Enhancement and safety of iomeprol-400 and iodixanol-320 in patients undergoing abdominal multidetector CTL Romano

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Enhancement and safety of iomeprol-400 and iodixanol-320 in patients undergoing abdominal multidetector CT

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ABSTRACT. The purpose of this study was to compare iomeprol-400 and iodixanol-320 for contrast enhancement and safety in patients undergoing liver multidetector CT (MDCT). 183 patients undergoing MDCT received equi-iodine (40 gI) iomeprol-400 ($n=91$) or iodixanol-320 ($n=92$) IV at 4 ml s^{-1}. Two off-site, independent, blinded readers determined the contrast density (in Hounsfield units (HUs)) in the abdominal aorta, inferior vena cava, portal vein and liver parenchyma during the arterial and portal phases. The mean contrast densities achieved were compared and 95% confidence intervals (CIs) estimated. Heart rate was measured at baseline and at post-dose peak, and a full safety assessment was performed. Study group demographics were comparable. Iomeprol-400 produced significantly greater enhancement of the aorta during the arterial phase (Reader 1: 337.3 HU *vs* 294.9 HU, 95% CI of difference (19.4, 65.5), $p=0.0004$; Reader 2: 325.7 HU *vs* 295.3 HU, 95% CI of difference (6.6, 54.3), $p=0.01$) and greater enhancement of the liver parenchyma during the portal venous phase (Reader 1: 115.1 H *vs* 108.6 HU, 95% CI of difference (0.27, 12.7), $p=0.04$; Reader 2: 115.2 H *vs* 109.3 HU, 95% CI of difference (–0.1, 11.8), $p=0.05$). Similar enhancement of the inferior vena cava and portal vein was noted. Comparably negligible increases in the mean heart rate were observed. Adverse events occurred in 1/91 (1.1%) subjects after iomeprol-400 and 4/92 (4.3%) subjects after iodixanol-320. In conclusion, iomeprol-400 produces greater arterial and portal phase enhancement and has a similarly negligible impact on heart rate and safety.

With the evolution of multidetector CT (MDCT), particularly 64-detector-row scanners, it is possible to reduce the scan time for the liver and upper abdomen to less than 5 s [1]. However, this has necessitated the development of protocols that ensure very rapid delivery of iodine. This can be achieved either by increasing the injection rate or by using contrast material with a higher concentration of iodine [1, 2]. Although it is generally not practical to increase injection rates much above 4–5 ml s^{-1}, higher concentration contrast media have been shown to provide delivery of a higher iodine flux (measured in gI s^{-1}) in a shorter period of time [1, 3–5].

Iomeprol is a non-ionic monomeric contrast medium whose low osmolality (726 mOsmol kg^{-1}) and viscosity permit the preparation of a formulation that contains an iodine concentration of 400 mg ml^{-1} (Iomeron®-400; Bracco Imaging, Milan, Italy) [6]. Conversely, iodixanol is a non-ionic dimeric contrast medium which, despite an osmolality similar to that of human plasma (290 mOsmol kg^{-1}) and the theoretical advantage of decreased contrast medium dilution in plasma, has an

increased viscosity compared with iodinated monomers at similar iodine concentrations [7]. The resulting commercial formulations of iodixanol are therefore limited to a maximum iodine concentration of 320 mg ml^{-1} (Visipaque^{TM}-320; GE Healthcare, Chalfont St. Giles, UK). To date, no studies have directly compared these two agents for multiphase MDCT of the liver. Conversely, comparisons of these agents for MDCT applications in the brain [8] and heart [9] have shown that the higher iodine concentration of iomeprol-400 results in markedly improved imaging performance owing to greater contrast enhancement. Improved imaging performance with iomeprol-400 compared with a monomeric agent containing 370 mgI ml^{-1} has also been demonstrated [10], suggesting that a higher iodine concentration is a determining factor for improved image quality.

Concerning the osmolality of iodinated contrast media, it has been suggested that agents that are isotonic with blood may be beneficial for contrast-enhanced MDCT applications because of a reduced effect on heart rate (HR) during the CT examination [11]. Although changes in HR may be of greater clinical significance for cardiac CT and CT angiography (CTA) because of possible interference with the acquisition of motion-free images [12–14], studies have yet to be performed to determine

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whether iomeprol-400 and iodixanol-320 have differential effects on HR during MDCT of the liver.

The present study (ACTIVE, Abdominal Computed Tomography: Iomeron®-400 *vs* Visipaque™-320 Enhancement) was designed to determine prospectively whether differences in iodine concentration impact the degree of attenuation of vascular and hepatic parenchymal structures when iomeprol-400 and iodixanol-320 are administered at an equi-iodine (40 gI) dose for multiphase MDCT of the liver, and to assess the effects of these two agents on HR during the CT examination.

Methods and materials

Study design

The study was a prospective, multicenter, double-blind, randomized, parallel group comparison of iomeprol-400 (400 mgI ml^{-1}) and iodixanol-320 (320 mgI ml^{-1}) in patients undergoing clinically indicated contrast-enhanced MDCT of the liver. The study was conducted at 12 centres in Europe and 4 centres in China according to Good Clinical Practice, and was performed in accordance with the Declaration of Helsinki (Helsinki, Finland, 1964) and all subsequent amendments. The Ethics Committee or Institutional Review Board of each participating centre approved the protocol, and all study subjects provided written informed consent at the time of study enrolment.

Study patients

Adult patients referred for a clinically indicated contrast-enhanced MDCT examination of the liver were consecutively enrolled at each study centre. All patients had moderate-to-severe renal impairment (stable baseline serum creatinine of 1.5–2.5 mg dl^{-1} and/or calculated creatinine clearance of 10–60 ml min^{-1} 1.73 m^{-2}). The impact of the two contrast agents on the incidence of contrast-induced nephropathy in this patient population has been reported elsewhere [15].

Subjects were ineligible and were excluded from the study if they had a history of hypersensitivity to iodine-containing compounds, a suspicion of hyperthyroidism or thyroid malignancy, unstable renal function, acute renal failure requiring dialysis, severe congestive heart failure (New York Heart Association Class III–IV), uncontrolled diabetes, or were a pregnant or lactating female. Subjects were also excluded (i) if they had undergone, or were scheduled to undergo, any other radiological procedure utilizing X-ray contrast media from 72 h before to 7 days after study agent administration; (ii) if they had received an investigational compound within 30 days prior to enrolment; or (iii) if they had any medical condition or other circumstance that would significantly decrease the chances of obtaining reliable data or achieving post-dose follow-up examinations.

Contrast injection protocol

All clinical trial sites were provided with a computer-generated balanced randomization scheme, along with drug accountability logs. Subjects were randomized to receive either iomeprol-400 or iodixanol-320 intravenously at an equi-iodine dose of 40 gI (corresponding to 100 ml of iomeprol-400 or 125 ml of iodixanol-320). Both agents were warmed to 37°C and injected at a rate of 4 ml s^{-1} (a 25 s injection for iomeprol-400 and a 31.2 s injection for iodixanol-320), followed by a 20 ml bolus of normal saline administered at the same rate. Based on the contrast administration protocol, the iodine delivery rates were 1.6 g s^{-1} for iomeprol-400 and 1.28 g s^{-1} for iodixanol-320.

Imaging protocol

MDCT of the liver was performed using scanners with 16 or more detector rows and a 0.5 s rotation time. The recommended parameters for arterial phase scanning on 16-slice scanners were: 140 kVp, 380 mA, 1.75 pitch, 17.5 mm per rotation table speed, and 0.85 slice profile. Similar parameters were recommended for scanning during the portal venous phase apart from a reduced mA of 250. Acquisition of the hepatic arterial phase was bolus triggered and the scan delay for the portal venous phase was 20 s after the start of the arterial phase acquisition. Given the multicentre design of the study, 16-detector-row MDCT scanners from a variety of manufacturers were used (Toshiba aquilon 16; Siemens Sensation 16; GE Lightspeed 16), with the result that slight variations of the above parameters were employed at different centres. However, the parameters used were always selected to obtain as precise an image timing and as high an image quality as possible. Variations of the above scanning parameters were also required for 64-slice scanners. Typical arterial and portal venous phase parameters for 64-slice MDCT were: 120 kVp, 400 mA, 1.0 pitch, 10.1 mm per rotation table speed, and 0.6 slice profile.

Image evaluation

Quantitative assessment of contrast enhancement was performed by two off-site independent and fully blinded readers in accordance with standards established by the US Food and Drug Administration, by the European Regulatory Authorities, and by the State Food and Drug Administration of China. Prior to assessment, both readers first determined whether the image sets were technically adequate for quantitative assessment; if a reader considered an image set to be technically inadequate, no further evaluation was made of that image set. Quantitative determination of contrast density was thereafter performed independently by the two blinded readers at regions of interest (ROIs) positioned on the abdominal aorta (1 cm, mid-lumen, level of the coeliac axis, in the arterial phase), the main portal vein (1 cm (or elliptical equivalent), mid-lumen, mid-portion, in the portal venous phase), the inferior vena cava (IVC; 1 cm, mid-lumen, at the level of mid-portion of main portal vein, in the portal venous phase) and the normal liver parenchyma (1 cm, approximately mid-right lobe, excluding visible portal or vascular structures). Measurements were made in Hounsfield units during
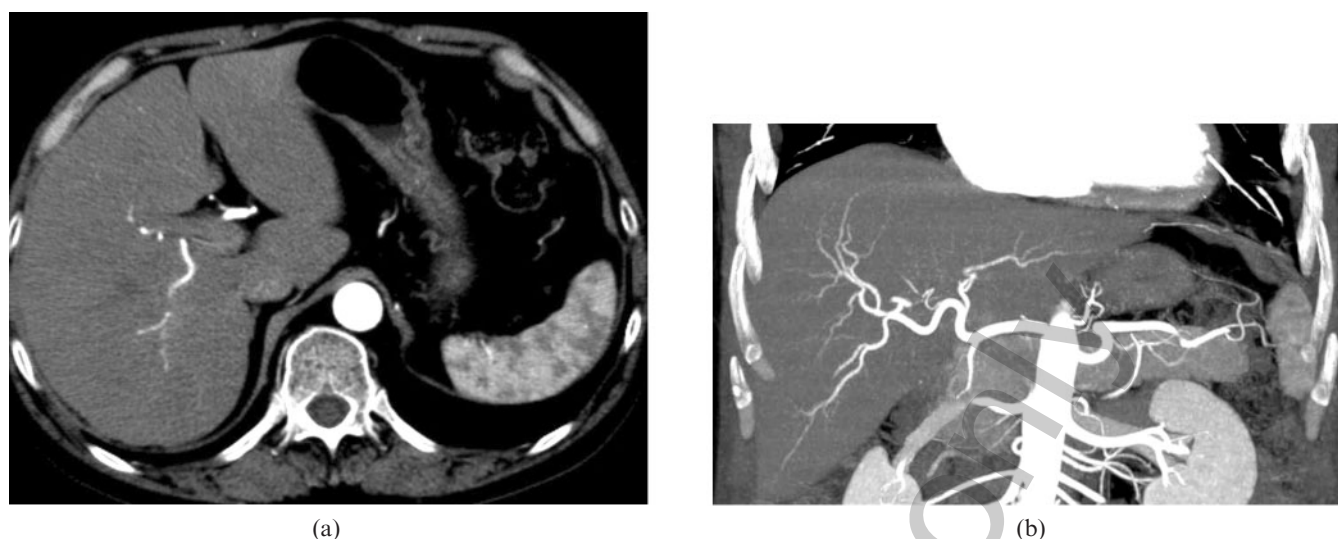
(a)

(b)

Figure 1. (a) The higher iodine delivery rate achievable with iomeprol-400 permits marked enhancement of arterial vessels and clear differentiation against the liver parenchyma. (b) The maximum intensity projection reconstruction reveals strong contrast between arterial vessels and liver parenchyma, leading to clear evaluation of the lumen of the hepatic artery and its branches.

both the arterial and portal venous phases of the MDCT examination.

Qualitative evaluation of contrast enhancement was performed by a single, on-site blinded reader in terms of the quality of contrast enhancement and the quality of anatomic visualization provided by the contrast medium. Grading of image quality was performed using a 5-point scale in which 1=poor, 2=insufficient, 3=fair, 4=good and 5=excellent.

Heart rate evaluations

Heart rate readings were obtained with the patient in the supine position on the CT table. Baseline HR was taken within 5 min prior to injection of contrast medium. The peak post-dose HR was thereafter determined by means of continuous HR monitoring from the time of injection until the patient left the CT table.

Adverse event monitoring

Subjects were monitored for adverse events from the time they entered the study until 2 h after contrast medium administration. An adverse event was defined as any untoward medical occurrence in a subject administered any dose of an investigational product. The time and duration of adverse events was recorded, as was the relationship (if any) to contrast medium administration. Separately, patients were monitored by telephone for any delayed adverse events occurring from 2 h to 7 days after contrast administration.

Statistical methodology

A total of 100 subjects (50 subjects for each investigational product) was required to allow the demonstration of an effect size of about 55% to 65% of the phenomenon variability (difference in the contrast-enhanced CT

examination between the two agents) with a power of ~0.80–0.90 with an unpaired Student's t-test performed at significance level of 0.05 (two-sided). To allow for subjects with missing or incomplete data, 120 subjects were scheduled to be enrolled. However, the final enrolment (184 subjects) was greater than planned because additional patients were required to better compare the incidence of contrast-induced nephropathy after the two contrast agents [15]. The larger numbers of patients in the two study groups served to strengthen the findings of this study.

Statistical analyses were performed using SAS® Version 8.2. Statistical testing was performed using two-sided tests at the 0.05 level of significance with 95% confidence limits.

Demographic data (sex, age, age group, weight, height and race) and baseline patient clinical information (diabetes, hypertension, other) were summarized for the two study groups. The comparability of the groups was tested using the unpaired t-test for age, weight and height; the χ^2 test for sex, age group and race; and the Mantel–Haenszel test for risk factors (diabetes, hypertension).

The incidence of delayed (2 h to 7 days after contrast administration) hypersensitivity-type cutaneous/subcutaneous adverse reactions was summarized by study group. Fisher's exact test was used to compare the incidence rate of subjects with delayed hypersensitivity after drug administration between the two treatment groups.

HR at baseline (within 5 min prior to injection of contrast medium), the post-dose peak and the change from baseline were summarized by study group. Analysis of covariance (ANCOVA) was performed to compare the change from baseline between groups, with baseline HR being treated as a covariate. The proportion of subjects in each group with predefined increases in HR (<5 beats per minute (bpm), ⩾5 bpm but <10 bpm; ⩾10 bpm but <15 bpm; ⩾15 bpm but <20 bpm; ⩾20 bpm) was compared using the χ^2 test.

Table 1. Patient demographics and procedural characteristics

Characteristic	Iomeprol-400 (n=91)	Iodixanol-320 (n=92)	p-Value[a]
Sex, n (%)			0.16
Male	68 (74.7)	60 (65.2)	
Female	23 (25.3)	32 (34.8)	
Age (years)			0.95
Mean (SD)	66.9 (13.97)	66.8 (11.96)	
Minimum, maximum	21, 92	34, 86	
Age group, n (%)			0.92
18–64 years	33 (36.3)	34 (37.0)	
⩾65 years	58 (63.7)	58 (63.0)	
Weight (kg)			0.40
Mean (SD)	67.1 (12.42)	68.7 (13.20)	
Minimum, maximum	30, 98	44, 106	
Height (cm)			0.81
Mean (SD)	165.9 (8.05)	166.2 (8.44)	
Minimum, maximum	148, 182	148, 188	
Race, n (%)			0.83
White	64 (70.3)	66 (71.1)	
Asian	27 (29.7)	26 (28.3)	
Risk factors, n (%)			
Diabetes	23 (25.3)	12 (13.0)	0.04
Hypertension	60 (65.9)	50 (54.3)	0.11
Other	61 (67.0)	58 (63.0)	0.57
β-blocker use, n (%)	13 (14.3)	11 (12.0)	0.64
Volume of contrast agent (ml)			<0.0001
Mean (SD)	100.0 (0.00)	124.3 (3.74)	
Minimum, maximum	100.0, 100.0	100.0, 125.0	
Iodine (g)			0.0963
Mean (SD)	40.0 (0.00)	39.8 (1.20)	
Minimum, maximum	40.0, 40.0	32.0, 40.0	
Iodine (g)/body weight (kg)			0.3813
Mean (SD)	0.6 (0.13)	0.6 (0.11)	
Minimum, maximum	0.4, 1.3	0.4, 0.9	

SD, standard deviation.
[a]Age, weight, height: unpaired t-test; sex, age group, race: χ^2 test; risk factors: Mantel–Haenszel test

Descriptive statistics were used to summarize the contrast density measurements for the two study groups. The contrast densities achieved by the two contrast media in each of the four ROIs (proximal abdominal aorta during the arterial phase; and main portal vein, IVC and normal liver parenchyma during the portal venous phase) were compared using ANCOVA, with the standard deviation of each ROI taken as covariate. The least square mean (LS$_{means}$), standard error, the difference in LS$_{means}$ between the two contrast media, and its

95% confidence intervals were estimated from the ANCOVA model. On-site qualitative assessment of contrast enhancement was compared using the unpaired t-test.

Results

A total of 184 subjects were enrolled and randomized to receive iomeprol-400 or iodixanol-320 between July

Table 2. Summary of adverse events (all dosed subjects)

Description	Iomeprol-400 (n=91)		Iodixanol-320 (n=92)	
	All adverse events	Related adverse events	All adverse events	Related adverse events
Total number of adverse events[a]	1	1	6	5
		Number (%) of subjects		
Subjects with any adverse event[b]	1 (1.1)	1 (1.1)	4 (4.3)	3 (3.3)
Injection site reaction	0	0	1 (1.1)	1 (1.1)
Nausea	0	0	1 (1.1)	1 (1.1)
Vomiting	0	0	1 (1.1)	1 (1.1)
Lymphoedema	0	0	1 (1.1)	0
Generalized spasm	0	0	1 (1.1)	1 (1.1)
Urticaria	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)

Related adverse events include ''probably related'', ''possibly related'', or ''relationship unknown''.
[a]Subjects who experienced more than one adverse event within a preferred term were counted once.
[b]Subjects who had more than one event are counted once.

Table 3. Heart rate change from pre-dose (baseline) to post-dose peak by study group

Characteristic		Iomeprol-400 (*n*=91)	Iodixanol-320 (*n*=92)	*p*-Value
Heart rate (bpm)				
Pre-dose	Mean (SD)	78.2 (16.79)[a]	78.5 (15.27)	
Post-dose peak	Mean (SD)	85.5 (19.75)[b]	83.5 (15.99)	
Change	Mean (SD)	7.5 (11.75)[b]	5.0 (8.67)	0.12[c]
	<5 bpm or negative	40 (46.0)	51 (55.4)	
Heart rate change from pre-dose	≥5 bpm and <10 bpm	17 (19.5)	18 (19.6)	
to post-dose, *n* (%)	≥10 bpm and <15 bpm	16 (18.4)	11 (12.0)	0.65[d]
	≥15 bpm and <20 bpm	7 (8.0)	7 (7.6)	
	≥20 bpm	7 (8.0)	5 (5.4)	

SD, standard deviation.
[a]*n*=89.
[b]*n*=87.
[c]ANCOVA model with pre-dose heart rate as covariate.
[d]Mantel–Haenszel χ^2 test.

2005 and November 2006. Of the 184 randomized subjects, 183 received contrast (iomeprol-400, *n*=91; iodixanol-320, *n*=92). The majority of the 183 subjects included in the efficacy analysis were male (69.9%) and white (71.0%). The two study groups were comparable with regard to sex, age, weight, height, race and the proportion of subjects receiving *β*-blocker administration (Table 1). Hypertensives accounted for 60.1% of the study population, while 19.1% of the population was diabetic. The proportion of subjects with hypertension and other risk factors were similar between the two contrast agent groups; however, there was a greater proportion of diabetics in the iomeprol-400 group than in the iodixanol-320 group (25.3% *vs* 13.0%, *p*=0.04). All subjects in both study populations had a history of at least one medical abnormality reported prior to enrolment in the study. The history of abnormality by anatomical system were generally evenly distributed between the iomeprol-400 group and the iodixanol-320 group, with the exception of abnormalities in cardiovascular history, which were reported more frequently in the iomeprol-400 group (82.4% *vs* 64.1%).

Safety assessments

One (1.1%) of the 91 dosed subjects in the iomeprol-400 group and 4 (4.3%) of the 92 dosed subjects in the iodixanol-320 group experienced adverse events following contrast medium administration (Table 2). One local adverse event (injection site reaction (exudation of contrast agent)) was reported in the iodixanol-320 group. Adverse events considered by the investigator to be related to contrast medium administration were reported for one subject (1.1%) in the iomeprol-400 group and three subjects (3.3%) in the iodixanol-320 group. All reported adverse events were mild or moderate in intensity. No patient died, had a serious adverse event, or discontinued as a result of adverse events. Four subjects receiving iodixanol-320 experienced delayed skin reactions, as opposed to one subject with iomeprol-400. The delayed skin reactions were characterized by widespread erythematous areas or maculopapular rashes, appearing between 1 day and 12 days after contrast medium administration and persisting for up to 5 days.

Changes in heart rate

The mean HR increased slightly and comparably following contrast medium administration (by 7.5 bpm for iomeprol-400 and 5.0 bpm for iodixanol-320; *p*=0.12; Table 3). The proportion of subjects in each group having increases of <5 bpm, ≥5 bpm to <10 bpm, ≥10 bpm to <15 bpm, ≥15 bpm to <20 bpm, or ≥20 bpm was also comparable (*p*=0.65).

On-site qualitative assessment

All of the images were assessed as technically adequate by the on-site investigators at each centre. The quality of enhancement and anatomic visualization was assessed as good or excellent in 96.7% (88/91) of the images for iomeprol-400 and 97.8% (90/92) of the images for iodixanol-320. The mean score was comparable between the two agents: 4.74±0.513 for iomeprol-400 and 4.72±0.499 for iodixanol-320 (*p*=0.80).

Off-site quantitative assessment

Nearly all the images (93.4–100.0% for iomeprol-400 and 98.9–100.0% for iodixanol-320) were assessed as technically adequate by the off-site readers. Iomeprol-400 resulted in significantly (*p*≤0.01; both readers) greater arterial phase enhancement of the abdominal aorta (Table 4; Figure 1). Iomeprol-400 also led to greater enhancement of normal liver parenchyma during the portal venous phase (Figure 2). The greater parenchymal enhancement was significant for Reader 1 (*p*=0.04) and of borderline significance for Reader 2 (*p*=0.05). No significant difference was noted between the two study groups regarding enhancement of the IVC or portal vein during the portal venous phase.

Discussion

The goals of multiphase hepatic MDCT imaging are several-fold: to achieve maximal contrast enhancement during the early arterial phase; to improve visualization of hypervascular lesions during the late arterial phase prior to hepatic parenchymal enhancement; and, finally,
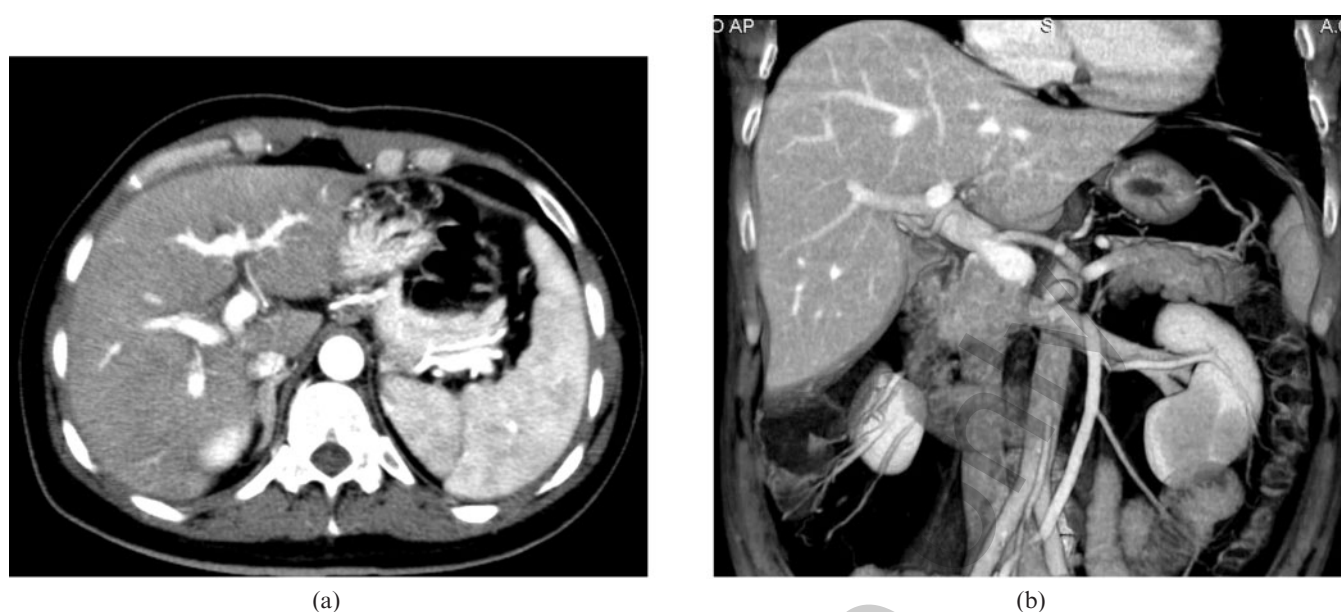
(a)   (b)

Figure 2. (a) The use of iomeprol-400 leads to marked enhancement of the portal vessels and liver parenchyma during the portal venous phase, leading to clear distinction of the large intraparenchymal veins. (b) The maximum intensity projection reconstruction reveals strong contrast between the portal vessels and liver parenchyma, leading to clear depiction of the external and internal morphology of the portal system.

to achieve maximal enhancement of the hepatic parenchyma during the portal venous phase to better delineate hypovascular masses prior to contrast equalization. Early vascular enhancement is determined by the rate of iodine influx, which is in turn related to the iodine concentration of the contrast medium and the injection rate [2, 16]. Conversely, because of substantial broadening of the contrast bolus upon entering the liver through the portal vein, hepatic parenchymal enhancement relies less on the iodine flow rate and more on the total dose of iodine administered [2, 16].

The higher iodine delivery rates possible with the use of higher concentration contrast media allow for more

pronounced arterial phase vascular opacification and increased contrast between hypervascular lesions and normal liver tissue during the hepatic arterial phase [4, 16–23]. Subsequent enhancement of the liver parenchyma may also be greater, owing to the faster delivery of iodine and greater iodine flux. Although preliminary studies to evaluate the usefulness of iomeprol-400 for CT of the liver have been performed [3, 24], little information is available on the use of this agent compared with standard-concentration contrast media for this application. However, valuable information is available regarding the use of equi-iodine (39 gI at 5 m s^{-1}) iomeprol-400 compared with iomeprol-300 for MDCT imaging of the

Table 4. Contrast density (HU) by contrast agent, off-site blinded reader and ROI

Region of interest	Reader	Parameter	Iomeprol-400	Iodixanol-320	Difference (Iomeprol/ iodixanol)	95% CI of the difference	*p*-Value
Abdominal aorta, arterial phase	1	*n*	85	89			
		Mean ± SE	337.3±8.3	294.9±8.2	42.4	(19.4, 65.5)	0.0004
	2	*n*	91	89			
		Mean ± SE	325.7±8.5	295.3±8.6	30.5	(6.6, 54.3)	0.01
Main portal vein, portal phase	1	*n*	89	90			
		Mean ± SE	181.4±4.9	186.1±4.8	−4.8	(−18.3, 8.8)	0.49
	2	*n*	91	90			
		Mean ± SE	180.0±4.5	187.2±4.6	−7.2	(−19.9, 5.5)	0.27
Inferior vena cava, portal phase	1	*n*	90	89			
		Mean ± SE	128.0±3.8	131.6±3.8	−3.6	(−14.2, 7.1)	0.51
	2	*n*	91	90			
		Mean ± SE	122.3±3.4	128.7±3.4	−6.4	(−15.9, 3.0)	0.18
Liver parenchyma, portal phase	1	*n*	90	90			
		Mean ± SE	115.1±2.2	108.6±2.2	6.5	(0.27, 12.7)	0.04
	2	*n*	91	90			
		Mean ± SE	115.2±2.1	109.3±2.1	5.9	(−0.1, 11.8)	0.05

n and the mean are summarized from the raw data. Mean, standard error (SE), the difference and its 95% confidence interval (CI), and *p*-values are estimated from the analysis of covariance (ANCOVA) model in which the standard deviation (SD) of the region of interest (ROI) is treated as covariate. The mean value represents the least square mean from the model by adjusting for the variability (SD) of contrast density of the ROI. HU, Hounsfield units.

pancreas [25], and the benefits of the higher iodine concentration of iomeprol-400 compared with contrast media containing a moderately high (350–370 mgI ml⁻¹) iodine concentration have also been demonstrated for coronary CTA [9, 10]. However, it should be noted that the contrast medium volume and injection rate were kept constant in these latter studies [9, 10], resulting in a variable total dose of iodine among the groups.

Our study compared the arterial and portal venous phase enhancement achieved by equi-iodine doses (40 gI) of iomeprol-400 and iodixanol-320 injected at the same rate (4 m s⁻¹). In terms of quantitative enhancement, the two blinded readers found that iomeprol-400 provided significantly greater enhancement of the abdominal aorta in the arterial phase. As equal doses of iodine were administered and the two contrast media were injected at the same rate, the principal difference between the two groups lay in the higher rate of iodine delivery achieved with iomeprol-400 (1.6 g s⁻¹) compared with iodixanol-320 (1.28 g s⁻¹). Although the iso-osmolar agent iodixanol-320 may be expected theoretically to suffer less from plasma dilution, any potential benefit attributable to this effect was insufficient to outweigh the more rapid iodine flux achieved with iomeprol-400. To achieve parity of iodine delivery and arterial contrast enhancement for an equivalent overall dose of 40 gI over an identical injection time of 25 s, the lower concentrated iodixanol-320 would need to have been administered at a 20% increased injection rate (5 m s⁻¹ rather than 4 m s⁻¹). Although this may be achievable for many patients undergoing MDCT of the liver, it is unlikely that this rate of administration would be achievable for all patients referred for MDCT, especially if doses higher than 40 gI are needed. A specific advantage of the more concentrated iomeprol-400 in this setting is therefore the possibility to achieve increased iodine delivery at an equivalent injection rate over a shorter injection time. Further studies might usefully be performed to compare these two contrast media at an equivalent iodine delivery rate, not only in terms of image quality and the magnitude of contrast enhancement, but also in terms of patient tolerability and adherence to administration protocol. It may also be of interest to investigate the possible haemodynamic effects of the higher injection volume and rate required with iodixanol-320 (125 ml) compared with iomeprol-400 (100 ml) at an equivalent dose.

Previous studies have indicated that enhancement of the hepatic parenchyma is independent of iodine flow rate and dependent solely on the total dose of iodine administered [2, 16]. Given that all patients in our study received the same total dose of iodine, a surprising finding was that iomeprol-400 provided greater enhancement of the normal liver parenchyma during the portal venous phase. Additional work is certainly warranted to further investigate these findings.

Regarding the influence of contrast medium administration on HR, our results revealed no significant differences between iomeprol-400 and iodixanol-320 in terms of the maximal mean HR alterations from baseline or the specific post-dose timeframe during which the maximal HR change occurred. A recent comparison of iomeprol and iodixanol in patients undergoing conven-

tional cardiac or peripheral angiography with intra-arterial contrast media administration similarly revealed only minimal and clinically insignificant effects on HR and no differences between contrast media [26].

Certain applications of MDCT, such as coronary angiography, require a steady slow HR (<65 bpm) and are highly sensitive to cardiac motion [12–14]. Although angiographic studies suggest that ionic contrast media have greater effects on haemodynamic parameters than non-ionic contrast media and that high-osmolar contrast media result in more variability of HR than do low-osmolar contrast media [27–30], it is not at all clear that osmolality has an effect on HR in the setting of intravenous administration. It has recently been suggested that iso-osmolar contrast media may provide an advantage over low-osmolar contrast media in terms of the effect on HR [11, 31]. However, several published studies have been unable to confirm a differential impact on HR between the iso-osmolar agent iodixanol and at least two different non-ionic low-osmolar agents [26, 32]. Although HR is not a primary concern for MDCT of the liver, further work may be of value to confirm the findings of our study in patients undergoing cardiac MDCT.

A final consideration concerns the safety profile of the two agents. Although the number of patients evaluated in the two groups was too small to draw any firm conclusions regarding the overall incidence of adverse events associated with these two contrast media, it was of interest that delayed skin reactions were associated more with iodixanol-320 than with iomeprol-400. This observation is consistent with previous reports of a greater incidence of delayed adverse events with iodixanol than with other iodinated agents [33, 34].

In conclusion, iomeprol-400 provides significantly greater enhancement in the arterial phase and improved enhancement of hepatic parenchyma in the portal venous phase compared with iodixanol-320 at the same iodine dose when administered to patients undergoing clinically indicated MDCT of the liver. The effects of iomeprol-400 and iodixanol-320 on HR appear modest and similar in subjects undergoing MDCT.

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