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Analysis of iodinated X-ray contrast agents in water samples by ion chromatography and inductively-coupled plasma mass spectrometry

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Abstract

In this paper, an analytical method for the determination of six iodinated X-ray contrast agents (amidotrizoic acid, iohexol, iomeprol, iopamidol, iopromide, and ioxitalamic acid), iodide, and iodate in water samples is presented. The method is based on a separation of the analytes by ion chromatography (IC) and a subsequent detection by inductively-coupled plasma mass spectrometry (ICP-MS). The method was optimised with respect to separation conditions (column type and eluent composition) and extensively validated. Without pre-concentration of the samples, limits of detection below 0.2 μg/l could be achieved whereby reproducibility was below 6% for all compounds under investigation.

Keywords: X-ray contrast agents; Iodinated; Water analysis; Iodide; Iodate; Ion chromatography; Inductively-coupled plasma mass spectrometry

1. Introduction

Nowadays, the occurrence of pharmaceutical residues in the environment is a well-recognised problem. Due to an incomplete elimination, residues of pharmaceutical products have been detected in effluents of wastewater treatment plants (WWTPs) as well as in surface and groundwaters (see e.g. [1–4] and literature cited therein). Among the pharmaceutical compounds most often found in the aquatic environment were iodinated contrast agents like amidotrizoic acid, iopamidol, or iopromide [4,5]. These compounds are widely used in X-ray diagnostics for the imaging of organs or blood vessels by enhancing the contrast to the surrounding tissue [6]. During X-ray examinations, contrast agents are applied in doses up to 200 g per person and are rapidly excreted unchanged [6]. Due to the high dosages applied, the lack of human metabolism and their persistence in WWTPs [6–9], iodinated X-ray contrast agents are released in considerable amounts into the aquatic environment. Depending on the wastewater fraction, concentration levels found in German rivers range from few ng/l up to several μg/l. Even in groundwaters these compounds have been detected, mainly due to leaking waste water pipes [4].

In general, iodinated contrast agents can be classified into two different groups in reference to the ionic or non-ionic nature of the compound. Table 1 gives an overview on the chemical structures, CAS numbers and molecular weights of the iodinated compounds under investigation. Most of the iodinated X-ray contrast agents used today are 2,4,6-triiodobenzene derivatives with ionic or at least very polar side chains resulting in a high water solubility of the respective compound.

Most of the methods for the environmental analysis of iodinated X-ray contrast agents described in literature are based on the use of liquid chromatography and tandem mass spectrometry (LC-MS-MS) and a previous enrichment of the samples by means of a solid-phase extraction procedure. Hirsch et al. developed a method using Isolute ENV+ material for the pre-concentration of the samples and subsequent analysis by LC-ESI-MS-MS (ESI: electrospray ionisation), which enabled the determination of the compounds under investigation in the low ng/l range [10]. Putschew et al. proposed another analytical method based on a sequential solid-phase extraction for the isolation of iopromide, iohexol, amidotrizoic acid, iotrolan and some of their possible metabolites, using LiChrolut EN and Envi-Carb as extraction materials and

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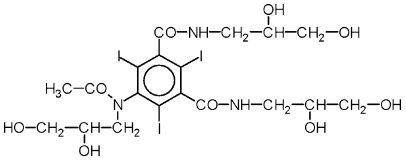
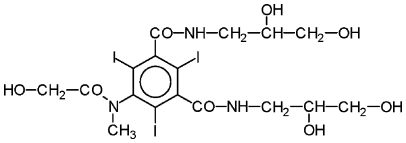
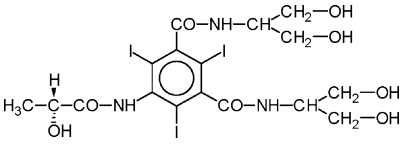
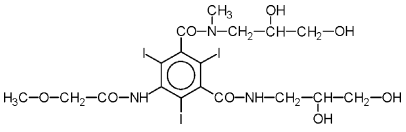
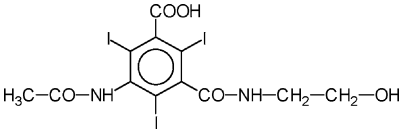
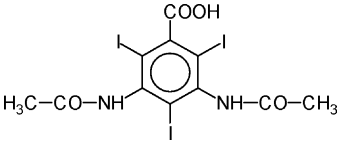
Table 1
Chemical structure, CAS number and molecular weight (MW) of the iodinated X-ray contrast agents under investigation (CAS: chemical abstract service)

Compound	Chemical structure	CAS no.	MW in g/mol
Iohexol		66108-95-0	821.14
Iomeprol		78649-41-9	777.09
Iopamidol		62883-00-5	777.09
Iopromide		73334-07-3	791.11
Ioxitalamic acid		28179-44-4	643.94
Amidotrizoic acid		131-49-7	623.98

subsequent analysis by LC-MS-MS [11]. For the analysis of amidotrizoic acid, iopamidol, iopromide, and iomeprol an extraction procedure using purely LiChrolut EN material which is combined to a LC-ESI-MS-MS method is also described in literature [12]. For the evaluation of laboratory-scale experiments, the analysis of amidotrizoic acid and iopromide by ion-pair reversed-phase HPLC-UV without any sample preconcentration step is described by Kalsch [13]. Using this method, however, limits of detection were in the mg/l range.

Alternatively, iodinated contrast agents can be considered as organic bound halogens, which, therefore, contribute to the sum of adsorbable organically bound halogens (AOX). Thus, by measuring the AOX, X-ray contrast agents can be determined indirectly. Gartiser and Kümmerer, e.g., studied the composition of the effluents of several German hospitals and found levels of AOX of about 0.3–0.9 mg/l which they mainly attributed to iodinated X-ray contrast media [14,15]. Oleksy-Frenzel et al. as well as Putschew et al. also used the determination of the sum of the adsorbable organic iodine compounds (AOIs) in effluents of municipal WWTPs and surface waters to monitor the occurrence of iodinated X-ray contrast agents and their behaviour during riverbank filtration [16–18]. In their paper, Putschew and al. compared the AOI data to concentration levels of X-ray contrast agents determined by LC-MS-MS and found that only part of the AOIs is represented by the identified contrast agents.

All of these analytical methods, however, need complex and time-consuming sample treatment. Especially for accompanying laboratory-scale experiments on the fate of X-ray contrast media, e.g. during drinking water treatment, fast and robust analytical methods which need no time-consuming sample pre-treatment are required. Furthermore, the additional determination of the inorganic iodine species iodide and iodate as potential metabolites of X-ray contrast agents during bio-degradation or oxidation experiments would be beneficial.

As it is well known that the coupling of ion chromatography (IC) and inductively-coupled plasma mass spectrometry (ICP-MS) provides a powerful tool for the simultaneous determination of inorganic and organic species of an element in water samples, a IC-ICP-MS method for the determination of iodinated X-ray contrast agents in water samples was developed and optimised.

2. Experimental

2.1. Chemicals

Amidotrizoic acid (diatrizoic acid) was purchased from Sigma–Aldrich Chemie (Taufkirchen, Germany), iohexol, iopamidol, and ioxitalamic acid from Promochem (Wesel, Germany). An iomeprol standard was provided as a courtesy by Byk Gulden (Konstanz, Germany), and a iopromide standard by Schering (Berlin, Germany). Purity of all chemicals was at least 99%. Potassium iodide and potassium iodate were purchased in analytical reagent quality from Merck (Darmstadt, Germany). From all compounds stock solutions in ultra-pure water were prepared which were further diluted either in tap water or ultra-pure water as needed.

Sodium carbonate and sodium hydrogencarbonate used for the preparation of the eluent solvents were of analytical grade and also obtained from Merck. *p*-Cyanophenol which was added to the carbonate-hydrogencarbonate eluent to improve peak shape of strongly retarded compounds was purchased from Fluka (Sigma–Aldrich Chemie, Taufkirchen, Germany). Sodium hydroxide as a 50% solution in water was purchased from J.T. Baker (Mallinckrodt Baker, Deventer, The Netherlands) and was of 'Baker Analyzed' grade. For the preparation of the eluents as well as for the preparation of the stock solutions of the analytes ultra-pure water with a resistance of 18.2 MΩ was used (Milli-Q plus, Millipore, Schwalbach, Germany).

2.2. Equipment

A scheme of the whole experimental set-up for the determination of iodinated X-ray contrast agents by IC-ICP-MS is presented in [19]. For separation of the analytes, a DX 300 ion chromatograph from Dionex (Idstein, Germany) was used. As a rule, the samples were injected without further pre-treatment. Ion-chromatographic separation was done either on an AS9-HC column or on an AS16 column (both purchased from Dionex). AS9-HC is a high-capacity anion-exchange column which was designed for the analysis of inorganic anions and oxyhalides like bromate, chlorite and chlorate. AS16 is a high-capacity, hydroxide-selective anion-exchange column which was especially designed for the fast determination of polarisable anions like thiosulfate or iodide. Compared to the AS9-HC column the anion-exchange capacity of the AS16 column is about four times higher. Both separation columns were used with a guard column of the same type. Following the instructions of the column manufacturer, a carbonate-hydrogencarbonate eluent was used for the analysis with the AS9-HC column and a sodium hydroxide eluent for the analysis with the AS16 column. Details on the chromatographic conditions are summarised in Table 2.

For reducing the salt content of the eluent prior to the inlet of the ICP-MS system, an ASRS-Ultra II suppressor from Dionex was used. In order to achieve a minimum of background, the suppressor was run in the so-called external water mode, i.e. the water needed for electrolytic generation of anions was supplied by an external source. The current for electrolysis turned out to be a key-factor for low background noise and was adjusted according to composition and concentration of the eluent as well as to the life-time of the suppressor.

ICP-MS detection was done by an ELAN 6000 instrument (Perkin-Elmer SCIEX, Rodgau, Germany), whereby the effluent of the suppressor unit was directly coupled to the cross-flow nebulizer system of the ICP-MS unit. Details on the ICP-MS system and its operating conditions are given in Table 3. Detection of the X-ray contrast agents was done

Table 2
IC conditions for the determination of iodinated X-ray contrast agents, iodide and iodate

Instrument	DX-300
Sample volume	100 μl
Flow rate	1 ml/min
Suppressor	ASRS-Ultra II
Suppression mode	AutoSuppression; External Water mode
Pre-column	IonPac AG9-HC (50 mm × 4 mm)
Separation column	IonPac AS9-HC (250 mm × 4 mm)
Eluents	A: 0.8 mM Na_2CO_3/2 mM $NaHCO_3$
	B: 30 mM Na_2CO_3/5 mM $NaHCO_3$/100 mg/l *p*-cyanophenol
Time table	0–12 min: 100% eluent A
	12–30 min: 100% eluent B
	30–40 min: 100% eluent A
Pre-column	IonPac AG16 (50 mm × 4 mm)
Separation column	IonPac AS16 (250 mm × 4 mm)
Eluents	A: 5 mM NaOH
	B: 50 mM NaOH
Time table	0–6 min: 100% eluent A
	6–15 min: 100% eluent B
	15–25 min: 100% eluent A

Table 3
ICP-MS parameters for the determination of iodinated X-ray contrast agents, iodide and iodate

ICP-MS	Perkin-Elmer Elan 6000
RF power	1150 W
Plasma gas	Argon
Plasma gas flow	15 l/min
Auxiliary gas flow	1 l/min
Nebulizer gas flow	0.85 l/min (cross-flow)
Detector mode	Pulse counting
Lens	Lens scan enabled
Data acquisition	
m/*z*	126.9
Scanning mode	Peak hopping
Measurement unit	Counts
Sweeps/reading	1
Readings/replicate	960 (AS9-HC)
	406 (AS16)
Replicates	1
Dwell time	2500 ms
Integration time	2400 s (AS9-HC)
	1020 s (AS16)

via the mass of the iodine atom which is 127 with a natural abundance of almost 100%.

Data acquisition was done by the ELAN 6000 software v. 2.3.2. Evaluation of the acquired data, however, was performed with the TotalChrom software v. 6.2.1 (Perkin-Elmer, Boston, MA, USA). For transfer of the ELAN 6000 data to a chromatographic data format, an additional software tool to the ELAN 6000 software supplied by Perkin-Elmer SCIEX was used.

3. Results

3.1. Optimisation of separation conditions

Figs. 1 and 2 present the separation of the six X-ray contrast agents under investigation, iodine and iodate applying the chromatographic conditions given in Table 2. It can be easily seen that for the separation of the X-ray contrast agents, the chromatographic performance of the AS16 separation column with the hydroxide eluent (Fig. 2) is better compared to the AS9-HC column (Fig. 1), although the total time of analysis is even longer for the AS9-HC column.

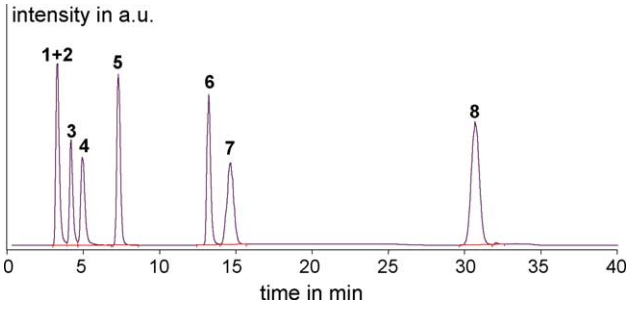


Fig. 1. Ion chromatogram of a 10 μg/l standard solution in tap water of six iodinated X-ray contrast agents, iodide and iodate applying the chromatographic conditions given in Table 2 (AS9-HC column). Peaks: 1 = iohexol; 2 = iomeprol; 3 = iopamidol; 4 = iopromide; 5 = iodate; 6 = ioxitalamic acid; 7 = amidotrizoic acid; 8 = iodide.

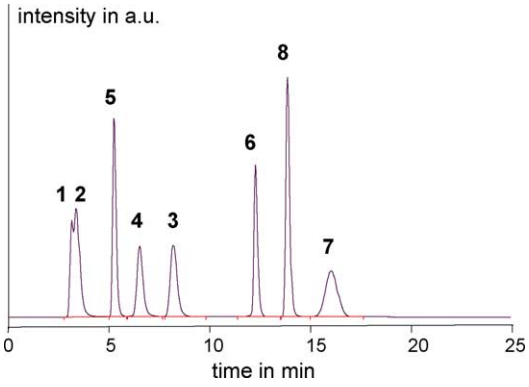


Fig. 2. Ion chromatogram of a 10 μg/l standard solution in tap water of six iodinated X-ray contrast agents, iodide and iodate applying the chromatographic conditions given in Table 2 (AS16 column). Peaks: 1 = iohexol; 2 = iomeprol; 3 = iopamidol; 4 = iopromide; 5 = iodate; 6 = ioxitalamic acid; 7 = amidotrizoic acid; 8 = iodide.

Using the AS9-HC column and the carbonate-hydrogencarbonate eluent, there is a complete overlapping of the peaks of iohexol and iomeprol, which can be explained by the structural similarity of the two compounds. Even by changing the composition of the eluent (concentration of carbonate and hydrogencarbonate as well as the ratio of the two concentrations), no separation of the two compounds could be achieved. All other compounds under investigation are well separated. Using the AS9-HC column and the carbonate-hydrogencarbonate eluent, elution time of the iodide peak was ca. 31 min. When increasing the concentration of eluent B, faster elution of the iodide peak and, thus, a shorter total time for analysis could be achieved. However, separation of the iohexol, iopromide, iopamidol and iopromide peaks deteriorated at the same time and also the equilibration time for eluent A increased. Thus, the conditions given in Table 2 represent the optimum conditions for the AS9-HC column with respect to minimum time of analysis and maximum separation of the analytes.

When using an AS16 separation column and a sodium hydroxide eluent, at least a marginal separation of the iohexol peak and the iopromide peak could be achieved (see Fig. 2). A better separation of the two peaks was not possible, even by further decreasing the sodium hydroxide concentration in the eluent. The peaks of the other iodine-containing compounds are well separated whereby the order of elution of some species is different to the AS9-HC column. Especially, the iodate peak is shifted to lower retention times eluting now before the peaks of iopamidol and iopromide. The same is true for the iodide peak which now elutes before the amidotrizoic acid peak. Using the optimum chromatographic conditions given in Table 2, time for a complete analysis could be shortened to 25 min (including equilibration time before starting the next run).

In order to prove the sensitivity of the method, Fig. 3a gives a chromatogram of a 1 μg/l standard solution in tap water. All target compounds give good signal to noise ratios at this concentration level even without additional sample pre-concentration. Further improvement of sensitivity can be achieved by increasing the injected sample volume. For comparison, Fig. 3b–d present chromatograms of the same 1 μg/l standard solution in tap water as given in Fig. 3a but with 250 μl, 500 μl, and 1 ml sample loops instead of a 100 μl loop. It can be seen that peak height as well as signal to noise ratio of the peaks significantly increase, thus indicating a higher sensitivity of the method. For validation, the method was used with a 100 μl sample loop as described in Table 2. For analysis of environmental samples, however, the 1 ml sample loop was used in order to achieve better sensitivity.

3.2. Validation of the analytical methods

Validation of the method was done for the analytical conditions given in Table 2 (AS16 separation column and sodium

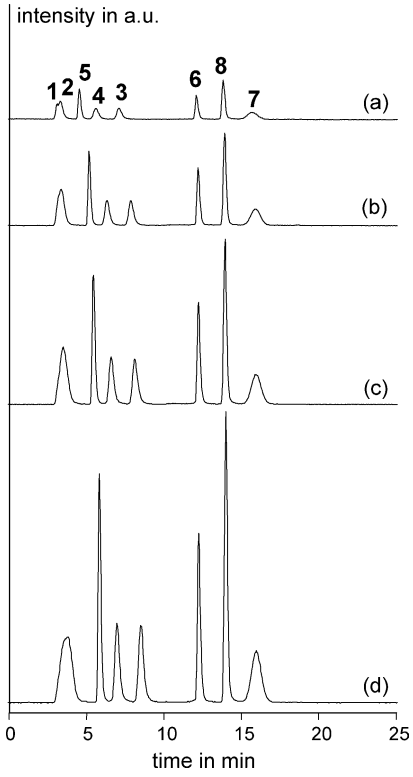


Fig. 3. Ion chromatogram of a 1 μg/l standard solution in tap water of six iodinated X-ray contrast agents, iodide and iodate. Peaks: 1 = iohexol; 2 = iomeprol; 3 = iopamidol; 4 = iopromide; 5 = iodate; 6 = ioxitalamic acid; 7 = amidotrizoic acid; 8 = iodide. (a) Chromatographic conditions as given in Table 2. (b) Chromatographic conditions as given in Table 2 but with a sample volume of 250 μl. (c) Chromatographic conditions as given in Table 2 but with a sample volume of 500 μl. (d) Chromatographic conditions as given in Table 2 but with a sample volume of 1 ml.

hydroxide eluent) and Table 3. The validation procedure of the selected analytical method for the determination of the six iodinated X-ray contrast agents, iodide and iodate comprised the determination of the parameters limit of detection and limit of determination, linearity, and repeatability. For the calculation of the performance parameters, a calibration was carried out in spiked tap water with ten concentration levels in the range of 1 to 10 μg/l. In parallel the non-spiked tap water was analysed in order to prove that the target compounds under investigation were not present in detectable amounts. From the resulting calibration curve the regression coefficient was calculated for each single compound, characterising the linearity of the calibration function. Furthermore, the limits of detection and determination were calculated according to the German standard method DIN 32645 [20]. For the determination of the repeatability, six tap water samples spiked at a concentration level of 1 μg/l were analysed in parallel. From the results the standard deviation was calculated for each compound.

In Table 4, the resulting validation data are presented. It can be seen that the performance data for all of the iodine-containing compounds under investigation are excellent. Regression coefficients are >0.999, indicating an excellent linearity of the calibration function in the concentration range from 1 to 10 μg/l. Additional measurements proved that this linearity holds true up to concentration levels of 100 μg/l. Values for relative standard deviation were below 6% for all compounds, indicating a good repeatability of the method. This result could be mainly attributed to the simplicity of the complete method and the robustness of the analytical instrumentation used. As it can be also seen from the data given in Table 4, limits of detection as well as limits of determination were far below 1 μg/l for all iodine-containing compounds.

Table 4
Performance parameters for the determination of iodinated X-ray contrast agents, iodide and iodate by IC-ICP-MS (*r*: regression coefficient; RSD: relative standard deviation; lod: limit of detection; LOD: limit of determination; for details see text)

	r	RSD in %	lod in μg/l	LOD in μg/l
Iohexol	0.9996	1.0	0.21	0.75
Iomeprol	0.9999	2.7	0.11	0.39
Iopamidol	0.9997	1.6	0.17	0.61
Iopromide	0.9998	3.8	0.16	0.58
Ioxitalamic acid	0.9998	3.9	0.13	0.47
Amidotrizoic acid	0.9997	5.4	0.17	0.60
Iodide	0.9998	2.1	0.21	0.77
Iodate	0.9998	2.5	0.13	0.48

As already mentioned in Section 3.1, sensitivity of the method could be further increased by using larger sample loops. Table 5 gives limits of detection and limits of determination for the six X-ray contrast agents under investigation that could be achieved with a 1 ml sample loop. Calculated of the data was done according to DIN 32645 from a calibration in tap water between 0.1 and 1 μg/l [20]. The data in Table 5 clearly prove the increase of sensitivity due to the use of the larger sample loop even if a direct comparison with the values given in Table 4 is not feasible due to the different calibration range used for the calculation of the validation parameters.

In order to check for matrix effects, the repeatability study was performed at a 5 μg/l level with MilliQ water, tap water, and surface water from river Rhine (Table 6). The higher concentration level compared to the previous study was chosen to avoid interferences with low levels of X-ray contrast agents already present in the surface water sample. In addition to the determination of relative standard deviations, relative recoveries were calculated for tap water and surface water taking the MilliQ water data as reference value. The results

Table 5
Limit of detection (lod) and limit of determination (LOD) for six iodinated X-ray contrast agents by IC-ICP-MS in tap water (1 ml sample loop; for details see text)

	lod in μg/l	LOD in μg/l
Iohexol	0.02	0.07
Iomeprol	0.03	0.10
Iopamidol	0.03	0.12
Iopromide	0.04	0.13
Ioxitalamic acid	0.03	0.11
Amidotrizoic acid	0.03	0.12

Table 6
Performance parameters for the determination of iodinated X-ray contrast agents, iodide and iodate by IC-ICP-MS in MilliQ water, tap water, and surface water (RSD: relative standard deviation ($c = 5$ μg/l, $N = 5$); rec: recovery; for details see text)

	MilliQ water		Tap water		Surface water	
	RSD in %	rec in %	RSD in %	rec in %	RSD in %	rec in %
Iohexol	1.1	100	1.0	99	0.94	98
Iomeprol	1.0	100	0.83	96	0.93	95
Iopamidol	2.3	100	2.0	103	1.6	109
Iopromide	1.5	100	1.6	98	1.1	94
Ioxitalamic acid	2.0	100	1.2	98	2.2	97
Amidotrizoic acid	1.9	100	2.3	97	1.6	96
Iodide	1.0	100	0.9	97	1.8	95
Iodate	1.9	100	1.3	94	1.1	94

of this study prove that the repeatability data for all analytes under investigation are comparable. The relative standard deviations are below 2.5% in all cases and no significant trend between the different matrices can be observed. Furthermore, there are no significant differences in recoveries for the tap water and the surface water compared to the MilliQ water. Thus, from the results of this study it can be concluded that the analytical method for the determination of X-ray contrast agents, iodide and iodate does not suffer from significant matrix effects when analysing surface water instead of tap water.

In conclusion, the validation data presented prove that the methods established is well suitable for the reliable determination of iodinated X-ray contrast agents, iodide and iodate in water samples.

3.3. Comparison of methods

In Table 7 data on the occurrence of iodinated X-ray contrast agents in three surface water samples are given. Samples 1 and 2 were taken from two locations at river Rhine and sample 3 from a sampling site at river Main. Concentration levels found in these samples are typical for surface waters influenced by municipal wastewater discharges. The concentration levels given in Table 7 were determined with the IC-ICP-MS method (using a 1 ml sample loop, an AS16 column and the respective chromatographic conditions given in Table 2) as well as with an HPLC-MS-MS method following solid-phase extraction (SPE) which is described in detail in [12]. As the calibration range for the IC-ICP-MS method was between 0.1 and 1 μg/l, no data below 0.1 μg/l are reported.

Table 7
X-ray contrast agents in surface water samples – comparison of methods (concentrations in μg/l)

	IC-ICP-MS without sample pre-treatment	LC-ESI-MS-MS after solid-phase extraction [12]
Sample 1		
Iohexol	<0.1	0.03
Iomeprol	0.12	0.10
Iopamidol	<0.1	0.09
Iopromide	0.18	0.20
Amidotrizoic acid	0.13	0.15
Sample 2		
Iohexol	<0.1	0.05
Iomeprol	<0.1	0.08
Iopamidol	0.22	0.18
Iopromide	<0.1	0.09
Amidotrizoic acid	0.18	0.18
Sample 3		
Iohexol	<0.1	0.09
Iomeprol	<0.1	0.05
Iopamidol	0.13	0.15
Iopromide	0.15	0.17
Amidotrizoic acid	0.44	0.40

The data in Table 7 prove clearly that the concentrations determined with the IC-ICP-MS are comparable to the concentration levels determined by the much more time consuming SPE-HPLC-MS-MS method. Differences are below 25% in all cases whereby no trend of the IC-ICP-MS method towards overestimation or underestimation of the concentration levels can be identified. The SPE-HPLC-MS-MS method, however, still offers a significantly higher sensitivity (limits of detection for all compounds are below 10 ng/l [12]) due to the sample pre-concentration step allowing the analysis even of very small amounts of X-ray contrast agents. Furthermore, specificity of the IC-ICP-MS method is low compared to the SPE-HPLC-MS-MS method due to the fact that only the presence of iodine atoms is detected in the mass spectrometer. Taking into account the limited separation power of the ion chromatographic system, false positive results due to interferences with other iodine-containing compounds cannot be completely excluded. On the other hand, the IC-ICP-MS method offers the possibility of detecting other iodine-containing compounds besides the target analytes, and thus, the determination of a kind of group parameter for iodine-containing compounds present in a water sample becomes feasible.

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