Iodinated contrast agents: physicochemical properties and renal retention

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Purpose

The differences in the physicochemical properties of x-ray contrast agents (CA) may have an important relevance for renal safety as suggested by recent publications [1,2]. Previous studies reported prolonged renal retention times for iso-osmolar, dimeric compared to low-osmolar, monomeric CA [3,4] and suggested a correlation between iodine exposure and elevated expression of biomarkers for renal damage [5]. At comparable iodine concentrations the low-osmolar CA have lower viscosities and higher osmolalities than the iso-osmolar CA. During their renal excretion CA are concentrated in the renal tubuli. Thereby, the degree of tubular CA enrichment depends on the osmolality of the CA and the osmolality of the tubular sections they pass through, as the CA osmolality is relevant to counteract the water reabsorption in the tubules [3].

The aim of this study was to investigate the impact of the physicochemical properties of CA on renal retention, systematically. Therefore, different formulations of a non-ionic, dimeric CA with varying osmolalities were compared to a non-ionic, monomeric, low-osmolar CA and an ionic, low-osmolar, dimeric CA by monitoring the iodine retention up the 24h post injection (p.i.) with computed tomography.

Methods and Materials

Han-Wistar rats (n=6 per group) received an intravenous injection of low-osmolar iopromide (Ultravist 300, Bayer Pharma), iso-osmolar iodixanol (Visipaque 320, GE Healthcare), a hypo-osmolar solution of iodixanol drug substance (320 mgI/mL), a low-osmolar iodixanol/mannitol mixture (300 mgI/mL) and ionic, low-osmolar ioxaglate meglumine/ sodium (Hexabrix 320, Covidien) at a dosage of 4 g I/kg body weight. The physicochemical properties of the CA in-vitro are shown in figure 1.

The renal iodine concentration was monitored by imaging the lower abdomen of the animals using a 64-slice CT scanner (80 kV, 100 mAs). To assess the early CA kinetic in the kidney the first 300 s p.i. were imaged dynamically (#t= 10 s). Additional measurements were performed at 2 h, 4 h, 6 h and 24 h p.i. to determine the renal CA retention over 24 h.

For image analysis a region of interest was manually drawn around each kidney on one centrally located slice for each time point. After a difference to baseline transformation the renal CA exposure was calculated using the trapezoidal rule. A calibration factor of 48 HU per mgI/mL was used to convert the CT-signal to iodine concentrations.

Images for this section:
**Fig. 1:** Overview of physicochemical contrast agent properties in vitro. All contrast agent formulations used in the present comparative study are presented with their viscosities and their respective osmolalities.
Results

In the case of the administered low-osmolar iopromide and the ionic, low-osmolar ioxaglate a rapid clearance from the kidneys was observed starting immediately after administration. In contrast, before the onset of clearance of the hypo- and iso-osmolar iodixanol formulations an increase in the renal iodine concentration was observed during the first 300 s after administration (Figure 2). This increase was markedly reduced for the low-osmolar iodixanol formulation.

Obvious differences in renal excretion were also observed at later time points. The renal iodine concentrations were higher for the hypo- and iso-osmolar formulated iodixanol than for the low-osmolar iopromide and ioxaglate (Figure 3). At 24 hours p.i. highly elevated CT signals were still observed in the renal cortex of animals injected with hypo- and iso-osmolar iodixanol formulations while it reached baseline level after administration of iopromide (Figure 4).

These differences became especially relevant considering the renal CA exposure over 24 hours (Figure 5). Iso-osmolar iodixanol showed a 7.2 fold higher iodine exposure than low-osmolar iopromide. Lowering the osmolality of iodixanol (drug substance) resulted in a slightly higher exposure (10.6%), whereas an osmolality increase to the level of iopromide by adding mannitol led to a 40.1% reduction of iodine exposure. In contrast, the ionic, dimeric ioxaglate showed a 2 fold iodine exposure than iopromide.

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**Fig. 1:** Overview of physicochemical contrast agent properties in vitro. All contrast agent formulations used in the present comparative study are presented with their viscosities and their respective osmolalities.

![Graph showing CT numbers over time](image)

**Fig. 2:** Renal CT signals measured over the first 300 s post injection of iodixanol 320 (red), of a hypo-osmolar formulation of iodixanol drug substance (brown), of a low-osmolar formulation of iodixanol/mannitol (pink), of ioxaglate meglumine/sodium 320 (green) and of iopromide 300 (blue). The vertical lines represent the standard deviations.

![Graph showing CT numbers over time](image)

**Fig. 3:** Renal CT signals measured over time up to 24h post injection of iodixanol 320 (red), of a hypo-osmolar formulation of iodixanol drug substance (brown), of a low-osmolar formulation of iodixanol/mannitol (pink), of ioxaglate meglumine/sodium 320 (green) and of iopromide 300 (blue). The vertical lines represent the standard deviations.
Fig. 4: Representatative CT-images 24h post injection show iodine retention in the kidney. The frames indicate the different osmolalities of the CA formulations.
Fig. 5: Renal exposure to contrast agent within the first 24 hours after injection of iodixanol 320 (red bar), of a hypo-osmolar formulation of iodixanol drug substance (brown bar), of a low-osmolar formulation of iodixanol/ mannitol (pink bar), of ioxaglate meglumine/ sodium 320 (green bar) and of iopromide 300 (blue bar). The vertical lines represent the standard deviations.
Conclusion

The prolonged renal retention and higher renal CA exposure observed for the hypo- and iso-osmolar, dimeric CA formulations appear to be due to their low osmolality. The faster excretion of the low-osmolar, monomeric CA is promoted through its higher intrinsic osmolality. This is demonstrated by the observation that the prolonged renal retention of hypo- and iso-osmolar, dimeric CA is largely compensated by increasing the osmolality to the level of low-osmolar CA using the osmodiuretic mannitol. We additionally prove this theory by showing efficient renal excretion for the ionic, low-osmolar CA which despite of its dimeric molecule structure exhibits a high intrinsic osmolality.

During renal CA excretion the osmolality determines the degree of CA enrichment during its passage through the tubular system, e.g. a low CA osmolality causes a high CA concentration [3]. This is especially relevant as high tubular iodine concentrations are associated with strongly enhanced CA viscosities [3]. The resulting elevated tubular filtrate viscosities in turn reduce the tubular flow and hence, prolong the renal CA retention for dimeric, iso-osmolar and hypo-osmolar CA [2]. With the present results we demonstrate the importance of the physicochemical properties and identify the osmolality of CA as a key factor for their fast and efficient renal excretion.

References


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