FULL PAPER

Compensatory biliary and urinary excretion of gadobenate ion after administration of gadobenate dimeglumine (MultiHance®) in cases of impaired hepatic or renal function: a mechanism that may aid in the prevention of nephrogenic systemic fibrosis?

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Objective: To determine whether increased elimination of gadobenate ion via the hepatobiliary pathway might compensate for reduced/absent elimination via the urinary pathway in the event of compromised renal function, as a possible protective mechanism against nephrogenic systemic fibrosis (NSF).

Methods: 15 male Crl:CD® R(SD)Br rats (Charles River Italia, Como, Italy) randomized to three treatment groups: (1) animals with occluded bile ducts, (2) animals with occluded renal vessels and (3) control animals, each received $0.25 \, mmol \, kg^{-1}$ of bodyweight of gadobenate dimeglumine (MultiHance®; Bracco Imaging SpA, Milan, Italy). Urine and bile were collected from $0-30$, $30-60$, $60-120$, $120-240$ and $240-480 \, min$ after gadobenate dimeglumine administration prior to exsanguination. Determinations of gadobenate ion in blood, bile and urine were performed by high-performance liquid chromatography.

Gadolinium (Gd^{3+}) levels in excised liver and kidneys were determined by X-ray fluorescence.

Results: The recovery of gadobenate ion in the urine of rats with bile duct occlusion was significantly higher than that in the urine of normal rats ($89.1 \pm 4.2\%$ *vs* $60.6 \pm 2.8\%$; $p < 0.0001$). Conversely, mean recovery in the bile of rats with renal vessel occlusion was significantly higher than that in the bile of normal rats ($96.16 \pm 0.55\%$ *vs* $33.5 \pm 4.7\%$; $p < 0.0001$). Gadobenate ion was not quantifiable in any group $8 \, h$ post-injection.

Conclusion: Compensatory elimination may be an effective means to overcome compromised renal or hepatobiliary elimination.

Advances in knowledge: The absence of NSF in at-risk patients administered with gadobenate dimeglumine may in part reflect greater Gd^{3+} elimination via the hepatobiliary route.

Nephrogenic systemic fibrosis (NSF) is a rare, systemic fibrosing disorder characterized by thickening and induration of the skin, flexion contractures and impaired mobility of the nearby joints, as well as fibrosing changes in connective tissues of internal organs.[1,2] Although the first cases of NSF were identified in 1997 and the first published report of 14 cases appeared in 2000,[3] it was not until 2006 that a possible association with exposure to gadolinium (Gd^{3+})-based contrast agents (GBCAs) became apparent.[4] By December 2012, 815 distinct cases of NSF had been reported in 200 articles in the peer-reviewed literature, the vast majority of which [595/815 (73.0%)] were observed in the USA.[5]

Most theories on the mechanism behind the development of NSF have focused on GBCA molecular structure and stability as factors determining an increased risk with some agents relative to others.[6,7] Thus, the non-ionic, open-chain (linear) GBCAs, gadodiamide and gadoversetamide, have the lowest kinetic stability and highest propensity to release Gd^{3+} and, as a group, have been associated with the greatest number of unconfounded cases of NSF (approximately 78% with gadodiamide and 1.3% with gadoversetamide).[5] Conversely, the macrocyclic GBCAs, gadoterate meglumine, gadobutrol and gadoteridol, have the highest kinetic stability and least propensity to release free Gd^{3+} and, as a group, have been associated with very few unconfounded cases [none with gadoteridol, very few (0.7%) with gadobutrol or gadoterate meglumine].[5] Based on these observations, the European Medicines Agency (EMA)

and UK Medicines and Healthcare Products Regulatory Agency (MHRA) introduced a classification scheme for GBCAs based on observed and perceived risk for NSF.[8,9] Thus, the macrocyclic GBCAs are categorized as low risk for NSF while the non-ionic, open-chain (linear) GBCAs are categorized as high risk. Also included in the category of high-risk agents is gadopentetate dimeglumine because of a comparatively high number of unconfounded NSF cases associated with this agent (approximately 20% of published unconfounded cases[5]).

Of particular interest, however, are gadobenate dimeglumine (MultiHance®; Bracco Imaging SpA, Milan, Italy), gadofosveset trisodium and gadoxetate disodium that are categorized as having intermediate risk for NSF.[8,9] Although these agents are ionic, open-chain GBCAs like gadopentetate dimeglumine, no unconfounded cases of NSF have yet been reported for any of these agents.[5] The principal molecular difference between these agents and gadopentetate dimeglumine is that each possesses an aromatic group on the contrast-effective molecule, whereas gadopentetate dimeglumine does not.[10] Among the unique features conferred by this aromatic moiety is that each of these three GBCAs are taken up by functioning hepatocytes to a greater or lesser extent and excreted via the hepatobiliary route into the bile and, ultimately, the faeces.[11–20] The degree to which these agents are eliminated via the hepatobiliary route is species dependent. Thus, in human subjects with normal renal and liver function, between 2% and 4% of the injected dose of gadobenate dimeglumine is eliminated by this route, while the remainder is eliminated into the urine via the kidneys.[19,20] Conversely, hepatobiliary elimination of gadobenate dimeglumine in animals has been shown to range between approximately 25% and 55% of the injected dose depending on the species, with rats demonstrating the greatest biliary excretion followed by dogs, rabbits and monkeys.[21] The possibility to eliminate Gd^{3+} via the hepatobiliary pathway is clearly potentially highly advantageous in patients with severe chronic kidney disease [CKD; Stage 4 or 5 according to the CKD classification of the US National Kidney Foundation;[22] glomerular filtration rate (GFR) $<30\,ml\,min^{-1}\,1.73\,m^{-2}$ or renal failure] or end-stage renal disease who are at risk of developing NSF but who nevertheless require a contrast-enhanced MRI examination for diagnostic purposes.

Compensatory elimination of Gd^{3+} has previously been demonstrated in rats with severely impaired liver and kidney function after administration of gadoxetate disodium.[23] The aim of our study was to determine whether compensatory elimination of Gd^{3+} occurs similarly in rats with impaired hepatic or renal function after administration of gadobenate dimeglumine.

METHODS AND MATERIALS
Animals
15 male Crl:CD® R(SD)Br rats (weight at treatment, 240–320 g; Charles River Italia, Como, Italy) were used for the study. Animals were quarantined for at least 4 days prior to treatment (three animals per cage; each cage: 59 × 38 × 20 cm) and were maintained *ad libitum* on 4Rf21-GLP pellets (Mucedola, Milan, Italy) certified as being without oestrogenic activity and as having contaminant levels within acceptable

limits. Tap water sterilized by ultraviolet irradiation and filtered through 1.0- and 0.2-m filters was similarly available *ad libitum* throughout the study. Environmental conditions were controlled and monitored throughout the quarantine period (temperature, 21.7 °C; relative humidity, 53.3%; air change, 15–20 h^{-1}; lighting automatically controlled to give a 12-h photoperiod per day).

Following the quarantine period, the 15 animals were randomly assigned to three treatment groups (5 animals per group): (1) animals to undergo bile duct occlusion and assessment of urinary excretion; (2) animals to undergo renal vessel occlusion and assessment of biliary excretion; and (3) control (normal) animals for assessment of normal urinary and biliary excretion. The treatments applied to animals in Groups 1 and 2 resemble the human pathological condition of biliary occlusion and of end-stage renal failure or bilateral nephrectomy, respectively.

All animals were fasted for 16–18 h prior to testing but were not deprived of drinking water. All animal procedures were conducted according to national and international guidelines (Italian D.L. No. 116 of 27 January 1992 and Directive 2010/63/EU) on the use of animals for experimental purposes. No validated non-animal alternatives are known that would meet the objectives of the study.

Surgical procedures
Urinary excretion in rats with bile duct occlusion
Animals were anesthetized by intraperitoneal injection of sodium pentobarbital at 30 mg kg^{-1}; if necessary further aliquots of anaesthetic were injected to maintain anaesthesia throughout the experimental period. After laparotomy, the common bile duct was isolated and a silk wire ligation made just near the mouth of the common bile duct into the duodenum. An Intramedic® PE 50 polyethylene catheter (Becton, Dickinson and Co., Parsippany, NJ) was inserted into the urinary bladder. Two ligatures were made, the first to fasten the catheter to the wall of the bladder and the second to reduce the volume between the mouth of the ureter and the catheter. The abdominal cavity was closed with sutures, and the animal placed on a surgical table warmed to 37 °C to keep the body temperature within physiological limits. The right femoral vein was exposed by making a cut through the skin in the region overlying the joint of the hind limb to the trunk of the body. This was where gadobenate dimeglumine was to be injected.

Biliary excretion in rats with renal vessel occlusion
Animals were similarly anesthetized by intraperitoneal injection of sodium pentobarbital at 30 mg kg^{-1} with top-up injections of anaesthetic administered as and when necessary to maintain anaesthesia throughout the experimental period. Laparotomy was performed and the common bile duct cannulated with an Intramedic PE 50 polyethylene catheter. The renal arteries and veins of both kidneys were isolated and ligated with silk wire. Thereafter, closure of the abdominal cavity with sutures, maintenance of body temperature at 37 °C and exposure of the right femoral vein for injection of gadobenate dimeglumine was performed as described above.

Biliary and urinary excretion in normal rats

Similar surgical procedures were performed as described above except that Intramedic PE 50 polyethylene catheters were inserted into both the common bile duct and urinary bladder.

Dosing and sampling procedures

Gadobenate dimeglumine (0.5 M) was injected at a dose of 0.25 mmol kg^{-1} into the right femoral vein of all animals at a rate of 6 ml min^{-1}. Injection volumes were calculated on the basis of dose and animal weight. All injections were performed 30 min after surgical treatment, once healing had occurred and the animals had stabilized. The timings for contrast injection following surgical intervention were consistent across animals and treatment groups.

Bile was collected for 30 min before the injection of gadobenate dimeglumine. Thereafter, both urine and bile were collected during the following periods: 0–30, 30–60, 60–120, 120–240 and 240–480 min after gadobenate dimeglumine administration. After the sampling period, *i.e.* at 480 min after gadobenate dimeglumine administration, the animal was exsanguinated through the abdominal aorta and blood collected for the assay of gadobenate ion by high-performance liquid chromatography (HPLC) and for determination of total plasma bilirubin. The liver and kidneys were excised for the assay of Gd^{3+} by X-ray fluorescence (XRF).

High-performance liquid chromatography analysis of gadobenate ion in bile, urine and plasma

All bile, urine and plasma samples collected during the study were stored at $-20\,^{\circ}\text{C}$ until the day of analysis. HPLC analysis of gadobenate ion was performed as described elsewhere.[24] Quantification was performed in duplicate by interpolation from calibration curves. The calibration curve was determined by assaying standard solutions of gadobenate dimeglumine over a range of concentrations from 10 to 1000 µg gadobenate ion per millilitre.

The working standard solutions of gadobenate dimeglumine were prepared with the same batch that was used in the treatments. A check of the precision and accuracy of the HPLC method was performed during the study with standard control samples containing 26.2, 262, 450 and 900 µg gadobenate ion per millilitre in bile, plasma and urine. The method detection limits for gadobenate ion in bile, urine and plasma were 1.1, 5.1 and 0.73 µg gadobenate ion per millilitre, respectively.

X-ray fluorescence analysis of gadolinium in liver and kidneys

The amounts of gadobenate ion in the liver and kidneys were calculated in terms of Gd^{3+} concentration since it is well established that neither *in vivo* dissociation nor metabolism of gadobenate ion occurs.[16]

The excised livers and kidneys of all animals were stored at $-20\,^{\circ}\text{C}$ until the day of analysis. All samples were weighed, lyophilized and digested in a microwave oven by suspending the sample in nitric acid. Gd^{3+} was then assayed by XRF according to standard procedures.[25] Quantification was performed in duplicate by interpolation from calibration curves. The calibration curve was determined by assaying standard solutions of gadobenate dimeglumine over the range of concentrations from 8 to 1591 µg Gd^{3+} ml^{-1}. The working standard solutions of gadobenate dimeglumine were prepared with the same batch that was used in the treatments. An internal standard solution of 0.2 M manganese(II) chloride (E. Merck, Darmstadt, Germany) was prepared. A check of the precision and accuracy of the XRF method was performed during the study with standard control samples containing 39.31 and 393.1 µg Gd^{3+} ml^{-1} in bile and urine. The limit of quantification of the XRF method was 5 µg Gd^{3+} ml^{-1}.

Assay of bilirubin

Blood samples were centrifuged (15 min; 4000 rpm) and the plasma supernatant used for the assay of free, bound and conjugated bilirubin. The assay was performed using a standardized colourimetric method based on the reaction of bilirubin with 2,5-dichlorophenyl diazonium salt and absorbance measurement at 550 nm. The assay was performed using a Cobas® Miras AutoAnalyser (Hoffmann-La Roche, Basel, Switzerland) and kit no. 19717 for assay of total bilirubin (E. Merck).

Statistical analysis

The cumulative biliary and urinary excretion (expressed as percent of the administered dose), the biliary and urinary concentration and excretion rates of gadobenate ion and the biliary flows were calculated. All values were expressed as mean ± standard deviation.

Analysis of variance for repeated measures was applied to verify that (1) there was no difference between the effects of gadobenate dimeglumine in normal animals and animals with renal vessel or bile duct occlusion; (2) that there was no difference between the effects of the times; and (3) that there was no effect of the time × animal condition interaction. The chosen significance level was $\alpha = 0.05$.

To verify the hypothesis that, at a certain time, the effects of the compound on the two groups of animals are the same, the least square means were compared with a series of *post hoc* t-tests. Again, the chosen significance level for each pairwise comparison was $\alpha = 0.05$.

Finally, in order to normalize the distribution and homogenize the group variances, data for percentage biliary excretion and percentage urinary excretion were transformed with the function $2\arcsin\sqrt{}$. Similarly, data (χ) for biliary flow and urinary excretion rate were transformed with the function $\ln(\chi)$ and biliary excretion rate and urinary concentration with the function $\sqrt{(\chi)}$.

RESULTS

Analysis of variance for repeated measures revealed no significant differences between the effects of gadobenate dimeglumine in normal animals and in animals with renal vessel or bile duct occlusion ($p \leq 0.01$), between the effects of the times ($p \leq 0.01$) or for the effects of the time × animal condition interaction ($p \leq 0.006$) for any determination.

Analytical procedures

The precision and accuracy of the HPLC method was $\pm 2\%$ and $\pm 1\%$, respectively, for the quantification of gadobenate ion in plasma, and $\pm 1.3\%$ and $\pm 2\%$, respectively, for the quantification of gadobenate ion in urine and bile. Similarly, the precision and accuracy of the XRF method was in both cases $\pm 2\%$ for the quantification of Gd^{3+} in the liver and kidneys.

Urinary excretion in rats with bile duct occlusion

The urinary excretion of gadobenate ion was significantly ($p < 0.0001$) higher in rats with bile duct occlusion than in normal rats at all time points during the period between 60 and 480 min after injection. The mean recovery (0–480 min) of gadobenate ion in the urine of rats with bile duct occlusion was $89.1 \pm 4.2\%$, while in the urine of normal rats it was $60.6 \pm 2.8\%$.

A comparison of the mean cumulative urinary excretion (percentage of administered dose) over time is shown in Figure 1a.

In normal animals, the urinary concentration of gadobenate ion peaked at $128 \pm 27\ \mu mol\ ml^{-1}$ between 0 and 30 min after injection (Table 1). Conversely, in animals with bile duct occlusion, the urinary concentration peaked at $146 \pm 12\ \mu mol\ ml^{-1}$ between 30 and 60 min after injection. The urinary concentration of gadobenate ion was significantly ($p \leq 0.002$) higher in rats with bile duct occlusion than in normal animals at time points between 30 and 120 min after injection (Table 1).

The urinary excretion rates for gadobenate ion were maximal for both groups between 0 and 30 min after injection (2.69 ± 0.58 and $2.6 \pm 1.1\ \mu mol\ min^{-1}\ kg^{-1}$ for control rats and rats with

Figure 1. Cumulative urinary (a) and biliary (b) excretion of gadobenate^{2-} (percentage of injected dose) after intravenous injection of $0.25\ mmol\ kg^{-1}$ gadobenate dimeglumine to rats ($n = 5$ per group) with bile duct occlusion (a) or urinary vessel occlusion (b).
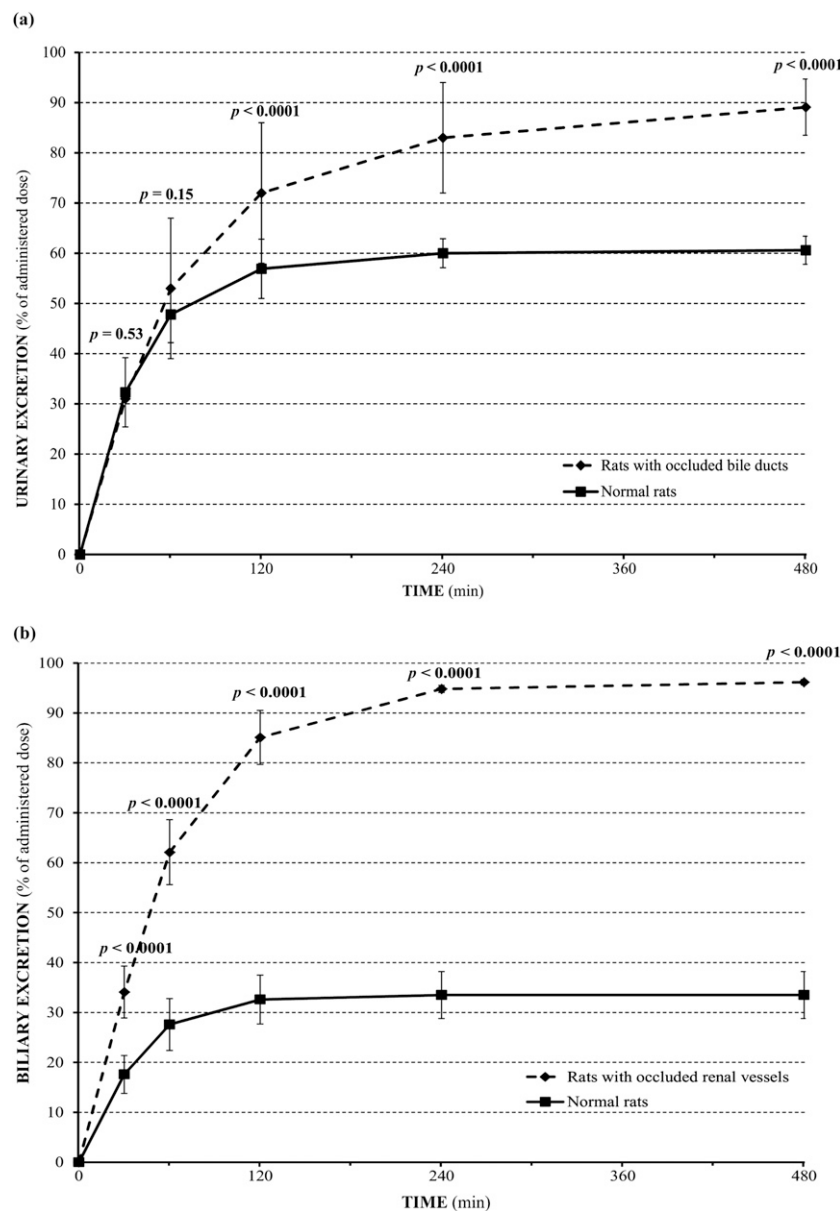
Table 1. Urinary concentration and excretion rate of gadobenate ion after intravenous administration of $0.25\,\text{mmol}\,\text{kg}^{-1}$ of bodyweight of gadobenate dimeglumine to normal rats and rats with bile duct occlusion ($n = 5$)

Time period (min)	Urinary concentration ($\mu\text{mol}\,\text{ml}^{-1}$)		Urinary excretion rate ($\mu\text{mol}\,\text{min}^{-1}\,\text{kg}^{-1}$)	
	Normal rats	Rats with bile duct occlusion	Normal rats	Rats with bile duct occlusion
0–30	128 ± 27	98 ± 24	2.69 ± 0.58	2.60 ± 1.1
	$p = 0.032$		$p = 0.74$	
30–60	95 ± 18	146 ± 12	1.29 ± 0.60	1.9 ± 0.5
	$p = 0.001$		$p = 0.246$	
60–120	41.3 ± 5.9	75 ± 20	0.38 ± 0.12	0.79 ± 0.14
	$p = 0.002$		$p = 0.052$	
120–240	8.4 ± 9.7	14.7 ± 8.4	0.066 ± 0.074	0.23 ± 0.14
	$p = 0.088$		$p = 0.001$	
240–480	0.54 ± 0.45	3.1 ± 2.5	0.006 ± 0.006	0.063 ± 0.052
	$p = 0.138$		$p < 0.0001$	

bile duct occlusion, respectively). The urinary excretion rate for gadobenate ion was significantly ($p \le 0.001$) higher in rats with bile duct occlusion between 120 and 480 min after injection (Table 1).

Biliary excretion in rats with renal vessel occlusion
The biliary excretion of gadobenate ion was significantly ($p < 0.0001$) higher in rats with renal vessel occlusion than in normal rats at all time points after gadobenate dimeglumine injection. The overall mean recovery (0–480 min) of gadobenate ion was $96.16 \pm 0.55\%$ in the bile of rats with renal vessel occlusion compared with $33.5 \pm 4.7\%$ in the bile of normal rats. A

comparison of the mean cumulative biliary excretion (percentage of administered dose) over time is shown in Figure 1b.

Peak values for gadobenate ion concentration occurred for both groups between 0 and 30 min after gadobenate dimeglumine administration ($16.6 \pm 1.9\,\mu\text{mol}\,\text{ml}^{-1}$ for control animals; $20.6 \pm 2.4\,\mu\text{mol}\,\text{ml}^{-1}$ for animals with renal vessel occlusion) (Table 2). Likewise, the biliary excretion rate of gadobenate ion peaked for both groups between 0 and 30 min after administration ($1.47 \pm 0.31\,\mu\text{mol}\,\text{min}^{-1}\,\text{kg}^{-1}$ for control animals; $2.84 \pm 0.44\,\mu\text{mol}\,\text{min}^{-1}\,\text{kg}^{-1}$ for animals with renal vessel occlusion). Significantly ($p \le 0.008$) higher values were noted at all

Table 2. Biliary concentration and excretion rate of gadobenate ion and biliary flow after intravenous administration of $0.25\,\text{mmol}\,\text{kg}^{-1}$ of bodyweight gadobenate dimeglumine to normal rats and rats with renal vessel occlusion ($n = 5$)

Time period (min)	Biliary concentration ($\mu\text{mol}\,\text{ml}^{-1}$)		Biliary excretion rate ($\mu\text{mol}\,\text{min}^{-1}\,\text{kg}^{-1}$)		Biliary flow ($\mu\text{l}\,\text{min}^{-1}\,\text{kg}^{-1}$)	
	Normal rats	Rats with renal vessel occlusion	Normal rats	Rats with renal vessel occlusion	Normal rats	Rats with renal vessel occlusion
0–30	16.6 ± 1.9	20.6 ± 2.4	1.47 ± 0.32	2.84 ± 0.44	88 ± 12	137.2 ± 5.4
	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	
30–60	11.8 ± 2.0	19.89 ± 0.92	0.83 ± 0.13	2.34 ± 0.11	71 ± 11	117.5 ± 4.2
	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	
60–120	3.4 ± 0.72	11.7 ± 1.0	0.208 ± 0.032	0.96 ± 0.10	62 ± 10	82.2 ± 7.4
	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	
120–240	0.34 ± 0.13	2.8 ± 1.3	0.019 ± 0.006	0.20 ± 0.10	58.7 ± 7.4	70.4 ± 5.3
	$p = 0.008$		$p < 0.0001$		$p = 0.002$	
240–480	0 ± 0	0.25 ± 0.15	0 ± 0	0.014 ± 0.007	53.5 ± 5.5	57.3 ± 6.8
	$p = 0.784$		$p = 0.037$		$p = 0.243$	

time points up to 240 min post-injection for biliary gadobenate ion concentration and at all time points up to 480 min post-injection for biliary excretion rate (Table 2). Similar findings were noted for biliary flow, which peaked for both groups between 0 and 30 min after administration ($88 \pm 12\,\mu mol\,min^{-1}\,kg^{-1}$ for control animals; $137.2 \pm 5.4\,\mu mol\,min^{-1}\,kg^{-1}$ for animals with renal vessel occlusion; $p \leq 0.002$ at all time points up to 240 min post-injection).

Gadobenate ion retention

Gadobenate ion was not quantifiable in plasma ($<5\,\mu g$ gadobenate ion per millilitre) in any group 8 h after gadobenate dimeglumine administration. Assuming a plasma volume in rats of $40.4\,ml\,kg^{-1}$,[26] the residual content of gadobenate ion in plasma at 8 h post-injection was therefore $<0.12\%$ of the injected dose for both normal animals and for animals with bile duct occlusion and renal vessel occlusion.

Gd^{3+} retention in the liver and kidneys at 8 h after gadobenate dimeglumine administration accounted, respectively, for $0.27 \pm 0.38\%$ and $0.57 \pm 0.34\%$ of the injected dose for rats with bile duct occlusion; $0.40 \pm 0.26\%$ and $0.59 \pm 0.92\%$ of the injected dose for rats with renal vessel occlusion; and for $0.43 \pm 0.06\%$ and $0.42 \pm 0.15\%$ of the injected dose for normal rats (Figure 2).

The total plasma bilirubin level was higher in rats with bile duct occlusion ($30.0 \pm 5.8\,\mu mol\,l^{-1}$) than in rats with renal vessel occlusion ($7.5 \pm 2.1\,\mu mol\,l^{-1}$) and in normal rats ($4.0 \pm 2.9\,\mu mol\,l^{-1}$).

DISCUSSION

This study shows that compensatory elimination of gadobenate ion through either the urinary or hepatobiliary pathway occurs from rats whose normal excretory function has been compromised by ligation of either the common bile duct or renal vessels. Specifically, our study shows that at 8 h after injection almost 90% of the injected dose of gadobenate dimeglumine is excreted via the kidneys in animals with occluded bile ducts compared with approximately 60% in normal animals. Conversely, approximately 96% of the injected dose is excreted via the hepatobiliary pathway in animals with occluded renal vessels compared with approximately 34% in normal animals. Importantly, the residual content of gadobenate ion in plasma at 8 h post-injection was in all cases $<0.12\%$ of the injected dose, while assessments of Gd^{3+} retention in the liver and kidneys revealed minimal differences between rats with occluded bile ducts/renal vessels and normal rats. These data are in agreement with those of Mühler et al[23] and suggest that compensatory elimination may be a physiological mechanism to overcome compromised biliary/renal excretion. In support of this conclusion are previous data that reveal almost identical values for the plasma half-life of elimination of gadobenate ion in normal rats with ligated biliary duct (31.1 ± 1.2 min) or renal vessels (31.2 ± 1.2 min).[27] Taken together, these data suggest that compensatory elimination may be a realistic means to eliminate GBCAs that are taken up by functioning hepatocytes and excreted in the bile.

That a similar mechanism might exist in humans is suggested by the results of Swan et al[28] who evaluated the safety and pharmacokinetics of gadobenate dimeglumine in subjects with moderate or severe renal impairment (defined as creatinine clearance of 31–60 and 10–30 ml min^{-1}, respectively). They demonstrated that at 216 h after administration of 0.2 mmol kg^{-1} of bodyweight of gadobenate dimeglumine, the mean Gd^{3+} recovery in the urine and faeces of subjects with moderate renal impairment accounted for 74% and 6% of the injected dose, respectively, while in subjects with severe renal impairment, the mean Gd^{3+} recovery at 216 h post-injection accounted for 69% and 8% of the injected dose, respectively. Clearly, the level of

Figure 2. Residual gadolinium (Gd^{3+}) levels in liver and kidney at 8 h post-injection of 0.25 mmol kg^{-1} gadobenate dimeglumine to normal rats and to rats with bile duct occlusion or urinary vessel occlusion ($n = 5$ per group). The residual Gd^{3+} levels after 8 h accounted for $<0.6\%$ of the injected dose in all groups and were similar across groups (see inset).
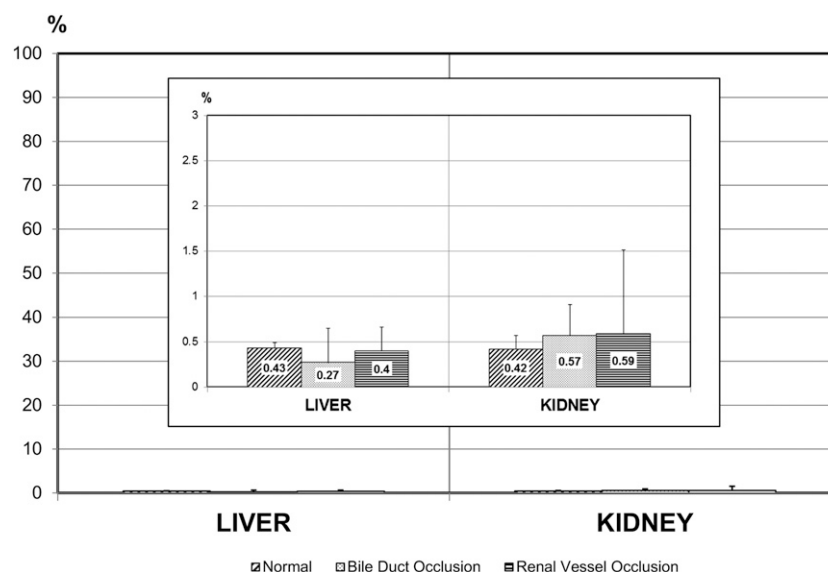
hepatobiliary elimination in both cases was up from the 2–4% determined for healthy volunteers with normal renal function[19,20] and increased with increasing degree of renal impairment. Studies on patients with impaired liver function have shown no deleterious effects on the elimination of gadobenate dimeglumine,[29] possibly reflecting the fact that urinary elimination accounts for approximately 96% of the injected dose in patients with normal renal function.

The potential clinical impact of a compensatory mechanism of elimination in patients with severe renal impairment at risk of NSF is enormous. As noted elsewhere,[30,31] NSF is primarily observed in patients exhibiting fulminant renal impairment; among 732 (90%) of 815 published unconfounded cases reported between January 2000 and December 2012 in which the type and degree of renal impairment prior to NSF onset was reported, patients with Stage 5 kidney disease (GFR: $<15\,ml\,min^{-1}\,1.73\,m^{-2}$) accounted for 644 (88%) cases, while patients with acute renal failure accounted for a further 72 (10%) cases.[5] Just 15 (2%) cases were reported in patients with Stage 4 kidney disease (GFR: $15–29\,ml\,min^{-1}\,1.73\,m^{-2}$) and just 1 (0.1%) in a patient purported to have Stage 3 CKD (GFR: $30–59\,ml\,min^{-1}\,1.73\,m^{-2}$). The comparatively few cases of NSF among patients with estimated GFR (eGFR) $>15\,ml\,min^{-1}\,1.73\,m^{-2}$ suggest that an eGFR above this level (i.e. approximately 10% residual kidney function) is sufficient to protect against NSF in the vast majority of cases.[30,31] As recently suggested by Heverhagen et al,[32] a 5% elimination via the hepatobiliary pathway, converted, corresponds to an eGFR of approximately $6\,ml\,min^{-1}$ $1.73\,m^{-2}$ via the kidney. By analogy, based on the findings of Swan et al,[28] a hepatobiliary elimination of approximately 8% in patients with severe renal insufficiency (eGFR: $<15\,ml\,min^{-1}$ $1.73\,m^{-2}$) would correspond to an eGFR of approximately $10\,ml\,min^{-1}\,1.73\,m^{-2}$. Although not much for a healthy subject with normal renal function, this level of elimination via the hepatobiliary pathway would already account for approximately two-thirds of the Gd^{3+} excretion needed to markedly reduce the risk of NSF in at-risk patients. Assuming that liver function and hepatobiliary elimination are not compromised in such patients, these data suggest that a residual eGFR of little more than $5\,ml\,min^{-1}\,1.73\,m^{-2}$ may be sufficient to safeguard against NSF in most patients administered gadobenate dimeglumine, particularly if haemodialysis is undertaken immediately after the MRI procedure.

Although the above considerations are valid for gadobenate dimeglumine given its level of hepatobiliary elimination,[19,20,28] they are perhaps less relevant for gadoxetate disodium that already undergoes 50% elimination by the hepatobiliary pathway even in subjects with normal renal function.[13–15] Likewise, such considerations are not valid for other GBCAs that are not taken up by functioning hepatocytes to any appreciable extent and are not eliminated via the hepatobiliary pathway. Apart from stability issues, this might in part explain why unconfounded cases of NSF have been reported for gadopentetate dimeglumine[5] despite a fundamentally similar molecular structure (ionic, linear, missing only the aromatic group) to that of gadobenate dimeglumine.[33,34] Similarly, it might also partly explain why unconfounded cases of NSF have been reported for one of the more kinetically stable macrocyclic GBCAs, gadobutrol,[35,36]

although it should be pointed out that these cases have been the subject of some debate.[37,38] Notably, in the case of gadobutrol its two-fold higher concentration in the vial (commercially available as a $1.0\,M$ formulation compared with the $0.5\,M$ formulations of all other GBCAs) is potentially problematic in patients at risk of NSF because of the possibility of excess dosage (a two-fold higher dose of Gd^{3+} if equal volumes are injected) if care is not taken to lower the volume administered.[32,39]

A second advantage conferred by the aromatic group on gadobenate dimeglumine, apart from a capacity for uptake by functioning hepatocytes, is increased r1-relaxivity relative to that of other GBCAs.[40,41] This increased r1-relaxivity is the result of weak, transient interaction of the $gadobenate^{2-}$ molecule with serum albumin,[42,43] mediated by the aromatic (benzyloxymethyl) group, which slows the tumbling rate of the complex, leading to stronger relaxation enhancement effects and hence greater signal intensity enhancement on T_1 weighted images.[44] Numerous intra-individual crossover studies across a range of clinical applications have demonstrated improved image quality and better diagnostic performance for gadobenate dimeglumine relative to comparator GBCAs when both agents are administered at an equivalent approved dose of $0.1\,mmol\,kg^{-1}$ of body weight.[45–51] Other studies, particularly for MR angiography (MRA) applications, have demonstrated equivalent or even superior image quality and diagnostic performance for a single dose of gadobenate dimeglumine compared with a double dose of gadopentetate dimeglumine.[52–56] This is potentially very important for patients at risk of NSF who require a contrast-enhanced MRA examination for diagnostic purposes. Higher doses of GBCAs have frequently been used in these patients because of the risk of insufficient contrast enhancement for accurate visualization and diagnosis if the GBCA dose is too low.[57–60] This has particularly been the case for patients undergoing MRA of the peripheral run-off vasculature because of the larger field of view, smaller size of the vessels and greater susceptibility to flow alterations if vessels are heavily diseased. Unfortunately, such patients are frequently elderly and have associated renal insufficiency or end-stage renal disease.[61,62] To administer high GBCA doses to these patients would be inadvisable because of the established greater risk of NSF with high GBCA doses.[5–7,30–32,63–66] In these patients, the opportunity to obtain diagnostic images with a lower dose of a GBCA that is excreted in part by the hepatobiliary pathway would be potentially highly beneficial. Preliminary studies have looked to assess the potential of lower doses of gadobenate dimeglumine for MRI procedures in patients at risk of NSF.[67]

A final consideration concerns the classification of GBCAs by the EMA and MHRA.[8,9] It is ironic that there should be fewer (zero) unconfounded cases of NSF among the group of GBCAs considered at intermediate risk of NSF than among the group considered at low risk of NSF, and it is worth bearing in mind that other regulatory authorities include gadobenate dimeglumine with the macrocyclic GBCAs in the group considered at low risk of NSF.[68,69]

In summary, this study shows that compensatory elimination of gadobenate ion through either the urinary or hepatobiliary

pathway occurs from rats whose normal excretory function has been compromised. Although there is evidence of a similar mechanism in humans,[28] it should be borne in mind that the normal level of biliary excretion is much greater in rats than in humans[21] and that further studies in humans are needed before firm conclusions can be drawn. Nevertheless, a similar compensatory mechanism in humans combined with the possibility to administer a lower overall dose to patients at heightened risk of NSF and greater awareness and care by the radiological community in general may explain in part why no unconfounded cases of NSF have yet been reported for this agent, despite many millions of administrations[32] across a wide range of approved indications.[16]

CONFLICTS OF INTEREST

Authors Miles Andrew Kirchin and Gianpaolo Pirovano are employees of Bracco, the manufacturers of gadobenate dimeglumine.

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