

Premedication of patients for prior urticarial reaction to iodinated contrast medium

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Abstract

Purpose: The purpose of this study was to determine whether premedication of patients with a history of urticaria after low osmolality contrast media (LOCM) results in fewer subsequent reactions, and if a benefit is seen, to determine which premedication regimen results in the fewest reactions.

Materials and methods: The subsequent contrast enhanced studies of patients who experienced urticaria after intravenous LOCM between 2002 and 2009 were reviewed to determine whether an additional reaction occurred. Patients undergoing subsequent studies received either no premedication, or premedication with diphenhydramine alone, corticosteroid alone, or corticosteroid plus diphenhydramine. Reactions occurring without premedication were termed repeat reactions and reactions occurring after premedication were termed breakthrough reactions.

Results: Fifty patients with a history of urticaria after LOCM met the inclusion criteria and underwent 133 subsequent contrast enhanced studies. Repeat reactions occurred in 7.6% (5/66) of subsequent studies in patients receiving no premedication. Breakthrough reactions occurred in 8% (2/25), 46% (12/26), and 44% (7/16) of subsequent studies in patients receiving premedication with diphenhydramine, corticosteroid, and corticosteroid plus diphenhydramine, respectively. All subsequent reactions consisted of urticaria as the most severe manifestation; no hemodynamic instability or respiratory compromise occurred. In multivariate analysis, premedication with corticosteroid was significantly associated with higher rate of breakthrough reaction relative to no premedication (OR 14.3, 95% CI: 4.1–50.4), as was premedication with corticosteroid plus diphenhydramine (OR 8.3, 95% CI: 1.8–37.9).

Conclusion: The results suggest that premedication of patients with a history of urticaria after LOCM may not be necessary.

Key words: Iodinated contrast reaction—Contrast reaction—Premedication—Urticaria—Corticosteroid—Antihistamine

The incidence of anaphylactoid reactions to iodinated contrast media has been extensively studied. Recent large-scale studies have reported the incidence of reaction to low osmolality contrast media (LOCM) as ranging from 0.5% to 3% [1–5]. The rate of severe reactions is extremely low from 0.01% to 0.04% [3–6]. However, considering that over 15 million intravenous iodinated contrast enhanced studies are performed each year [5], a significant number of reactions occur.

Historically, after a patient experienced a reaction to iodinated contrast, corticosteroids, antihistamines, or a combination of both were administered prior to repeat contrast administration in attempts to prevent reactions. The most widely used premedication protocols, the Lasser protocol and the Greenberger protocol, were originally studied as prevention of reactions to ionic contrast media and showed a significant decrease in reactions [7–9]. The Lasser protocol includes two doses of methylprednisolone 32 mg orally administered 12 and 2 h prior to imaging. The Greenberger protocol includes three doses of prednisone 50 mg orally administered 13, 7, and 1 h prior to imaging. Diphenhydramine (25–50 mg) may or may not be included with the corticosteroids in either protocol.

LOCM was subsequently shown to have a significantly better safety profile than high osmolar ionic contrast media, with far fewer and less severe associated

reactions, and has been used almost exclusively since its advent [1–4]. However, reactions to LOCM do occur, and the same premedication regimens have been used in attempts to prevent reactions to LOCM [8, 10, 11]. It has been shown that patients with previous reactions to contrast have a four to six times increased risk of having a repeat reaction [5, 12]. Additionally, concern exists that subsequent exposures can lead to increasingly severe reactions, including anaphylaxis. Studies have shown repeat reactions can occur even after premedication [10, 11, 13, 14], however, these studies have grouped all reactions together, be they mild or severe. To our knowledge, no studies focusing on patients with urticaria as their only manifestation have been conducted to establish the rate of repeat reaction and usefulness of premedication in preventing breakthrough reactions.

The purpose of this study was to determine whether premedication of patients with a history of urticaria after LOCM results in fewer subsequent reactions, and if a benefit is seen to determine which premedication regimen results in the fewest reactions. This would aid physicians in providing safe and timely contrast administration.

Materials and methods

Institutional review board approval was obtained for this retrospective review. Health Insurance Portability and Accountability Act guidelines were followed and informed patient consent was not required. No external funding was received to support this research and no study authors have industry or other ties to report.

Study patients

At our institution, reactions to iodinated contrast have been documented in a radiology database since 2002. This database was searched for patients having a new reaction to intravenous contrast consisting of urticaria as the most severe manifestation from 2002 through 2008. Patients whose first reaction occurred prior to 2002 or at another institution ($n = 15$) were excluded, as firsthand details regarding these reactions were not available. Patients determined to receive steroid chronically as treatment for a medical condition ($n = 8$) were also excluded. The remaining patients were reviewed to identify those who underwent additional contrast enhanced studies from the time of their index study through 2009 (Fig. 1). These patients' electronic medical records, including radiology reports, nursing records, and clinic visit notes, were reviewed to determine if and how they were premedicated for the subsequent study and whether they had a subsequent reaction. Patient characteristics such as gender and age were noted. Additionally, risks factors cited in the literature as possible predisposing factors for contrast reactions were noted, including number of other medication allergies and history of asthma.

Reaction type

Index and subsequent reaction type were classified using the suggested classification system in the ACR Manual on Contrast Media, Version 9, Table 3 [15].

Reaction severity

Index reactions were classified as mild if they required observation only and moderate if they required treatment with diphenhydramine and/or hydrocortisone for symptom control [2]. Subsequent reactions were categorized using the same system. If a patient experienced more severe symptoms during a subsequent reaction, such as hypotension or respiratory compromise, the reaction was classified as severe. If a subsequent reaction occurred after receiving premedication, it was identified as a breakthrough reaction. If a subsequent reaction occurred without premedication, it was labeled a repeat reaction.

Premedication regimen

No policy existed at our institution requiring premedication for a history of isolated urticarial reaction to LOCM. Some referring physicians prescribed premedication and instructed the patient to take it prior to arriving for the exam. Some opted not to premedicate or may not have been aware of a prior reaction. The final decision as to how to proceed was left to the discrimination of the performing radiologist. Some radiologists chose to perform the test without premedication, some administered diphenhydramine prior to giving contrast, and some elected to postpone the test so that corticosteroid could be given.

Whether or not premedication was given and the type of premedication administered was determined by reviewing the contrast reaction database and the electronic medical chart. Our institution is a single-system medical environment sharing a centralized electronic medical record and any medications prescribed by the referring physician for premedication were accessible for review. The radiology nurses routinely confirm a patient has taken the premedication as directed prior to imaging. In addition, any medications given at the time of an exam, including diphenhydramine, are charted in the electronic record.

Studies were assigned to one of the four premedication categories including no premedication, diphenhydramine alone (25–50 mg orally or intravenously 1 h prior to imaging), corticosteroid alone (two doses of methylprednisolone 32 mg orally administered 12 and 2 h prior to imaging), or combined corticosteroid plus diphenhydramine.

Statistical analysis

The percent of patients experiencing hives reaction was summarized overall and by premedication type both for the first subsequent scan and for all subsequent scans

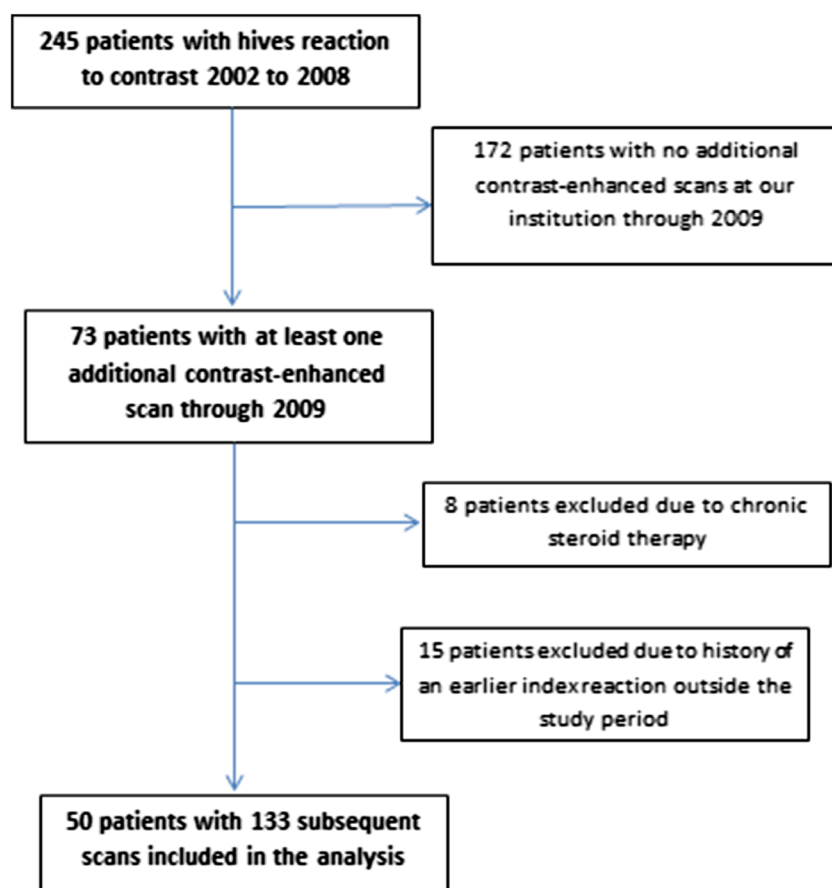


Fig. 1. Consort diagram of patient population.

combined. 95% confidence intervals were calculated for each estimate, using Wilson score intervals for the first subsequent scan results and a generalized linear model for the all subsequent scan estimates. Generalized linear models were implemented using PROC GENMOD in SAS, which allowed us to account for multiple scans within patient. Odds ratios with 95% confidence intervals were estimated for each premedication category relative to no premedication using logistic regression for the first subsequent scan results and generalized linear models with logit link and binomial distribution for the all subsequent scan results. Tests of association between potential explanatory variables and the outcome of hives on subsequent scan, as well as the choice to premedicate with corticosteroids, were performed using data from all subsequent scans and again using the generalized linear model approach to account for the correlation among multiple scans from the same patient. Multiple logistic regression was performed similarly to adjust for potential confounders in assessing the impact of premedication choice on the hives outcome. Analysis was performed using SAS (Version 9.2, SAS Institute Inc.). p -values < 0.05 were considered statistically significant.

Results

Of the 299,413 contrast enhanced scans performed from 2002 through 2008, 245 patients had a reaction involving hives as

the most severe manifestation. After excluding patients not meeting the inclusion criteria, there were 50 patients having urticaria for the first time after a non-premedicated contrast enhanced study (see Table 1). In these 50 patients, 133 contrast-enhanced scans were performed. The median number of subsequent studies was 2, with a range of 1 to 11. The rates of reaction vs. premedication type for the first study after the index reaction and for all subsequent studies are given in Table 2. It is noted that 19 of the 50 patients (38%) had at least one repeat or breakthrough reaction during 26 of the 133 studies (19.5%). Table 3 shows the associations of factors with decision to premedicate with corticosteroids during the subsequent studies. Table 4 shows the odds ratio of having a breakthrough reaction for the various premedication regimens compared to having a repeat reaction without premedication, after adjustment for age, gender, asthma, and occurrence of urticaria on most recent prior study.

No subsequent reactions were more severe than urticaria. Thirteen reactions were treated with diphenhydramine for symptomatic relief. No reactions included compromised respiratory or hemodynamic status and none required hospitalization.

Discussion

In our study, the rate of repeat reaction in patients' previously experiencing urticaria undergoing additional

Table 1. Characteristics of the patients that had contrast enhanced scans after an index urticarial reaction to iodinated contrast

Characteristic	<i>n</i> = 50
Age at index scan, yrs, median (range)	61.5 (28, 88)
Male, <i>n</i> (%)	27 (54%)
Asthma, <i>n</i> (%)	2 (4%)
Medication allergies, <i>n</i> (%)	
None	26 (52%)
1–3	22 (44%)
≥4	2 (4%)
Severity of index reaction, <i>n</i> (%)	
Mild	29 (58%)
Moderate	21 (42%)
Number of contrast enhanced scans subsequent to index reaction, <i>n</i> (%)	
1	23 (46%)
2	13 (16%)
3–5	7 (14%)
≥6	7 (14%)

Table 2. Urticarial reactions by premedication choice for scans occurring subsequent to index reaction

Premedication category	<i>n</i>	<i>n</i> (%) with urticaria	95% CI ^a	Unadjusted OR ^b (95% CI)
<i>1st subsequent scan</i>				
No premedication	23	3/23 (13%)	4.5–32%	Reference
Diphenhydramine	7	1/7 (14%)	2.6–51%	1.1 (0.1, 12.8)
Corticosteroids	10	5/10 (50%)	24–76%	6.6 (1.2, 37.8)
Corticosteroids and diphenhydramine	10	4/10 (40%)	17–69%	4.4 (0.8, 25.6)
Total	50	13/50 (26%)	16–40%	
<i>All subsequent scan</i>				
No premedication	66	5/66 (7.6%)	0–16%	Reference
Diphenhydramine	25	2/25 (8.0%)	0–18%	1.1 (0.2, 6.6)
Corticosteroids	26	12/26 (46%)	26–66%	10.5 (2.9, 37.5)
Corticosteroids and diphenhydramine	16	7/16 (44%)	20–67%	9.5 (2.0, 44.4)
Total	133	26/133 (20%)	11–28%	

^a Confidence interval (CI) calculated using the Wilson score method^b Odds ratio (OR) estimated using a generalized linear model to account for multiple scans within patient**Table 3.** Univariate association of patient characteristics with choice to premedicate with corticosteroids

	OR (95% CI)	<i>p</i> -value
Age, per 10 years increase	1.0 (0.7, 1.6)	0.84
Female vs. male	1.6 (0.6, 4.4)	0.36
Moderate vs. mild index reaction	1.7 (0.6, 4.9)	0.34
Number of other medication allergies		0.92
None	1.0 (Reference)	
1–3	0.8 (0.3, 2.3)	
≥4	1.0 (0.05, 17.6)	
Asthma	7.4 (2.6, 21.3)	0.0002
Urticaria on most recent prior scan	3.0 (1.5, 5.9)	0.001

contrast enhanced studies without premedication was 7.6% (5/66). To our knowledge, this rate has not been reported previously. Davenport et al. [10] reported the rate of reaction in patients with a prior reaction to contrast at 12%, however, all of these patients were premedicated. As was demonstrated in that study and Freed et al. the repeat and breakthrough reactions in our study were similar to the index reaction in manifestation and severity. Our study did not have any patients who developed a more severe reaction than urticaria upon

subsequent contrast exposure. These results are important in that the majority of patients who were not premedicated did not have a repeat reaction, and when they did, it was similar to the index reaction.

Next we investigated whether premedication further decreased the reaction rate in these patients. The unexpected finding of our study was that the rates of breakthrough reactions with premedication were similar or higher than the rate of repeat reaction without premedication. The rate of breakthrough reaction after diphenhydramine was similar to that of no premedication at 8.0%. The rates of breakthrough reaction after corticosteroid and corticosteroid plus diphenhydramine, believed to be increasingly aggressive premedication regimens, actually increased, and are significantly higher than previously reported [10]. We are unsure why this occurred. Statistical analysis showed these groups were not different with regards to age or gender. We did find that urticaria on the most recent study trended toward association with experiencing a reaction on subsequent LOCM exposure (OR 3.3, *p* = 0.06) and was statistically associated with being given corticosteroid premedication

Table 4. Association of premedication with urticaria on subsequent scans

	Adjusted OR ^a (95% CI)	<i>p</i> -value
Premedication		
No premedication	Reference	
Diphenhydramine only	1.2 (0.2, 7.3)	0.85
Corticosteroids only	14.3 (4.1, 50.4)	<0.0001
Corticosteroids and diphenhydramine	8.3 (1.8, 37.9)	0.006

^a Adjusted for age, gender, asthma, and urticarial on most recent prior exam

before subsequent contrast exposure (OR 7.4, $p = 0.0002$). It may be that patients who had multiple episodes of urticaria were predisposed for some unknown reason, and these were the patients that physicians tended to prescribe corticosteroids. Asthma was also significantly associated with being given corticosteroid premedication (OR 3.0, $p = 0.001$), however there were only two patients with asthma in our study. After adjustment was made for the effects of age, gender, urticaria on most recent study, and asthma, there remained an association of premedication with corticosteroids alone or in combination with diphenhydramine, with higher rate of breakthrough reaction.

The patients in our study had a higher rate of breakthrough reactions than reported by Davenport et al. [10] who found 88% of LOCM injections did not result in a breakthrough reaction. One potential explanation for the discrepancy in the rate of breakthrough reactions is that our study consisted only of patients with urticaria. The previous studies have looked at the rate of breakthrough reaction after all types of index reactions combined, including reactions such as bronchospasm, for example, that generally occur at a much lower rate than urticaria and therefore decrease the reported overall reaction rate.

These results raise questions about the basic mechanism of immediate allergic reaction to LOCM. The currently accepted model identifies marginated basophils in the post-capillary venules, which are sensitive to rapid changes in the osmolar environment, as the mediator-containing cell responsible for triggering reactions [16]. This led to the concept of prophylactic treatment with corticosteroid, to demarginate the basophil population of cells making them less available to release histamine, and antihistamine, to block the cardiovascular system effects of histamine released by basophils [17]. After the adoption of near exclusive use of LOCM, reaction rates decreased by 90% to 95% which further supported the theory of osmolar environmental shifts as the mechanism of reaction. Reactions continue to occur, and, as is well documented elsewhere and shown in our study, some patients continue to experience reactions even after receiving premedications designed to target basophils and block the effects of histamine. This raises the possibility that urticaria may be occurring via an entirely different mechanism unrelated to basophils.

We believe, important observations can be drawn from the results of our study. Importantly, most patients with a history of urticarial reaction to LOCM who did not receive premedication did not have a subsequent reaction. Also, when patients did experience reactions, they were similar to the index reaction. Finally, premedication did not decrease the odds of repeat reaction on subsequent scans. Given the results of this study, our radiology department implemented a practice guideline stating premedication of patients having a prior hives reaction is not required. Use of premedication is, of course, left to the discrimination of the referring physician and the performing radiologist after review of the patient's symptoms and severity. The new guideline has been in place for over 2 years, and anecdotally we have not identified a change in the frequency or severity of reactions.

Limitations of the study include the retrospective nature and lack of randomization for premedication regimen. Because the rate of reaction to LOCM is very low, there are a relatively small number of patients in the study. We do not have information as to why certain premedication regimens were given to which patients. Additionally, there may be factors not captured in this study which affect the likelihood of having a reaction to LOCM or influence the choice to premedicate and with which regimen.

Further research is needed to elucidate the mechanism of reaction to contrast and to determine the true relationship between urticaria and anaphylaxis. While a prospective study may ultimately be required to validate the findings, the results of our study suggest that premedication of patients with a prior urticarial reaction to LOCM may not be necessary. As always, it is prudent for radiology personnel performing studies with contrast to be aware of prior reactions, be knowledgeable in reaction recognition and treatment, and have necessary medications and equipment readily available.

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