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Quantification of gadodiamide as Gd in serum, peritoneal dialysate and faeces by inductively coupled plasma atomic emission spectroscopy and comparative analysis by high-performance liquid chromatography

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Abstract

An inductively coupled plasma atomic emission spectroscopy (ICP-AES) method for determination of gadodiamide as Gd in serum, peritoneal dialysate and faeces was developed. The within-day and between-day precision for determination of Gd in serum and peritoneal dialysate were 0.60–2.9 and 1.8–4.4%, respectively, and the accuracy was 98.0–99.3%. The quantification limits in serum and peritoneal dialysate were 6.5 and 1.6 μM Gd, respectively. The within-day and between-day precision determination of gadolinium in faeces were 1.0–5.3 and 2.2–7.9%, respectively, and the accuracy was 104–116%. The quantification limit was 11 nmol Gd/g dry weight. For the high-performance liquid chromatography (HPLC) method, the within-day precision in determination of gadodiamide in peritoneal dialysate was 1.2% and the accuracy was 103%. The quantification limit was 0.9 μM Gd. Comparative analysis of gadodiamide in serum and peritoneal dialysate from severely impaired renal patients by ICP-AES and HPLC revealed no metabolism of chelator or transmetallation of gadolinium, even in samples obtained as long as 7 days after dosing. Furthermore, the ICP-AES determination of Gd in faeces allows for the determination of faeces content of Gd corresponding to less than 0.1% of a clinical dosage of a Gd-based contrast medium.

Keywords: Gadodiamide; Inductively coupled plasma atomic emission spectroscopy; Serum; Peritoneal dialysate; Faeces

1. Introduction

The active compound of the magnetic resonance (MR) contrast medium gadodiamide injection (Omniscan®; Nycomed Imaging, Oslo, Norway) is a non-ionic, low-osmolal gadolinium

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(Gd) chelate containing 500 mM Gd-diethylenetriamine pentaacetic acid-bis-methylamide (GdDTPA-BMA) and 25 mM calcium-diethylenetriamine pentaacetic acid-bis-methylamide. The gadolinium complex is highly water soluble. Pharmacokinetic studies in rats, rabbits and monkeys [1–3], and man [4,5], have shown that GdDTPA-BMA is distributed in the extracellular fluid and entirely excreted from the body through the kidneys by glomerular filtration, with an elimination half-life in man of 80–100 min. These findings strongly indicate that gadolinium is excreted from the body as a complex. This is in contrast to intravenously (i.v.) administered free Gd [6,7] that is primarily distributed to the intracellular compartment and excreted very slowly (over months) from the body.

From in vitro studies with gadodiamide, it has been claimed that a weak stability of the gadolinium complex should lead to retention of gadolinium in the body and urinary excretion of zinc [8,9], and it has been questioned if this is caused by transmetallation of gadolinium in gadodiamide with endogenous zinc. However, gadodiamide injection has proved to be a safe contrast medium in more than 2 million MR examinations of the central nervous system, spine and a number of other organs. Data from healthy subjects [4] and patients with moderately reduced renal function [10] gave no evidence of metabolism of GdDTPA-BMA. Separate studies in rats using ^{14}C-labelled ligand have shown [11,12] that the gadolinium moiety of GdDTPA-BMA is not exchanged by endogenous metals and that the ligand is not metabolised. In the present study, inductively coupled plasma atomic emission spectroscopy (ICP-AES) has been established and validated as a sensitive method for determination of gadolinium in serum, peritoneal dialysate and faeces. Moreover, the in vivo biostability of gadodiamide was investigated in patients with severely reduced renal function by combining analysis of gadolinium by ICP-AES and gadodiamide by high-performance liquid chromatography (HPLC). The pharmacokinetics and safety results are presented elsewhere [13].

2. Experimental

2.1. Materials

2,7 - Bis(*o* - arsenophenylazo) - 1,8 - dihydroxynaphthalene-3,6-disulfonic acid (Arsenazo III) was purchased from Tokyo Kasei Kogyo Co., Japan, and GdDTPA-BMA was produced by Nycomed Imaging AS (Oslo, Norway). The peritoneal fluid used, Dianeal®, was produced by Baxter Healthcare Corporation (Allerød, Denmark). Water was purified by reversed osmosis, ion exchanged and filtrated through 0.45 μm filter using a Millipore Milli Q system. Hydrochloric acid, perchloric acid, nitric acid and acetic acid were pro analysis quality products from Merck (Germany). Triethylamine was of analytical grade. Seronorm™ animal reference serum was supplied by Nycomed Pharma AS (Oslo, Norway). Spectrascan element standards with 1000 μg Gd/ml and 1000 μg scandium (Sc)/ml were supplied by Teknolab AS (Drøbak, Norway).

2.2. Patients and sampling of blood and peritoneal dialysate

The biostability of gadodiamide was studied in three groups of patients: nine with severely reduced renal function (SRRF) not undergoing renal replacement therapy, having a [51-chromium] ethylenediamine tetraacetic acid clearance of 2–10 ml/min per 1.73m^2 body surface area; nine undergoing hemodialysis (HD); and nine patients on continuous ambulatory peritoneal dialysis (CAPD). Thus, a total of 27 patients were enrolled, each receiving gadodiamide of 0.5 mmol/ml, 0.1 mmol/kg body weight. The patient demographic characteristics are given elsewhere [13].

Blood samples were taken from all the patients immediately prior to contrast administration. Thereafter, the SRRF patients had blood samples taken at 12 h, and 1, 2, 3, 4, and 5 days after injection of gadodiamide. One baseline 'spot' faeces sample and all faeces for 5 days after contrast administration were collected. The HD patients had blood samples taken at 1, 2 and 3 h after administration of gadodiamide. During the first

HD session, blood samples were taken just prior to start of dialysis and 1, 2 and 3 h later, as well as at the end of dialysis. Moreover, blood samples were taken just before and after the next three dialysis sessions at 3, 5, and 8 days following the injection of gadodiamide. Finally, the CAPD patients had blood sampled at 30 min, and 1, 2, 3, 4 and 5 h following the injection of gadodiamide. Dialysate was collected at baseline and 5 h after gadodiamide was given. Thereafter, blood and dialysate were collected at day 2, 3, 5, 8 or 9, 11 or 12, and once between days 19 and 22 after gadodiamide administration.

Within 1 h after blood and peritoneal dialysate sampling, serum and dialysate samples were prepared and stored at −70°C until analysis. Total gadolinium in serum and dialysate samples was determined by ICP-AES. Gadodiamide in serum was determined by HPLC in a low molecular weight fraction prepared as described previously [14], and gadodiamide in peritoneal dialysate was determined by the HPLC method for urine samples [14]. Faeces samples were stored at −20°C until further treatment and analysis for total gadolinium content by ICP-AES.

2.3. Determination of gadolinium in serum and peritoneal dialysate by ICP-AES

The total amount of gadolinium in serum and peritoneal dialysate samples was quantified by ICP-AES using the gadolinium 342.247 nm emission line. The instrumental plasma power was 1000 W, and the plasma, auxiliary and nebulizer flow were 15, 1.0 and 1.0 l/min, respectively. The pump rate was 1.0 ml/min and the viewing height was 17 mm. The monochromator had 3600 lines/mm grating, and the gain on the photomultiplicator tube was 800 and 450 V for Gd and Sc, respectively. The survey and peak windows were both 0.020 nm, and the sampling time was 500 ms. Myers–Tracy signal compensation was used, i.e. simultaneous signal compensation with separate filter monochromators using scandium at 424.683 nm and argon at 415.865 nm. A manual background correction for Gd of −0.044 to +0.058 nm was used. The samples were diluted ten times with 0.1 N HCl and analysed by ICP-AES on a Perkin Elmer Plasma 2000 Atomic emission spectrophotometer with an AS91 autosampler (Perkin Elmer Co., Norwalk, CT) using a linear standard calibration curve. The calibration standards were prepared from commercial standards. Sc was added to samples and standards to perform Myers–Tracy signal compensation and internal standardisation. The Sc 361.384 nm emission line was used.

2.4. Determination of gadolinium in faeces by ICP-AES

The faeces samples were dried at 60°C for 24–48 h until a stable dry-weight was obtained. Approximately 1.0 g dried material was added to 12.0 ml nitric acid and 5.0 ml perchloric acid [15], and 1250 μg Sc (for internal standard and Myers–Tracy compensation).

The samples were digested on a Tecator Digestion system 40 programmable heating block (Tecator AB, Hoganes, Sweden), for 17 h with a gradual increase of the temperature to 200°C. The digested samples were diluted to 25.0 ml with water before analysis on the ICP-AES using the parameters already described for Gd in serum and peritoneal fluid. A manual background correction for Gd of +0.043 nm was used.

2.5. Determination of gadodiamide in peritoneal dialysate by HPLC

The peritoneal dialysate concentration of gadodiamide was determined using the method previously described for serum and urine samples [14], except that dialysate samples were analysed directly without any further centrifugation, filtration or dilution. Calibration and control samples were prepared from stock solutions in commercial peritoneal fluid similar to that performed in serum and urine [14]. The calibration standards contained 2.00–800 μM gadodiamide, whereas the control samples contained about 5.00, 100 and 400 μM gadodiamide.

2.6. Data handling

ICP-AES data were transferred into a Microsoft Excel spreadsheet for regression analysis and calculation of sample concentrations. The detector signal from the HPLC analyses was collected using Perkin Elmer Access-Chrome chromatographic software for integration, regression analysis and calculation of the sample concentrations. Statistical analysis was performed by using a one-sided t-test; $P < 0.05$ was considered as statistically significant.

3. Results and discussion

3.1. Selection of ICP-AES method parameters

It is important to keep the concentration of acid low to prevent precipitation of the proteins in the serum samples, but also high enough to prevent any precipitation of the internal standard. Others have diluted serum samples with water or dilute acid [16]. By using 0.01 or 0.1 M HCl, no precipitation was observed in the serum samples even after 8 days at room temperature. The serum and peritoneal dialysate samples in the present study were therefore diluted ten times with 0.1 N HCl before analysis.

Gadolinium was determined in sera and peritoneal dialysate by using the most sensitive emission line for gadolinium at 342.247 nm. This emission line has few spectral interferences from elements in sera or peritoneal dialysate. A small spectral background shift from matrix elements in the sera was compensated for by using background corrections at -0.044 nm and $+0.058$ nm around the emission line. The gadolinium 342.247 nm emission line has a nearby iron emission line at 342.266 nm that may have an effect, but the concentration of iron in sera and peritoneal dialysate is far too low to give any effect on the analyte signal.

For the analysis of faecal samples, the same instrumental parameters as for the serum and peritoneal dialysate samples were used. The relatively high iron emission at 342.266 nm in the faeces samples interfered with the upper background correction point and only the lower background correction point was used for these analyses. The iron emission at 342.266 nm did not interfere with the gadolinium 342.247 nm emission line. Background correction at $+0.060$ nm was also performed on the scandium internal standard at 361.384 nm to correct for a small spectral background shift from the sample matrix.

3.2. Validation of ICP-AES determination of gadodiamide as Gd in serum, faeces and peritoneal dialysate samples

The validation of the present ICP-AES method was performed essentially as described elsewhere [17]. The test samples were obtained by adding known amounts of gadodiamide to serum, peritoneal dialysate and faecal predose samples. The determination of Gd in serum showed good within-day precision, 1.4–2.9% ($n = 5$ or 6), and between-day precision, 1.8–4.4% ($n = 17$ or 18), in the concentration range 12–589 and 11–291 μM Gd, respectively. The accuracy was 98.0–99.3% (Table 1). The method was linear in the tested concentration range of 0–590 μM (linear regression correlation coefficient, $r = 0.9997$). The detection and quantification limits of Gd, defined as three and ten times the standard deviation of a non-spiked serum sample, were 1.9 and 6.5 μM, respectively.

For determination of Gd in peritoneal dialysate, the within-day precision was 0.6–0.8% and the between-day precision was 2.1–2.2% in the concentration range 8.9–89 and 18–90 μM Gd, respectively (Table 1). The accuracy was 98.0–103%. The method was linear in the tested concentration range 0–90 μM (linear regression correlation coefficient, $r = 1.0000$). The detection and quantification limits of Gd were 0.5 and 1.6 μM, respectively.

For gadolinium in spiked faeces samples, the within-day precision was 1.0–5.2% and the between-day precision was 2.2–7.9% in the concentration range 120–1431 and 179–358 nmol Gd/g dry weight of faeces, respectively (Table 1). The accuracy was 99.2–116%. The detection and quantification limits were 3 and 11 nmol Gd/g, respectively. The method was linear in the tested

Table 1
Within-day and between-day precision and accuracy data of the ICP-AES method for determination of gadodiamide as Gd in serum, peritoneal dialysate and faeces

Matrix	Added concentration of gadodiamide[a]	Within-day precision			Between-day precision			Recovery (%)
		Found concentration of Gd[a]	*n*	RSD (%)	Found concentration of Gd[a]	*n*	RSD (%)	
Serum	0	<2	6	–	<2	6	–	–
	2.94	2.93	5	16	–	–	–	98.3
	11.8	11.6	5	1.4	11.1	17	4.4	98.0
	58.9	58.2	6	1.9	–	–	–	98.7
	295	290	6	2.9	291	18	1.8	98.5
	589	585	6	1.9	–	–	–	99.3
Peritoneal dialysate	8.90	8.85	5	0.81	–	–	–	98.1
	17.9	17.7	3	0.60	17.8	6	2.1	98.9
	89.4	88.0	5	0.67	89.9	11	2.2	98.9
Faeces	0	<3	6	–	–	–	–	–
	17.9	19.8	1	–	–	–	–	105
	35.8	40.1	6	5.3	–	–	–	109
	179	207	1	–	185	4	7.9	104
	358	398	6	1.0	398	9	2.2	111
	1431	1661	1	–	–	–	–	116

[a] Measured as μM for serum and peritoneal dialysate, and nmol/g for faeces.

concentration range 0–1430 μM (linear regression correlation coefficient, $r = 0.9998$). The precision in the determination of Gd in patient faeces samples was 5.2–18% ($n = 5$), which indicates a certain inhomogeneity of Gd in faeces.

3.3. Validation of HPLC determination of gadodiamide in dialysate

For the quantification of gadodiamide in the dialysates, the HPLC method for the analysis of gadodiamide in urine was used [14]. The chromatographic profile of gadodiamide spiked into peritoneal dialysate (Fig. 1) is nearly identical to that of gadodiamide in urine [14], where minute amounts of the hydrolysis products Gd-diethylenetriamine pentaacetic acid-monomethylamide (GdDTPA-MMA) and GdDTPA were seen in the chromatogram at the time point indicated with the arrows in the chromatograms. The quantification limit was 0.9 ± 0.2 μM (mean ± SD; $n = 6$). Repeatability and accuracy were determined at three different gadodiamide concentrations ($n = 6$) to be 1.2 and 103%, respectively. Compared with aqueous samples, gadodiamide was stable in peritoneal fluid at room temperature for at least 24 h, i.e. less than 2% decrease in recovered gadodiamide.

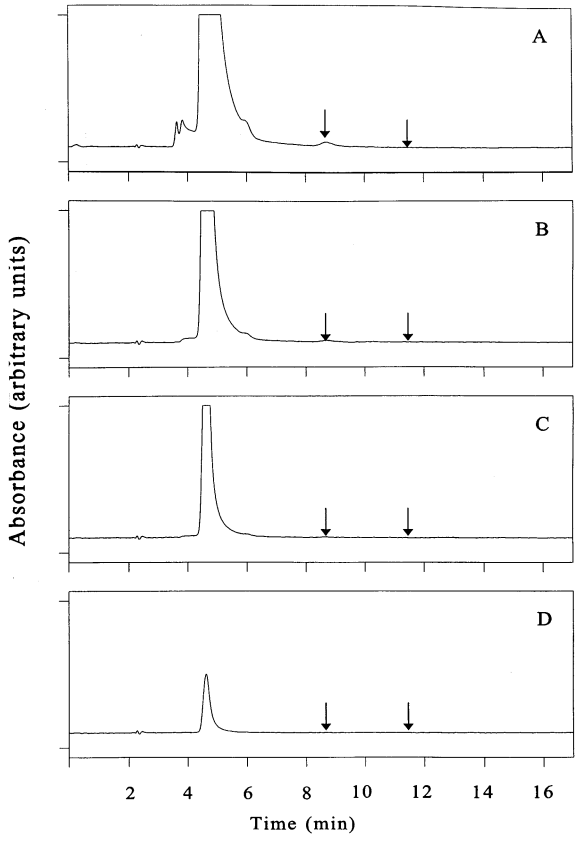

Fig. 1. Representative HPLC chromatograms of gadodiamide in dialysate samples obtained (A) 4–6 h, (B) 1 day, (C) 3 days and (D) 5 days after dosing. The arrows indicate the retention time for the potential hydrolysis products GdDTPA-MMA and Gd-DTPA.

3.4. Elimination of gadodiamide in faeces

Analysis of faeces collected for 5 days after dosing of gadodiamide injection recovered 2.0 ± 1.6% of the administered dose. Even though there was still some gadolinium present in the faeces 5 days after dosing, faecal excretion will certainly decrease in the following days since less than 10% of the administered dose was present in the extra cellular fluid compartment at that time. Similar data from patients dosed with iodinated X-ray contrast agents iohexanol and iohexol showed that about 10% of the contrast agent was recovered in faeces [18] during the first 5 days after dosing, which indicates that gadodiamide is less accessible to liver uptake and bile elimination than the X-ray contrast agents.

In a previous study of the excretion of gadodiamide from patients with moderately reduced renal function, it was found that 0.4% of the i.v. administered dose was recovered in faeces [10] during the first 5 days after dosing. Thus, these findings confirm the overall experience with the pharmacokinetics of gadodiamide in humans, showing that the substance was essentially completely excreted through the kidneys [4,5] and that liver elimination was negligible even in patients with SRRF. Moreover, this result is in agreement with the finding in animals that gadodiamide, to a very small extent, is taken up by the liver cells [19].

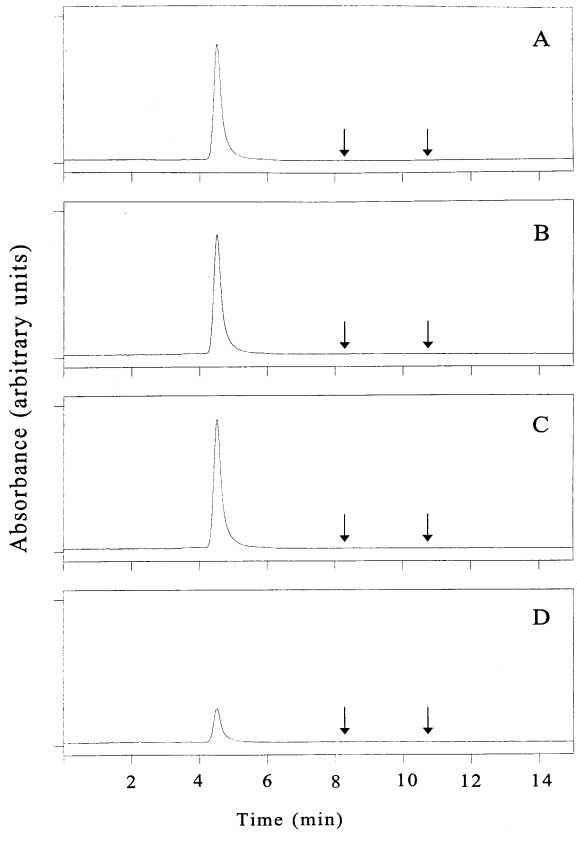

Fig. 2. Representative HPLC chromatograms of gadodiamide in processed serum samples obtained (A) 1 h, (B) 1 day, (C) 3 days and (D) 5 days after dosing. The arrows indicate the retention time for the potential hydrolysis products GdDTPA-MMA and Gd-DTPA.

3.5. Determination of biostability of gadodiamide in serum

Determination of gadodiamide in serum samples from patients with SRRF opens the possibility to study the in vivo biostability of gadodiamide in humans. In contrast to subjects with a normal renal function, the compound in these patients can be expected to circulate in the body for several days. For that reason, serum samples were taken from a group of end-stage renal patients undergoing either HD or CAPD, for investigation of in vivo biostability of gadodiamide. The stability was investigated by determining the total gadolinium content by ICP-AES in selected non-processed serum samples and gadodiamide by HPLC in low-molecular weight fraction of the same serum samples [14]. Similar concentrations of gadolinium and gadodiamide should indicate that gadodiamide is stable in vivo. The present data revealed that the difference in concentrations determined by the two methods was negligible, i.e. 1.2 ± 0.5 μM (mean ± SD; $n = 9$) 1 h after dosing, and 0.9 ± 0.8 μM ($n = 9$), 1.7 ± 1.2 μM ($n = 9$) and 0.7 ± 0.9 μM ($n = 8$) 2, 4 or 7 days after dosing, respectively (Table 2). These data strongly indicate that there is no free gadolinium (Gd^{3+}) or gadolinium bound to high molecular weight chelators such as serum proteins, or to low molecular weight compounds like citrate. Moreover, the chromatographic profile of gadodiamide in serum showed that the gadolinium complex was unchanged even 7 days after dosing (Fig. 2). Thus, it can be concluded that all gadolinium in human serum of patients with SRRF is present as gadodiamide.

Interestingly, Puttagunta et al. [9] reported that urinary excretion of Zn increased after administration of 0.1 mmol/kg gadopentetate dimeglumine injection or gadodiamide injection, and interpreted this as evidence of in vivo Zn–Gd transmetallation. Gadodiamide injection contains 25 mM Caldiamide, the calcium complex with DTPA-BMA that will chelate zinc and thus increase urinary zinc excretion. This Zn–Ca transmetallation has been shown to occur in vivo in rats dosed with a formulation of gadodiamide injection containing radiolabelled caldiamide [20]. This transmetallation can also easily be explained by the difference in thermodynamic stability of the Ca and Zn chelates [21].

3.6. Determination of biostability of gadodiamide in dialysate

The possibility of biotransformation of gadodiamide in dialysate was investigated in selected samples obtained from the first bag of dialysate taken from the CAPD patients 4–6 h after dosing and in selected samples obtained from dialysate obtained from these patients 2, 4 and 7 days after dosing. As for the serum samples, on the selected days after dosing, the average difference between

Table 2
Serum and dialysate concentration of total gadolinium and gadodiamide in selected samples from patients undergoing HD and CAPD dosed with 0.1 mmol/kg b.w. gadodiamide injection.

Sample type	Parameter	Day 0[a]			Day 2[b]			Day 4			Day 7		
		Gd	GD (μM)	Δ_0	Gd	GD (μM)	Δ_2	Gd	GD (μM)	Δ_4	Gd	GD (μM)	Δ_7
Serum (HD)	Mean	25.5	24.4	1.2	25.7	24.8	0.9	22.2	20.5	1.7	8.2	7.4	0.7
	SD	3.53	3.42	0.50	9.66	9.35	0.75	10.78	9.89	1.23	5.43	4.93	0.87
	n			10			10			10			9
	t value						<0.00			1.19			<0.00
	P						–			>0.05			–
Serum (CAPD)	Mean	39.3	36.5	2.8	45.0	43.1	1.9	54.5	52.1	2.4	14.2	12.3	2.0
	SD	11.6	11.3	0.7	10.2	10.9	1.3	17.7	17.6	1.3	5.4	5.0	0.4
	n		11			10			11			11	
	t value						<0.00			<0.00			<0.00
	P						–			–			–
Dialysate (CAPD)	Mean	179.7	178.8	0.9	98.4	100.3	−1.8	40.4	42.8	−2.4	8.6	8.9	−0.3
	SD	71.5	65.8	10.8	22.1	21.0	4.8	13.1	13.6	2.7	2.8	3.3	1.3
	n			11			11			11			11
	t value						<0.00			<0.00			<0.00
	P						–			–			–

[a] Serum samples diluted ten times.
[b] Serum samples diluted three times.

the gadolinium and the gadodiamide concentration was determined. The difference in gadolinium and gadodiamide concentration was negligible, i.e. 0.9 ± 10.8 μM ($n = 11$) on the day of dosing, and -1.8 ± 4.8 μM ($n = 11$), -2.4 ± 2.7 μM ($n = 11$) and -0.3 ± 1.3 μM ($n = 11$) 2, 4 or 7 days after dosing, respectively (Table 2). Thus, the data indicate that all gadolinium in the dialysate of patients undergoing CAPD was present as gadodiamide.

The HPLC chromatograms (Fig. 2) of dialysate show two small peaks that contribute about 5% of that of gadodiamide. This is similar to what has previously been reported regarding gadodiamide in urine [14], and is most probably due to the high content of calcium or magnesium in the dialysis dialysate.

4. Conclusions

In conclusion, an ICP-AES method for determination of gadolinium in serum, peritoneal dialysate and faeces has been documented and the method applied to samples from severely impaired renal patients. The serum and peritoneal samples has been analysed for gadodiamide by a published HPLC method. A comparison of Gd and gadodiamide findings in serum and peritoneal dialysate from these patients revealed no metabolism of chelator or transmetallation of gadolinium even in samples obtained as long as 7 days after dosing. Furthermore, the ICP-AES determination of Gd in faeces allows for the determination of faeces content of Gd corresponding to less than 0.1% of a clinical dosage of a Gd-based contrast medium.

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