

Intravenous Corticosteroid Premedication Administered 5 Hours Before CT Compared with a Traditional 13-Hour Oral Regimen¹

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Purpose:

To determine if the allergic-like breakthrough reaction rate of intravenous corticosteroid prophylaxis administered 5 hours before contrast material-enhanced computed tomography (CT) is noninferior to that of a traditional 13-hour oral regimen.

Materials and Methods:

Institutional review board approval was obtained and informed consent waived for this retrospective noninferiority cohort study. Subjects ($n = 202$) who completed an accelerated 5-hour intravenous corticosteroid premedication regimen before low-osmolality contrast-enhanced CT for a prior allergic-like or unknown-type reaction to iodine-based contrast material from June 1, 2008, to June 30, 2016, were identified. The breakthrough reaction rate was compared by using the Farrington and Manning noninferiority likelihood score to test subjects premedicated with a traditional 13-hour oral regimen (2.1% [13 of 626]). All subjects were premedicated for a prior allergic-like or unknown-type reaction to iodine-based contrast material. A noninferiority margin of 4.0% was selected to allow for no more than a clinically negligible 6.0% breakthrough reaction rate in the cohort that received 5-hour intravenous corticosteroid prophylaxis.

Results:

The breakthrough reaction rate for 5-hour intravenous prophylaxis was 2.5% (five of 202 patients; 95% confidence interval: 0.8%, 5.7%), which was noninferior to the 2.1% (13 of 626 patients; 95% confidence interval: 1.1%, 3.5%) rate for the 13-hour regimen ($P = .0181$). The upper limits of the confidence interval for the difference between the two rates was 3.7% (0.4%; 95% confidence interval: -1.6%, 3.7%), which was within the 4.0% noninferiority margin. All breakthrough reactions were of equal or lesser severity to those of the index reactions (two severe, one moderate, and one mild reaction).

Conclusion:

Accelerated intravenous premedication with corticosteroids beginning 5 hours before contrast-enhanced CT has a breakthrough reaction rate noninferior to that of a 13-hour oral premedication regimen.

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Although modern low- and iso-osmolality iodine-based contrast media are generally well tolerated, there is an inherent risk of adverse reactions (1–3). In patients at risk of an allergic-like reaction to contrast media, the American College of Radiology (3) recommends pretreatment with corticosteroids. The most common regimen is premedication over 13 hours (4). It consists of 50 mg of oral prednisone administered at 13 hours, 7 hours, and 1 hour before computed tomography (CT) and 50 mg of oral diphenhydramine 1 hour before CT (3–6). However, in some patients who are at risk for a reaction to contrast media, waiting 13 hours is not desirable (4,7), either because medical urgency makes a timelier radiologic examination necessary or the care is being performed in a high-risk environment with collateral risk (eg, inpatient hospitalization) (8).

In such cases, an accelerated intravenous (IV) corticosteroid-based regimen has been recommended (3), although the efficacy of such regimens is not well studied (7). The existing radiologic literature on this topic, to our knowledge, consists of a single case series published in 1986 of 10 subjects who were premedicated with a variety of IV corticosteroid-based regimens that lasted up to 9 hours (7). No larger or controlled series is available. Despite this limited knowledge, the frequent clinical need for accelerated prophylaxis has overwhelmed the lack of efficacy data (4), and accelerated

premedication such as that used in the Greenberger et al case series (7) has been adopted in the United States in appropriate clinical scenarios (7).

It would be useful to know whether use of a rapid premedication regimen is associated with an increased rate of reactions in at-risk patients, or whether it is noninferior to the longer 12- or 13-hour oral regimens. The purpose of our study was to determine if the allergic-like breakthrough reaction rate of 5-hour IV corticosteroid prophylaxis is noninferior to that of a traditional 13-hour oral regimen.

Materials and Methods

Institutional review board approval was obtained, and informed consent was waived for this Health Insurance Portability and Accountability Act-compliant retrospective noninferiority cohort study. None of the subjects who received an accelerated regimen had been involved in a previously published study, and no external funding was used.

Study Population

The breakthrough reaction rate for a cohort of patients who received accelerated 5-hour IV corticosteroid prophylaxis before contrast material-enhanced CT for a prior allergic-like or unknown-type reaction to iodine-based contrast media was compared with a previously published breakthrough reaction rate from the same institution for a similar group of subjects who

received a 13-hour oral premedication regimen for the same indication (2.1%; 13 of 626) (9). Two methods were used to identify the 5-hour IV study cohort between the dates of June 1, 2008, and January 1, 2016. Data on subjects who received 13-hour oral prophylaxis were derived from a prior study (9). The accrual dates were similar for both cohorts (9). For subjects who had received more than one premedication regimen, only the first regimen was chosen for inclusion.

The first method for subject identification was an electronic query of all notes signed in the electronic medical record system between the study dates to identify subjects with free-text documentation of having received a rapid corticosteroid premedication regimen. Capitalization-insensitive search terms used included: “urgent steroid prep,” “emergent steroid prep,” “rapid steroid prep,” “1-hour steroid prep,” “1 hour steroid prep,” “one hour steroid prep,” “5-hour steroid prep,” “5 hour steroid prep,” and “five hour steroid prep.” This was done to account for practitioners who placed premedication orders in piecemeal fashion (ie, each dose and/or medication separately) and did not use a preset electronic order set. A total of 253 subjects were identified by using this first method. The second method for subject identification was an electronic query of the order entry

Advances in Knowledge

- The breakthrough reaction rate for 5-hour intravenous prophylaxis was 2.5% (five of 202 patients; 95% confidence interval [CI]: 0.8%, 5.7%), which was noninferior to the 2.1% (13 of 626 patients, 95% CI: 1.1%, 3.5%) rate for the 13-hour regimen when a 4.0% noninferiority margin was used ($P = .0181$).
- All breakthrough reactions were of equal or lesser severity than were the index reactions (two severe, one moderate, one mild).

Implications for Patient Care

- Our data support the replacement of a 13-hour oral premedication regimen with a 5-hour intravenous premedication regimen in patients with competing medical priorities (eg, inpatients, those in emergency departments).
- Faster premedication should reduce the indirect harms of premedication in hospitalized patients at high risk for reactions to contrast media.

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Abbreviation:

IV = intravenous

Author contributions:

Guarantors of integrity of entire study, B.M.M., M.S.D.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, B.M.M., R.H.C., J.H.E., M.S.D.; clinical studies, B.M.M., M.S.D.; statistical analysis, B.M.M., S.K., M.S.D.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

system to find subjects who had been prescribed a predesigned prophylaxis order set used to place orders for a standardized 5-hour premedication regimen. A total of 342 subjects were identified by using this second method. Twenty-two subjects were found with both methods, for an overall total of 573 individual subjects.

A single coauthor (B.M.M., an abdominal radiology fellow with 1 year of experience) performed a manual review of the medication administration records for the 253 subjects who had been identified by means of the keyword search to verify that an IV corticosteroid premedication regimen before contrast-enhanced CT actually was administered. Manual review was not necessary for the second capture method because the medication order entry system was used to identify the subjects. An electronic query of the radiology information system was performed for all subjects to ensure that each underwent contrast-enhanced CT within 24 hours of the time when the orders for corticosteroid premedication were signed.

During this manual review and radiology information system query, 197 subjects were excluded for one of the following reasons: (a) no contrast-enhanced CT performed within 24 hours ($n = 124$), (b) receipt of premedication for 10 hours or longer despite initial documentation indicating that an accelerated regimen was planned ($n = 21$), (b) premedication performed before an examination other than CT (coronary angiography [$n = 17$], visceral angiography [$n = 11$], magnetic resonance imaging [$n = 15$], fluoroscopy [$n = 3$], myelography [$n = 1$]), (d) subject received oral rather than IV premedication ($n = 4$), and (e) spurious matching of search terms ($n = 1$). This resulted in 376 individuals who received premedication before contrast-enhanced CT with IV corticosteroids administered for 9 hours or fewer and who represented all accelerated regimens used during the study period for any indication. This population ($n = 376$) was explored for secondary outcomes. From this group, 73 subjects were excluded for the primary

end point for premedication of other than 5 hours in duration, and 101 were excluded for the primary end point for premedication being given for an indication other than a prior allergic-like or unknown-type reaction to contrast material. This resulted in 202 subjects for the primary end point who had received accelerated 5-hour IV corticosteroid premedication before contrast-enhanced CT for a prior allergic-like or unknown-type reaction to iodine-based contrast material (Figure). Subjects who received 13-hour oral prophylaxis were part of a prior study (9), and additional details on that cohort can be found in that reference.

For all included subjects, a combined manual and electronic review of the electronic medical records was conducted by one coauthor (B.M.M.) to record subject sex, race, and age; history of asthma or of allergic-like reaction to iodine-based contrast material (and for those who did have a prior reaction to contrast material, the manifestations of the prior reaction); number of mild, moderate, and severe allergies to classes of substances; and number of reactions or intolerances of unknown type to classes of substances. The iodine-based contrast agent used with each CT examination also was recorded. Contrast material dosing was fixed (80–125 mL) and was dependent on protocol. Details regarding subject demographics are presented in Table 1, and details regarding subject allergy history are presented in Table 2.

Premedication

During the study period, premedication before IV contrast-enhanced CT was recommended at our institution for subjects meeting one or more of the following indications: (a) prior allergic-like or unknown-type reaction to iodine-based contrast media, (b) prior allergic-like or unknown-type reactions to four or more unique classes of allergens, (c) one or more severe allergy, or (d) asthma treated with two or more medications.

At our institution, the 13-hour premedication regimen originally recommended by Greenberger and colleagues

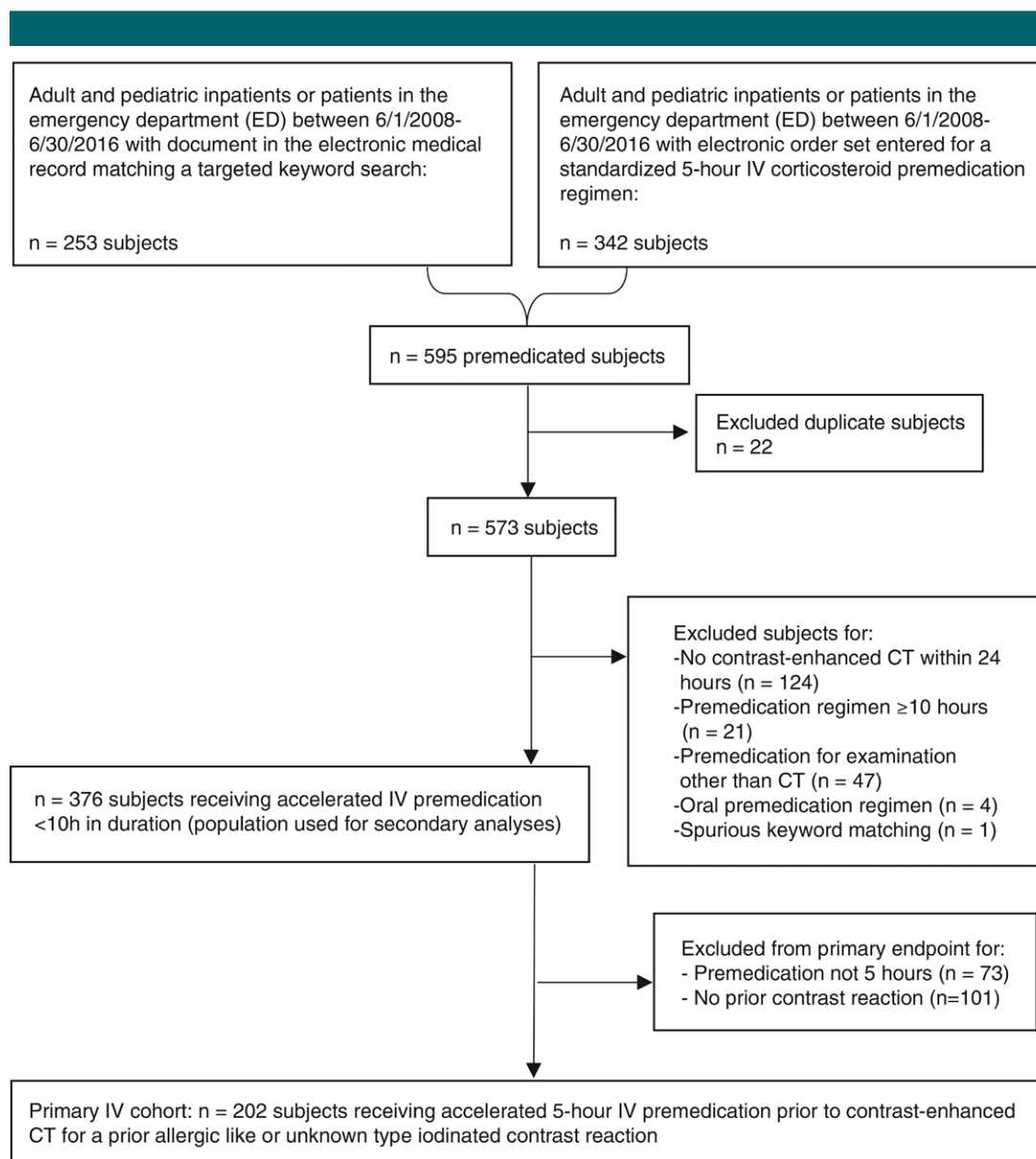
(5,6) and listed in the American College of Radiology Manual on Contrast Media, version 10.2 (3), is used for subjects who are medically able to wait 13 hours, while subjects at high risk of reaction with an urgent need for contrast-enhanced CT are recommended for an intention-to-treat 5-hour IV corticosteroid premedication protocol consisting of 200 mg of IV hydrocortisone administered at 5 hours and 1 hour before CT (total, 400 mg of hydrocortisone administered by means of IV) and 50 mg of IV diphenhydramine administered 1 hour before CT (3,7). This is the same accelerated regimen that was used in the case series by Greenberger et al (7) and was advocated in the American College of Radiology Manual on Contrast Media, version 10.2 (3).

Although institutional policy recommends this 5-hour regimen as the urgent alternative to the 13-hour regimen, medical need may require modification of this. In some urgent situations, the regimen is truncated to 1 hour (200 mg of IV hydrocortisone and 50 mg of IV diphenhydramine 1 hour before CT), and in some less-urgent situations, an additional dose of IV hydrocortisone is given at 9 hours before CT (total IV hydrocortisone, 600 mg). When truncated, the ordering service is informed that there are no published efficacy data for premedication regimens of less than 5 hours, and only a small case series supports the 5-hour regimen (7).

Breakthrough Reactions

A breakthrough reaction was defined as an allergic-like reaction to IV iodine-based contrast material that occurred despite premedication (3,10–13). Only allergic-like breakthrough reactions were considered for this study; physiologic reactions were ignored, because they are not considered relevant to corticosteroid prophylaxis (3). The American College of Radiology Manual on Contrast Media, version 10.2 (3), was used to define and grade allergic-like reactions.

Breakthrough allergic-like reactions in the study patients were identified by searching a prospective electronic database compiled in real time by the



Flowchart for the 5-hour IV cohort. Historical data were used for the 13-hour oral cohort (9).

Department of Radiology quality assurance monitor. This database represents transcription of paper versions of adverse event forms that are completed by a resident, fellow, or attending radiologist each time there is a perceived adverse event associated with contrast material administration (eg, significant physiologic reactions, allergic-like reactions, or extravasation events). This process has been a stable method of tracking and monitoring reaction

rates at the study institution for more than 15 years. A manual review of the paper forms was also performed for a sample (43%, 130 of 303 patients) of the 5-hour IV cohort to ensure that the transcribed database included all breakthrough reactions. No discrepancies were identified.

Data Analysis

Continuous data were summarized as means and ranges. Categorical data

were summarized with rates and percentages. The primary outcome was a comparison of the breakthrough reaction rate for the cohort of patients who received 5-hour IV prophylaxis before contrast-enhanced CT for a prior allergic-like or unknown-type of reaction to iodine-based contrast material to the breakthrough reaction rate of subjects premedicated with a traditional 13-hour oral regimen prior to contrast-enhanced CT for the same

Table 1

Demographic Data

Characteristic	5-Hour IV Regimen (n = 202)	13-Hour Oral Regimen (n = 626)	P Value
Sex			
Male	81 (40)	229 (37)	.40
Female	121 (60)	397 (63)	
Mean age (y)	58 (11–86)	57 (5–97)	.79
<18 years	2 (1)	3 (0.5)	
18–65 years	126 (62)	379 (60)	
>65 years	74 (37)	244 (39)	
Race			.02*
Other	17 (8)	26 (4)	
Asian	2 (1)	4 (0.6)	
Black	24 (12)	76 (12)	
White	156 (77)	519 (83)	
Hispanic	3 (1)	1 (0.2)	
Asthma	43 (21)	69 (11)	.0004*
Contrast agent administered			.005*
Iopamidol 370	121 (60)	299 (48)	
Iopamidol 300	73 (36)	303 (48)	
Iopamidol 250	0 (0)	1 (0.2)	
Iopromide 300	4 (2)	2 (0.3)	
Iodixanol	1 (0.5)	4 (0.6)	
Unknown	3 (1)	17 (3)	

Note.—Unless otherwise indicated, data are number of patients, with percentages in parentheses. The 13-hour oral cohort was derived from the study by Mervak et al (9).

* Indicates a significant difference.

indication (2.1%, 13 of 626) (9). Non-inferiority was assessed with the one-way Farrington and Manning likelihood score test. By using a 3:1 accrual rate, the noninferiority margin was 4.0%, with acceptance of no more than a 6.0% clinically negligible breakthrough reaction rate in the 5-hour IV cohort. Post hoc power calculation also was performed by using a one-way Farrington and Manning test with an α of .025, demonstrating 74% power at a 4.0% threshold, 84% power at a 4.5% threshold, and 91% power at a 5.0% threshold. The 95% confidence interval of the difference between the two breakthrough reaction rates (5-hour IV and 13-hour oral) was calculated and compared with the predefined 4.0% noninferiority margin. Demographic and atopic risk factor data were compared between the 5-hour IV cohort and the 13-hour oral cohort with the χ^2 test for categorical data and Mann Whitney *U* test for nonparametric continuous data, and 95% confidence

intervals were calculated to show the precision of our estimates.

Secondary exploratory analyses without hypothesis testing were performed on the overall cohort of subjects who were premedicated for any indication by using an accelerated IV regimen less than 9 hours in duration ($n = 376$) or the 13-hour oral regimen ($n = 1051$) (9). Breakthrough reaction rates were calculated and stratified according to length of premedication and history of a prior allergic-like or unknown-type reaction to iodine-based contrast media. Accelerated premedication at the study institution was intended to last 5 hours, but because of clinical circumstances (eg, clinical urgency, CT scanner accessibility, patient stability or accessibility), sometimes lasted for a shorter or longer period of time. Nine hours was selected as the upper limit for the accelerated cohort for these secondary comparisons, because the dosing schedule of the accelerated regimen is every 4 hours, and a 9-hour

upper limit would capture subjects who received an additional dose (5 + 4 hours) without reaching the 13 hours of the oral regimen.

Results

Subject sex ($P = .40$) and age ($P = .79$) were not significantly different between the 5-hour IV and 13-hour oral prophylaxis cohorts (Table 1). There were minor differences in subject race that were statistically significant ($P = .02$) (Table 1), and subjects who received 5-hour IV prophylaxis were more likely to have asthma (21% [43 of 202] vs 11% [69 of 626], $P = .0004$) (Table 1). There were minor differences in the administered concentration of the contrast agent and the contrast agent itself that were statistically significant but unlikely to be clinically meaningful (Table 1). More than 96% of each cohort received iopamidol.

There was no significant difference between the 5-hour IV and 13-hour oral cohorts in the proportion of subjects with a prior moderate ($P = .35$) or severe ($P = .30$) reaction to iodine-based contrast media (Table 2). Significantly more subjects receiving a 13-hour oral regimen had a prior reaction to iodine-based contrast material of unknown type (38% vs 15%, $P < .0001$), and significantly more subjects who received an accelerated IV regimen had a prior mild reaction to iodine-based contrast material (51% vs 34%, $P < .0001$). Both cohorts had a similar number of allergies or unspecified reactions to substances other than iodine-based contrast material (5-hour IV mean, 2.3 [range, 0–11] vs 13-hour oral mean, 2.3 [range, 0–31]; $P = .90$).

Primary End Point

The breakthrough reaction rate for the 5-hour IV cohort was 2.5% (five of 202; 95% confidence interval: 0.8%, 5.7%), which was noninferior to the 2.1% (13 of 626, 95% confidence interval: 1.1%, 3.5%) rate for the 13-hour oral cohort ($P = .0181$). The upper limit of the 95% confidence interval for the difference between the two rates was 3.7% (0.4% [95% confidence interval: -1.6%,

Table 2

Allergy and Reaction History

Characteristic	5-Hour IV Regimen (n = 202)	13-Hour Oral Regimen (n = 626)	P Value
Prior mild allergic-like reaction to iodine-based contrast material	103 (51)	210 (34)	<.0001*
Limited urticaria	94 (47)	194 (31)	
Limited cutaneous edema or erythema	8 (4)	13 (2)	
"Scratchy" throat	0 (0)	0 (0)	
Nasal congestion	0 (0)	1 (0.2)	
Sneezing or conjunctivitis	1 (0.5)	2 (0.3)	
Prior moderate allergic-like reaction to iodine-based contrast material	42 (21)	112 (18)	.35
Diffuse urticaria	15 (7)	37 (6)	
Diffuse erythema, normotensive	0 (0)	2 (0.3)	
Facial edema without dyspnea	3 (1)	17 (3)	
Throat tightness without dyspnea	2 (1)	11 (2)	
Bronchospasm without hypoxia	22 (11)	45 (7)	
Prior severe allergic-like reaction to iodine-based contrast material	26 (13)	63 (10)	.30
Diffuse edema, facial edema with hypoxia	1 (0.5)	1 (0.2)	
Diffuse erythema with hypotension	0 (0)	1 (0.2)	
Laryngeal edema with stridor or hypoxia	0 (0)	0 (0)	
Bronchospasm with hypoxia	1 (0.5)	0 (0)	
Hypotension and tachycardia	24 (12)	61 (10)	
Prior unknown-type reaction to iodine-based contrast material	31 (15)	241 (38)	<.0001*
Prior allergic-like or unknown-type reaction to iodine-based contrast material	202 (100)	626 (100)	.99
Allergies or unspecified reactions, not iodine-based contrast material†	2.3 (0–11)	2.3 (0–31)	.90
Mild allergies	1.6 (0–8)	0.6 (0–7)	
Moderate allergies	0.7 (0–10)	0.3 (0–9)	
Severe allergies	0.3 (0–5)	0.2 (0–5)	
Unspecified reactions	0.6 (0–8)	1.2 (0–31)	
Allergies (any severity)	1.8 (0–11)	1.1 (0–11)	

Note.—Unless otherwise indicated, data are number of patients, with percentages in parentheses. Reaction types were derived from the American College of Radiology Manual on Contrast Media version 10.2 (3). The 13-hour oral cohort was derived from the study by Mervak et al (9).

* Indicates a significant difference.

† Data are mean number of reactions per subject, with the range in parentheses.

3.7%]), which was within the 4.0% noninferiority margin. Two of the five breakthrough reactions in the 5-hour IV cohort were severe, one was moderate, and two were mild. All ($n = 5$) breakthrough reactions were of equivalent or lesser severity than were the index reactions; however, even when the reaction was of equivalent severity, it did not necessarily manifest with the same symptoms (Table 3). One subject was treated with epinephrine for a severe reaction. No subjects died.

Secondary Analyses

Breakthrough reaction rates for secondary outcomes are shown in Table 4. No breakthrough reactions occurred in subjects in the accelerated IV cohort (< 9 hours) who were premedicated for

any reason other than a prior reaction to contrast material (0%, 0 of 133). The reaction rates for all subgroup comparisons were similar, ranging from 0.0% to 2.5%.

Discussion

We have shown that the breakthrough reaction rate to 5-hour IV premedication (2.5%) is noninferior to the breakthrough reaction rate for a traditional 13-hour oral regimen (2.1%). The upper limit of the 95% confidence interval for the difference between the breakthrough reaction rate point estimates was 3.7%. This indicates that the breakthrough reaction rate of the 5-hour IV cohort was likely less than 5.8% (3.7% [upper limit] + 2.1% [rate of 13-hour oral cohort] =

5.8%) and was statistically less than our prespecified clinically negligible threshold of 6.0%. These data demonstrate that 5-hour IV premedication has similar efficacy in preventing breakthrough reactions to that of the traditional 13-hour oral regimen. There were two additional similarities between the 5-hour IV and 13-hour oral regimens: Neither regimen prevented all moderate and severe breakthrough reactions (10–13), and breakthrough reactions usually were of equivalent or lesser severity than were index reactions (11).

The available literature on the efficacy of accelerated IV corticosteroid premedication consists, to our knowledge, of a case series (7) published in 1986 of 10 subjects who were pretreated with a variety of IV corticosteroid

Table 3

Breakthrough Reactions After 5-Hour IV Premedication for a Prior Reaction to Iodine-based Contrast Material

Reaction Variable	Patients with Breakthrough Reactions				
	1	2	3	4	5
Indication for premedication					
Prior allergic-like reaction to iodine-based contrast media	Yes	Yes	Yes	Yes	Yes
Prior unknown-type reaction to iodine-based contrast media	...	...	...	...	...
≥ 4 reactions to other substances	Yes	...	...	...	Yes
One severe allergy to other substances	...	Yes	Yes	Yes	...
≥ 2 severe allergies to other substances	Yes	...	...	...	...
Asthma	...	...	...	...	...
Allergic-like reaction severity and type					
Mild					
Limited urticaria	...	...	I, B	...	B
Limited cutaneous edema or erythema	...	...	...	...	...
"Scratchy" throat	...	...	...	...	...
Nasal congestion	...	...	...	...	...
Sneezing or conjunctivitis	...	...	...	...	...
Moderate					
Diffuse urticaria	...	...	...	...	...
Diffuse erythema, normotensive	...	...	...	...	...
Facial edema without dyspnea	...	...	...	...	...
Throat tightness without dyspnea	...	...	...	...	...
Bronchospasm without hypoxia	...	B	...	...	I
Severe					
Diffuse edema, facial edema with hypoxia	I, B	...	...	...	...
Diffuse erythema with hypotension	...	...	...	...	...
Laryngeal edema with stridor or hypoxia	...	...	...	B	...
Bronchospasm with hypoxia	...	...	...	...	...
Hypotension and tachycardia	...	I	...	I	...
Breakthrough reaction treatment					
Observation only	...	...	...	...	...
Oxygen (≥ 5 L by facemask)	...	Yes	...	Yes	...
Intravenous fluids	...	...	...	...	...
Diphenhydramine	...	...	...	...	Yes
Other antihistamine	...	...	Yes	...	...
Corticosteroids	...	...	Yes	Yes	...
Albuterol	...	Yes	...	...	...
Epinephrine	Yes	...	...	...	...

Note.—I = index reaction, B = breakthrough reaction. No subjects died.

regimens lasting up to 9 hours and a case series published in 2008 of six subjects who were pretreated with IV corticosteroids with or without antihistamines less than 1 hour before coronary angiography (14). No subject in either cohort experienced a breakthrough reaction. The authors of the 1986 case series (7) concluded that rapid premedication was feasible and recommended a regimen consisting of 200 mg of IV

hydrocortisone administered immediately, followed by subsequent doses of 200 mg of IV hydrocortisone every 4 hours until the contrast material is administered, along with administration of 50 mg of IV diphenhydramine 1 hour before contrast material administration. This was the 5-hour intention-to-treat regimen used in our study.

Although the efficacy of accelerated IV premedication has not, to our

knowledge, been demonstrated previously in larger series, it has been known for many years that allergic-like reactions are not reduced by administering a single dose of oral corticosteroids within 2 hours of iodine-based contrast material administration (15). In 1987, Lasser et al (15) tested a 2-hour oral premedication regimen consisting of 32 mg of methylprednisolone before IV high-osmolality iodine-based contrast material (no longer used for IV administration), and they were unable to show superiority of this regimen over placebo in a randomized design; the longer 12-hour oral regimen tested in that study (15) was efficacious. Therefore, there is a minimum premedication duration below which corticosteroids are ineffective in reducing the incidence of reactions to contrast material. The minimum time for oral regimens is unknown, but is longer than 2 hours (15). Similarly, the minimum time for IV regimens is also unknown, but on the basis of the data in our study, it appears that a 5-hour IV regimen is similarly efficacious to a 13-hour oral regimen.

Despite limited data to support it, the American College of Radiology Manual on Contrast Media version 10.2 (3) and many radiology practices (4) recommend use of the same or similar IV regimen (3,7) as that analyzed in this study, because many clinical situations arise in which the acute need for a contrast-enhanced CT examination makes prolonged prophylaxis impractical. In an effort to do something to minimize risk in this setting, practitioners often elect to use a shorter prophylaxis regimen with little evidentiary support (7). As of 2009, accelerated IV regimens were being used in urgent or emergent situations by 29% (20 of 69) of surveyed radiologists (4).

Minimizing the duration of prophylaxis is advantageous to accelerate diagnosis in emergent situations but also to reduce the indirect harms prophylaxis can induce in high-risk settings (eg, inpatient ward, intensive care unit) (8). Specifically, it has been shown (8) that inpatients undergoing 13-hour oral prophylaxis have a significantly longer hospital length of stay (median, 25

Table 4

Secondary Analyses of All Accelerated Regimens of Less than 9 Hours

Cohort	Accelerated IV Regimen	13-Hour Oral Regimen
5-hour IV regimen (<i>n</i> = 303)	1.7 (5/303)	1.2 (13/1051)
Prior reaction to iodine-based contrast material*	2.5 (5/202)	2.1 (13/626)
No prior reaction to iodine-based contrast material	0.0 (0/101)	0.0 (0/425)
All accelerated IV regimens (<i>n</i> = 376)	1.3 (5/376)	1.2 (13/1051)
Prior reaction to iodine-based contrast material	2.1 (5/243)	2.1 (13/626)
No prior reaction to iodine-based contrast material	0.0 (0/133)	0.0 (0/425)

Note—Data are percentage of patients who experienced a breakthrough reaction, with proportions in parentheses. Data for the 13-hour oral regimen were derived from the study by Mervak et al (9).

* Primary end point.

hours), a significantly longer time from admission to CT (median, 25 hours), significantly more hospital-acquired infections, and significantly greater health care–related costs compared with similar patients who also are imaged with contrast-enhanced CT but do not receive prophylaxis.

On the basis of such data (8) and the results of our study, institutions may want to consider the use of an accelerated IV regimen instead of a longer oral regimen for all indicated patients with competing medical priorities (eg, emergent examinations, inpatient examinations, examinations in the emergency department) for whom use of an IV regimen is not an added burden (as it might be in an outpatient setting). Although traditionally such a practice change would be preceded by data from a phase III study, no such level of evidence exists for the current practice of 13-hour prophylaxis (16). In fact, no studies have shown that prophylaxis against reactions to contrast material reduces permanent morbidity or mortality in patients at high risk of an adverse reaction who receive modern intravascular media (17). In the largest randomized trial for modern iodine-based contrast agents, investigators (16) tested prophylaxis in patients at average risk of a reaction, and the trial was underpowered to detect an effect on moderate or severe reaction rates. Assuming that prophylaxis does reduce the likelihood of severe reactions, which some experts agree that it may

(3), we believe that the number needed to treat to prevent one reaction is likely quite high (8). In fact, one estimate of the number needed to treat to prevent one lethal reaction with 13-hour oral prophylaxis in a population of patients who have had a prior reaction to iodine-based contrast material is approximately 50 000 patients (8).

Our study had limitations. Due to the retrospective nature of the study design, it is possible that there were uncontrolled covariates or missing data that could have led to bias. However, the 5-hour IV and 13-hour oral cohorts had similar risk factors, and the methods used to track reactions have been a reliable source of recordkeeping at the study institution for more than 15 years. Of the differences that were observed between cohort risk factors, the 5-hour IV cohort had a significantly greater proportion of subjects with asthma and a significantly greater proportion of subjects with a confirmed prior allergic-like reaction to iodine-based contrast material, which indicates that if bias related to these covariates was present, it worked against the study conclusions (ie, the 5-hour IV cohort had greater confirmed atopic risk factors than did the 13-hour oral cohort). It is likely that the greater proportion of unknown-type index reactions in the 13-hour oral cohort explains the greater proportion of mild allergic-like index reactions in the 5-hour IV cohort (ie, unknown reactions are most likely unclassified mild allergic-like

reactions). This is because the proportion of subjects with prior moderate and severe reactions was similar ($P = .35$ and $P = .30$, respectively), and mild reactions are much more common than are moderate and severe reactions (1–3).

We did not test to determine whether a regimen shorter than 5 hours is effective and cannot comment on the efficacy of premedication in advance of CT in general. We are only able to state that the 5-hour IV regimen was noninferior to the 13-hour oral regimen within a 4.0% noninferiority margin. As we mentioned previously, the minimum premedication duration necessary for effective prophylaxis (IV or oral) remains unknown. Finally, there is growing evidence that alternative measures such as changing from one low-osmolality iodine-based contrast medium to another low-osmolality iodine-based contrast medium may be more efficacious than is prophylaxis (18,19). Because of limitations in historical data with respect to accurately identifying the agent responsible for the index reaction, we were unable to analyze this effect in our study.

In conclusion, 5-hour IV corticosteroid premedication has a breakthrough reaction rate that is noninferior to that of a traditional 13-hour oral regimen and can be used as a substitute, with a clinically and statistically insignificant risk of reaction in populations with competing medical priorities (eg, inpatients, patients in the emergency department). Although these data do not add information to the larger discussion about premedication efficacy in general, they may be used to conclude that a 5-hour IV regimen is at least not substantially less effective than the commonly used 13-hour oral regimen.

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