

Rate of Contrast Material Extravasations and Allergic-like Reactions: Effect of Extrinsic Warming of Low-Osmolality Iodinated CT Contrast Material to 37°C¹

Matthew S. Davenport, MD
Carolyn L. Wang, MD
Mustafa R. Bashir, MD
Amy M. Neville, MD
Erik K. Paulson, MD

Purpose:

To retrospectively determine whether extrinsic warming of the low-osmolality contrast material iopamidol to 37°C prior to intravenous administration at computed tomography (CT) affects extravasation and allergic-like reaction rates.

Materials and Methods:

The need to obtain informed patient consent was waived for this HIPAA-compliant and institutional review board-approved analysis. All adverse events related to the intravenous administration of iopamidol during CT examinations occurring 200 days before (period 1) and 200 days after (period 2) the cessation of extrinsic contrast material warming (37°C) for intravenous injections of less than 6 mL/sec at Duke University Medical Center (Durham, NC) were retrospectively reviewed. Adverse event rates were compared by using χ^2 statistics.

Results:

There were 12 682 injections during period 1 (10 831 injections of iopamidol 300 and 1 851 injections of iopamidol 370) and 12 138 injections (10 064 injections of iopamidol 300 and 2 074 injections of iopamidol 370) during period 2. Adverse event rates for iopamidol 300 were not affected by extrinsic warming (extravasation rates: 0.30% [32 of 10 831] in period 1 vs 0.23% [23 of 10 064] in period 2, $P = .64$; allergic-like reaction rates: 0.39% [42 of 10 831] in period 1 vs 0.46% [46 of 10 064] in period 2, $P = .74$; overall adverse events: 0.68% [74 of 10 831] in period 1 vs 0.69% [69 of 10 064] in period 2, $P = .99$). Discontinuation of extrinsic warming was associated with significantly increased extravasation and overall adverse event rates for iopamidol 370 (extravasation rates: 0.27% [five of 1 851] vs 0.87% [18 of 2 074], $P = .05$; allergic-like reaction rates: 0.16% [three of 1 851] vs 0.39% [eight of 2 074], $P = .42$; overall adverse events: 0.43% [eight of 1 851] vs 1.25% [26 of 2 074], $P = .02$).

Conclusion:

Extrinsic warming (to 37°C) does not appear to affect adverse event rates for intravenous injections of iopamidol 300 of less than 6 mL/sec but is associated with a significant reduction in extravasation and overall adverse event rates for the more viscous iopamidol 370.

©RSNA, 2011

¹From the Department of Radiology, University of Michigan Health System, 1500 E Medical Center Dr, B2A209P, Ann Arbor, MI 48103 (M.S.D.); Department of Radiology, Duke University Medical Center, Durham, NC (M.R.B., A.M.N., E.K.P.); and Department of Radiology, University of Washington Medical Center, Seattle, Wash (C.L.W.). Received June 18, 2011; revision requested August 8; revision received August 9; final version accepted September 12. Address correspondence to M.S.D. (e-mail: matdaven@med.umich.edu).

Extrinsic warming of room-temperature iodinated contrast material to human body temperature (37°C) is known to reduce contrast material viscosity (1–4), and results of some studies (4,5) have shown that the practice can improve contrast material delivery rates with both hand and power injections through intravenous catheters. However, to our knowledge, only one study (6) has shown that warming iodinated contrast material prior to intravenous administration actually confers a reduction in the risk of adverse events (12% vs 10% for high-osmolality contrast material [HOCM]). These results are contested by those of a well-controlled double-blind study by Turner et al (7), who found that warming HOCM prior to excretory urography provided no benefit. To our knowledge, the relatively few studies investigating the relationship between adverse events and contrast material warming have focused on HOCM, which has been replaced by low-osmolality contrast material (LOCM) at most institutions for intravascular studies owing to its improved side-effect profile (1).

Our review of the literature revealed no studies that evaluated the benefit of contrast material warming on the adverse event risk of LOCM. The benefit of warming LOCM prior to intravenous use for the purpose of adverse event risk reduction remains uncertain. Additionally, contrast material warming (if performed) has logistic and financial side effects. Contrast material is considered a medication and therefore is subject to review by the Joint Commission, which mandates daily temperature logs and

documentation of tight temperature control for warmed contrast material.

The purpose of our study was to retrospectively determine whether extrinsic warming of the LOCM iopamidol to 37°C prior to intravenous administration affects extravasation and allergic-like reaction rates.

Materials and Methods

Approval of the institutional review board of Duke University Medical Center (Durham, NC) was obtained and informed patient consent was waived for this Health Insurance Portability and Accountability Act–compliant retrospective analysis.

Subjects

All contrast material-enhanced computed tomographic (CT) examinations performed in all patients (children and adults) at Duke University Medical Center from March 14, 2010, through September 30, 2010 ($n = 12684$, period 1), and from October 1, 2010, through April 19, 2011 ($n = 12142$, period 2), were identified by means of an electronic query of our institutional billing records. Examinations enhanced by the intravenous administration of iodixanol were excluded because of the small number of injections for noncardiac CT applications during the study (period 1, $n = 2$; period 2, $n = 4$). The study was designed to include two study periods: (a) 200 days immediately prior to the cessation of extrinsic iodinated contrast material warming (to 37°C) at our institution (period 1, from March 14, 2010, through September 30, 2010) and (b) 200 days immediately after the cessation of contrast material warming (period 2, from October 1, 2010, through April 19, 2011). The use of contrast material warmers was discontinued at our institution on October 1, 2010, for all

intravenous contrast-enhanced studies with power injection rates of less than 6 mL/sec. This decision was unrelated to and made prior to the inception of this study. Contrast material warming for power injections at rates less than 6 mL/sec was stopped at our institution on September 30, 2010, because of insufficient published evidence of its efficacy and the increasing regulatory requirements governing the practice.

All adverse events ($n = 229$) in patients of all ages (children and adults) related to the administration of contrast material during a CT examination from March 14, 2010, to April 19, 2011, were identified by means of a query of our institutional electronic adverse event reporting system. This system is used for the generalized reporting of all adverse events in the hospital system, including adverse events related to radiologic studies. Adverse events related to oral contrast material ($n = 7$), gadolinium-based contrast material ($n = 31$), iodixanol ($n = 1$), and iodinated contrast material administered for cardiac CT ($n = 2$), as well as adverse event reports filed to document inaccurate scanning protocols ($n = 7$; eg, contrast material administered when not indicated), physiologic adverse events

Advance in Knowledge

- Discontinuation of extrinsic warming (to 37°C) did not appear to affect adverse event rates for intravenous injections of iopamidol 300 of less than 6 mL/sec ($P = .64$ –.99), but was associated with an approximate tripling of extravasation ($P = .05$) and overall adverse event rates ($P = .02$) for the more viscous iopamidol 370.

Implication for Patient Care

- Extrinsic warming (to 37°C) of iopamidol 300 may not be necessary for injection rates less than 6 mL/sec, but is recommended for iopamidol 370.

Published online before print

10.1148/radiol.11111282 Content code: CT

Radiology 2012; 262:475–484

Abbreviations:

HOCM = high-osmolality contrast material
LOCM = low-osmolality contrast material
PICC = peripherally inserted central venous catheter

Author contributions:

Guarantors of integrity of entire study, M.S.D., C.L.W.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.S.D., C.L.W.; clinical studies, M.S.D., M.R.B., E.K.P.; statistical analysis, M.S.D., M.R.B.; and manuscript editing, all authors

Funding:

This research was supported by a National Institutes of Health Clinical Translational Science Award (grant UL1RR024986).

Potential conflicts of interest are listed at the end of this article.

($n = 3$), and preinjection intravenous catheter malfunction ($n = 1$) were excluded. Adverse events related to iodixanol were excluded because of the relatively small number of injections of iodixanol administered for noncardiac CT during the study period. Injections related to cardiac CT were excluded because this contrast material was warmed during both study periods. Physiologic adverse events were excluded because these events are in general not reported in our institution's electronic adverse event tracking system. The resulting adverse events ($n = 177$) were subdivided by occurrence date (period 1, $n = 82$; period 2, $n = 95$) and were categorized by type (allergic-like reaction and contrast material extravasation) according to previously published guidelines (8).

Contrast Media

The following iodinated contrast media were in use at our institution for intravenous contrast-enhanced CT applications during the study period: iopamidol 300 (Isovue, 300 mg iodine per milliliter, viscosity = 8.8 cP at 20°C and 4.7 cP at 37°C; Bracco Diagnostics, Princeton, NJ) and iopamidol 370 (Isovue, 370 mg I/mL, viscosity = 20.9 cP at 20°C and 9.4 cP at 37°C; Bracco Diagnostics).

Iopamidol 300 was the primary iodinated contrast material used for general intravenous contrast-enhanced CT applications. Iopamidol 370 was used for CT angiographic studies. The choice of iodinated contrast material depended on the protocol and the physician. Relative contraindications to the use of iodinated contrast material included prior severe allergic-like reaction to iodinated contrast material, acute kidney injury, and severe chronic kidney disease. All iodinated contrast material was extrinsically warmed to a target of 37°C during period 1; all contrast material was kept at room temperature during period 2. The range of recorded temperatures for warmed iodinated contrast material during period 1 was 36.1–40.0°C (measured daily).

Contrast Medium Administration

Intravenous contrast material administered during CT was injected through

either a previously placed indwelling intravenous catheter or an intravenous catheter placed by the Department of Radiology nursing staff. Peripheral intravenous catheters from 16 to 20 gauge are standard for the referring services, and 20-gauge peripheral intravenous catheters are preferentially placed by Department of Radiology nursing staff members when no access is available. Twenty-two-gauge intravenous catheters are placed in patients with difficult-to-access or small veins, and 14-gauge intravenous catheters are placed by the referring services for clinical infusions requiring a high flow rate. Peripheral intravenous catheters placed by the Department of Radiology nursing staff are preferentially placed in the antecubital fossa; if this site is not accessible, an alternative site in one of the arms is chosen at the nurse's discretion. Intravenous catheters are not placed in sites of marked edema, cellulitis, known deep venous thrombosis, or an open wound or if there has been a history of ipsilateral lymph node dissection.

Alternative catheters for injection include power peripherally inserted central venous catheters (PICCs) suitable for power injection of contrast material, standard PICCs (PICCs suitable only for hand injection of contrast material), indwelling central venous catheters (only for hand injection of contrast material), and tunneled catheters suitable for power injection of contrast material (access was obtained by the referring service).

Intravenous contrast material is power injected unless there is a contraindication (ie, inadequate or inappropriate venous access). In cases of venous access that was not suitable for power injection (eg, central line, non-power PICC, tenuous intravenous catheter) the contrast material was instead hand injected by a resident, fellow, or attending radiologist. Rates of power injection ranged from 2 to 8 mL/sec. Most contrast-enhanced CT applications in the head, neck, chest, abdomen, pelvis, and extremities used intravenous injection rates of 3–4 mL/sec. CT angiography employed intravenous injection rates of 4–5 mL/sec for most

applications other than cardiac CT angiography, which instead employed rates of 6–8 mL/sec. Most power injections and some hand injections were accompanied by use of an extravasation detection accessory (E-Z-Em, Westbury, NY) to limit the volume of contrast material extravasation should an extravasation event occur.

Adverse Events

Allergic-like reactions were graded by severity (by M.S.D., an abdominal imaging fellow) according to a previously published algorithm (8). All allergic-like manifestations were recorded for each allergic-like reaction to iodinated contrast material. The following data were recorded: type and presence of corticosteroid premedication, history of allergic-like reaction to iodinated contrast material, number of additional allergies, number of severe allergies, history of asthma, contrast material reaction treatment, clinical outcome (within 2 weeks to 8 months from the event), whether the patient's allergy record was updated in the electronic medical record system within 7 days, type and dose of contrast material, and contrast material injection rate. Symptoms of hoarseness, throat itching and/or tingling, and difficulty swallowing were scored as laryngeal symptoms, regardless of severity.

The following data were recorded for each iodinated contrast material extravasation event: contrast material dose and type, contrast material injection rate, use of an extravasation detection accessory, vascular access location and gauge, extravasation volume, extravasation treatment, and clinical outcome (within 2 weeks to 8 months from the event).

Power Calculation

A power analysis was conducted to determine sample size adequacy for this noninferiority study (to answer the question "Are adverse event rates due to nonextrinsically warmed iodinated contrast material noninferior to those due to extrinsically warmed iodinated contrast material?"). The following assumptions were used: noninferiority

margin, 0.004 (0.4%); reference population (extrinsically warmed iopamidol 300 or 370) adverse event rate, 0.004 (0.4%, used for both extravasations and allergic-like reactions); power, 80%; and significance level, .05. This yielded a target sample size of 3079 for each of the arms of our study (eg, warmed iopamidol 300, warmed iopamidol 370, nonwarmed iopamidol 300, nonwarmed iopamidol 370). Reference population adverse event rates were determined by using published data (1,8–10) and historic internal quality assurance adverse event data.

Statistical Analysis

Nominal data (contrast material type, extravasation detection accessory use, vascular access characteristics, type of premedication, history of asthma, treatment methods, clinical outcome, electronic update of the patient's medical record after an allergic-like reaction) and ordinal data (allergic-like reaction severity) were summarized by counts and percentages. Interval data (contrast material dose, injection rate, extravasation volume, number of allergies, number of severe allergies) were summarized by means and ranges. χ^2 Statistical analyses were performed to compare the adverse event rates (by type and aggregate) of period 1 and period 2. A two-tailed *t* test was used to compare the contrast material extravasation volumes (in period 1 vs period 2). Two-tailed *t* tests were also used to compare the mean contrast material injection rates for warmed versus nonwarmed iopamidol 300 and 370. The Fisher exact test was used to compare the allergic-like reaction severity ratios (mild vs moderate or severe) in period 1 and period 2. *P* < .05 was considered to indicate statistical significance for all statistical tests. Calculations were made by using software (Excel; Microsoft, Redmond, Wash).

Results

Eighty-two adverse events after intravenous iopamidol administration occurred in 81 patients (47 female patients [mean age, 51 years; range, 1–79 years] and

34 male patients [mean age, 53 years; range, 19–85 years]) during period 1 (*n* = 74 for iopamidol 300, *n* = 8 for iopamidol 370), and 95 adverse events after intravenous iopamidol administration occurred in 92 patients (66 female patients [mean age, 52 years; range, 4–90 years] and 26 male patients [mean age, 55 years; range, 14–90 years]) during period 2 (*n* = 69 for iopamidol 300, *n* = 26 for iopamidol 370).

Table 1 indicates the number of contrast-enhanced CT examinations and adverse event rates by type (extravasations, allergic-like reactions) in periods 1 and 2 for each contrast material (iopamidol 300 and iopamidol 370). The adverse event rates for iopamidol 300 according to type and in aggregate for period 1 and period 2 were not significantly different (*P* = .64–.99). However, there were significantly more extravasation events (*P* = .05) and overall adverse events (*P* = .02) related to iopamidol 370 in period 2 than in period 1. This demonstrates that although extrinsic warming of iopamidol 300 to 37°C does not affect extravasation and allergic-like reaction rates, extrinsic warming of the more viscous iopamidol 370 to 37°C is associated with a reduction in adverse events. Interestingly, the mean injection rate of extravasated warmed iopamidol 370 (mean, 4.6 mL/sec; range, 4.0–5.0 mL/sec) was significantly greater (*P* = .04) than the mean injection rate of the extravasated nonwarmed iopamidol

370 (mean, 4.1 mL/sec; range, 3.0–5.0 mL/sec). The mean injection rates for extravasated warmed versus nonwarmed iopamidol 300 were not significantly different (*P* = .39).

Tables 2 and 3 describe the relevant patient characteristics, injection characteristics, adverse event manifestations, treatment, and clinical outcome of the allergic-like reactions and contrast material extravasations (respectively) for intravenous iopamidol 300 and 370 during periods 1 and 2. No patient required placement of an advanced airway for laryngeal symptoms (eg, hoarseness, throat itching and/or tingling, difficulty swallowing), and all laryngeal symptoms resolved after medical therapy (with one or more of the following: intravenous diphenhydramine, intravenous corticosteroids, intravenous famotidine, inhaled albuterol, inhaled oxygen) or observation. No patient with laryngeal symptoms received epinephrine.

One 63-year-old male patient in period 1 developed pulseless electrical activity after the intravenous administration of 150 mL of warmed iopamidol 300, necessitating cardiopulmonary resuscitation (CPR). He had underlying cardiac disease, an infected sternotomy wound, multiple medical comorbidities, and one allergy to a substance other than contrast material. CPR returned the patient to normal sinus rhythm, but reopened the infected sternotomy

Table 1

Comparison of Adverse Event Rates in Period 1 with Those in Period 2

Contrast Material and Parameter	Period 1 (Warming)		Period 2 (No Warming)		P Value*
	No.	Rate (%)	No.	Rate (%)	
Iopamidol 300					
Injections	10 831		10 064		
Extravasations	32	0.30	23	0.23	.64
Allergic-like reactions	42	0.39	46	0.46	.74
Overall adverse events	74	0.68	69	0.69	.99
Iopamidol 370					
Injections	1851		2074		
Extravasations	5	0.27	18	0.87	.05
Allergic-like reactions	3	0.16	8	0.39	.42
Overall adverse events	8	0.43	26	1.25	.02

* Calculated with χ^2 test.

Table 2

Summary of Allergic-like Reactions after Intravenous Administration of Iopamidol during CT Examinations in Periods 1 and 2

Parameter	Iopamidol 300*										Iopamidol 370†									
	Period 1 (Warming)					Period 2 (No Warming)					Period 1 (Warming)					Period 2 (No Warming)				
	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum
Total Patients	42	...	...	...	...	46	...	...	...	...	3	...	...	...	...	8	...	...	...	...
Unique female patients	25	60	...	...	...	30	65	...	...	...	2	67	...	...	...	6	75	...	...	...
Female patient age (y)	...	...	49	3	79	...	...	51	18	79	...	...	42	31	53	...	...	41	4	90
Unique male patients	17	40	...	...	...	13	28	...	...	...	1	33	...	...	...	2	25	...	...	...
Male patient age (y)	...	...	53	19	82	...	...	54	14	90	...	...	61	61	61	...	...	51	42	60
Contrast material dose (mL)	...	...	145	20	200	...	...	143	75	175	...	...	108	75	150	...	...	79	30	125
Unknown dose	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Injection rate (mL/sec)	...	...	3.2	2.5	5.0	...	...	3.1	2.0	5.0	...	...	4.7	4	5	...	...	3.9	3	4
Unknown injection rate	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Hand injection	5	12	...	...	...	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Risk factors																				
Iodinated contrast material allergy	5	12	...	...	...	9	17	...	...	...	0	0	...	...	...	1	13	...	...	...
No. of additional allergies	...	...	0.9	0	10	...	...	1.2	0	7	...	...	1.0	0	3	...	...	1.3	0	3
No. of severe allergies	...	...	0.2	0	6	...	...	0.04	0	1	...	...	0.3	0	1	...	...	0.1	0	1
Asthma	9	21	...	...	...	6	13	...	...	...	1	33	...	...	...	0	0	...	...	...
Premedication†																				
5-Hour regimen	1	2	...	...	...	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
13-Hour regimen	4	10	...	...	...	7	17	...	...	...	0	0	...	...	...	2	25	...	...	...
Manifestation(s)																				
Pruritis	24	57	...	...	...	31	67	...	...	...	3	100	...	...	...	7	88	...	...	...
Hives	24	57	...	...	...	21	46	...	...	...	2	67	...	...	...	1	13	...	...	...
Facial swelling	1	2	...	...	...	1	2	...	...	...	0	0	...	...	...	1	13	...	...	...
Nasal congestion	2	5	...	...	...	4	9	...	...	...	0	0	...	...	...	2	25	...	...	...
Sneezing	5	12	...	...	...	8	17	...	...	...	0	0	...	...	...	4	50	...	...	...
Erythema	3	7	...	...	...	2	4	...	...	...	0	0	...	...	...	0	0	...	...	...
Dyspnea	7	17	...	...	...	5	11	...	...	...	0	0	...	...	...	2	25	...	...	...
Laryngeal symptoms	7	17	...	...	...	7	15	...	...	...	0	0	...	...	...	2	25	...	...	...
Anaphylactic shock	1	2	...	...	...	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Severity of reaction																				
Mild	33	79	...	...	...	41	89	...	...	...	3	100	...	...	...	6	75	...	...	...
Moderate	8	19	...	...	...	5	11	...	...	...	0	0	...	...	...	2	25	...	...	...
Severe	1	2	...	...	...	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...

Table 2 (continues)

Table 2 (continued)

Summary of Allergic-like Reactions after Intravenous Administration of Iopamidol during CT Examinations in Periods 1 and 2

Parameter	Iopamidol 300*						Iopamidol 370†					
	Period 1 (Warming)			Period 2 (No Warming)			Period 1 (Warming)			Period 2 (No Warming)		
	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)
Treatment												
None recorded	18	43	...	...	...	28	61	...	...	...	3	38
Intravenous or oral diphenhydramine	22	52	...	...	...	15	33	...	...	...	4	50
Intravenous famotidine	3	7	...	...	...	1	2	...	...	...	0	0
Oxygen	5	12	...	...	...	2	5	...	...	...	0	0
Inhaled albuterol	2	5	...	...	...	1	2	...	...	...	0	0
Intravenous fluids	2	5	...	...	...	1	2	...	...	...	0	0
Intravenous corticosteroids	5	12	...	...	...	1	2	...	...	...	0	0
Intravenous epinephrine	1	2	...	...	...	0	0	...	...	...	0	0
Emergency department transfer	0	0	...	...	...	1	2	...	...	...	1	13
Cardiopulmonary resuscitation	1	2	...	...	...	0	0	...	...	...	0	0
Outcome												
Return to baseline	41	98	...	...	...	46	100	...	...	...	8	100
Long-term morbidity‡	1	2	...	...	...	0	0	...	...	...	0	0
Allergies updated¶	36	86	...	...	...	41	89	...	...	...	7	88

* There were 10 831 iopamidol 300 injections in period 1 and 10 064 injections in period 2.

† There were 1851 iopamidol 370 injections in period 1 and 2074 injections in period 2.

‡ The 5-hour regimen consisted of 60 mg of solumedrol administered intravenously 1 and 5 hours prior to contrast material administration, with optional intravenous coadministration of 50 mg of diphenhydramine 1 hour prior to contrast material administration. This premedication regimen is used in urgent clinical scenarios. The 13-hour regimen consisted of 50 mg of prednisone administered orally 1, 7, and 13 hours prior to contrast material administration, with optional oral coadministration of 50 mg of diphenhydramine 1 hour prior to contrast material administration.

§ Cardiopulmonary resuscitation reopened an infected postoperative sternal wound that required repeat surgical débridement. The patient died 2 months later of complications related to the infected sternal wound and other medical comorbidities.

¶ No. of patients for whom the adverse event information in the electronic medical record was updated within 7 days of the allergic-like event to reflect that an allergic-like reaction occurred.

Table 3

Summary of Iopamidol Extravasations during CT Examinations in Periods 1 and 2

Parameter	Iopamidol 300*						Iopamidol 370†								
	Period 1 (Warming)			Period 2 (No Warming)			Period 1 (Warming)			Period 2 (No Warming)					
	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum
Total	32	...	...	...	...	23	...	...	...	...	5	...	...	...	...
Patients															
Unique female patients	18	56	...	...	...	15	65	...	...	...	2	40	...	...	...
Female patient age (y)	...	...	56	1	78	...	...	55	24	88	...	...	65	63	...
Unique male patients	13	41	...	...	...	8	35	...	...	...	3	60	...	...	...
Male patient age (y)	...	...	51	19	85	...	...	59	45	73	...	...	57	40	...
Vascular access															
Intravenous, upper arm	1	3	...	...	...	1	4	...	...	...	1	20	...	...	...
Intravenous, antecubital fossa	22	69	...	...	...	17	74	...	...	...	4	80	...	...	...
Intravenous, forearm	6	19	...	...	...	5	22	...	...	...	0	0	...	...	...
Intravenous, wrist	1	3	...	...	...	0	0	...	...	...	0	0	...	...	...
Port catheter	1	3	...	...	...	0	0	...	...	...	0	0	...	...	...
Central line	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Power PICC	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Right side	18	56	...	...	...	16	70	...	...	...	3	60	...	...	...
Left side	12	38	...	...	...	7	30	...	...	...	2	40	...	...	...
Unknown location	1	3	...	...	...	0	0	...	...	...	0	0	...	...	...
22 gauge	1	0	...	...	...	9	0	...	...	...	0	0	...	...	...
20 gauge	26	81	...	...	...	19	83	...	...	...	4	80	...	...	...
18 gauge	1	3	...	...	...	3	13	...	...	...	1	20	...	...	...
16 gauge	1	3	...	...	...	1	4	...	...	...	0	0	...	...	...
14 gauge	1	3	...	...	...	0	0	...	...	...	0	0	...	...	...
Unknown gauge	1	3	...	...	...	0	0	...	...	...	0	0	...	...	...
Contrast material dose (mL)	...	...	114	20	175	...	...	112	19	200	...	...	81	32	150
Unknown dose	2	6	...	...	...	0	0	...	...	...	0	0	...	...	...
Injection rate (mL/sec)	...	...	3.1	2.0	4.0	...	...	3.2	2.0	5.0	...	...	4.6	4.0	5.0
Unknown rate	2	6	...	...	...	2	9	...	...	...	0	0	...	...	...
Hand injection	2	6	...	...	...	2	9	...	...	...	0	0	...	...	...
Extravasation detection	27	84	...	...	...	19	83	...	...	...	5	100	...	...	...
Extravasation accessory used															
Extravasation															
Volume (mL)	...	...	49	10	150	...	...	56	3	150	...	...	47	30	75
Unknown volume	6	16	...	...	...	1	4	...	...	...	0	0	...	...	...
"Small" volume‡	2	8	...	...	...	1	4	...	...	...	1	20	...	...	...

Table 3 (continues)

Table 3 (continues)

Table 3 (continued)

Summary of Iopamidol Extravasations during CT Examinations in Periods 1 and 2

Parameter	Iopamidol 300*						Iopamidol 370†								
	Period 1 (Warming)			Period 2 (No Warming)			Period 1 (Warming)			Period 2 (No Warming)					
	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum	No.	Rate (%)	Mean	Minimum	Maximum
Treatment															
Ice	25	78	...	...	...	21	91	...	...	...	5	100	...	...	...
Warmth	1	3	...	...	...	1	4	...	...	...	0	0	...	...	...
Extremity elevation	21	66	...	...	...	18	78	...	...	...	5	100	...	...	...
None recorded	5	16	...	...	...	1	4	...	...	...	0	0	...	...	...
Surgical consultation	2	6	...	...	...	4	17	...	...	...	0	0	...	...	...
Surgery	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...
Outcome															
Return to baseline	32	100	...	...	...	23	100	...	...	...	5	100	...	...	...
Long-term morbidity	0	0	...	...	...	0	0	...	...	...	0	0	...	...	...

* There were 10 831 Iopamidol 300 injections in period 1 and 10 064 injections in period 2.

† There were 1851 Iopamidol 370 injections in period 1 and 2074 injections in period 2.

‡ "Small" was the qualitative description provided in the electronic incident report; a quantitative assessment of the extravasated volume was not available.

wound, necessitating a return to the surgical suite for débridement. The patient died approximately 2 months later of complications related to the infected sternotomy site and other medical comorbidities.

The allergic-like reaction severity ratios in period 1 (33 mild, eight moderate, one severe) and period 2 (41 mild, five moderate, none severe) for Iopamidol 300 were similar ($P = .4$). The allergic-like reaction severity ratios were also similar for Iopamidol 370 (period 1: three mild, none moderate, none severe; period 2: six mild, two moderate, none severe [$P = .63$]), but the number of reactions was low. There was no significant difference in the volume of extravasated contrast material between period 1 and period 2 for either Iopamidol 300 (mean: 49 vs 56 mL, respectively; $P = .59$) or Iopamidol 370 (mean: 47 vs 43 mL, respectively; $P = .76$). With only one exception (one severe allergic-like reaction to Iopamidol 300 in period 1), all adverse events in all study arms eventually resolved, with the patient returning to his or her usual state of health.

Discussion

Extrinsic warming of iodinated contrast material to 37°C reduces contrast material viscosity and has been advocated to decrease the frequency of adverse events related to intravenous administration (1–3,6,11,12) and to improve iodinated contrast material delivery (4,5). However, studies demonstrating efficacy of a reduction in adverse risk from contrast material warming are scant, and the magnitude of demonstrable effect (when able to be shown at all [7]) has been small (6). To our knowledge, there are no published data that demonstrate an adverse event risk reduction conferred by extrinsic warming of LOCM; all studies to date have involved HOCM. Institutions that do warm contrast material are subject to regulation of this practice by the Joint Commission, with daily quality control required for each warming device. It is

important to determine what effect (if any) the warming of LOCM has on adverse event rates.

In 1996, Vergara et al (6) published the only series, to our knowledge, that documents a reduction in adverse events after the extrinsic warming of intravenous contrast material. They conducted a nonrandomized longitudinal observation study in which patients were intravenously injected with one of four contrast material and temperature combinations as part of routine clinical practice. The contrast material and temperature combinations were introduced sequentially and without overlap. The authors demonstrated a reduced rate of adverse events in extrinsically warmed (37°C) HOCM (sodium meglumine, Angiovisc; Schering, Berlin, Germany) compared with the same HOCM at room temperature. The warmed contrast material had an overall adverse event rate of 10%, compared with 12% for the room temperature contrast material ($P < .05$). However, Vergara et al did not include a comparison of room temperature LOCM with warmed LOCM. Additionally, the adverse event profile of the nonwarmed contrast medium was weighted toward mild allergic-like and physiologic events (32% of adverse events were graded as moderate or severe for the room temperature cohort vs 45% for the warmed cohort). This implies that the minor (albeit statistically significant) increase in the combined allergic-like and physiologic event rate was dominated by an increased number of mild severity events. Extravasation events were not reported, and the authors did not separate allergic-like and physiologic events.

The nonrandomized clinical observations of Vergara et al (6) are challenged by the earlier double-blind work of Turner et al (7), who compared data in 50 patients randomized to receive warmed (37°C) intravenous HOCM (iothalamate meglumine, Conray-30; Mallinckrodt, St Louis, Mo) with data in 50 patients randomized to receive the same intravenous HOCM at room temperature. This study also evaluated only allergic-like and physiologic adverse events and found no difference

in the adverse event rates between the warmed and room temperature HOCMs. However, the study was likely underpowered. The authors did not report extravasation events.

Our study analyzed the effect of iopamidol warming (to 37°C) on the rates of allergic-like reactions, contrast material extravasations, and overall adverse events. We found no significant change in any of these adverse event rates for iopamidol 300 when our institution discontinued extrinsic warming of iodinated contrast material for contrast material injection rates of less than 6 mL/sec. Warming of iodinated contrast material to body temperature for intravenous injections at these rates appeared to play no role in reducing adverse event rates.

This was not true for iopamidol 370. Discontinuation of extrinsic contrast material warming was associated with an approximate tripling in the extravasation (0.27% [five of 1851] vs 0.87% [18 of 2074], $P = .05$) and overall adverse event (0.43% [eight of 1851] vs 1.25% [26 of 2074], $P = .02$) rates for iopamidol 370. This likely relates to the higher dynamic viscosity of iopamidol 370 (20.9 cP at 20°C and 9.4 cP at 37°C) relative to that of iopamidol 300 (8.8 cP at 20°C and 4.7 cP at 37°C). When iopamidol 370 is warmed to body temperature (37°C), its dynamic viscosity becomes similar to that of nonwarmed iopamidol 300 (9.4 cP vs 8.8 cP, respectively). As an apparent result of this, the extravasation and overall adverse event rates of iopamidol 370 are reduced significantly with extrinsic warming and approximate that of nonwarmed iopamidol 300 (extravasation rate: 0.27% [five of 1851] for warmed iopamidol 370 vs 0.23% [23 of 10064] for nonwarmed iopamidol 300; overall adverse event rate: 0.43% [eight of 1851] for warmed iopamidol 370 vs 0.69% [69 of 10064] for nonwarmed iopamidol 300). This conclusion is supported by the significantly lower ($P = .04$) mean intravenous injection rate of extravasated nonwarmed iopamidol 370 when compared with the mean intravenous injection rate of extravasated warmed iopamidol 300. Extravasations

of nonwarmed iopamidol 370 occurred with greater frequency and at lower injection rates.

Although cessation of extrinsic contrast material warming for iopamidol 370 resulted in a significant increase in the number of adverse events, there was no significant difference in adverse event severity for any temperature and contrast material combination. We found no significant difference in the mean volume of extravasated contrast material or in allergic-like reaction severity. Additionally, patients experiencing adverse events in period 1 had outcomes similar to those of patients in period 2. This reinforces the fact that LOCMs are extraordinarily safe. In our series, only one adverse event after 24820 intravenous injections of iopamidol (300 and 370) resulted in permanent morbidity.

The iopamidol adverse event rates in our series (range of rate of allergic-like events: 0.16% [three of 1851] to 0.46% [46 of 10064]; range of rate of extravasations: 0.23% [23 of 10064] to 0.87% [18 of 2074]) are similar to those in other published series. Published rates of allergic-like reaction to LOCM are 0.18%–0.93% (9,13,14), while published extravasation rates for LOCM are 0.25%–0.7% (9,10,12). This suggests that our adverse event reporting system for contrast material extravasations and allergic-like reactions is fairly robust and similar to that of other large published trials.

There were several limitations to these data. First, Department of Radiology staff members at our institution are directed to report all contrast material extravasation and allergic-like reaction events but do not routinely report physiologic adverse events (eg, nausea, vomiting, tingling sensations, sensations of warmth, vasovagal reactions). This is because the occurrence of a physiologic adverse event would not necessarily result in a future treatment change (ie, would not require future corticosteroid premedication or contraindicate future contrast material administration). Therefore, we cannot comment on the effect of extrinsic contrast material warming on physiologic

adverse event rates nor on subjective feelings of patient discomfort during the injection. However, we can provide good evidence that warming has no effect on the occurrence or severity of contrast material extravasations or allergic-like reactions for iopamidol 300.

Second, the iopamidol 370 arms of our study ($n = 1851$ in period 1, $n = 2074$ in period 2; target size = 3079) were underpowered for noninferiority analysis. Therefore, although we did not find a significant difference in the allergic-like reaction rates between warmed and nonwarmed iopamidol 370, it is possible that our study was not adequately powered to detect such an effect. However, we did detect significant increases in extravasation and overall adverse event rates for nonwarmed iopamidol 370 compared with its warmed counterpart. On the basis of this significant finding, extrinsic warming for iopamidol 370 and other agents with a similarly high dynamic viscosity (eg, iodixanol [viscosity, 26.6 cP at 25°C and 11.8 cP at 37°C]) will be reinstated at our institution to maintain patient safety. Therefore, it is unlikely that we will ever have sufficient noninferiority data to adequately test the allergic-like reaction rates of nonwarmed iopamidol 370 against its warmed counterpart.

Finally, we did not include a control group of patients exposed to intravenous iopamidol who did not experience an adverse event. Such a control group would have allowed identification of additional risk factors unrelated to extrinsic warming that contribute to the development of allergic-like reactions and contrast material extravasations; however, this was not the aim of this study. We were primarily interested in

determining whether extrinsic warming of iopamidol had an effect on the adverse event rate for intravenous injections.

In summary, extrinsic warming (to 37°C) does not appear to affect adverse event rates for intravenous injections of iopamidol 300 of less than 6 mL/sec but is associated with a significant reduction in extravasation and overall adverse event rates for the more viscous iopamidol 370.

Disclosures of Potential Conflicts of Interest:

M.S.D. No potential conflicts of interest to disclose. **C.L.W.** No potential conflicts of interest to disclose. **M.R.B.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution receives grant support from Bracco Diagnostics. Other relationships: none to disclose. **A.M.N.** No potential conflicts of interest to disclose. **E.K.P.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is a research consultant for and stockholder in Siemens and is affiliated with ZONARE Medical Systems. Other relationships: none to disclose.

References

1. American College of Radiology. Manual on contrast media. 7th ed. Reston, Va: American College of Radiology, 2010.
2. Brunette J, Mongrain R, Rodés-Cabau J, Larose E, Leask R, Bertrand OF. Comparative rheology of low- and iso-osmolarity contrast agents at different temperatures. *Catheter Cardiovasc Interv* 2008;71(1):78–83.
3. Halsell RD. Heating contrast media: role in contemporary angiography. *Radiology* 1987; 164(1):276–278.
4. Hazirolan T, Turkbey B, Akpınar E, et al. The impact of warmed intravenous contrast material on the bolus geometry of coronary CT angiography applications. *Korean J Radiol* 2009;10(2):150–155.
5. Hughes PM, Bisset R. Non-ionic contrast media: a comparison of iodine delivery rates during manual injection angiography. *Br J Radiol* 1991;64(761):417–419.
6. Vergara M, Seguel S. Adverse reactions to contrast media in CT: effects of temperature and ionic property. *Radiology* 1996; 199(2):363–366.
7. Turner E, Kentor P, Melamed JL, Rao G, Zeitz HJ. Frequency of anaphylactoid reactions during intravenous urography with radiographic contrast media at two different temperatures. *Radiology* 1982;143(2): 327–329.
8. Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and severity of acute allergic-like reactions to i.v. nonionic iodinated contrast material in children. *AJR Am J Roentgenol* 2007;188(6):1643–1647.
9. Wang CL, Cohan RH, Ellis JH, Adusumilli S, Dunnick NR. Frequency, management, and outcome of extravasation of nonionic iodinated contrast medium in 69,657 intravenous injections. *Radiology* 2007;243(1):80–87.
10. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *AJR Am J Roentgenol* 2001; 176(6):1385–1388.
11. Pugh ND. Haemodynamic and rheological effects of contrast media: the role of viscosity and osmolality. *Eur Radiol* 1996;6(Suppl 2): S13–S15.
12. Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. *Radiology* 2010; 256(1):32–61.
13. Jacobs JE, Birnbaum BA, Langlotz CP. Contrast media reactions and extravasation: relationship to intravenous injection rates. *Radiology* 1998;209(2):411–416.
14. Callahan MJ, Poznauskis L, Zurakowski D, Taylor GA. Nonionic iodinated intravenous contrast material-related reactions: incidence in large urban children's hospital—retrospective analysis of data in 12,494 patients. *Radiology* 2009;250(3):674–681.