Frequency and Severity of Adverse Effects of Iodinated and Gadolinium Contrast Materials: Retrospective Review of 456,930 Doses

Christopher H. Hunt[1]
Robert P. Hartman
Gina K. Hesley

OBJECTIVE. The purpose of this study was to determine the frequency and characteristics of adverse effects of low-osmolar iodinated and gadolinium contrast agents in a single-center experience with a large number of cases.

MATERIALS AND METHODS. A retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium contrast materials administered from 2002 through 2006 was conducted. Adverse effects were identified through the use of radiologist and nurse event recording. Adverse effects were examined for type and severity of reaction, treatment required, and outcome.

RESULTS. A total of 456,930 contrast doses (298,491 low-osmolar iodinated, 158,439 gadolinium) were administered over the study period. A total of 522 cases of adverse effects (0.11% of total) were identified (458 low-osmolar iodinated, 64 gadolinium). The most common adverse effects were hives (274, 52.5%) and nausea (92, 17.6%). Of all adverse effects, 79 of low-osmolar iodinated and 15 of gadolinium contrast material necessitated treatment. Most treatments were performed in the radiology department alone. Only 16 cases of adverse effects necessitated transfer for further observation or treatment. Epinephrine was used to manage an adverse effect in nine instances. Thirty-two of the adverse effects of low-osmolar iodinated contrast material (6.9%) occurred in patients with a history of allergy who received premedication. Only two of these premedication reactions necessitated transfer to the emergency department. The one death in the study period occurred after administration of low-osmolar iodinated contrast material. The patient had no symptoms during the contrast administration or imaging but died suddenly within 30 minutes of receiving the dose.

CONCLUSION. Both iodinated and gadolinium contrast agents are associated with a very low rate of adverse effects. Most adverse effects are mild and can be managed in the radiology department. Transfer for additional treatment or observation is rarely needed.

Introduced in the 1920s, iodinated contrast agents have evolved into one of the most frequently administered IV medications in hospitals and outpatient facilities [1]. Revolutionizing radiologists' ability to differentiate soft-tissue densities, this advance has come with the added risk of adverse contrast effects. Although physiologic responses such as nausea and vomiting used to be ubiquitous with high-osmolar contrast agents, serious adverse effects were rare enough to allow widespread use. Immediate adverse effects of high-osmolar contrast media have been reported among 12.7% of patients [2]. With the advent of low-osmolar contrast material, this number has decreased to 3.1% of patients. Overall, mortality was estimated at one death per 100,000 examinations on the basis of findings from 1991 [2]. With the widespread use of low-osmolar agents, the incidence of adverse effects likely has changed, as have the features of these events.

With the introduction of gadolinium as a contrast agent for MRI, another source of contrast-related adverse effects was introduced [3–5]. In addition, patients with a history of reaction to an iodinated contrast agent appear to be at increased risk of gadolinium allergy. In the most extensive review of gadolinium reactions reported [6] as of this writing, four of 36 patients with gadolinium reactions also had an allergy to an iodinated contrast agent. The four patients were 80% of patients who needed treatment of an adverse effect. As a result, this patient population appears to be at greater risk, and better definition of the population and their reactions is warranted.

Keywords: contrast reactions, gadolinium, iodinated contrast

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[1]All authors: Department of Radiology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. Address correspondence to C. H. Hunt (hunt.christopher@mayo.edu).

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Contrast-related adverse effects, though rare, continue to pose a risk to patients. Although there has been an overall decrease in the percentage of patients who experience adverse effects, in part because of the advent of low-osmolar iodinated contrast material and use of premedication, risk continues to be associated with the use of low-osmolar iodinated and of gadolinium-based agents [7–14]. Although many studies have documented the risk of adverse effects of older high-osmolar iodinated contrast media, few studies have been conducted to examine the risk of low-osmolar iodinated contrast material. In addition, given the diverse techniques used, there is a need to examine the risk of acute adverse effects associated with use of IV gadolinium contrast media.

The findings in this study represent the sum of a 4-year experience with gadolinium and low-osmolar iodinated contrast agents at our institution. Because the study was performed at a single center, there are limitations to generalizing the results. Specifically, brands of contrast agents vary, as does the level of training in the management of contrast-related adverse effects by nursing staff, technologists, and radiologists. We believe the number of cases and length of this study make the findings useful in the modern age of low-osmolar iodinated and gadolinium contrast agents.

Materials and Methods

After receiving institutional review board approval, we performed a retrospective review of all cases of adverse effects of administration of low-osmolar iodinated and gadolinium contrast agents that occurred from 2002 to 2006. All IV doses administered in the outpatient, inpatient, and emergency departments of our tertiary referral center were included. Demographic data and information regarding the type of adverse effect, severity of the effect, treatment, and outcome were obtained from the clinical history, physician and nursing notes, and radiology report (Table 1). We included only acute adverse effects in this study. Adverse effect was defined as a reaction occurring in the radiology suite during contrast administration or within 30 minutes of administration. In our experience, delayed adverse effects (> 30 minutes after injection) are exceedingly rare and are usually self-limited. In addition, because of the nature of our database, incomplete capture of these events likely would have occurred, making estimation of their frequency unreliable.

We classified the severity of adverse effects according to guidelines in the American College of Radiology Manual on Contrast Media version 6.0 (2008, http://www.acr.org) as mild, moderate, or severe (Table 2). Although this system is a uniform way of comparing our results with those of other studies, it should be noted that nausea and vomiting are considered a mild effect in this classification. Although nausea and vomiting are recorded as an adverse effect for the purposes of our database, at our institution in the absence of other symptoms, nausea and vomiting would not be considered an anaphylactoid contrast reaction and would not preclude future administration of contrast media. Infiltration of the injection site and isolated effects on the extremity (e.g., coolness, local pain) at the injection site were not included.

TABLE 1: Demographic Characteristics of Patients with Contrast-Related Adverse Effects

Characteristic	Male	Female	Both Sexes
Agent			
Low-osmolar iodinated contrast material	178	280	458
Gadolinium contrast material	24	40	64
Total	202	320	522
Age (y)			
Mean ± SD	55 ± 18	51 ± 17	52 ± 17
Range	9–88	15–89	9–89
Average no. of medication allergies	1	1	1

Note—Fifteen patients had history of shellfish allergy.

Results

From 2002 to 2006, a total of 456,930 contrast doses were administered. Among these doses, 298,491 were of low-osmolar iodinated and 158,439 were of gadolinium contrast material. No high-osmolar iodinated contrast agents were used at our institution during this period. A total of 522 adverse effects were identified (0.114% of all doses). Four hundred fifty-eight of these adverse effects were associated with low-osmolar iodinated contrast material, for an adverse effect rate of 0.153% for these doses. Sixty-four adverse effects were reported with gadolinium contrast material (0.0404% of doses of these agents).

The overwhelming majority of adverse effects were mild, represented by nausea and vomiting and mild rash (Table 3). Most of the adverse effects, 91.9% associated with low-osmolar iodinated and 87.5% with gadolinium contrast material, were managed with observation or diphenhydramine. The need for more aggressive treatment, including transfer to an emergency department or administration of epinephrine, was rare. Seven patients who had a severe adverse effect after administration of low-osmolar iodinated contrast material needed epinephrine, constituting 1.5% of events related to these agents. Two patients who had a severe adverse effect after administration of gadolinium contrast material needed epinephrine, constituting 3.1% of all events related to these agents. Ten patients with adverse effects of low-osmolar iodinated and six patients with adverse effects of gadolinium contrast material, 2.2% and 9.4%, respectively, needed transfer to the emergency department (Table 4).

One death presumed caused by low-osmolar iodinated contrast material was reported at our institution from 2002 to 2006. The patient, a 79-year-old man, had no symptoms immediately after contrast administration and the imaging examination; however, while waiting for transport, he experienced sudden cardiovascular collapse, and attempts at resuscitation were unsuccessful. Although the contrast agent was not directly implicated in the death, because of the proxim-

TABLE 2: Classification of Severity of Adverse Effects

Severity	Effect
Mild	Nausea, vomiting
	Urticaria
Moderate	Symptomatic urticaria
	Mild bronchospasm
	Vasovagal reaction
	Tachycardia
	Diffuse erythema
Severe	Cardiovascular collapse
	Moderate or severe bronchospasm
	Laryngeal edema
	Loss of consciousness
	Seizure

TABLE 3: Severity of Adverse Effects of Contrast Agents

Severity	Low-Osmolar Iodinated (*n* = 458)	Gadolinium (*n* = 64)	Total (*n* = 522)
Mild	374 (81.6)	49 (76.6)	423 (81.0)
Moderate	69 (15.1)	11 (17.2)	80 (15.3)
Severe	15 (3.3)[a]	4 (6.3)	19 (3.6)

Note—Values are numbers of patients with percentage in parentheses.
[a]One death.

ity of the death to contrast administration (< 20 minutes), the patient was included in this study. Owing to this death, the mortality in our study was 0.00034% of doses of low-osmolar iodinated contrast material. No deaths were reported with the use of gadolinium contrast material.

Thirty-four patients who had an adverse effect of low-osmolar iodinated contrast material at our institution had a self-reported history of iodine allergy. Thirty-two of these patients (6.9% of the 458 with adverse effects of these agents) received steroid premedication, and 23 of the 32 (71.8%) had a mild adverse effect, seven (21.9%) a moderate adverse effect, and two (6.2%) a severe adverse effect that necessitated transfer. Two patients were not pretreated with any agent, and both had mild adverse effects that were managed with observation only.

Three patients who had an adverse effect of gadolinium contrast material had a history of reaction to contrast media. Two of these patients had a history of an adverse effect of iodinated contrast medium. One of these patients experienced symptomatic urticaria that necessitated treatment with diphenhydramine. The other had the severe adverse effect of laryngeal edema and needed transfer. Only one patient who had an adverse effect of gadolinium contrast material had a self-reported history of allergy to gadolinium contrast material. This patient had a mild adverse effect and was treated with observation only.

On average, the patients experiencing a contrast-related adverse effect reported only one previous medication allergy (range, 1–10). Only 15 patients (2.9%) experiencing an adverse effect had a reported history of shellfish allergy.

Discussion

Our adverse effect rate with low-osmolar iodinated contrast material was 0.153% among 298,491 doses, a significant decrease from the rate reported with high-osmolar iodinated contrast media. Most of these adverse effects were mild or moderate in severity and were managed with observation or diphenhydramine. The need for patient transfer or epinephrine administration was rare. All radiology physicians and nurses at our institution undergo specific, mandatory training in the management of contrast reactions. We believe this training enhances our ability to effectively manage adverse effects in the radiology suite and decreases the need for transfer.

The mortality in our study was 0.00034% for administration of low-osmolar iodinated contrast material. This rate is in keeping with the previously reported mortality associated with use of these agents [14]. Although this mortality is lower than with high-osmolar contrast media, risk still exists, even among patients without a history of contrast reactions. Although no deaths occurred in the gadolinium contrast material group in this study, given the low mortality due to adverse contrast effects, absence of risk should not be inferred.

Our adverse effect rate with gadolinium contrast material was 0.0404% among 158,439 doses, in keeping with the 0.0003–1.2% range reported in the literature [4, 5]. Although adverse effects due to gadolinium were less frequent than those due to low-osmolar iodinated contrast material, the events associated with gadolinium contrast material were more often deemed severe and necessitating treatment with epinephrine, transfer to the emergency department, or both.

Although it has been suggested [15] that certain demographic features, such as multiple medication allergies, are associated increased risk of adverse effects, our study did not confirm that supposition. Among our patients with adverse effects, the average number of medication allergies was one. In addition, only 15 of our patients (3.3%) with adverse effects of low-osmolar iodinated contrast material had a history of shellfish allergy. We believe this finding lends further evidence to the concept that a shellfish allergy constitutes no greater risk of reaction to low-osmolar iodinated contrast material than does any other food allergy. Although questions about food allergies remain a part of our routine preexamination screening, the utility of the answers appears severely limited.

Pretreatment with corticosteroids has been found to effectively decrease the incidence of serious adverse effects of contrast media [8, 9, 11]. Although corticosteroid pretreatment regimens vary at our institution, the most common regimen is 32 mg of methylprednisolone orally 12 and 2 hours before contrast administration. In addition, the clinician or radiologist may elect to administer 25 or 50 mg of diphenhydramine immediately before the examination. We have found this regimen effective, but as our data show, reactions to both low-osmolar iodinated and gadolinium contrast agents continue to occur in spite of pretreatment. Although most of the adverse effects of low-osmolar iodinated contrast material that occurred despite pretreatment were mild, moderate and severe adverse effects did occur at a rate sufficient to warrant both patient counseling and close observation in the radiology suite.

There were limitations to this study. First, the study was a retrospective review that required self-reporting by either the radiologist or a nurse. Although many departmental measures were taken to raise awareness about this reporting, there was inherent selection bias toward more accurate reporting of more severe events. In addition, information about subsequent adverse effects or previous contrast-related adverse effects at other institutions was

TABLE 4: Management of Adverse Effects of Contrast Agents

Treatment	Low-Osmolar Iodinated (*n* = 458)	Gadolinium (*n* = 64)	Total (*n* = 522)
Observation only	365 (79.7)	49 (76.6)	414 (79.3)
Diphenhydramine only	56 (12.2)	7 (10.9)	63 (12.1)
Additional medication	23 (5.0)	8 (12.5)	31 (5.9)
Received epinephrine	7 (1.5)	2 (3.1)	9 (1.7)
Transfer from radiology suite for care	10 (2.2)	6 (9.4)	16 (3.1)

Note—Values are numbers of patients with percentage in parentheses.

not available. We believe these limitations, although not insignificant, only minimally affected the results of the study and are inherent in most retrospective studies.

Although the advent of low-osmolar iodinated contrast material and use of pretreatment regimens have decreased the overall incidence of contrast-related adverse effects, these effects continue to occur. In this single-center retrospective study, we found the rate of adverse effects to be 0.1535% for low-osmolar iodinated and 0.0404% for gadolinium contrast doses. Although most of these adverse effects can be successfully managed in the radiology suite, many with observation alone, severe adverse effects can necessitate aggressive treatment and transfer for emergency care. Careful review of reporting and treatment protocols is necessary to prevent morbidity and mortality.

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