms of iodine per molecule. It has resulted in **non-ionic dimers**, which have the same (iodixanol) or almost the same (iotrolan) osmolality as plasma independent of concentration. They are referred to as **"iso-osmolal" contrast media (IOCM)**.

Gd-CM are made up by chelates consisting of a gadolinium atom bound to a ligand, e.g. diethylenetriaminepentaacetate (DTPA), bis-methylamide-DTPA (BMA-DTPA), tetraaza-cyclododecane tetraacetic acid (DOTA), etc. All Gd-CM comes in a 0.5M concentration except for gadobutrol, which is available in a 1.0M solution. The concentration refers both that of Gd-atoms and Gd-CM molecules, since there is only one Gd-atom per molecule, *Figure 4*.

Gd-CM are also water-soluble and may also be characterized as ionic and non-ionic. Ionic compounds consisting of one anion (CM molecule) and two cations (meglumine), e.g.

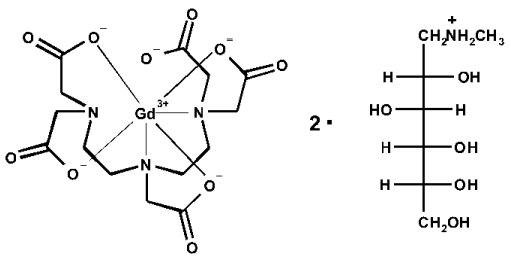

Figure 4. Ionic Gd-chelate (gadopentetate dimeglumine - Magnevist®)

dimeglumine gadopentetate or gadobenate, have an osmolality about seven times that of plasma, while those consisting of only one cation, e.g. monomeglumine gadoterate, has an osmolality about five times that of plasma. Gadobutrol is a non-ionic agent but with an osmolality 5.5 times that of plasma. All these types of Gd-CM may be referred to as HOCM. The non-ionic agents gadodiamide and gadoteridol has an osmolality only about two to three times that of plasma and may thus be referred to as LOCM.

Contrast media pharmacokinetics

Both I- and Gd-CM have high water solubility, low fat solubility, low binding to plasma proteins, are rapidly distributed in the extracellular space, have very small intracellular distribution and their body clearance is dominated by glomerular filtration (32-36), *Table 1*. These are the factors determining their pharmacokinetics, i.e. volumes of distribution and elimination half-life.

When CM molecules reach the systemic circulation, the molecules quickly equilibrate across capillary membranes (except an intact blood-brain barrier) (37,38). In the first phase of distribution, the increase in intravascular osmolality from plasma hyperosmotic HOCM and LOCM causes hypertonic effects, i.e. a rapid fluid shift across capillary membranes toward the hyperosmolal (intravascular) compartment. As the CM molecules pass through the capillary bed, there is rapid movement through capillary pores into the interstitial, extravascular space, as well as glomerular filtration into the renal tubules (39-43). The plasma concentration of CM follows a bi-exponential decay curve, *Figure 5*. The first exponential term represents the mixing of the CM in the plasma volume and then its distribution into the interstitial space. The second exponential term represents the clearance of CM molecules from the body (44).

The clearance of CM is primarily by means of glomerular filtration, i.e. renal clearance (32,48,54-57). The clearance of CM molecules is usually described by their half-life elimination time, i.e. the time required for elimination of 50% of the agent from the body. The clearance of CM from the plasma can be readily measured and has been regarded a reliable index of GFR (32,48,54-57).

Elimination half-life is not a direct indicator of the rate of CM removal, but is rather a dependent variable related to two independ-

Table 1. Pharmacokinetic properties of iodine and gadolinium contrast media in healthy human volunteers.

Contrast media	Plasma half-life (minutes)	Distribution volume (L/kg)	Body clearance
Iohexol* (36)	121 (108-126)	0.27 (0.24-0.28)	122 (118-128) mL/min (median value corresponds to 1.6 mL/min/kg#)
Gadopentetate ** (34)	95 (87-103)	0.26 (0.23–0.28)	1.9 (1.6-2.1) mL/min/kg
Gadodiamide** (35)	78 (62-94)	0.19 (0.18-0.21)	1.8 (1.4-2.2) mL/min/kg

*All values are median and 95% confidence interval.

**All values are mean and standard deviation.

#Calculated from the median values of plasma half-life and distribution volume using formula 2.

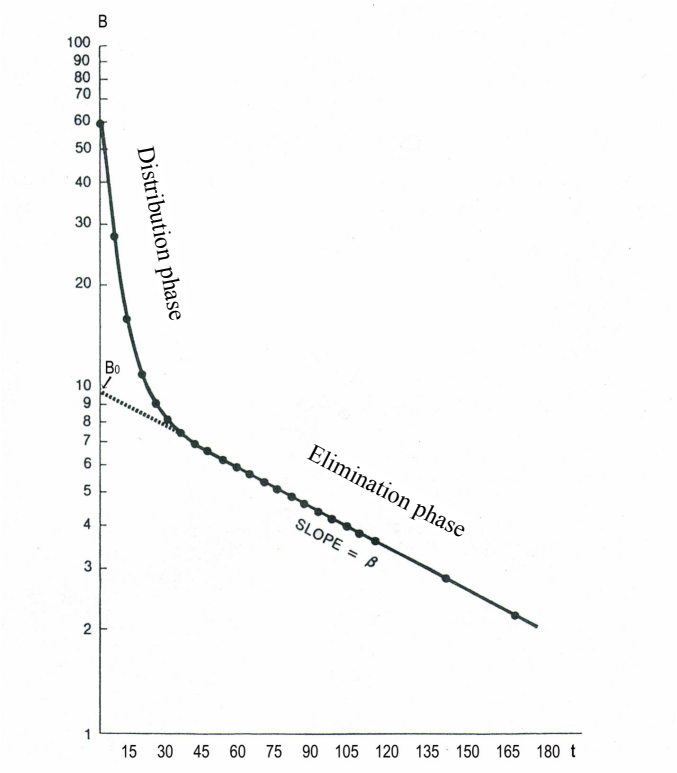

Figure 5. Schematic plasma concentration curve following rapid intrarterial injection of CM. Vertical axis B – plasma concentration of CM (log scale). Horizontal axis t – time in minutes after start of injection (linear scale). B_0 = zero time intercept of elimination phase of plasma concentration of CM curve when extrapolated back to time zero (i.e. after distribution equilibrium theoretically has been attained)
B_t = plasma concentration at time t minutes after injection of CM
$B_t = B_0\ e^{-\beta t}$
We name the value of t as T½ when Bt is equal to half the value of B_0
$B_0 / 2 = B_0\ e^{-\beta t}$
$T½ = \ln 2 / \beta$
Half – life is commonly used pharmacokinetic characteristic of drug (CM in this case)

ent pharmacokinetic factors, i.e. pharmacokinetic volume of distribution (V_d) and total body clearance (Cl). The V_d is the hypothetical volume term relating the total amount of CM in the body to its concentration in serum or plasma. Although V_d is a fictitious volume, it reflects the extent of CM distribution in vivo (58). It is sometime called the "apparent volume of distribution" and can be determined as:

V_d = Dose/Concentration (59).

The relationship between elimination half-life (T1/2), V_d, total body clearance (Cl) and GFR can be expressed as follows:

$$T1/2 = \frac{\ln 2 \times Vd}{Cl} \quad \Leftrightarrow \quad \mathrm{Cl}\ (\approx \mathrm{GFR}) = \frac{\ln 2 \times Vd}{T1/2} \qquad (1)$$

and volume of distribution may be calculated using the formula:

$$Vd = \frac{Dose \; x \; T1/2}{(AUC \; x \; ln2 \; x \; weight)} \qquad (2)$$

where Ln = natural logarithm (ln2=0.693), V_d = volume of distribution (mL/kg body weight), Dose = contrast medium (e.g. mg iodine), AUC = area under the time-plasma concentration curve (minutes*mg I/mL) from time of injection to infinity, T½ = plasma half life elimination time (minutes) of GFR marker and finally weight in kg.

In healthy human volunteers iohexol, gadodiamide and gadopentetate had similar, but not identical, volumes of distribution, half-life and total body clearance *Table 1*.

In summary by measuring the plasma half-life elimination time of CM following their injection, it is possible to evaluate the nephrotoxic effect of a CM by measuring its own effect on renal function.

Glomerular filtration

The kidneys are just 0.4% of the body's total mass, yet they handle 1.2-1.3 L of blood each minute, accounting for approximately 20-25% of total cardiac output. The basic functioning unit of the kidney is the **nephron**, *Figure 6*. The size of the kidneys in various species is largely determined by the number of nephrons they contain. There are approximately 1.3 million nephrons in each human kidney (60).

The movement of water and solute across the glomerular capillary wall to form an ultrafiltrate of plasma is called glomerular filtration; the rate at which this occurs is called the glomerular filtration rate (GFR). The normal GFR for humans is about 125 mL/min or 180 L/day (60 times plasma volume), whereas the normal urine is only approximately 1.5 L/day. Thus, more than 99% of the filtrate is reabsorbed (44).

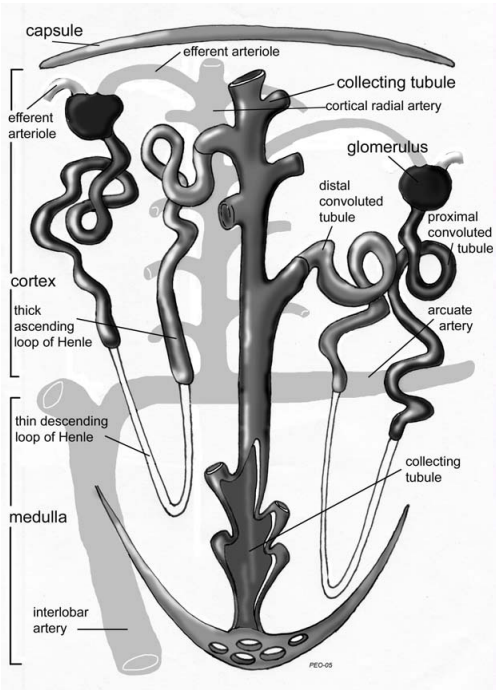

Figure 6

Contrast medium concentrations and moles

Comparison of toxic properties between Gd- and I-CM at equal attenuating concentrations is complicated by the fact that the concentration is given in number (mmoles) of CM molecules per mL on vials containing Gd-CM and in weight (mg) of the attenuating atom (iodine) per mL on I-CM vials.

The SI definition of a mole (abbreviated mol) is the amount of substance containing the same number of chemical units (atoms, molecules or other specified entities) as the number of atoms in exactly 12 g of the carbon isotope ^{12}C. The number of entities in one mole is approximately 6.022 x10^{23}, i.e. Avogadro's number.

The mass of an iodine atom, a gadolinium atom, an iohexol molecule and a dimeglumine-gadopentetate molecule is 126.9, 157.3, 821.1, and 938 u respectively. So, 12 grams (g) of ^{12}C, 126.9 g of iodine and 157.3 g of

gadolinium atoms all contain 6.022 x 10^{23} or one mole of atoms. Similarly 821.1 g of iohexol and 938 g of dimeglumine-gadopentetate corresponds to 6.022 x 10^{23} or one mole of CM molecules. For the sake of simplicity the number of moles of a substance is its weight in gram divided by the mass of its constituent atoms expressed in atomic mass units.

Gd-CM such as gadopentetate, and gadodiamide are commercially available at a concentration of 0.5 mmol/mL (= 0.5 mol/L = 0.5 molar = 0.5M). Gadobutrol is the only Gd-CM available at concentration of 1.0 mmol/mL (=1.0 mol/L = 1.0 molar = 1.0M). The molar concentration of the Gd-CM refers both to the number of complete CM-molecules and to the number of attenuating Gd-atoms since there is only **one Gd-atom in each Gd-CM molecule**.

The mass of an iodine atom is 126.9 u. Subsequently one mmol of iodine corresponds to 126.9 mg and a 0.5M solution to 63.5 mg I/mL (0.5*126.9). Thus, an I-CM solution with a concentration of only 63.5 mg I/mL contains the same number of attenuating atoms as all commercially available 0.5M Gd-CM. Assuming that iodine and gadolinium atoms attenuate x-rays to the same extent, then 63.5 mg I/mL would be equal-attenuating with a 0.5M Gd-CM solution. Non-ionic monomeric I-CM, such as iopromide or iohexol contains **three iodine atoms per I-CM molecule**. Hence, the number of CM molecules per mL will be only one-third the number of iodine atoms.

In summary if iodine and gadolinium atoms attenuate x-rays to the same extent, then an I-CM solution with an iodine concentration as low as 63.5 mg I/mL would be equal attenuating with all presently available 0.5M Gd-CM solutions AND the number of potentially nephrotoxic monomeric I-CM molecules would only be 1/3 (0.5/3=0.17M) the number of Gd-CM molecules.

X-ray attenuation

K-edge and characteristic radiation

Attenuation is the reduction in the intensity of an x-ray beam as it traverses matter by either absorption or deflection of photons from the beam (61). The intensity of a beam is the product of the number and energy of the photons. X-ray photons may interact with orbital electrons or the nucleus of atoms. In the diagnostic energy range, the interactions are always with orbital electrons. The attenuation of photons in any materia including iodine and gadolinium atoms decreases with increasing photon energy. However, a sudden increase in photon attenuation, the so called **K-edge**, occurs at a photon energy just above the binding energy of the K shell electron (the innermost shell) of the atom, *Figure 7*. The photon disappears, giving up all its energy to the electron, so called photoelectric absorption of the photon. When a photon transfers all of its energy to the K shell electron, the electron will be released from the atom. The resulting K shell electron void will be filled by an outer shell electron, usually from the adjacent L shell. As an electron drops into the K shell the atom can release the excess energy in the form of an x-ray photon. The energy of this photon is characteristic of each element and these X-rays are therefore called **characteristic radiation**. X-ray fluorescence technique utilizes characteristic radiation emitted from e.g. iodine and gadolinium to measure their plasma concentrations and has been used in the present investigations. The three x-ray contrast media iodine, barium and gadolinium have K shell binding energies for absorption of x-rays of 33.2, 37.4 and 50.3 keV, respectively. Similar sudden increases in attenuation may also be found at lower energies for other shells than the K shell. The general term for this phenomenon is absorption edge.

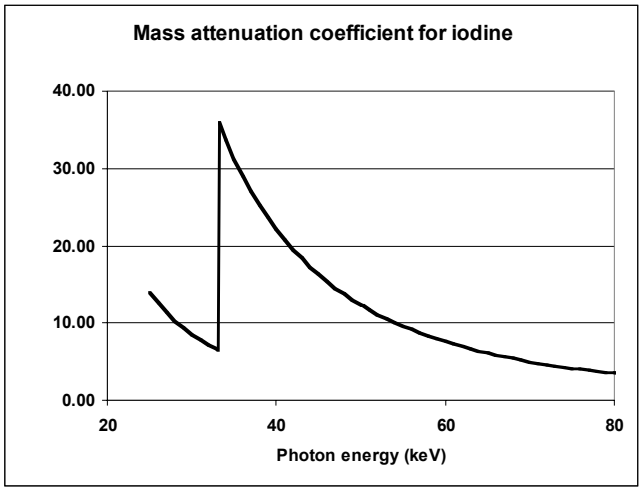

Figure 7. Mass attenuation coefficient for iodine illustrating the K-edge located at 33.2 keV

Attenuation of x-ray photons by gadolinium and iodine atoms

Attenuation increases with the atomic number Z of an element (iodine Z=53, gadolinium Z=64) but, as already mentioned, decreases with the energy (keV = kiloelectronvolt) 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 gadolinium. At all other photon energies the opposite prevails.

A rule of thumb, states that in a spectrum of photon energies coming out of a filtered x-ray tube, the most common energies are at a level about one half of their maximum. When an x ray tube peak kilovoltage (kV_p) is set to 120-140 kV_p, as for CT, the most common photon energies in the spectrum are about 70-80 keV. This is above the K-edge for gadolinium, where the attenuation by gadolinium is about twice that by iodine. So a rough estimate for the complete spectrum of photon energies out of an x-ray tube used for CT suggests, that gadolinium attenuates twice as much radiation as iodine, i.e. a 0.5M Gd-CM would result in the same x-ray attenuation as a 1.0M I-CM = 126.9 mg I/mL An I-CM molecule containing three iodine atoms would then still attenuate 1.5 times the amount of radiation as a Gd-CM molecule with only one Gd-atom.

For XRA the peak kilovoltage commonly applied varies between 70-90 kV_p. Therefore a large part of the x-ray spectrum, *Figure 8*, 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. 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 the human body and reach the detector. Thus, a rough integration of the spectrum of photon energies at a tube setting of 80 kV_p indicates that the attenuation would be approximately the same for iodine and gadolinium atoms; i.e. 0.5 mmol/mL of a Gd-agent would be equal attenuating with 63.5 mg I/mL. Using an image intensifier with a cesium iodide input screen in "an experimental and theoretical x-ray imaging performance", it was found that for x-ray spectra above 72±6 kV "radiographic contrast" obtained by gadolinium atoms generally exceeded that of iodine atoms and vice versa below that value (62).

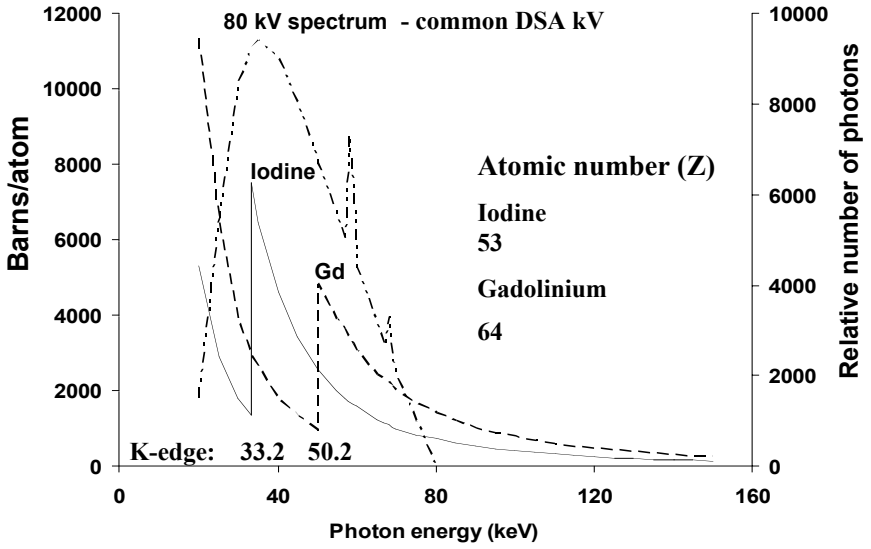

Figure 8. Illustration of the relative number of photons in a 80 kilovolt (kV) polychromatic X-ray spectrum (dotted and dashed line) in relation to the attenuation of iodine (I, solid line) and gadolinium (Gd, dashed line) measured in barns/atom at different photon energies (kiloelectronvolt = keV).

In summary an I-CM molecule containing three iodine atoms would theoretically attenuate 1.5 times the number of x-ray photons as a Gd-CM at 120 kV_p and three times the number of photons at about 70-80 kV_p.

Contrast medium toxicity

Toxic reactions to contrast media may be attributed to the CM molecule (chemotoxicity), osmotoxicity, composition if ions in ionic CM or added ions in non-ionic CM, viscosity, etc. Osmotic effects from rapid injections of highly concentrated CM solutions have long been regarded as one of the major mechanisms behind adverse CM reactions. The development of LOCM and IOCM has resulted in CM with a decreased osmolality in relation to attenuating capacity, i.e. an increased **ratio** between attenuating and osmotic particles.

The "ratio concept" of iodine and gadolinium contrast media

The ratio between the number of iodine or gadolinium atoms and the number of osmotic active particles in the CM solution results in a single measure to describe attenuating capacity in relation to possible osmotoxicity; i.e. relative attenuation per osmotic active particle.

Ionic monomeric I-CM, e.g. sodium diatrizoate, have three iodine atoms per two particles in solution (one sodium ion and one CM molecule diatrizoate), i.e. a ratio of 1.5 (3:2). Non-ionic monomeric I-CM, e.g. iohexol, have three iodine atoms per particle (one non-dissociable monomeric CM molecule) therefore a ratio of 3 (3:1). The ionic monoacidic dimer ioxaglate has six iodine atoms per two particles in solution (one cation and one CM molecule as anion), i.e. a ratio of 3 (6:2). The non-ionic dimer iodixanol has six iodine atoms per particle (one non-dissociable dimeric CM molecule) and thus a ratio of 6 (6:1).

The ionic monomeric Gd-CM dimeglumine gadopentetate contains one attenuating atom per three ions in solution and has a ratio 0.33

(1:3) [one anion (gadopentetate) containing one gadolinium atom and two cations (meglumine) containing no gadolinium], while meglumine gadoterate contains only one meglumine cation resulting in a ratio of 0.5 (1:2). The non-ionic gadodiamide and gadobutrol have a ratio of 1 (1:1; one gadolinium atom in one non-dissociable CM molecule).

The differences in ratio between e.g. gadopentetate (1:3) and iodixanol (6:1) means that for each osmotic active particle, iodixanol contain 18 times the number of attenuating atoms compared with gadopentetate.

In summary if gadolinium and iodine atoms should have the same attenuating capacity, gadopentetate would deliver 18 times more osmotic active particles (with potential osmotic side-effects) than iodixanol for the same diagnostic density. The corresponding figure for gadoterate would be 9 and for gadodiamide 6 times.

Osmolality

The osmolality of a solution is the measurement of the number of its particles in a solution per kilogram of water. It can be described as a measurement of the number of molecules that can crowd out or displace water molecules in a kilogram of water (63). The unit of osmolality is osmole or milliosmole/kg H_2O (Osm or mOsm/kg H_2O).

Human plasma has an osmolality of about 0.29 Osm/kg H_2O, salt water from the Baltic Sea in south Sweden (outside Ystad or Trelleborg) an osmolality equal to that of plasma, while salt water from the open ocean measures 1.01 Osm/kg H_2O. The osmolality of 0.5M Gd-LOCM and the highest concentrations of I-LOCM (350-400 mg I/mL) reaches about 0.8 Osm/kg H_2O, while the osmolality of 0.5M Gd-HOCM and the highest concentrations of I-HOCM (370 mg I/mL) are about 2.0 Osm/kg H_2O. CM osmolality is related to the nephrotoxic effects of the media. There are two aspects of this statement:

1) The higher the osmolality of the CM is in the syringe the higher hypertonic effects will be on e.g. blood cells and vessel walls in the kidney downstream to the point of injection into the renal artery.
2) The other aspect of osmolality is related to osmotic load.

Osmotic load

Ionic and non-ionic I- Gd-CM are all filtered through the glomerula and reach the tubular lumen. The CM-molecules in the tubules, contrary to surrounding water molecules, resist absorption to the blood and try to keep water inside the lumen, i.e. they function as osmotic diuretics and constitute an **osmotic load** (64). Note that the magnitude of this osmotic load depends on the total dose of CM molecules and is independent of their concentration, hyper- or iso-osmolal relative to plasma at the site of injection. At equal doses of iodine the ionic monomeric diatrizoate (ratio 1.5) represents the highest osmotic load, the non-ionic monomeric iohexol (ratio 3.0) represents half the osmotic load of diatrizoate and the non-ionic dimeric iodixanol (ratio 6.0) half the load of iohexol.

Viscosity

Viscosity is described as a resistance to flow. It is perceived as "thickness", e.g. water is "thin", while corn syrup is "thick". The SI unit of viscosity is pascal-second (Pa·s). At 20°C water has viscosity 1.0 mPa·s, blood 1.5-1.7 mPa·s, while corn syrup has a viscosity of 74.6 mPa·s. One of the former HOCM, Hypaque M (462 mg I/mL) had a viscosity of 34.7 mPa·s at 25°C and 19.5 mPa·s at 37°C. Modern CM such as the non-ionic dimeric iodixanol at 320 mg I/mL and non-ionic monomeric iomeprol at 400 mg I/mL reaches viscosities of 25.4 and 27.5 mPa·s, respectively, at 20°C and 11.4 and 12.6 mPa·s, respectively, at 37°C. As comparison the corresponding figures for the non-ionic Gd-CM

0.5M gadodiamide and 1.0M gadobutrol are 2.8 and 8.0 at 20°C and 1.9 and 5.0 at 37°C. In angiography, there is often a need for fast injections of large volumes of CM through narrow catheters. Therefore the viscosity of angiographic CM should not be too high. Accordingly, in an ideal angiographic CM both osmolality and viscosity should be low (31).

Contrast media induced nephropathy (CIN)

Almost 100% of an intravascular dose of CM is normally excreted through the kidneys by glomerular filtration. Thus, the kidneys are obviously one of the main target organs for contrast media induced nephropathy. Major risk factors include impaired renal function, especially when combined with diabetes mellitus and other risk factors, reduction in effective intravascular volume and decreased renal perfusion (dehydration, congestive heart failure, hypotension, liver cirrhosis), and concurrent use of other nephrotoxic drugs.

CIN is most commonly defined as an acute impairment of renal function manifested by an absolute increase in serum-creatinine concentration of at least 0.5 mg/dL (44.2 μmol/L) or a relative increase of at least 25% from the base-line value occurring within three days following CM administration in the absence of alternative etiology (3,65-68). Using these definitions prospective controlled studies in patients without risk factors have reported an incidence of I-CM induced nephropathy varying from 0 to 10% (1). Incidence among patients with diabetes has been reported to be 9-40% in patients with mild-moderate and 50-90% in those with severe chronic renal impairment (69)

CIN is regarded a common cause of hospital-acquired acute renal failure (70-73). The clinical course of CIN may vary. Often there is only a transient increase in serum-creatinine with a return to base-line values within 1 or 2 weeks. Occasionally, oliguria or anuria starts within 24 hours, necessitating temporal or chronic dialysis. Renal failure requiring dialysis has been reported in 2-15% in patients with pre-existing renal impairment (3,69,72). CIN defined as a s-creatinine increase >25% has been shown to be associated with a higher morbidity and mortality rate than a patient group from the same population and match for age and base-line s-creatinine who had similar CM procedures but did not develope CIN (69).

The use of I-LOCM, implying a decreased osmotic load to the kidneys, instead of I-HOCM has reduced the risk of CIN (2,3,73). In a recent study on patients with a combination of impaired renal function and diabetes mellitus, the IOCM iodixanol implied a lower risk of CIN compared with the LOCM iohexol (4). However CIN is still a burning issue because there is presently a tendency to expose an increasing number of patients to larger amounts of I-CM due to an expanding use of CT, XRA and vascular interventions, which all may require high doses of I-CM. Many of these procedures are performed in elderly patients with decreased renal function and diabetes mellitus.

CIN is almost exclusively associated with I-CM except for occasionally reported cases of renal failure after administration of Gd-CM (74-77). According to some authors Gd-CM may even *improve* glomerular filtration rate (GFR) in patients with impaired renal function (78).

The apparent non-nephrotoxic effects of Gd-CM for MRI compared with I-CM for XRA and CT may be explained by the fact that the molar doses of Gd-CM used in MRI are small, generally ≤0.3 mmol/kg b.w., in relation to the doses of I-CM used in radiography. As an example doses for XRA at about 300-400 mL 300 mg I/mL of HOCM and LOCM have been regarded safe in patients with normal renal function (71,79), though doses up to 800 mL 300 mg I/mL of LOCM

(80) and 1020 mL 320 mg I/mL of IOCM (81) have been given in some patients without any apparent renal effects. These iodine doses (300-800 mL, 300 mg I/mL, of monomers with 3 iodine atoms per molecule) correspond to 3.4-9 mmol I-CM molecules/kg in a 70 kg person. It means that at these iodine doses the number of I-CM molecules is 11-30 times the number of Gd-CM molecules at the dose of 0.3 mmol Gd-CM/kg b.w. and the number of I-atoms is 33-90 times the number of Gd-atoms.

In summary the commonly marked differences in clinically applied CM doses between MRI and radiographic examinations may at least to some extent explain the noted differences in CIN frequency.

Some possible factors in the pathophysiology of CIN

The pathophysiological mechanisms behind CIN are not fully elucidated but seem likely multifactorial and dependent on osmotic and chemotoxic effects of the CM. Recently CM viscosity has also been proposed as a pathogenic factor (82).

Osmotic factors have been considered to play a significant role in the development of CIN (1). The administration of plasma hyperosmotic CM may result in marked shrinkage and rigidification of red blood cells (83-85) and vascular endothelial injuries with platelet aggregration (86,87) may cause microcirculatory occlusions. Apart from the direct cellular exposure to the hypertonic solutions injected into the renal artery, the CM also represent an osmotic load to the kidneys with secondary diuresis and natriuresis (1,44,64). Osmotic load may activate the tubulo-glomerular feedback mechanism mediating vasoconstrictive agents, increase medullary oxygen demand for active reabsorption of the increased tubular sodium load resulting in hypoxic injuries and/or increase intratubular pressure with elevation of interstitial pressure and secondary vascular compression beneath the rigid renal capsule. A non-osmolality-dependent release of vasoconstrictors has also been postulated (1).

It has recently been claimed that plasma isoosmotic dimeric I-CM such as iodixanol and iotrolan may increase tubular fluid viscosity due to filtration of high viscous CM into the tubules in combination with a lower osmotic diuresis allowing higher tubular concentration compared with LOCM and HOCM. It was suggested that augmented tubular viscosity increases resistance to tubular flow resulting in raised intratubular pressures, diminished GFR and decreased medullary blood flow due to compression of peritubular vessels from increased hydrostatic pressure within the tubules (88).

A direct cytotoxic effect on renal tubular cells may also be caused by CM (89,90).

General toxicity of contrast media

Intravenous (i.v.) general toxicity (i.v. LD_{50})

Statements have been made that the rate of adverse side effects is lower with Gd-CM than with I-CM (29). However, these statements do not make any referral to the large differences in the number of CM molecules administrated in MR and x-ray imaging. Acute i.v. toxicity in experimental animals has been evaluated and demonstrate marked differences in general toxicity between the two types of CM. The LD_{50} is a standardized rough measure for expressing and comparing the general toxicity of chemical substances in pre-clinical studies. It is the dose that kills 50% of the animals tested (LD = "lethal dose"). The lower the LD_{50}, the more toxic the chemical substance is.

Intravenous LD_{50} in mice for gadopentetate and gadodiamide is 6 and 25 mmol Gd/kg mouse, respectively (29), while for the nonionic monomeric I-CM iopromide and iohexol it is about 18-20 g I/kg b.w., i.e. 142-158 mmol I/kg mouse (18 000-20 000/126.9

u). Thus, one needs 6-25 times more iodine atoms (carried in the body of I-CM molecules) than gadolinium atoms (carried in the body of Gd-CM molecules) to reach the dose at which 50% mortality occurs. According to these LD_{50} studies in mice Gd-CM would be 6-25 times more toxic to the body as a whole than non-ionic monomeric I-CM, providing that iodine and gadolinium atoms are equal attenuating at about 70-80 kV_p during an XRA study.

When comparing the general toxicity of equal attenuating concentrations of Gd-and I-CM for CT at approximately 120-140 kV_p (when the attenuation by one gadolinium atom is about twice that by one iodine atom), the toxicity of Gd-CM would be about 3-12 times higher than the toxicity of ratio 3.0 I-CM.

Animal models

Animal models used before

CIN is difficult to induce in animals. This is similar to the clinical situation in which CIN rarely occurs in patients with normal kidney function, but develops in the presence of other renal insults, particularly those that lead to a reduction in renal perfusion (91, 92). Normal and healthy animals seem to tolerate even extremely high doses of CM without any effect on renal function (93). To sensitize the animals and thereby producing effects after CM injection similar to those observed in patients at risk, a variety of renal insults have been used such as drug administration (94-96), salt and water depletion (97), ischemia by the occlusion of renal arteries (98,99) and also including multiple insults such as uninephrectomy with drug administration or salt depletion (94) or uninephrectomy with temporal ischemia (100,101).

Present animal model

We used a porcine model, designed to provoke an acute CM-induced renal failure after selective injection of high doses of Gd- and I-CM into the right renal artery of one kidney. A left-sided nephrectomy was performed, a prerequisite for using plasma half-life elimination time of the injected CM as a GFR marker to measure renal function of the CM-exposed right kidney. In a pilot study we injected CM into the patent right renal artery. Since we did not notice any decline in the renal function, temporary occlusion of the right renal artery was added to potentiate the effect of the CM.

Aims of the study

General aim

To confront the statement that Gd-CM are less nephrotoxic than I-CM when used in radiographic examinations.

Specific aims

1. To review the current literature and analyze the properties of Gd- and I-CM concerning their x-ray attenuation, general toxicity and nephrotoxicity (Paper I)

2. To determine in vitro equal attenuating concentrations of Gd- and I-CM for XRA and CT at various x-ray spectra. (Paper II)

3. To compare the nephrotoxicity of equal volumes of equi-molar and equal attenuating concentrations of Gd- and I-CM following their injections in to the renal artery of a temporarily ischemic kidney (Paper III).

4. To investigate the role of osmolality of CM on renal toxicity in the same porcine model as in Paper III (Paper IV).

5. To compare the nephrotoxicity of equal volumes of gadolinium HOCM (ratio 0.33) and LOCM (ratio 1) with commercially available plasma iso-osmotic iodine LOCM (ratio 3) and IOCM (ratio 6) in the same porcine model as in Paper III (Paper V).

6. To investigate renal histomorphological changes caused by the Gd- and I-CM in the pigs studied in Paper III-V and to correlate these changes with the effects on renal function that occurred in the same pigs.

Material and methods

Phantom study (Paper II)

Iodine concentration

The concentration of iodine (mg/mL or mmol/mL) in the present paper always refers to the iodine atom, not to the I-CM molecule, unless otherwise stated.

CT measurements

Four 20 mL syringes were filled with 0.01, 0.02, 0.05 and 0.1 mmol/mL of I-atoms and four other with the same concentrations of Gd-atoms. The syringes were scanned (Siemens Somatom Sensation 16) at 80, 100, 120 and 140 kV_p in air and in a 30 cm (diameter) circular phantom of polystyrene, *Figure 9a and b*. A fifth syringe containing distilled water was included in all scans as a constancy reference.

Measurements on RF, XRA and DX systems

Six syringes were filled with iohexol at concentrations of 35, 50, 70, 90, 110 and 140 mg I/mL. Another syringe was filled with 0.5M gadodiamide and yet another two with distilled water. The syringes were placed in drilled holes in a slab of polypropene plastic. For each series of exposures at various kV_p the phantom was loaded with syringes containing gadodiamide, water and one syringe containing one of the iohexol concentrations. The syringes with I- and Gd-CM were placed beside each other in the middle with a water-filled syringe on each side, *Figure 10a*. This slab was symmetrically surrounded with plexiglass plates (polymethylmetacrylate, PMMA), forming a phantom corresponding to a total equivalent thickness of 20 cm ("thick phantom") or 13 cm ("thin phantom") of water.

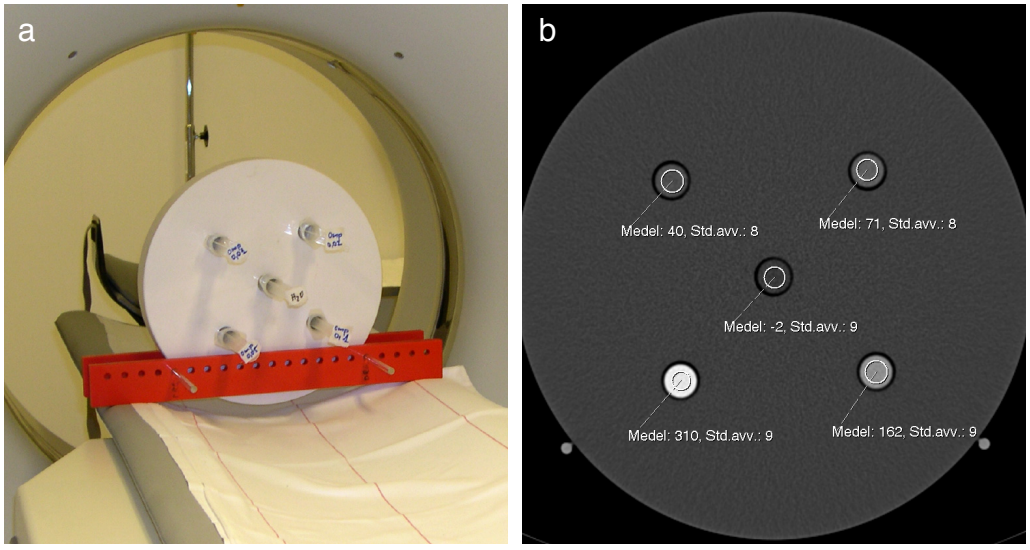

Figure 9. Four syringes filled with 0.01, 0.02, 0.05 and 0.1M gadolinium atoms surrounding a centrally placed syringe with distilled water and all placed in a 30 cm diameterpolystyrene phantom (a) and a computed tomographic image (b) exposed at 120 kV_p for density measurements in Hounsfield numbers ("Medel" = mean number in the region of interest).

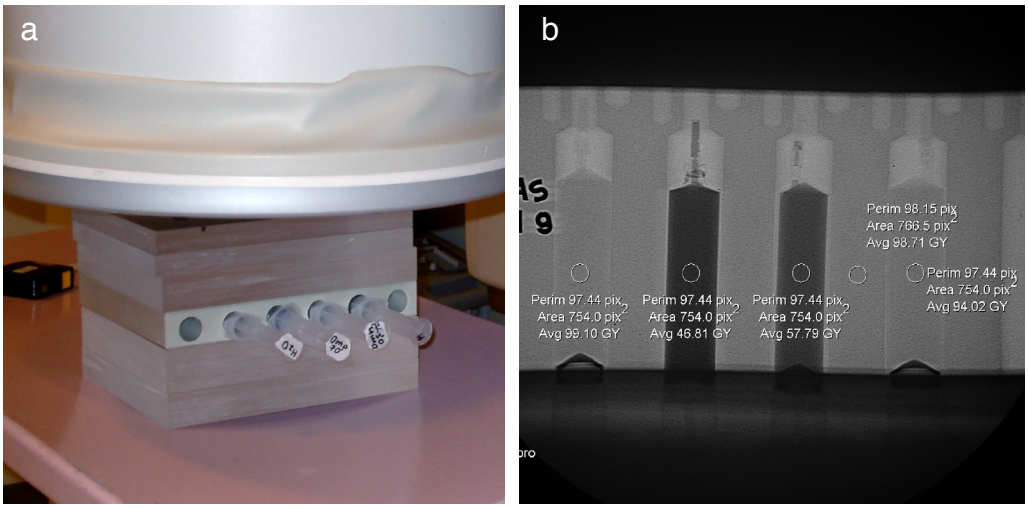

Figure 10. Four syringes filled from left to right with distilled water, iohexol 70 mg I/mL, 0.5M gadodiamide and distilled water placed in a thick phantom equivalent to 20 cm water in a MultiDiagnost 4 radiofluoroscopy system (a) and an X-ray image of the phantom following exposure demonstrating measurments of relative contrast (b)

Exposures were made at 52, 60, 70, 81, 96 and 117 kV_p with a radiofluoroscopy (RF) unit (Philips MultiDiagnost 4) and a Direct-Digital (DX) unit (Philips DigitalDiagnost). For the dedicated x-ray angiography (XA) unit (Philips Integris V3000) it was not possible to set exposure parameters manually. Using different preconfigured programs exposures for the thick phantom were obtained at 65 and 69 kV_p and for the thin phantom at 55 and 62 kV_p. Density measurements were performed with a ROI placed in the centre of the syringes and influence by the heel effect was avoided, *Figure 10b*. For the RF, DX and XRA systems the attenuation properties of the contrast agents were evaluated using the relative contrast value *Crel* :

$$C_{rel} = \frac{|P_{ph} - P_{CA}|}{P_{ph}} \qquad (3)$$

P_{ph} = mean pixel value in a ROI over the phantom material close to the syringe

P_{CA} = mean pixel value in a ROI centrally inside the image of the syringe

Animal studies (Paper III-VI)

Animal preparation

The experiments were performed on 64 (Paper III), 48 (Paper IV) and 40 (Paper V) healthy Swedish landrace male pigs with a mean weight of 21 kg (range 16-23 kg), 21 kg (range 16-29 kg) and 23 kg (range 18-28 kg), respectively. After each experiment the right kidney was removed and a histomorphological analyze was performed. The kidneys from totally 144 of the 152 animals (the gadodiamide group in paper V not evaluated) were studied (Paper VI).

Following general anaesthesia the right femoral artery was dissected free and an 8-9 F was inserted and connected to a pressure transducer for continuous recording of the arterial pressure. Intra-arterial pH, pO_2 and pCO_2 were also monitored during the experiment. An introducer was inserted into the right internal jugular vein for injection of heparin (5000 IU/mL) and blood sampling. A bolus dose of heparin (30 IU/kg) was given and the introducers were flushed with heparinized saline (5000 IU in 1000 mL of saline) to prevent clotting.

A left-sided nephrectomy was performed through a subcostal incision. After surgery a 60 minute calibration period was used to monitor the pigs for hemodynamic stability. A 4F Cobra catheter was inserted, via the right femoral artery introducer, into the right renal artery. The catheter was then exchanged over a guide wire for a 5F balloon occlusion catheter, *Figure 11*. Then an additional i.v. dose of 200 IU/kg heparin was given to prevent thrombotic occlusion of the renal artery during the subsequent balloon occlusion. The occlusion balloon was inflated for a period of 10 minutes (except NaCl-3 group) to produce both renal ischemia and prolonged contact between the test solution and the renal vessels.

Test solutions (Paper III-VI)

Details of the test solutions are given in the *Table 2*. Each pig was randomized to receive one test solution, at a dose of 3 mL/kg b.w. and at a rate of 20 mL/min into the right renal artery through the occlusion catheter during the first 3 minutes of a 10 minute ischemic period. In the animals subjected to saline in NaCl-1 group, a total dose of 3 mL iohexol (300 mg I/mL) was injected intravenously as a GFR marker. In NaCl-2 and NaCl-3 groups totally 3 mL of iohexol 300 mg I/mL was added as GFR marker to the saline dose injected into the right renal artery.

Preparation of mannitol/iohexol solutions (Paper IV)

Crystalline mannitol ($C_6H_{14}O_6$; molecular weight 182.17) was added to a 0.18M iohexol solution in an iterative process until osmolalities (vapor pressure measurement) of the mannitol/iohexol solutions (*mannitol/io*) at 37° C were attained almost equal to the osmolality of 0.5M solutions of gadopentetate, gadodiamide and iohexol, *Table 2*. The reason for using an iohexol solution as solvent was to utilize iohexol as GFR-marker. The three *mannitol/io* solutions were named *mannitol/io 1.96* (iso-osmotic to 0.5M gadopentetate), *mannitol/io 0.82* (iso-osmotic to 0.5M gadodiamide) and *mannitol/io 0.43* (iso-osmotic to 0.5M iohexol).

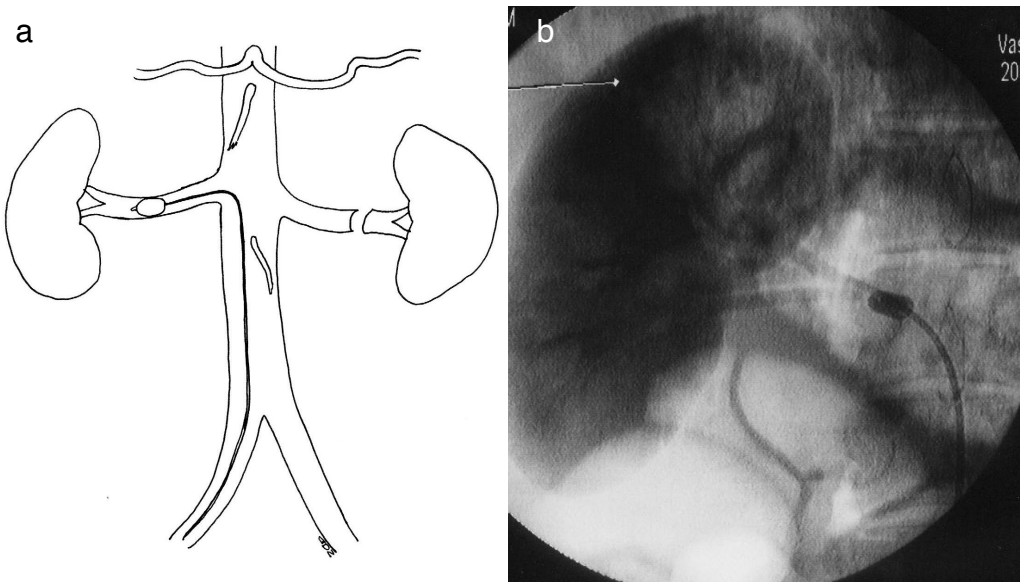

Figure 11. Schematic illustration of the present animal model (a). Nephrogram showing the ballon-catheter inflated in the right renal artery during the 10 minute period of ishemia (b)

Table 2. Molarity of contrast medium (CM) molecules and gadolinium (Gd) and iodine (I) atoms in the various testsolutions and the osmolality and viscosity of the solutions.

Test solutions (injected at a dose of 3 mL/kg body weight)	**CM molecules** [molarity (M)]	**Gd or I atoms** [molarity (M) (mg/mL)	**Osmolality** (Osm/kg H_2O) 37°C	**Viscosity**[1] (mPa·s) 20°C	37°C
Dimeglumine gadopentetate (Magnevist®, Schering AG, Berlin, Germany)	0.5M	0.5M (79 mg Gd/mL)	1.96[1]	4.9	2.9
Mannitol/iohexol 1.96[3]	0.153M iohexol	0.460M (58 mg I/mL)	1.96[2]	NM	NM
Gadobutrol (Gadovist®, Schering AG)	1.0M	1.0M (158 mg Gd/mL)	1.60[1]	8.9	5.0
Gadodiamide (Omniscan™, Amersham Healthcare AS, Oslo, Norway)	0.5M	0.5M (79 mg Gd/mL)	0.78[1]	2.8	1.9
Mannitol/iohexol 0.82[3]	0.179M iohexol	0.54M (68 mg I/mL)	0.82[2]	NM	NM
Iohexol [Omnipaque™ 300 or 350 mg I/mL (Amersham Healthcare AS)] diluted with H_2O	0.5M	1.5M (190 mg I/mL)	0.40[1]	~3.8[4]	~2.4[4]
Mannitol/iohexol 0.43[3]	0.182M iohexol	0.55M (69 mg I/mL)	0.82[2]	NM	NM
Iopromide (Ultravist®, Schering AG)	0.39M	1.18M (150 mg I/mL)	0.34[1]	2.30	1.50
Iodixanol (Visipaque™, Amersham Healthcare AS)	0.20M	1.18M (150 mg I/mL)	0.29[1]	2.70	1.70
Iodixanol	0.42M	2.52M (320 mg I/mL)	0.29[1]	25.4	11.4
Iohexol (Omnipaque ™ 140 mg I/mL) diluted with saline	0.18M	0.55M (70 mg I/mL)	0.29[1]	<2.37[5]	<1.5[5]
NaCl-1[6]			0.29[1]		
NaCl-2[7]			0.29[1]		
NaCl-3[8]			0.29[1]		

NM=not measured.

1) According to the manufacturer.
2) Measured with a Vapor Pressure Osmometer 5500 XR.
3) Mannitol was dissolved in a 0.18M iohexol (70 mg I/mL) obtained by diluting iohexol 140 mg I/mL (Omnipaque™ 140) with an equal volume of sodium chloride.
4) Viscosity according to manufacturer of iohexol 190 mg I/mL.
5) Viscosity according to manufacturer of iohexol 140 mg I/mL is 2.3 mPa·s at 20°C and 1.5 mPa·s at 37°C.
6) Total 3 mL of iohexol 300 mgI/mL injected i.v. (v.jugularis) as GFR marker.
7) Total 3 mL of iohexol 300 mg I/mL added as GFR marker to the saline solution injected into the right renal artery.
8) No ischemia; 3 mL of iohexol 300 mg I/mL added as GFR marker to the saline dose injected into the right renal artery.

Note: osmolality = osmoles per kg water (solvent); molarity= moles per liter solution (solute+solvent).

Plasma half-life of the contrast media (Paper III-V)

Plasma half-life elimination time of the CM was used as an index of their effect on GFR. The larger a CM-induced depression of GFR is, the lower the body clearance of the GFR-marker (the contrast medium) from plasma will be with subsequent prolongation of its plasma half-life elimination time. CM plasma half-life was calculated by using a one compartment model and linear regression analysis of logarithmic plasma concentrations (32) in the period one to three hours post-injection, i.e. elimination phase, *Figure 5*. In other words the half-life elimination time was calculated from the slope β of the plasma concentration curve using relationship: $T1/2 = \ln 2/\beta$. Thus a hybrid of a one-compartment model and two-compartment model has been used.

Determination of contrast medium concentrations in plasma (Paper III-V)

Four-mL blood samples were drawn up to 180 minutes to determine the plasma CM concentration using x-ray fluorescence technique (102-104).

Plasma half-life/attenuation and osmotic load/attenuation indexes (Paper V)

Plasma half-life relative to iodixanol 320 mg I/mL was calculated by dividing the median plasma-half-life time for each CM by that of iodixanol 320 mg I/mL. In a similar way osmotic load relative to iodixanol 320 mg I/mL were calculated for each test solution, i.e. the total number (mosmoles) of osmotic active particles injected per kg b.w. Osmotic load may correspond to the number of CM molecules injected of a non-ionic CM or the number of cations and anions of an ionic CM providing no apparent formation of molecular aggregates in their highly diluted state in the total extracellular fluid. This does not exclude formation of loose aggregates of CM molecules at the high CM concentrations in a syringe or in a concentrated bolus of CM-molecules.

The attenuation relative to iodixanol 320 mg I/mL was then calculated for the various CM based on in vitro measurements in Paper II. At 120 kV_p CT a 0.5M Gd-CM was assumed to be equal attenuating with 110 mg I/mL and at 70-90 kV_p XRA equal attenuating with 70 mg I/mL. The relative plasma half-life and osmotic load, respectively, were divided by the relative attenuation for each CM. The resulting plasma half-life/attenuation and osmotic load/attenuation indexes were compared with the index of 1 for iodixanol 320 mg I/mL.

Radiograms

Four radiograms were obtained 1, 3 (end of injection), 10 (end of ischemic period) and 30 minutes after the start of injection using a C-arm equipment (BV 300 PLUS, Philips, Netherlands). X-ray tube peak potential was set to 70 kV_p. An extra radiogram 3 hours after injection was obtained in animals injected with gadopentetate, *mannitol/io 1.96* and gadobutrol. The radiograms were subjectively analyzed with regard to CM excretion or retention of CM within the renal parenchyma (without excretion), i.e. a "persistent nephrogram". The density of the radiograms was compared as they appeared at the end of injection of the various CM.

Histomorphological evaluation (Paper VI)

Two samples of the right kidney i.e. one slice of dorsal and ventral part of kidney were collected and immersion fixed in 10% neutral buffered formalin for histomorphological evaluation. After fixation, the tissue samples were trimmed, processed into paraffin wax, sectioned at a nominal thickness of 5 µm, stained with haemotoxylin and eosin and mounted under cover slips on glass slides then examined on a Leitz DMRD light microscope.

In the evaluation procedure both sections from the same animal were examined sequentially and all slides were read on at least two separate occasions (one original read and one review). The severity of histomorphological changes were graded subjectively as follows: 1= minimal, 2 = mild, 3 = moderate and 4 = marked. The observer (DG) was blinded to treatment except for the control groups (saline). All slides were subjected to comprehensive peer review by another pathologist (RD). On disagreement between the observers, the slides were reviewed to reach a consensus grading.

Statistics (Paper III-VI)

To evaluate any statistically significant differences in renal function caused by the various test solutions, as indicated by their individual plasma half-life elimination time, the non-parametric Mann-Whitney U-test was used. P-values of 0.05 or less were considered statistically significant (Paper III-V).

To evaluate any statistically significant differences of histomorphological changes between the various test solutions, the non-parametric Mann-Whitney U-test was also used. In order to reduce the risk of false positive findings, we only considered p-values of 0.01 or less as statistically significant (Paper VI).

Results

Phantom study (Paper II)

CT measurements

The equal attenuating concentration ratios for different kV_p with and without phantom material as well as the concentrations of iodine in mg/mL giving the same attenuation as 0.5M Gd are given in *Figure 12*. It was found that 0.5M Gd corresponded to 93, 105, 110 and 112 mg I/mL with phantom and to 72, 85, 93 and 96 mg I/mL without phantom at 80, 100, 120 and 140 kV_p, respectively.

Measurements on RF, XRA and DX systems
As an example, the relative contrast values for 35-140 mg I/mL and 0.5 M Gd for the thick phantom imaged with the DigitalDiagnost are given in *Figure 13*. Similar figures were obtained for the thin phantom and for the MultiDiagnost 4. From such figures iso-attenuating concentration curves of iodine to 0.5M gadolinium can be found for different kV_ps. These results are presented in *Figure 14*. The curves are very similar, except for the MultiDiagnost 4 with the thick phantom, which clearly differs. However, when the experiment was repeated with the image processing parameters switched on, the system behaved similarly to the DigitalDiagnost. At about 70-90 kV_p, 0.5M Gd-CM were roughly equal attenuating with 70 mg I/mL for both systems. For the Integris V3000 system, the kV_p could only be varied within a very narrow interval. The equal attenuating concentrations of iodine to that of 0.5 M Gd were found to be: 35 mg I/mL at 60 kV_p with the thin phantom and 50 mg I/mL at 65-69 kV_p with the thick phantom.

Effects on renal function (Paper III-V)

Plasma-half life and GFR in unilaterally nephrectomized pigs

In Group 1 (Paper III) eight pigs were injected intravenously with 3 mL of iohexol 300 mg I/mL in connection with saline injection into the renal artery. Based on formula 2, these unilaterally nephrectomized pigs got a calculated median volume of distribution of

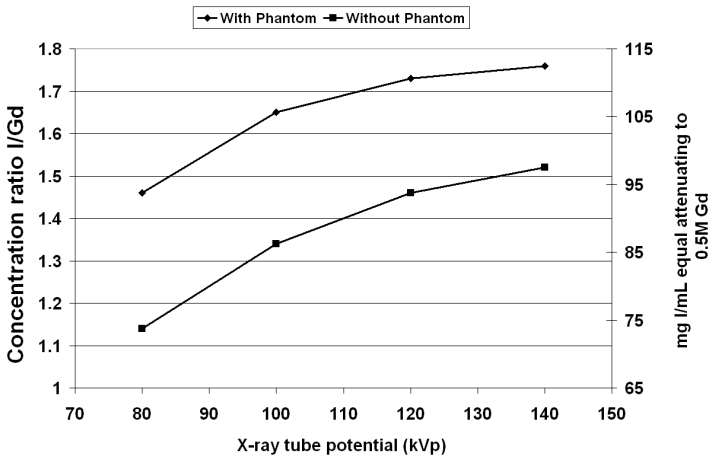

Figure 12. Left Y-axis: Iodine/gadolinium (I/Gd atoms) molar concentration ratio producing the same computed tomographic Hounsfield number at different X-ray tube voltages. Right Y-axis: Iodine concentrations (mg/mL) giving the same Hounsfield number as that of 0.5M gado-linium.

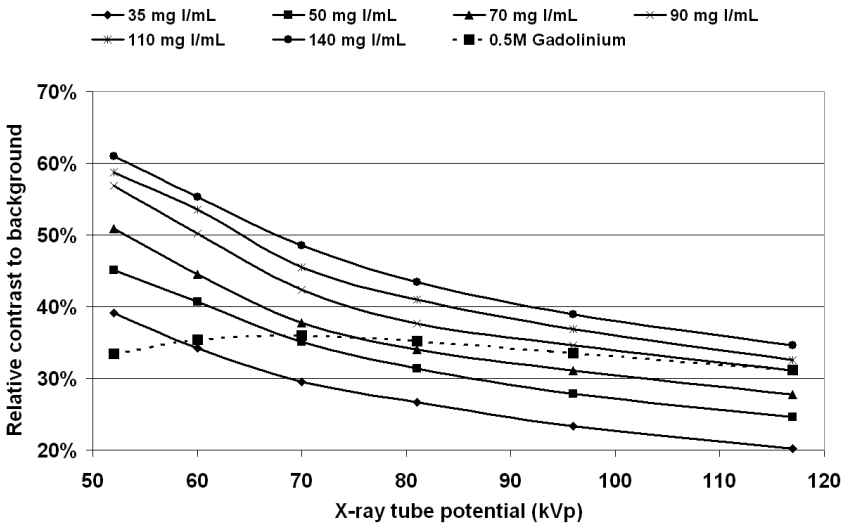

Figure 13. The relative contrast (as defined by equation 1) for 0.5M gadolinium and concentra-tions of iodine from 35–140 mg/mL at different kV_p for the DigitalDiagnost system with the thick phantom.

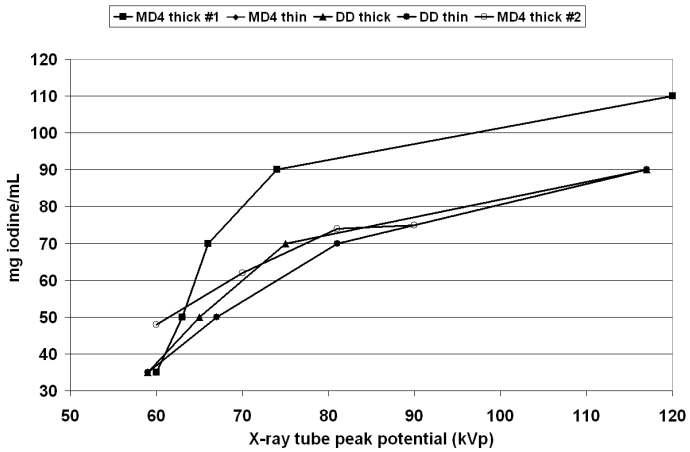

Figure 14. Concentration of iodine (mg/mL) giving the same relative contrast as that for 0.5M gadolinium at different kVps for the MultiDiagnost 4 (MD4; #1 without image processing pa-rameters, #2 repeated study with processing parameters) and DirectDigital (DD) systems (thin=thin phantom, thick= thick phantom). The curves for MD thin and DD thin are overlying each other.

iohexol that was 0.25 L/kg (range 0.24-0.31). This was of similar magnitude as in healthy human volunteers, *Table 1*. Using formula 1 and inserting the median values for volume of distribution (0.25 L/kg) and plasma half-life of the GFR marker in pigs subjected to saline (133 minutes) will result in a calculated median body clearance value of 13 mL/min/10 kg. Considering that the pigs had only one kidney these values fit well with the results of a previous study at our laboratory, in which body clearance of iohexol in normal pigs with two kidneys was 22 mL/min/10 kg (56).

Plasma-half life elimination time of the GFR marker vs. test solution

The plasma half-life results from all pigs in Paper III-V were pooled for each CM. The pooled results are summarized in *Figure 15* and the median values on the pooled figures of each test solution are given in *Table 3*. 0.5M gadopentetate, *mannitol/io 1.96* and 1.0M gadobutrol caused significantly longer plasma half-life time when compared with the results of the individual test solutions in each study. 0.5M gadodiamide caused significantly longer half-life than 0.5M iohexol (190 mg I/mL) and all plasma iso-osmotic I-CM tested from 70 to 320 mg I/mL. There was no significant difference in half-life between 0.5M gadodiamide and the iso-osmotic *mannitol/io 0.82*, while 0.5M iohexol (190 mg I/mL) caused a significantly longer half-life than its iso-osmotic counterpart, *mannitol/io 0.43*. The plasma half-life of all plasma iso-osmotic CM were in the same range as the plasma half-life of the GFR marker following injections of saline with and without ischemia. There was no significant difference between saline with and without ischemia.

Radiograms (Paper III-V)

Gadopentetate, *mannitol/io 1.96* and gadobutrol caused a persistent nephrogram up to three hours post-injection and without any visible of excretion of CM, *Figure 16-18*. Gadodiamide and all I-CM resulted in a transient nephrogram during the period of ischemia that had vanished 30 minutes post injection and instead CM excretion was seen. The density of the nephrograms in decreasing in order relative to injected CM was: iodixanol 320 > iohexol 190 > iodixanol 150 = iopromide 150 = 1.0M gadobutrol > 0.5M gadodiamide = 0.5M gadopentetate = iohexol 70.

Plasma half-life and osmotic load/ attenuation index (Paper III-V)

The plasma half-life/attenuation indexes for the Gd-CM were all higher than that of the I-CM at both 150 and 320 mg I/mL, Table 3. For the same attenuation 0.5M gadodiamide may appear about 5 and 7 times more nephrotoxic than iodixanol 320 mg I/mL at 120 kV_p CT and 70-90 kV_p XRA, respectively. The corresponding figures for 1.0M gadobutrol were 11 and 18 times and for 0.5M gadopentetate 35 and 56 times that of iodixanol 320 mg I/mL.

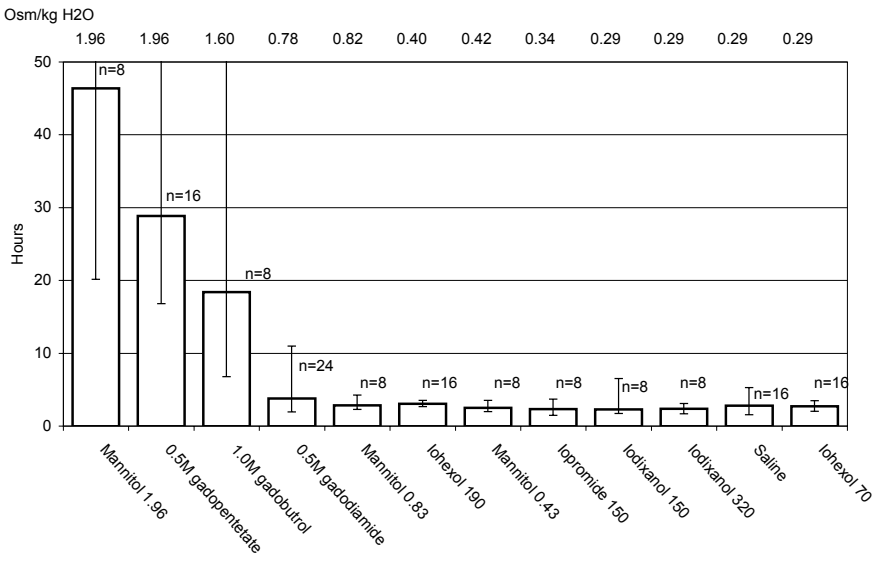

Figure 15. Pooled half-life results from all pigs in Paper III-V

Table 3. Concentration of CM molecules, number of attenuating atoms per CM molecule, osmolality, viscosity, attenuating capacity in terms of iodine, nephrotoxicity and osmotic load/attenuation index relative iodixanol 320 mg I/mL of the various contrast media.

Contrast media (3 mL/kg b.w.)	**Gado-pentetate**	**Gado-butrol**	**Gado-diamide**	**Iohexol 70**	**Iohexol 190**	**Iodixanol 150**	**Iodixanol 320**	**Iopromide 150**
CM molecules (mmol/mL)	0.5	1.0	0.5	0.18	0.5	0.20	0.42	0.39
Gd or I atoms per molecule	1	1	1	3	3	6	6	3
Osmolality at 37°C (Osm/kg)[1]	1.96	1.6	0.78	0.29	0.42	0.29	0.29	0.34
Viscosity (mPa·s)[1] 20°C	4.9	8.9	2.8	NM	NM	2.7	25.4	2.3
37°C	2.9	5.0	1.9	NM	NM	1.7	11.4	1.5
Median plasma half-life (min)	1730[2]	1103	228[2]	159[2]	180[2]	136	142	138
-relative iodixanol 320 mg I/mL	12.2	7.8	1.6	1.1	1.3	1.0	1	1.0
Osmotic load (mOsm/kg b.w.)	4.50	3.00	1.50	0.54	1.50	0.59	1.26	1.18
-relative iodixanol 320 mg I/mL	3.6	2.4	1.2	0.4	1.2	0.5	1	0.9
Attenuating capacity (mg I/mL)[3]								
CT at 120 kVp with phantom	110	220	110	70	190	150	320	150
-relative iodixanol 320 mg I/mL	0.34	0.69	0.34	0.22	0.59	0.47	1	0.47
XRA at 70-90 kVp	70	140	70	70	190	150	320	150
-relative iodixanol 320 mg I/mL	0.22	0.44	0.22	0.22	0.59	0.47	1	0.47
Plasma half-life/attenuation index[4]								
-CT at 120 kV	35.4	11.3	4.7	5.1	2.1	2.0	1	2.1
-XRA at 60-80 kVp	55.7	17.8	7.3	5.1	2.1	2.0	1	2.1
Osmotic load/attenuation index[4]								
-CT at 120 kVp	10.4	3.5	3.5	2.0	2.0	1.0	1	2.0
-XRA at 60-80 kVp	16.3	5.4	5.4	2.0	2.0	1.0	1	2.0

b.w.=body weight, CM=contrast media, Gd=gadolinium, I=iodine, CT= computed tomography, XRA=x-ray angiography, kVp=peak kilovoltage, NM=not measured

1) According to the manufactures
2) Median values of pooled results in paper III and IV.
3) Attenuating capacity of Gd-CM expressed in terms of iodine concentration according to the results in Paper III .
4) Plasma half-life/attenuation index was calculated by dividing median plasma half-life relative iodixanol 320 mg I/mL with the attenuating capacity in terms of mg I/mL relative iodixanol 320 mg I/mL; i.e. for CT with gadobutrol the plasma half-life/attenuation index became 7.8/0.69=11.3. In a similar way osmotic load/attenuation index was calculated.

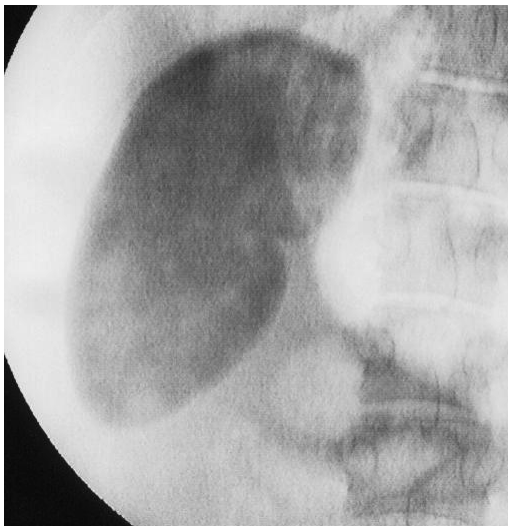

Figure 16. Persistent nephrogram three hours after injection of 0.5M gadopentate

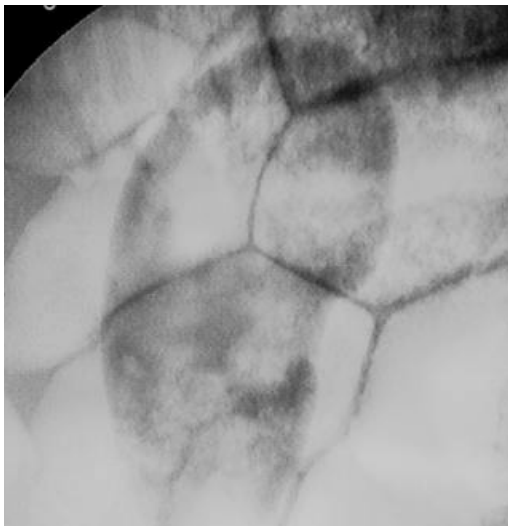

Figure 17. Persistent nephrogram three hours after injection of *mannitol/io 1.96*

The osmotic load/attenuation indexes for the Gd-CM were also higher than that of the I-CM at 150 and 320 mg I/mL. For the same attenuation the osmotic load of both 0.5M gadodiamide and 1.0M gadobutrol were 3.5 and 5.4 times higher than that of iodixanol 320 mg I/mL at 120 kV_p CT and 70-90 kV_p XRA, respectively, *Table 3*. The corresponding indexes for 0.5M gadopentetate rose to 10.4 and 16.3.

Histomorphological changes (Paper VI)

All the kidneys from pigs injected with gadopentetate, *mannitol/io 1.96* or gadobutrol were swollen and discoloured macroscopically *Figure 19*. The kidneys injected with all other CM and saline appeared macroscopically normal *Figure 20*. The histological findings are summarized in *Table 4*. The main findings were: 1) proximal tubular, *Figure 21* and glomerular necrosis, *Figure 22*, 2) haemorrhage/congestion of cortex, *Figure 23*, medulla, *Figure 24* and glomeruli, *Figure 23*, 3) proximal tubular vacuolation, *Figure 25* and 4) protein filled tubular in cortex, *Figure 26* and medulla.

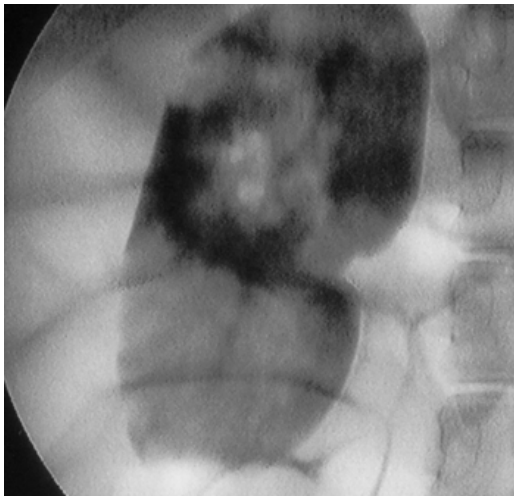

Figure 18. Persistent nephrogram three hours after injection of 1.0m gadobutrol

In general necrosis of proximal tubules and glomeruli as well as haemorrhage/congestion was statistically significantly greater in the kidneys injected with 0.5M gadopentetate, *mannitol/io 1.96* and 1.0M gadobutrol compared to all other groups. There was no or only minor necrosis or haemorrhage/congestion seen in the kidneys injected with iodixanol 150 and 320, iohexol 70 and saline.

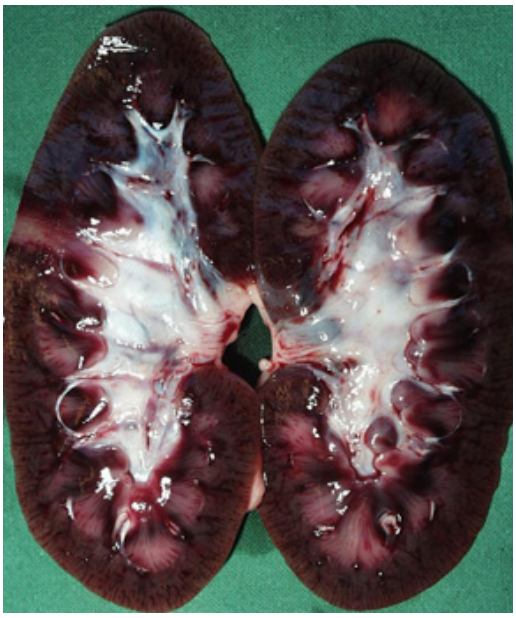

Figure 19. Macroscopic photograph of a kidney after administration of gadopentetate. The kidney is swollen and discoloured as a result of haemorrhage/congestion and necrosis.

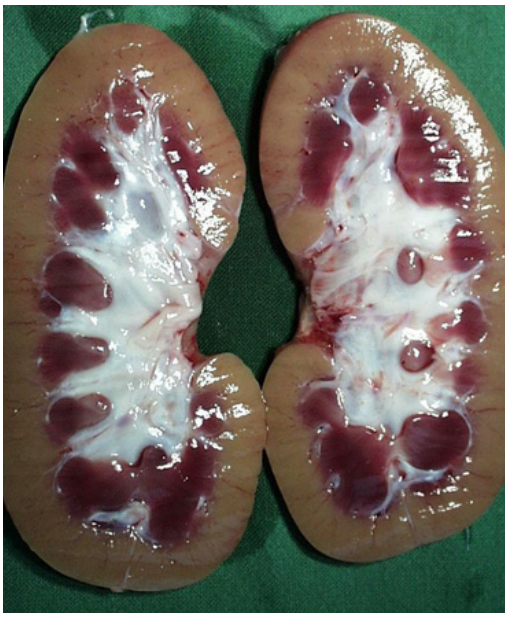

Figure 20. Macroscopic photograph of a kidney after administration of 0.5M gadodiamide. Normal appearance.

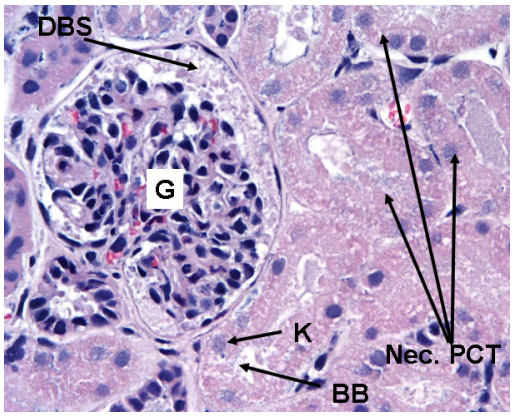

Figure 21. Gadopentetate-treated animal. Light micrograph, histological section of immersion-fixed kidney, cortex. H&E, x400 . Nec. PCT = Necrosis (coagulative) of the proximal convoluted tubules, DBS = presence of cellular debris in the urinary space (Bowman's space) of the glomeruli (G), not affected, DCT = Distal convoluted tubules, not affected, K = Karyolysis (Ghosting) of nuclei and loss of the (BB =) brush border are also seen.

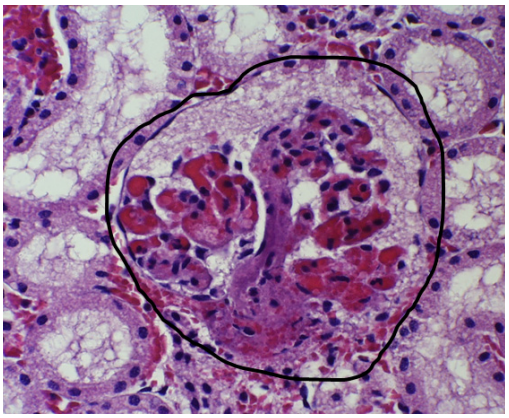

Figure 22. *Mannitol/io 1.96*-treated animal. Light micrograph, histological section of immersion-fixed kidney, cortex. H&E, x400. The marked area indicate glomerulus necrosis

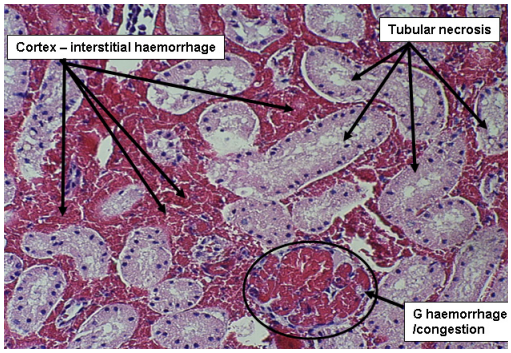

Figure 23. Gadobutrol-treated animal. Light micrograph, histological section of immersion-fixed kidney, cortex. H&E, x200. Haemorrhage and congestion of glomeruli and cortex. Necrosis of proximal convoluted tubules.

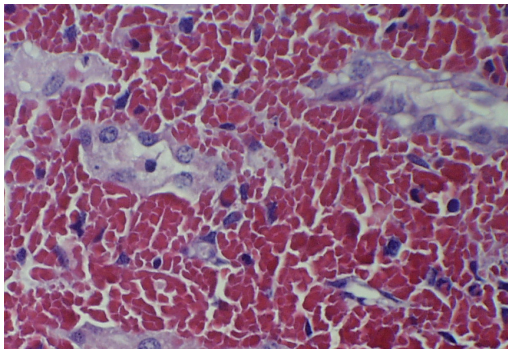

Figure 24. Gadopentetate-treated animal. Light micrograph, histological section of immersion-fixed kidney, cortex. H&E, x400. Haemorrhage of medulla.

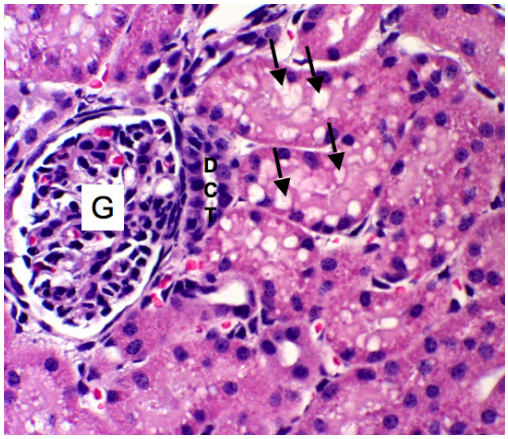

Figure 25. Gadodiamide-treated animal. Light micrograph, histological sections of immersion-fixed kidney, cortex. H&E, x400. Arrows indicate vacuoles within proximal convoluted tubules (PCT). G = glomerulus, not affected, DCT = distal convoluted tubular, not affected.

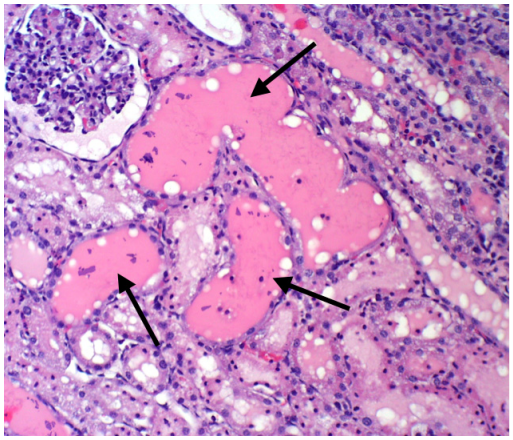

Figure 26. Gadobutrol-treated animal. Light micrograph, histological section of immersion-fixed kidney, cortex. H&E, x400. Arrows indicate protein filled tubules

Contrary to necrosis and haemorrhage/congestion, there was no proximal tubular vacuolation in the kidneys injected with gadopentetate, gadobutrol or *mannitol/io 1.96*. All other test solutions resulted in some degree of vacuolation. The pattern of protein filled cortical tubules resembled the proximal tubular vacuolation (*Table 4*).

Table 4 Results of histology. The severity of histomorphological changes were graded subjectively as follows: 1 = minimal, 2 = mild, 3 = moderate and 4 = marked. n = number of animals in the group. * = Osmolality [Osm/kg H_2O] according to manufacturer ; ** osmolality according to measurement using a Vapor Pressure Osmometer 5500 XR

	Necrosis								Haemorrhage/congestion												Vacuolation				Protein filled tubules							
	proximal tubular				glomeruli				cortex				medulla				glomeruli				proximal tubular				cortex				medulla			
Grade / CM	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Gadopentetate 1.96*, n=16				*16*	*8*	*3*	*5*			*9*	*7*		*4*	*6*	*5*	*1*	*8*	*6*	*2*													
Mannitol/io 1.96 1.96**, n=8				*8*		*4*	*3*	*1*		*6*	*2*		*1*	*5*	*2*			*4*	*4*						*2*							
Gadobutrol 1.60*, n=8				*8*	*1*	*1*	*4*	*2*		*4*	*4*			*2*			*1*	*1*	*6*							*1*	*3*	*2*		*2*	*2*	*3*
Gadodiamide 0.78*, n=16	*3*												*2*									*1*	*14*	*1*		*1*	*13*	*1*				
Mannitol/io 0.82 0.82**, n=8									*2*				*1*								*1*	*4*	*2*		*1*	*4*	*2*					
Iohexol 190 0.42*, n=16	*6*	*4*							*1*				*2*								*2*	*7*	*2*		*2*	*8*	*1*					
Mannitol/io 0.43 0.43**, n=8	*2*	*1*							*1*	*1*											*4*				*4*							
Iopromide 150 0.34*, n=8	*4*											*1*	*1*								*6*	*1*		*1*	*6*	*1*		*1*	*1*	*1*		*1*
Iodixanol 150 0.29*, n=8													*1*	*1*							*3*	*2*	*2*		*2*	*2*	*2*					
Iodixanol 320 0.29*, n=8																					*4*	*1*			*4*	*1*						
Iohexol 70 0.29*, n=16	*1*																				*3*	*4*			*3*	*4*						
NaCl 1 0.29*, n=8										*1*				*1*							*1*				*1*							
NaCl 2 0.29*, n=8																																
NaCl 3 0.29*, n=8																					*1*				*1*							

General discussion

The ideal choice of a radiographic intravascular CM is that with the lowest general toxicity and nephrotoxicity in relation to its ability to attenuate x-rays.

Several experimental animal models have been used to study CIN (1,96,100,101,105,106). We designed a porcine model with a high probability of CIN by injecting high doses of CM selectively into the renal artery during a period of ischemia. The model was partly chosen because the use of Gd-CM has been advocated to guide treatment of renal artery stenoses with balloon angioplasty and/or stent placement (10,17,18,107). The model may imitate a clinical situation where a patient undergoes renal arteriography/angioplasty implying selective CM injections and periods of renal ischemia.

We choose the pig as experimental model since their kidneys are morphologically and physiologically considered more similar to humans in comparison to other species (108-110) possibly with the exception of the dwarf water buffalo (111). It should be noted that there are differences among species in renal anatomy and physiology, e.g. relative medullary thickness, a determinant of the tubular concentrating ability (108). The relative medullary thickness in pigs is closer to that of human kidneys than in the dog and rat (108).

Crucial in animal studies is to evaluate if the model mirrors the situation seen in patients. To be valid an in vivo animal model should fulfil one main condition, i.e. the course of the experimental nephropathy should be comparable to the human CM-induced acute renal failure (ARF). Because human ARF is usually multifactorial, multiple insult models combining several factors that would not, by themselves, have caused any significant renal injury, appear to be more relevant clinically than single insult models (101,106). In a pilot study we initially injected CM into a patent right renal artery following left-sided nephrectomy. No effect on the renal function was registered and an occlusion of the right renal artery was added to produce ischemia. Then all CM hyper-osmolal to plasma decreased GFR with different severity. The mechanism behind the observed alterations of renal function in the present model may be multifactorial and dependent on chemo- and osmotoxicity of the CM and ischemia.

Effect on renal function and histomorphology

Saline was used as control. When saline was tested, a low dose of iohexol (total dose 3 mL 300 mg I/mL) was injected intravenously or into the renal artery as a marker of GFR. In the control groups no apparent renal impairment was encountered (Paper III), as indicated by the calculated GFR that in our unilaterally nephrectomized pigs receiving saline (Group 1 Paper III) was about half of the GFR in normal pigs with two kidneys in a previous study at the present laboratory (56). Ischemia per se did not seem to induce any effect on renal function in the present model.

Gadopentetate, *mannitol/io 1.96* and gadobutrol, with an osmolality 5.5 to 7 times that of human plasma all caused relatively severe histomorphological changes with necroses and haemorrhages/congestions which was accompanied with almost complete cessation of renal function in several animals. The major pathophysiological mechanism behind these changes may have been hypertonic effects on cell membranes injuring endothelial and red blood cells resulting in microcirculatory occlusions (83,84,86,87).

Injections of gadodiamide with an osmolality 2.7 times that of human plasma caused sub-

stantially less effect on renal function than the Gd-HOCM, a difference with a factor 5 to 12 in plasma half-lives. Though, the pooled figures resulted in a median plasma half-life of gadodiamide that was only 20-80% longer than that of the plasma iso- or slightly hyper-osmotic (iohexol 190, 1.4 times) I-CM, the differences were statistically significant. These differences may to a large extent be explained by their difference in osmolality, the tested I-CM having an osmolality of only 1-1.4 that plasma.

According to *Table 1* the median/mean half-lives of gadodiamide were shorter (78 minutes) than that of iohexol (121 minutes) in human volunteers. If this relation were similar in normal pigs, this may strengthen our conclusion that 0.5M gadodiamide really causes a more substantial depression of GFR than an equi-molar solution of iohexol (190 mg I/mL).

The results in the study comparing Gd- and I-CM with iso-osmotic mannitol solution (Paper IV) indicate that osmotoxicity seems to dominate at an intermediate (e.g. gadodiamide 0.78 Osm/kg H_20) or high (e.g. gadopentetate-1.96 Osm/kg H_20) level of hyper-osmolality, while chemotoxicity may prevail at a low level of hyper-osmolality relative to plasma as (e.g. iohexol 190 mg I/mL-0.40 Osm/kg H_20). The role of osmolality in CM nephrotoxicity has been observed in a number of animal studies using intra-arterial administration of CM (94,101,112-116).

The plasma iso-osmotic 0.18M iohexol (70 mg I/mL) had the same effect on GFR as injections of saline (Paper III). Iohexol at a concentration of 70 mg I/mL is roughly equal attenuating with 0.5M Gd-CM for XRA at 70-90 kV_p (29,117). Thus, for the same diagnostic efficacy iohexol 70 mg I/mL appeared less harmful to the kidneys than the two 0.5M Gd-CM tested, gadopentetate and gadodiamide. Injections of more than twice the CM molecular concentration of 0.18M iohexol, i.e. 0.39M iopromide (150 mg I/mL) and 0.42M iodixanol (320 mg I/mL) in study reported in Paper V, resulted in a plasma half-life that was similar to that of 0.18M iohexol as well as saline in our first study (Paper III). The lack of any detectable difference between 0.20M and 0.42M iodixanol (150 and 320 mg I/mL) may simply be due to the fact the threshold dose for a nephrotoxic effect has not been reached. These results indicate that injecting as much as 60 mL of the plasma iso-osmotic iodixanol 320 mg I/mL, almost equi-molar in molecular with 0.5M Gd-CM, into the renal artery of an ischemic porcine kidney did not have any toxic effect in the present animal model. These results do not support the theory that the high viscosity of iodixanol should be a significant pathogenetic factor in CIN.

The histomorphological renal findings following injections of the LOCM and IOCM also seemed to parallel their effects on renal function (Paper VI). Tubular and glomerular necrosis as well as hemorrhagic/congestion of the cortex, medulla and glomeruli was either absent or minimal contrary the findings in kidneys injected with gadopentetate, *mannitol/io 1.96* and gadobutrol. On the other hand, gadodiamide and all the I-CM caused vacuolation. The lack of co-variation between vacuolation and renal impairment indicate that vacuolation is unlikely to be a major factor in the pathogenesis of CIN.

Nephrotoxicity versus attenuation

When comparing the attenuation of x-rays by equal volumes of 0.5M gadopentetate, 0.5M gadodiamide and 0.5M iohexol (190 mg I/mL), i.e. equal number of CM-molecules per mL, it turns out that iohexol 190 attenuate a higher fraction of the x-ray spectrum at all practically used kV_ps in diagnostic radiology (29,117). Thus in our model one molecule iohexol represents both a lower nephrotoxicity and higher x-ray attenuation than one molecule of gadopentetate or gadodiamide.

In vitro attenuation measurements

The iodine concentrations equal attenuating with 0.5M Gd-CM at CT are in accordance with the rough theoretical estimates in the introduction and with most other studies presented in *Table 5*. As an example 0.5M Gd-CM were equal attenuating with 110 mg I/mL at 120 kV_p using a body phantom in our study compared to 93-120 mg I/mL found by most others authors, *Table 5*. Using the same conditions, this also means that 1.0M gadobutrol is roughly equal attenuating with 220 mg I/mL. The equal attenuating iodine concentration may vary with type of scanner, tube filtration, differences in phantoms used, etc. The equal attenuating iodine concentration of 172 mg I/mL relative to a 0.5M Gd-CM at 120 kV_p found by one author, *Table 5* cannot be accounted for.

Measurements on RF, XA and DX systems indicate that Gd-CM exhibits a maximum in its attenuation efficiency at approximately 70-80 kV_p. Our results are in accordance with a previous thorough experimental study (62) and indicate that at commonly used 70-90 kV_p for XRA, 60-80 mg I/mL seems roughly equal attenuating with 0.5M Gd-CM. However, if the tube voltage is lowered to 60 kV_p in thin patients or when performing femoral and lower leg angiography with the present dedicated angiographic equipment, the I-CM concentration may be diluted to 35 mg I/mL and still result in the same radiographic contrast as 0.5M Gd-CM at 60 kV_p. Below the 70-80 kV_p range the most common photon energies in the spectrum are found between the K-edges of iodine (33 keV) and gadolinium (50 keV), where the attenuation by iodine is more than twice that by gadolinium.

Common clinical CM volumes at body CT ranges from about 100-150 mL of 300 mg I/mL, i.e. a total dose of 30-45 gram iodine. In a recent study on using Gd-CM in chest CT including diagnosing acute pulmonary embolism in patients with renal impairment all examinations were considered diagnostic following injection of high clinical doses (0.4 mmol/kg b.w.) of 0.5M gadopentetate (mean volume 50 mL) (27,28). Thus, with the present scanner the same 50 mL volume of an equal attenuating iodine concentration of 110 mg/mL should have resulted in the same diagnostic quality. This means a total dose of only 5.5 gram of iodine; i.e. only 12-18% of the common clinical doses that may cause CM induced nephropathy. Furthermore, 50 mL 0.5M gadopentetate, a plasma high-osmotic ionic CM (1960 mOsm/kg H_2O), may result in an osmotic load of 3x25 mosmoles (3 osmotic active particles per CM molecule) reaching the kidneys, while 5.5 gram iodine of the plasma iso-osmotic non-ionic dimeric I-CM iodixanol only represents an osmotic load of 7.2 mosmoles. If osmotic load is a main pathophysiological mechanism behind CM nephropathy after i.v. CM administrations (64), then I-CM may in fact be much less nephrotoxic than Gd-CM when comparing the same volumes of equal attenuating concentrations. It should be noted that in a retrospective clinical study 2% of the patients undergoing MR-angiography and 9.5% of those undergoing XRA with more than 0.25 mmol/kg of gadopentetate developed severe CIN, i.e. oliguria or anuria (76).

Using the same high clinical Gd-CM dose as in the CT example above, 50 mL of 0.5M Gd-CM during X-ray angiography should be equal attenuating with injections of 50 mL of 35-80 mg I/mL at 60-90 kV_p. This corresponds to 2-5 grams of iodine. This is in the same range as the 10 mL 300 mg I/mL (1.5-3 gram iodine) used to determine glomerular filtration rate (GFR) by iohexol-clearance in patients with renal impairment and which is deemed harmless (55,118). In the "Iohexol cooperative study" a 2.4% rate of severe CM induced renal failure was reported following coronary angiography with iohexol in patients with pre-existing renal impairment (3), though the patients had received a 10-25 times higher mean iodine dose (140 mL 350 mg I/mL = 49 gram iodine) than the 2-5 grams in the present example.

Plasma half-life/attenuation and osmotic load/attenuation indexes

A plasma half-life/attenuation index could be used as a measure of nephrotoxicity in relation to attenuating capacity. We chose to relate this index to the plasma half-life and attenuating capacity of iodixanol 320 mg I/mL, since it has the highest attenuation of all CM tested and had the same short plasma half-life as the I-CM with only about half the iodine concentration. According to *Table 3* the plasma half-life/attenuation indices for the Gd-CM were all higher than that of the I-CM at both 150 and 320 mg I/mL. For the same attenuation gadodiamide may appear about 4 and 7 times more nephrotoxic than iodixanol 320 mg I/mL at 120 kV_p CT and 70-90 kV_p XRA, respectively. The corresponding figures for gadopentetate rose dramatically to 35 and 56 times that of iodixanol 320 mg I/mL.

It must be realized that "plasma half-life/attenuation index" is a rough tool to evaluate the potential of a CM to cause renal damage. If we compare iodixanol 320 mg I/ml with iodixanol and iopromide 150 mg I/ml in the present study, the higher concentration gets an index of one in *Table 3*, while the lower concentration gets an index of two. According to this difference in indices it would be a higher risk of renal damage with a lower CM concentration and dose, which hardly seems likely. Thus, the index relative e.g. iodixanol 320 mg I/mL can only be used for comparison with CM injected in doses above the threshold of renal damage indicated by an significantly higher plasma half-life than that caused by iodixanol 320.

If a CM is injected intravenously, it has to pass the heart and pulmonary circulation before reaching the kidneys. If injected intra-arterially into an organ remote from the kidneys it also has to pass at least one more capillary and venous system. In both cases substantial plasma dilution of the CM will occur. Thus, the hypertonic effects on endothelial and red blood cells, that may be a major pathophysiological nephrotoxic mechanism when plasma hyper-osmotic CM are injected directly into the renal arteries (83,84,86,87), will most likely be omitted. Instead osmotic load, i.e. the number of osmotic active particles that reach the kidneys may be the main harmful mechanism (64). However, the osmotic load/attenuation indexes for the Gd-CM were all still higher than that of the I-CM at both 150 and 320 mg I/mL, though not that high compared to the plasma half-life/attenuation index. For the same attenuation gadodiamide causes a 3.5 and 5.4 times higher osmotic load than iodixanol 320 mg I/mL at 120 kV_p CT and 70-90 kV_p XRA, respectively (*Table 3*). The corresponding osmotic load for gadopentetate is 10.4 and 16.3 times that of iodixanol 320 at equal attenuation.

It should be emphasized that the concentration of I-CM equal attenuating with 0.5 and 1.0M Gd-CM may vary somewhat and affect the plasma half-life/attenuation and osmotic load/attenuation indices depending on type of CT scanner and XRA equipment used. It may vary with X-ray tube filtration, chosen tube potential, post-processing of the digital detector signals as well as the size and composition of the body that the X-ray beam has to transmit. However, these variations will hardly reverse the indices to the advantage of the Gd-CM in relation to the I-CM in the present study.

Summary and conclusions

Summary

1. In vitro measurements indicate that 0.5M Gd-CM are equal attenuating with 60-80 mg I/mL at commonly used 70-90 kV_p XRA.

2. According to LD_{50} studies in mice, Gd-CM are 6 to 25 times more toxic than non-ionic monomeric I-CM, providing that iodine and gadolinium atoms are equally attenuating at about 72 kV_p during XRA.

3. In vitro CT measurements indicate that 0.5M Gd-CM are equal attenuating with about 70 and 90 mg I/mL without and with body phantom, respectively, at 80 kV_p and about 90 and 110 mg I/mL without and with phantom, respectively, at 120 kV_p.

4. At equal attenuation of x-rays a "high" dose (0.4 mmol/kg) of 0.5M Gd-CM (= 60 mL in a 75 kg person) may correspond to a total dose of "only" 6-7 grams of iodine at 120 kV_p body CT and to "only" 2-5 grams of iodine at 60-95 kV_p x-ray angiography.

5. In our pig model 0.5M Gd-CM at 70-90 kV_p renal arteriography are more nephrotoxic than equal attenuating iodine concentrations (≈70 mg I/mL) of non-ionic monomeric I-CM and also more nephrotoxic than roughly equi-molar molecular concentrations of non-ionic monomeric (190 mg I/mL) and dimeric (320 mg I/mL) I-CM.

6. The nephrotoxic effect of Gd-CM is correlated to their osmolality.

7. Plasma iso-osmotic non-ionic dimeric I-CM up to 320 mg I/mL seem to have an effect on GFR similar to that of saline without ischemia in this pig model and caused minimal histomorphological changes.

8. Gadolinium HOCM (gadopentetate and gadobutrol) caused marked necrosis and haemorrhage/congestion that correlated with the severe impairment of renal function caused by these agents in our model.

9. Vacuolation appears to be independent ofosmolality and viscosity of CM, and does not seem to be a pathogenetic factor in CM induced nephropathy.

Conclusions

1. Those advocating the use of Gd-CM instead of I-CM in patients with renal impairment have to show that Gd-CM are less nephrotoxic in humans than I-CM in equal volumes of equal attenuating concentrations.

2. As long as human studies are lacking, Gd-CM should not be substituted for I-CM for radiographic examinations in patients with renal impairment, since equal volumes of non-ionic monomers or dimers of I-CM with equal ability to attenuate X-rays are much less nephrotoxic in the only living subjects studied so far in this fashion, the pigs.

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Populärvetenskaplig sammanfattning

Kontrastmedel, som sprutas in i blodbanan, används vid både röntgen- och magnetkameraundersökningar för att förstärka skillnader mellan normal och sjuklig vävnad och därigenom förbättra säkerheten i diagnostiken av många sjukdomar. Vid röntgenundersökningar används jod, fast bundet till en molekyl, som kontrastmedel (I-KM). Det är väl känt att dessa kontrastmedel kan vara toxiska (giftiga) för njurarna och orsaka en försämring av njurfunktionen. Utsatta patienter är de som redan ha en nedsatt njurfunktion, särskilt om den är kombinerad med sockersjuka. Moderna I-KM är förvisso betydligt mindre njurtoxiska än I-KM, men kan fortfarande påverka njurfunktionen, samtidigt som allt fler äldre individer med nedsatt njurfunktion utsätts för både omfattande diagnostiska utredningar och behandlingar, som kräver stora mängder I-KM, t.ex. ballongvidgning av förträngningar av hjärtats kranskärl.

Gadoliniumbaserade kontrastmedel (Gd-KM) är en annan typ av kontrastmedel utvecklade för magnetkameraundersökningar (magnetisk resonanstomografi - MR). Här är det gadoliniumatomen som ger själva kontrasteffekten och den är också bunden till en molekyl. I samband med MR-undersökningar noteras ytterligt sällan någon påverkan på njurfunktionen. Gd-KM anses därför av många att i princip inte vara njurtoxiska. Gd-KM används därför allt mer som ersättning för I-KM hos patienter med nedsatt njurfunktion i samband med olika kärl- (angiografi) och skikt-röntgenundersökningar (datortomografi). Den påstådda låga njurtoxiciteten av Gd-KM baseras bl.a. på resultat från en studie, där låga doser av Gd-KM anpassade till MR jämfördes med betydligt högre doser av I-KM anpassade för angiografi och datortomografi. Skillnaden kan vara 10-30 gånger fler kontrastmedelsmolekyler av I-KM vid röntgenundersökningar jämfört med Gd-KM vid MR-undersökningar. Eftersom det enda ändamålet med kontrastmedel vid röntgenundersökningar är att absorbera (blockera) röntgenstrålar (fotoner) bör effekten på njurarna jämföras i doser som ger samma absorption av röntgenstrålar, s.k. ekvi-absorberande doser. Någon sådan jämförelse har aldrig gjorts. Avsikten med denna avhandling har därför varit att undersöka:

1. Vid vilken jodkoncentration är strålabsorptionen av jod densamma som för gadolinium i den vanligaste förekommande koncentrationen, 0,5M (mol/liter; mol anger antal gadoliniumatomer i detta fall).
2. Jämföra den generella toxiciteten av I- och Gd-KM i publicerade studier på djur.
3. Jämföra njurtoxiciteten av I- och Gd-KM i en experimentell djurmodell.

Ekvi-absorberande koncentrationer.

Kontrasteffekten av olika jodkoncentrationer jämfördes med ett 0,5M Gd-KM i ett fantom som simulerar en mänsklig kropp och med olika röntgenutrustningar och exponeringsdata (inställd spänning i röntgenröret). Det framkom då att jod och gadolinium absorberade grovt sett lika mycket röntgenstrålar vid vanligt förekommande exponeringsdata när man använder utrustning för kärlröntgen, dvs. 0,5M Gd-atomer motsvarar en jod-koncentration på ca 70 mg I/mL (=0,55M jodatomer).

Vid datortomografi, där man använder högre inställd spänning i röntgenröret än vid angiografi, visade det sig att gadolinium absorberar knappt dubbelt så mycket strålar som jod, dvs. det krävdes 110 mg I/mL (= 0.9M jodatomer) för samma strålabsorption som 0,5M Gd-atomer.

Vid röntgenundersökningar är det vanligt att man använder 100-300 mL av 300-400 mg I/mL, dvs. 30-120 gram jod. Femtio mL 0,5M Gd-KM betraktas närmast som en maximal dos till en normalstor individ. Denna dos skulle alltså ge samma kontrasteffekt som 50

mL 70 mg I/mL vid en kärlröntgenundersökning och 50 mL 110 mg I/mL vid en datortomografi. Den totala joddosen blir då 3,5 respektive 5,5 gram jod för att få samma diagnostiska kvalité som 0,5M Gd-KM vid en röntgenundersökning. Dessa doser, 3,5-5,5 gram jod, motsvarar alltså grovt sett endast 1/6 till en 1/30 av de joddoser som normalt användes vid röntgenundersökningar. Risken för njurskada, som är beroende av dosens storlek, torde alltså vara kraftigt reducerad vid så låga doser.

Generell toxicitet

En genomgång av publicerade djurstudier visar att den generella toxiciteten för Gd-KM är högre än för I-KM när man jämför i doser som ger samma strålabsorptiom. För kärlröntgen, där jod och gadolinium absorberar ungefär lika mycket röntgenstrålar, är Gd-KM 6-25 gånger mer toxiska än dagens I-KM. För datortomografi, där gadolinium absorberar dubbelt så mycket som jod, blir siffrorna halverade.

Egna studier avseende njurtoxicitet

Som djurmodell valde vi gris, vars njurar är de bland försöksdjur som anses mest lika människans, möjligen med undantag för dvärgvattenbuffel. Godkännande från etisk kommitté inhämtades. Djuren sövdes ned och därefter avlägsnades vänster njure. I artären till den kvarvarande högra njuren injicerades samma volym (60 mL) av olika I- och Gd-KM i olika koncentrationer samt koksalt som kontroll. Varje gris utsattes endast för en testlösning som injicerades i sammanlagt 8 grisar i varje studie, sammanlagt tre olika studier. Därefter mättes njurfunktionen (glomerulär filtration) under 60-180 minuter efter injektionen. När försöket var klart avlivades djuren genom en överdos av sömnmedel och njuren avlägsnades för mikroskopisk undersökning.
Det visade sig att samtliga Gd-KM gav en kraftigare försämring av njurfunktionen än samma injicerad volym av alla I-KM som testades, vilket inkluderade koncentrationerna 70 mg I/mL (samma strålabsorption som 0,5M Gd-KM vid kärlröntgen), 150 mg I/mL (något högre absorption än 0,5M Gd-KM vid datortomografi) och 320 mg I/mL, som ger avsevärt bättre kontrasteffekt (bättre diagnostisk kvalité) än Gd-KM. Efter injektion av vissa Gd-KM upphörde njurfunktionen helt och hållet, medan de allra flesta I-KM som testades hade ungefär samma effekt på njurarna som koksalt, alltså ingen påvisbar nedsättning av njurfunktionen. Påverkan på njurfunktion motsvarades också av förändringar i den mikroskopiska bilden. Gd-KM orsakade mer eller mindre allvarliga mikroskopiska förändringarna, medan I-KM, som hade samma effekt på njurarna som koksalt, inte uppvisade några allvarliga mikroskopiska förändringar.

Slutsatser

1. Innan man använder Gd-KM som ersättning för I-KM vid röntgenundersökningar på människor vid nedsatt njurfunktion, måste det göras kontrollerade studier som bevisar att Gd-KM är mindre njurtoxiska än I-KM i doser som ger samma kontrasteffekt och därmed samma diagnostiska utbyte, dvs. samma volym av koncentrationer som absorberar lika mycket röntgenstrålar.
2. I avsaknad av dylika studier måste det anses som kontraindicerat att ersätta I-KM med Gd-KM vid röntgenundersökningar på patienter med nedsatt njurfunktion. Gd-KM uppvisar i djurstudier en avsevärt högre toxicitet, såväl generellt som på njurar, jämfört med I-KM injicerade i samma volymer som Gd-KM men i koncentrationer som ger lika eller t.o.m. högre absorption av röntgenstrålar än Gd-KM.

Streszczenie popularnonaukowe

Jodowe środki kontrastowe (J-ŚK), ktore wstrzykuje się dożylnie lub dotętnicowo mogą być nefrotoksyczne (czyli mogą spowodować pogorszenie funkcji nerek) u pacjentów, którzy mają niewydolność nerek, szczególnie w połączeniu z cukrzycą. Nowoczesne J-ŚK są dużo mniej nefrotoksyczne niż J-ŚK starszej generacji. Niezależnie od tego mogą w dalszym ciągu działać negatywnie na funkcję nerek. Dożylne środki kontrastowe zawierające gadolinium (Gd-ŚK) stosowane w magnetycznej tomografii rezonansowej (MRI) są przez wielu uznawane jako znacznie mniej nefrotoksyczne niż J-ŚK. To przyczyniło się do stosowania Gd-ŚK, szczególnie w USA, jako środka kontrastowego zamiast J-ŚK w badaniach rentgenowskich typu angiografia (rentgen naczyniowy), rozszerzanie naczyń czy też tomografia komputerowa, u pacjentów z niewydolnością nerek. Tacy pacjenci sa szczegolnie podatni na szkodliwy wpływ środkow kontrastowych. Gd-ŚK stosuje się u tych pacjentów, żeby zmniejszyć ryzyko uszkodzenia nerek w związku z kontrastowym badaniem rentgenowskim. Dane na temat niskiej nefrotoksyczności Gd-ŚK oparto na podstawie wyniku jedynego badania, gdzie małe dawki Gd-ŚK, tzn. takie, jakie stosuje się w badaniach MRI zostały porównane z dużo większymi dawkami molekularnymi (cząstkowymi) J-ŚK, jakie stosuje się w angiografii czy w tomografii komputerowej. Jako że jedynym powodem dla którego używa się środków kontrastowych w badaniach rentgenowskich jest ich zdolność do pochłaniania promieniowania rentgenowskiego (hamowania fotonów), porównanie nefrotoksyczności różnych środków kontrastowych powinno przeprowadzać się w dawkach, które powodują pochłanianie przez nie promieniowania rentgenowskigo w takim samym stopniu . Takiego porównania jak dotąd nie przeprowadzono. Porównywanie nefrotoksyczności J-ŚK i Gd-ŚK jest tym bardziej skomplikowane, że stężenie Gd-ŚK podaje się w mmol/ml a stężenie J-ŚK podaje sie w mg jodu (I)/ml. Konieczne jest porównanie nefrotoksyczności tych preparatów stosowanych w tej samej dawce molekularnej. Jak dotąd nie ma Gd-ŚK, które w takim samym molekularnym stężeniu (jeżeli chodzi o liczbę cząsteczek) ma taką samą wysoką zdolność do hamowania fotonow jak J-ŚK. Przyczyną tego jest fakt, ze Gd-ŚK w swojej cząstce zawierają tylko jeden atom gadolinium, a cząstka J-ŚK zawiera trzy lub sześć atomów jodu. Obecnie Gd-ŚK stosuje się jedynie dożylnie w badaniach MRI. Dlatego są one stosowane w badaniach rentgenowskich w takich samych dawkach jak w MRI. Kiedy porównuje się nefrotoksyczność Gd-ŚK z nefrotoksycznością J-ŚK w takich samych dawkach cząstkowych i w dodatku w takim stężeniu, przy którym pochłaniaja tyle samo fotonów wydaje się, że bezpieczeństwo Gd-ŚK w badaniach rentgenowskich u pacjentow z niewydolnością nerek jest bardzo wątpliwe.

Tę wątpliwość zwiększa fakt, że nawet obecnie raportuje się przypadki pogorszonej funkcji nerek u takich pacjentów po przeprowadzonych badaniach kontrastowych z Gd-ŚK, które były użyte w dawkach dopuszczalnych dla MRI. Według naszej opinii nie powinno się stosować Gd-ŚK zamiast J-ŚK u pacjentow z niewydolnością nerek w badaniach rentgenowskich. Należy wziąć pod uwagę fizyczne i chemiczne właściwości obydwu grup środków kontrastowych, czego jak dotad nikt nie zrobil.

Przeprowadzilismy przegląd literatury światowej dotyczącej właściwości zarówno jodu jak i gadolinium w stosunku do ich przepuszczalnosci dla promieniowania rentgenowskiego i jednoczesnie ich toksyczności. Wyciagnęlismy wniosek, że mniejsza dawka molekularna J-ŚK daje równie dobrą diagnostyczną informację rentgenowską jak większa dawka molekularna Gd-ŚK. Gd-ŚK

mają wyższą osmotyczność niż plazma. Mają one w dodatku wyższą osmotyczność niż nowoczesne J-ŚK w dawkach, ktore hamują taka samą frakcję fotonów. Gd-ŚK są więc potencjalnie bardziej nefrotoksyczne niz J-ŚK. Ich ogolna toksyczność jako LD_{50} w wypadku zwierząt doświadczalnych jest zdecydowanie większa w porównaniu z dawkami J-ŚK pochłaniajacymi tyle samo fotonów co Gd- ŚK.

W modelach zrobionych z pleksu i z polistyrenu badaliśmy takie same molekularne dawki o tej samej zdolnosci do pochłaniania fotonów w obu grupach środków kontrastowych. Modele zawierały strzykawki wypełnione różnymi środkami kontrastowymi i zostały umieszczone w aparacie rentgenowskim jak przy angiografii lub w tomografie komputerowym.

Dzięki temu mogliśmy dokładnie zmierzyć stężenie jodu potrzebne do zahamowania takiej samej liczby fotonów jak porównywalne stężenie Gd-ŚK zależnie od zastosowanego wyposażenia rentgenowskiego i użytego napięcia lampy rentgenowskiej.

Nasze pierwsze doświadczenie na świniach poświęciliśmy na porównanie nefrotoksyczności Gd-ŚK i J-ŚK przez przeprowadzenie angiografii prawej tętnicy nerkowej po usunięciu lewej nerki. Dwa różne Gd-ŚK porównywaliśmy z różnymi stężeniami J-ŚK. Wszystkie środki kontrastowe wstrzykiwane były w takich samych cząstkowych dawkach o tej samej zdolności do hamowania fotonów przez cewnik zakończony balonem, który czopował prawą tętnicę przez 10 minut. Wpływ tej kombinacji środka kontrastowego i niedoboru tlenu na funkcje nerki analizowaliśmy przez pomiar stężeń środków kontrastowych we krwi. Gd-ŚK spowodowały dużo większe uszkodzenie nerki niż J-ŚK. Roztwór J-ŚK, który miał osmotyczność jak plazma i stężenie, które daje takie samo zahamowanie fotonow jak Gd-ŚK okazał się być zupełnie nieszkodliwy dla funkcji nerki. Doszliśmy do wniosku, że w naszym doświadczeniu osmotyczność Gd-ŚK była powodem uszkodzenia nerki. To potwierdza wcześniejsze obserwacje, że środki kontrastowe o wysokiej osmotyczności wpływają negatywnie na funkcje nerek.

Z tego też powodu w następnym doświadczeniu na tym samym modelu zwierzęcym porównywaliśmy środki kontrastowe z roztworami mannitolu, które miały tę samą osmotyczność co środki kontrastowe. Rezultaty z tego doświadczenia wskazują znowu na to, że osmotyczność Gd-ŚK może w znacznym stopniu być wytłumaczeniem ich negatywnego dzialania na funkcje nerek.

Wśród nowoczesnych środków kontrastowych znajdują się zarówno tzw."nisko"- i "izo"- osmotyczne preparaty. W naszym modelu zwierzecym , w trzecim doświadczeniu chcieliśmy zbadać, czy te tzw."izoosmotyczne", czyli mające taką samą osmotyczność jak plazma, środki kontrastowe są mniej szkodliwe w stosunku do funkcji nerki. Porównywaliśmy „izo"- i „niskoosmotyczne " J-ŚK z zarowno „nisko-" i „wysokoosmotycznymi" Gd-ŚK (nie ma jak narazie żadnych „izoosmotycnych" Gd-ŚK). Wyniki wykazały, że jeden z „izoosmotycznych" środków kontrastowych (koncentracja 320 mg J mg/ml) jest dużo łagodniejszy w stosunku do funkcji nerki niz Gd-ŚK i w dodatku daje diagnostycznie dużo lepszą jakość badania. Nasze „izoosmotyczne" J-ŚK były tak samo łagodne w stosunku do funkcji nerek jak „niskoosmotyczne" J-ŚK w stężeniu izotonicznym do plazmy (150 mg J/ml).

Poza analizą parametrów nerkowych krwi ocenialiśmy wygląd nerek i ich mikroskopijne zmiany histopatologiczne. Nerki, ktore pochodzily ze świń, które poddane były badaniu z Gd-ŚK i roztworem mannitolu o najwyższym stopniu osmotyczności były obrzmiałe i sine. Wszystkie inne nerki miały normalny wyglad. Gd-ŚK i roztwór mannitolu o najwyższym stopniu osmotyczności spowodowały martwicę kanalików

proksymalnych i kłębuszków nerkowych, zastój krwi i krwawienia w korze włącznie z kłębuszkami nerkowymi i rdzeniu nerki. Wszystkie inne środki kontrastowe i roztwory mannitolu spowodowały między innymi powstanie wakuoli, czyli struktur przypominajacych bańki mydlane w kanalikach proksymalnych. Można wyciągnąć z tego wniosek, że wakuole nie powstają z powodu osmotyczności użytych roztworów. W dodatku wydaje się, że wakuole nie mają żadnego związku z patologicznym działaniem na funkcję nerki. Wyniki analizy krwi w naszych poprzednich doświadczeniach wskazują na to, że im wyższa osmotyczność użytych środków tym większa ich szkodliwość na funkcje nerki. Nasze histologiczne wyniki potwierdzają to.

Opisy zmian histologicznych w nerkach spowodowanych środkami kontrastowymi u ludzi należą do rzadkości w literaturze naukowej. Niezależnie od tego opisano poprzednio wakuole i martwice w rdzeniu nerkowym.

Użyliśmy świnie w naszych doswiadczeniach z powodu, że ich nerki przypominają najbardziej ze wszystkich innych zwierząt zarówno budową jak i fizjologią ludzkie nerki. Musieliśmy oczywiście spreparować nasze zwierzęta tak, żeby sytuacja przypominała sytuację kliniczną, kiedy pacjent z obniżoną funkcją nerek poddawany jast badaniom czy zabiegom kontrastowym. Zabiegi takie jak rozszerzanie naczyń lub implantacja protez naczyniowych powodują okresowo niedobór tlenu, ktory działa szkodliwie na nerki.

Nasze wyniki z doświadczeń w tym modelu zwierzęcym są porównywalne z wynikami otrzymanymi w badaniach klinicznych. Środki kontrastowe z wysoką osmotycznością użyte u pacjentów z obniżoną funkcją nerek są bardziej szkodliwe na nerki niż środki, które maja taką samą osmotyczność jak plazma. W naszym modelu wykazaliśmy, że jeżeli się porównuje Gd-ŚK z J-ŚK w roztworach które dają taka samą diagnostyczną informację są one zdecydowanie bardziej nefrotoksyczne niz J-ŚK.

Uwazamy, że ci naukowcy, którzy rekomendują używanie Gd-ŚK zamiast J-ŚK u pacjentów z obniżoną funkcją nerek muszą rzeczywiście wykazać, że Gd-ŚK są mniej nefrotoksyczne u ludzi niz J-ŚK, jeżeli się używa ich tych samych objętościach i w tym samym stężeniu, które daje taką samą jakość badania rentgenowskiego.

Jak dotąd nie przeprowadzono takich klinicznych doświadczeń i dlatego należy uznać, że użycie Gd-ŚK zamiast J-ŚK jest przeciwskazane w badaniach rentgenowskich u pacjentów z obniżoną funkcją nerek, szczególnie że J-ŚK użyte w ilości mającej taką samą wartość diagnostyczną, okazują się być dużo mniej szkodliwe dla nerek u świni.

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