Gadolinium contrast media are more nephrotoxic than iodine media. The importance of osmolality in direct renal artery injections.

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Abstract

Purpose: To study the role of osmotoxicity in gadolinium (Gd) and iodine contrast media (CM) nephrotoxicity **in ischemic porcine kidneys.**

Material and methods: Test solutions: mannitol iso-osmotic to 0.5M gadopentetate (1.96 Osm/kg H_2O), 0.5M gadodiamide (0.78 Osm/kg H_2O) and 0.5M iohexol (190 mg I/ml, 0.42 Osm/kg H_2O). Each solution was injected (3 ml/kg BW) into the balloon-occluded (10-minutes) right renal artery of eight left-sided nephrectomized pigs. The plasma half-life of a GFR-marker was used to compare their effects on **GFR** 1-3 hours post-injection.

Results: The median half-lives of the GFR marker after injection of gadopentetate (1730 min) and mannitol 1.96 Osm/kg (2782 min) did not differ statistically **(p=0.28)**, but were significantly longer than after all other solutions ($p<0.001$). There was no significant difference ($p=0.06$) between gadodiamide (218 min) and mannitol 0.82 Osm/kg (169 min), while there was ($p=0.03$) between iohexol (181 min) and mannitol 0.43 Osm/kg (148 min). The difference between gadodiamide and iohexol was significant ($p=0.01$).

Conclusions: **Reduction in GFR, as a marker of nephrotoxicity,** induced by gadopentetate correlated with its high osmolality, while the effect of gadodiamide and iohexol may include chemotoxicity. Iohexol molecules were less nephrotoxic than the Gd-CM molecules and contain three times the number of attenuating atoms per molecule.

Key words: Angiography; Computed tomography; Contrast media; Osmolality; Renal impairment; Gadolinium.

Introduction

Gadolinium contrast media (Gd-CM), primarily intended for magnetic resonance imaging (MRI), are regarded by many as a less or even non-nephrotoxic alternative to iodine CM (I-CM) in patients with renal impairment undergoing x-ray angiography (XRA), and computed tomography (CT) [1-8], though this view has no scientific support. There are no human studies comparing their nephrotoxic effects at volumes and concentrations resulting in the same x-ray attenuation [9, 10]. The substitution of Gd- for I-CM appears contradictory not least in renal angiography/angioplasty procedures [1, 4, 11], **since osmotoxicity is an important factor in the pathophysiology** of contrast medium induced nephropathy (CIN) [12, 13] and direct injections of high-osmolal solutions, including CM, into the renal artery may be deleterious to the kidney [14-17]. The osmolality of e.g. the Gd-CM gadopentetate and gadobenate is about *seven times that of plasma* and similar to that of the previous generation of I-CM, the ionic monomeric "high-osmolal" CM (HOCM) at 300-370 mg I/ml. HOCM are nowadays regarded as contraindicated in patients with renal impairment [18]. Today's "low-osmolal" non-ionic monomeric I-CM (LOCM) and "iso-osmolal" non-ionic dimeric I-CM (IOCM) are available in plasma iso-osmolal solutions at 140-150 and 150-320 mg I/ml, respectively. LOCM are sometimes classified as ratio 3.0 and IOCM as ratio 6.0 CM. The ratio denotes the number of attenuating atoms per osmotic active particle in **an ideal** CM solution [19]. This hints at the attenuating capacity of a CM relative to its risk of causing complications due to osmotoxicity. The ratio of the ionic HOCM dimeglumine gadopentetate and gadobenate is 1:3 and the non-ionic LOCM gadodiamide and gadoteridol has a ratio of 1:1. Thus, in I-CM the number of attenuating "heavy" atoms is 3 to 18 times higher than the number of "heavy" atoms per each osmotic active particle in Gd-CM. Today's Gd-CM have a ratio similar to that of Selectan Neutral (1:1) and Uroselectan (1:2), the first I-CM introduced 80 years ago [19].

It was recently shown that the HOCM gadopentetate caused a severe depression of renal function when injected into renal arteries of ischemic porcine kidneys [20]. The LOCM gadodiamide caused a markedly less effect on glomerular filtration rate (GFR), but still significantly more than equal volumes of an equi-molar 0.5M molecular concentration of the ratio 3:1 I-CM iohexol (190 mg I/ml). Injections of 0.184M iohexol (70 mg I/ml), iso-osmolal relative to plasma and roughly iso-attenuating with 0.5M Gd-CM at commonly used x-ray tube potentials of 70-90 peak kilovoltage (kVp) during XRA [10], had no effect on renal function any different from that of saline. The nephrotoxic effect of the CM in these animal experiments [20] seemed to be related to their osmolality relative to plasma. Ranking the CM from the highest to the lowest osmolality [0.5M gadopentetate (1.96 mOsm/kg H_2O)>0.5M gadodiamide (0.78 mOsm/kg H_2O)>0.5M iohexol (0.42 mOsm/kg H_2O)>0.184M iohexol (0.29 mOsm/kg H_2O)] gave the same result as ranking them with regard to their ability to decrease GFR.

The aim of the present study was to investigate the role of osmolality on depression of renal function using the same experimental model as in the previous study [20], i.e. injections of test solutions into the artery to ischemic porcine kidneys. For that purpose the effects of 0.5M solutions of gadopentetate, gadodiamide, and iohexol were compared with those of mannitol solutions iso-osmotic to each of the three CM.

Material and methods

Animals

The experiments were performed on 48 healthy Swedish landrace male pigs, Swedish University of Agricultural Sciences (SLU), with a mean weight of 21 kg (range 16-29 kg). The study was approved by the local ethical committee. The pigs were acclimatized at the Department of Experimental Research, Malmö University Hospital, for 4-6 days prior to surgery. They were deprived of food for 15 hours before the experiment but had free access to water. After the experiment, all animals were killed by an overdose of pentobarbital and the right kidney was examined for the presence of multiple renal arteries.

Anesthesia, surgery and catheterization

Anesthesia, heparinization, monitoring and the catheterization procedure have been described in detail elsewhere [20]. In summary introducers were placed in the right femoral artery and right internal jugular vein. 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. Subsequently a 5F balloon occlusion catheter (Boston Scientific MediTech, Watertown, USA) was placed with its tip in the proximal part of the right renal artery. The occlusion balloon was inflated to occlude the renal artery for a period of 10 minutes to produce a transient renal ischemia, when the test solutions were injected through the end hole distal to the balloon.

Test solutions

Details of the test solutions are given in the Table 1. Each pig was randomized to receive one test solution, at a dose of 3 ml/kg body weight (BW) 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. **Each test solution was injected into eight pigs.** Henceforth the term hyper-osmolal is always in relation to plasma.

Preparation of mannitol/iohexol solutions

D-mannitol ($C_6H_{14}O_6$; molecular weight 182.17) is a polyol that forms water solutions with an osmotic coefficient, i.e. the ratio of osmolality to molality of 1:1 [21]. This means that a molecule of mannitol always makes the same contribution to osmolality, independent of the dilution state of the solution of which it is a part. Mannitol molecules act individually, not as dilution dependent aggregates. This property, together with its predominantly extracellular distribution in animals and its apparent lack of toxicity attributable to molecular interactions with biological substrates (chemotoxicity) has made D-mannitol solutions the preferred reference in the study of osmotic effects on cells, organs and whole organisms [21].

Crystalline mannitol was added to plasma iso-osmolal solutions of 0.184M iohexol (Omnipaque™ 140 mg I/ml diluted with saline to 70 mg I/ml) to produce mannitol/iohexol solutions (man/io) iso-osmolal to 0.5M gadopentetate, gadodiamide and iohexol, respectively (Table 1). The reason for using an iohexol solution as solvent was to utilize the iohexol molecules as GFR-marker. As the Gd- and I-CM solutions have an osmotic coefficient that is not equal to 1 (aggregation of CM-molecules depend on their concentration) the addition of mannitol had to be made as an iterative process to get the desired osmolality at 37˚ C (Vapor Pressure Osmometer 5500 XR, Wescot, Inc, Logan, Utah, USA) were attained almost equal to the three 0.5M CM-solutions. The solubility of mannitol is approximately 22 gram per 100 milliliter of water at 25° C. Because of this solubility limit of mannitol, the solutions corresponding to the osmolality of the two Gd-CM had to be heated to 37˚ C and sonicated to delay crystallization. The composition and osmolality of the three mannitol/iohexol solutions are given in Table 1. They were named man/io-1.96 (iso-osmolal to 0.5M gadopentetate), man/io-0.82 (iso-osmolal to 0.5M gadodiamide) and man/io-0.43 (iso-osmolal to 0.5M iohexol), where the figure denotes their mean measured osmolality in Osm/kg H_2O.

Determination of contrast medium concentrations in plasma

Ten venous blood samples of 4 ml each were drawn 15, 30, 45, 60, 75, 90, 105, 120, 150 and 180 minutes after the start of the test solution injection. Plasma concentration of the CM was determined with X-ray fluorescence technique as previously described [20].

Plasma half-life of the contrast media

Half-life of the plasma concentration of the CM present in each test solution was used for comparison of the effects of the solutions on GFR following their injections into the renal arteries. This is based on the knowledge that both types of CM have glomerular filtration as dominating mechanism of body clearance and similar volume of distribution (Vd) in the extracellular space [22, 23]. Thus, according to the equation:

plasma half-life (T1/2) = ln2*Vd/body clearance [24],

where ln2 is the natural logarithm (ln2=0.693),

possible differences in plasma half-life following injections of Gd- and I-CM into the renal arteries will mainly be dependent on different effects on GFR. The larger a depression of GFR is, the longer the plasma half-life will be. Plasma half-life of the CM was calculated during their elimination phase one to three hours after injection using a one compartment model and linear regression analysis of logarithmic plasma values [23].

Statistics

Statistically significant differences between each contrast medium and its osmotic man/io control were analyzed using the non-parametric Mann-Whitney U-test. The trend in plasma half-life elimination time caused by the different contrast media was tested by the non-parametric Jonckheere-Terpstra test. For that purpose the contrast media were ranked according to their osmolality in descending order: 1) 0.5M gadopentetate (1.96 Osm/kg H_2O), 2) 0.5M gadodiamide (0.78 Osm/kg H_2O) and 3) 0.5M iohexol (0.42 Osm/kg H_2O). If the trend test was significant, differences between contrast media, adjacent in the ranking,

were investigated further using the non- parametric Mann-Whitney U-test. All p-values ≤0.05 were considered statistically significant. All statistical analyses were conducted using SPSS for Windows, version 12.0.1 (SPSS Inc., Chicago, U.S.A.).

Results

All pigs remained stable during the course of the experiment regarding intra-arterial pressure, pH, pO_2 and pCO_2, and body temperature (38° C). A single right renal artery was present in all pigs.

The plasma half-life elimination time of the GFR-markers following each injection of the various test solutions into the renal artery are given in Table 2, and median and range is outlined in the Figure. There was no significant difference in plasma half-life of the GFR markers after injections of 0.5M gadopentetate and its osmotic control man/io-1.96 (p=0.28) or between 0.5M gadodiamide and its osmotic control man/io-0.82 (p=0.06). 0.5M iohexol on the other hand caused a significantly longer half-life of the GFR marker than did its osmotic control man/io-0.43 (p=0.03).

The plasma half-life elimination time decreased with decreasing osmolality of the CM (p for trend <0.001). The plasma half-life of 0.5M gadopentetate was significantly longer than that of 0.5M gadodiamide (p<0.001), which in turn had significantly longer half-life than 0.5M iohexol (p=0.01).

Discussion

The present study indicate that the depression of renal function caused by gadopentetate and gadodiamide was due to osmotoxicity since plasma half-life of the GFR marker did not differ significantly from that following injections of their osmotic controls man/io-1.96 and -0.82, respectively. It could be argued that the presence of iohexol molecules in the mannitol/iohexol solutions may have contributed to their nephrotoxic effects. This seems unlikely considering that the higher the osmolality of a mannitol/iohexol solution the lower was its fraction of iohexol molecules (Table 1) representing both osmotoxicity and chemotoxicity. At the same time the fraction of mannitol molecules representing osmotoxicity alone [21] increased. In addition, the concentration of iohexol in the man/io-1.96 and -0.82 solutions (0.153M and 0.179M, respectively, Table 1) was less or roughly equal to 0.184M iohexol, that has been shown to affect renal function no different from that of saline in this experimental model [20].

Intravascular injections of hyper-osmolal solutions containing substances that do not freely cross cell membranes, such as CM-molecules as well as cations in ionic CM, may exert *hypertonic effects* with extraction of water out of cells that may elicit various biological responses. Osmolality-dependent effects on the kidneys has been observed in a number of experimental studies following exposure of the renal arteries to hyper-osmolal solutions including I-CM [14-17, 25-29]. Depending on the doses and degree of hyper-osmolality of CM and if ischemia is applied or not, the CM may cause anything from a transient depression of renal blood flow and GFR to extensive macro- and microscopic changes with cessation of renal function. The depression of renal function caused by the gadopentetate and gadodiamide in the present study may have been secondary to hypertonically induced shrinkage and rigdification of red blood cells [30, 31] as well as endothelial cell injuries

resulting in platelet and fibrinogen accumulation producing microthrombi [32] resulting in obstruction of the microcirculation.

Apart from hypertonic effects, CM may also exert an osmotic load on the kidneys when reaching the tubular lumen. In the tubules the CM molecules resist absorption and thereby function as osmotic diuretics and constitute an osmotic load, which also results in natriuresis [13]. Osmotic load depends on the *total dose* of CM-molecules and possible CM-cations providing no association with each other or endogenous molecules [22], and is independent of their osmolality at the site of injection. Osmotic load may activate the tubulo-glomerular feedback mechanism mediating vasoconstrictive agents, increase medullar 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 [13, 33, 34]. In the present study the ionic 0.5M gadopentetate with the highest osmotic load [1.5 mOsm/ml, 0.5 mmol/ml*3 particles; one anion (gadopentetate) and two cations (dimeglumine)] had the highest nephrotoxicity, while the osmotic load of the non-ionic 0.5M gadodiamide and iohexol is the same (0.5 mOsm/ml; one non-ionic CM-molecule) and only one-third of that of gadopentetate.

0.5M iohexol depressed renal function significantly more ($p=0.03$) than man/io-0.43. The two solutions had the same osmolality and molarity of osmotic active particles. This may indicate that the higher nephrotoxicity of 0.5M iohexol, containing three times the number of iohexol molecules as man/io-0.43 (0.5M versus 0.182M, respectively, Table 1) may at least partially be caused by a chemotoxic effect of the iohexol molecules. In this context it should be noted that the difference in plasma-half life of the GFR marker between gadodiamide and its osmotic control man/io-0.82 was actually close to significant ($p=0.06$). When comparing

the median differences of the plasma half-life values, it turned out that the plasma half-life of the GFR markers following injection of gadodiamide was 29% longer than its osmotic control. For iohexol and its osmotic control the median difference was only 22%. Thus, it cannot be excluded that gadodiamide also exerts a chemotoxic effect. Such effects may include non-osmolality dependent release of vasoconstrictors such as endothelin [12] and direct cytotoxic effects on tubular cells [35-37].

The present investigation confirms the results of a previous study [20], that the two Gd-CM depressed renal function more than the equi-molar solution of iohexol. Following injection of gadopentetate there was a severe deterioration of renal function with a median plasma half-life of the GFR marker of almost 60 hours in the earlier and 30 hours in the present study. The corresponding figures for gadodiamide were only 4.3 and 3.6 hours, which in turn represented a 90 percent prolongation of plasma-half-life of the GFR marker as compared to when saline was injected [20]. Plasma half-life following injections of 0.5M iohexol was 3 hours in both studies with a 35% prolongation relative saline. The relatively small but significant difference between gadodiamide and iohexol may be explained by the higher osmolality of gadodiamide implying more pronounced hypertonic side effects at the site of injection and/or a higher chemotoxicity.

When comparing the number of attenuating atoms per CM molecule, Gd-CM contain only one Gd-atom while iohexol contain three I-atoms per molecule. In vitro studies have demonstrated that at equi-molar concentrations of CM molecules, I-CM attenuate a higher fraction of the x-ray spectrum than Gd-CM at all practically used kVp:s in diagnostic radiology [10]. Thus, one molecule iohexol represents both a lower nephrotoxicity according to the present animal model and higher x-ray attenuation than one molecule of gadopentetate or gadodiamide. In addition LD_{50} studies in mice demonstrate that the general toxicity of

gadodiamide and gadopentetate molecules is about three and nine times higher, respectively, than that of ratio 3.0 I-CM such as iohexol [9]. It should also be emphasized that Gd-CM was not designed for x-ray examinations but for MRI, which measures signal intensities. Its use in x-ray examinations and intra-arterial injections during XRA are not a part of the product description and the applied Gd-CM doses in x-ray examinations many times exceed that recommended by the manufactures. **Even at approved doses Gd-CM may be nephrotoxic in patients with decreased renal function [38] and its use as a substitute for I-CM in x-ray examinations has been discouraged by the Contrast Media Safety Committee of The European Society Of Urogenital Radiology [39].** Gd-CM are also much more expensive than I-CM, especially in iso-attenuating doses.

The present experimental results are to some extent comparable to those obtained in humans. Clinical studies indicate that the level of hyper-osmolality of CM plays an important role in CIN. Iodine-based LOCM has been shown to be less nephrotoxic than HOCM [40, 41]. The LOCM iohexol in turn implied a higher risk of CIN compared with the IOCM iodixanol in a recent study on high-risk patients with a combination of decreased GFR and diabetes mellitus [42].

One limitation of the present study is that plasma clearance of the CM as a direct expression of GFR could not be calculated according to the formula GFR=dose/AUC (AUC=area under the plasma concentration-time curve) [23]. This was due to the fact that the CM, the GFR marker, were injected selectively into the renal artery and an unknown fraction of the dose was filtered into the urine during the first pass through the kidneys and therefore never appeared in the general circulation to become a part of AUC. Instead we used plasma-half life of the CM as an indirect measure of GFR. This requires similar volumes of distribution of the three CM, but has to the best of our knowledge not been reported for pigs.

The volumes of distribution of iohexol was determined by us based on data from eight pigs injected *intravenously* with 3 ml of iohexol 300 mg I/ml in connection with saline injection into the renal artery in a previous work [20]. Since the Gd-CM were injected directly into the renal artery in that investigation, their volume of distribution could not be calculated according to the reasoning above about AUC. The volume of distribution of iohexol was calculated according to the formula:

Vd = Dose*T½:(AUC*ln2*weight) [24]

where Vd = volume of distribution of iohexol (ml/kg BW), Dose = mg iodine, T½= plasma half life elimination time (minutes) of iohexol in the period 1-3 hours post injection, AUC = area under the plasma concentration-time curve (minutes*mg I/ml) from time of injection to infinity, ln2 = natural logarithm (ln2 = 0.693) and finally weight in kg of the pig.

The *unilaterally nephrectomized pigs* (median weight 20 kg) had a median half-life of intravenously injected iohexol of 133 minutes (Table 2) resulting in a median volume of distribution of iohexol of 0.25 L/kg. This is close to the 0.27 L/kg calculated in healthy human volunteers for iohexol [43] as well as the 0.26 L/kg for gadopentetate [44]. However, the volume of distribution for gadodiamide was found to be somewhat lower in humans, i.e. 0.19L/kg [45]. This means that, if there were a similar difference in volume of distribution between iohexol and gadodiamide in pigs as in man, the plasma-half-life for gadodiamide would be shorter than that for iohexol for the same GFR (T1/2=ln2*Vd/GFR) prior to injection of the CM. Thus, the difference in plasma-half life following injection of gadodiamide and iohexol in the present study may actually indicate an even larger difference in depression of GFR to the advantage of iohexol.

Another limitation of the present study is the question to what extent the results may be applicable in humans. Still, there is no experimental model of CIN, whose validity in predicting effects in patients has been generally accepted. First, renal anatomy and physiology may differ between animal species and humans. However, porcine kidneys have been

considered most alike human kidneys with regard to anatomy and physiology with the exception of dwarf water buffalo [46]. Secondly, the injected volume (3 ml/kg BW) was much higher than the 5-10 ml (0.1 ml/kg BW in a 75 kg person) commonly used for a single selective renal artery injection in humans. However, large CM doses are required in animals, as well as humans, to injure normal kidneys. A large dose applied to a normal kidney may be equivalent to the injuring effect of a small dose to a kidney with poor function. Thirdly, applying a 10-minute period of ischemia, when injecting the CM, would be an extraordinary procedure in humans. As in humans, prior preconditioning of the kidneys of experimental animals is often necessary to make them susceptible to CIN. Transient ischemia is only one of many models of experimental preconditioning [47]. Selective renal artery injections with ischemia was chosen since Gd-CM has been advocated to guide treatment of renal artery stenoses with balloon angioplasty and/or stent placement [1, 4], and such procedures may imply multiple injections of CM with alternating periods of renal ischemia.

In summary, **the development of intravascular x-ray I-CM since the 1920s have resulted in a *factor 12 increase in ratio* between the number of attenuating atoms and osmotic active particles in an ideal solution from 1:2 to 6:1 with a parallel *increase in renal tolerance*. Gd-CM developed for MRI have been assumed to have a lower nephrotoxicity when used for radiological examinations, than presently used I-CM in spite of a *ratio* (no. of attenuating atoms per osmotic particle) that is 3 to 18 times lower than that of modern I-CM. This fact emphasizes that the use of Gd-CM as x-ray CM in azotaemic patients is unethical before the renal toxicity of the two types of media has been compared in animal studies.**

In the present porcine model iohexol had lower nephrotoxicity per molecule than gadopentetate and gadodiamide. With three attenuating I-atoms per molecule, iohexol will also result in better diagnostic radio-opacity at all levels of kVp used in clinical radiography

than a Gd-CM molecule with only one attenuating Gd-atom. The nephrotoxic effects of 0.5M iohexol and 0.5M gadodiamide with a low and intermediate level of hyper-osmolality, respectively, may be attributed to osmo- and/or chemotoxicity, while osmotoxicity seems to dominate the effect of gadopentetate with a high level of hyper-osmolality.

Legends

Figure: Plasma half-life elimination time (median and range) of GFR markers following injections into the occluded right renal artery of 0.5M gadopentetate, 0.5M gadodiamide, 0.5M iohexol (190 mg I/ml) and corresponding iso-osmotic mannitol/iohexol solutions: **man/io-1.96, man/io-0.82 and man/io-0.43. The upper range of 0.5M gadopentetate and man/io-1.96 not illustrated as it approaches infinity. Each test solution was injected in eight pigs in a non-crossover design.**

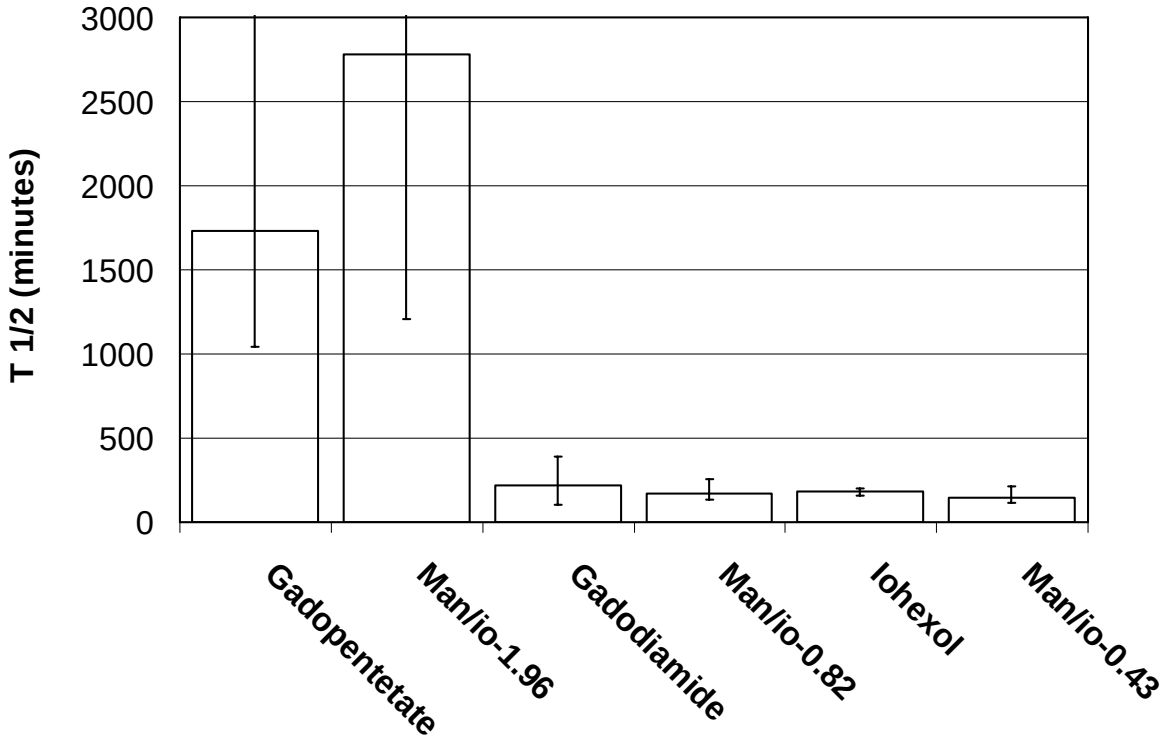
3000
2500
2000
1500
1000
500
0
T 1/2 (minutes)
Gadopentetate
Man/io-1.96
Gadodiamide
Man/io-0.82
Iohexol
Man/io-0.43

Table 1. Concentration of contrast medium (CM) molecules, attenuating atoms, mannitol and sodium chloride, and osmolality and total molarity of osmotic active particles of the test solutions.

Test solutions (3 ml/kg body weight)	**CM molecules** [molarity (M)] (iohexol molecules in percent of total molarity of osmotic particles)	**Gadolinium or iodine atoms** [molarity (M)] (mg/ml)	**Mannitol** [molarity (M)] (mannitol molecules in percent of total molarity of osmotic active particles)	**Sodium chloride** [molarity (M)]	**Mean osmolality**[1] (range) (Osm/kg H_2O)	**Total molarity of osmotic active particles**[2] [molarity (M)]
Dimeglumine gadopentetate (Magnevist®, Schering AG, Berlin, Germany)	0.5M	0.5M (79 mg Gd/ml)			1.96 (1.95-1.99)	1.5
Gadodiamide (Omniscan™, GE Healthcare AS, Oslo, Norway)	0.5M	0.5M (79 mg Gd/ml)			0.78 (0.76-0.79)	0.5
Iohexol (Omnipaque™ 350 mg I/ml, GE Healthcare AS, diluted with H_2O]	0.5M	1.5M (190 mg I/ml)			0.42 (0.41-0.43)	0.5
Mannitol/iohexol 1.96[3] (iso-osmolal with 0.5M gadopentetate)	0.153M iohexol (9 %)	0.460M (58 mg I/ml)	1.515M (84 %)	0.064M	1.96 (1.95-1.98)	1.796M
Mannitol/iohexol 0.82[3] (iso-osmolal with 0.5M gadodiamide)	0.179M iohexol (22 %)	0.538M (68 mg I/ml)	0.476M (59 %)	0.075M	0.82 (0.80-0.83)	0.805M
Mannitol/iohexol 0.43[3] (iso-osmolal with 0.5M iohexol)	0.182M iohexol (41 %)	0.547M (69 mg I/ml)	0.115M (26 %)	0.076M	0.43 (0.43-0.45)	0.449M

1. According to five measurements of each solution using a vapor pressure osmometer.
2. Summation of molecules (mannitol and CM) and ions (dimeglumine, sodium and chloride) in CM and mannitol/iohexol solutions.
3. Mannitol dissolved in a 0.184M iohexol solution (70 mg I/ml) obtained by diluting iohexol 140 mg I/ml (Omnipaque™ 140) with an equal volume of saline.
Note: osmolality = osmoles per kg water (the solvent); molarity= moles per liter solution (solute + solvent)

Table 2. Individual plasma half-life elimination times in minutes of glomerular filtration markers after injection of the various test solutions into the right renal artery in each pig. All contrast media had a 0.5M concentration of contrast medium molecules. The results of the saline group are from a previous investigation (using the same porcine model as in the present study), but where the GFR marker iohexol (3 ml, 300 mg I/mL) were injected intravenously [20] and could as such be used to calculate the volume of distribution of iohexol (see the present discussion). The values are ranked in ascending order from the top of the table. Median values and p-values are given.

	Gadopentetate (n=8)	**Man/io-1.96* (n=8)**	**Gadodiamide (n=8)**	**Man/io-0.82* (n=8)**	**Iohexol (n=8)**	**Man/io-0.43* (n=8)**	**Saline (n=8)**
	1044	1209	106	137	160	118	92
	1052	1597	201	146	161	129	106
	1194	1766	208	166	162	141	110
	1423	2437	217	168	179	147	131
	2036	3128	219	170	184	149	136
	4394	11321	245	175	187	155	138
	7681	25523	251	190	196	169	157
	∞#	∞#	391	253	199	210	167
Median	1730	2782	218	169	181	148	133
		p=0.28		p=0.06		p=0.03	
				p=0.01			

*Man/io=mannitol/iohexol solutions with the figures denoting their osmolality in Osm/kg H_2O.
#Plasma half-life time approaching infinity.

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