

Gender risk for anaphylactoid reaction to radiographic contrast media

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Background: Female predominance has been reported previously in series of anaphylaxis cases; however, no definite precedent has been established for greater risk of anaphylactoid reaction caused by contrast media infusion on the basis of gender.

Objective: This study was designed to determine whether greater risk for anaphylactoid reaction caused by intravenous contrast media infusion exists in association with female gender.

Methods: Rates of anaphylactoid and severe anaphylactoid reaction, according to gender, were determined in a sample of 5264 consecutive patients receiving conventional radiocontrast media during performance of computed tomography.

Results: Of 80 adverse reactions caused by contrast media infusion, 73 (1.39%) were classified as anaphylactoid in nature. Among 5191 patients who received intravenous contrast media without experiencing an anaphylactoid reaction, there were 2642 male patients (51%) and 2549 female patients (49%); reactors included 22 male patients and 51 female patients (odds ratio = 2.40, 95% confidence interval = 1.42 – 4.10, $p < 0.0005$). Female patients also comprised 21 of 22 cases of severe anaphylactoid reaction (odds ratio = 21.77, 95% confidence interval = 3.13 – 435.12, $p < 0.0005$).

Conclusion: Greater risk for anaphylactoid and severe anaphylactoid reaction exists in association with female gender. Further studies are needed to identify mechanisms that can explain this risk. The importance of these findings for cost-effective use of lower osmolality contrast media need to be determined. (*J ALLERGY CLIN IMMUNOL* 1995;95:813-7.)

Key words: Anaphylactoid reaction, anaphylaxis, female gender, radiographic contrast media

Radiocontrast media infusion is the most common cause of non-IgE-mediated anaphylaxis in the modern medical era.¹⁻³ Although risk reduction for adverse (including anaphylactoid and se-

Abbreviations used

CI: Confidence interval
OR: Odds ratio

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rious) reactions to contrast media can be achieved with use of lower osmolality contrast agents, increased cost associated with universal administration of these media would add 1.5 billion dollars or more to annual health care expenditures in the United States.²⁻⁴ Recent studies demonstrate that selective use of lower osmolality contrast media is an effective strategy,² with a calculated cost-utility ratio that compares favorably with other health care programs, such as screening and treatment for mild hypertension⁵; however, the "high risk" populations most appropriate for receiving these media are not clearly defined.

We have previously reported greater risk for anaphylactoid reaction caused by contrast media in association with asthma and with β -blocker expo-

sure.⁶ In addition, we have described greater risk for major and life-threatening reactions in persons with cardiovascular disorders (independent of asthma and β -blocker exposure) and greater risk for bronchospasm among patients with asthma and patients receiving β -blockers independent of underlying cardiovascular conditions.⁷ We also found an unexpected 2:1 ratio of female to male patients among reactors in both retrospective and concurrent case control studies. Because we did not tabulate the gender ratio of all patients who received contrast media without experiencing an anaphylactoid reaction, we were unable to validate the suggestion that gender can also influence likelihood of anaphylactoid reaction. To expand present knowledge regarding factors that may influence rate or severity of anaphylactoid reactions, we have retrospectively reviewed records to assign gender for all patients who received intravenous infusion of contrast media during our previously reported concurrent case-control study.⁷

METHODS

Adverse reactions were recorded in accordance with Quality Assurance guidelines. Reports describing adverse reactions during performance of computed tomography on a concurrent basis for a 6-month period were analyzed. Adverse reactions caused by contrast media were classified³ as anaphylactoid, vasovagal, or other (including hemodynamic) on the basis of clinical manifestations observed and recorded at the time of each reaction. An anaphylactoid reaction was defined as occurrence of one or more of the following within 20 minutes after infusion of contrast media: urticaria, angioedema, throat constriction or change in voice with or without stridor, chest tightness or wheezing with shortness of breath, hypotension (decline in systolic blood pressure of 30 mm Hg or more), syncope while in the supine position, and cardiac dysrhythmia or arrest associated with urticaria or angioedema. Anaphylactoid reactions were further classified as mild (reaction limited to urticaria or angioedema without need for treatment), moderate (reaction limited to urticaria or angioedema with need for treatment), or severe (throat constriction or stridor, bronchospasm, or hypotension); a subgroup of severe reactors who had major and life-threatening reactions (hypotension with or without need for subsequent hospitalization) was also identified. Vasovagal reactions were those characterized by symptoms such as nausea, emesis, flush, or generalized warmth. Other reactions included hemodynamic responses such as pulmonary edema or angina, nephrotoxicity, pain at injection site, anxiety, confusion, and various nonspecific responses.

A retrospective review of records maintained in the Department of Diagnostic Radiology at Henry Ford Hospital was carried out. Information obtained included documentation of contrast media infusion and agent

(conventional or low osmolality contrast media) administered, as well as gender, for all persons undergoing computed tomography procedures.

The magnitude of risk was calculated with the odds ratio (OR) and Cornfield's 95% confidence interval (CI).⁸ Significance of associations was computed with chi square analysis. A *p* value of less than 0.05 was accepted as statistically significant.

RESULTS

A sample of 5393 consecutive computed tomography procedures with contrast media infusion were studied; 5264 were carried out with conventional contrast agents. Of these 5264 infusions, adverse reactions were recorded in 80 cases, 73 (1.39%) of which were categorized as anaphylactoid. Mean age of reactors was 49.29 ± 17.6 years (mean age of male patients, 49.22 years; mean age of female patients, 49.32 years).

Of the 5191 patients who received conventional intravenous contrast media without experiencing an anaphylactoid reaction, there were 2642 male patients (51%) and 2549 female patients (49%). Among 73 reactors, there were 22 male patients (30%) and 51 female patients (70%), indicating statistically significant risk for anaphylactoid reaction in association with female gender (OR = 2.40, 95% CI = 1.42 – 4.10, *p* < 0.0005). Table I displays the distribution of women and men over four response categories. When associations between each level of severity and gender were examined, female patients had no statistically significant elevation in risk for mild or moderate anaphylactoid reaction. Of the 22 reactors (30.1%) who experienced severe anaphylactoid reactions, 11 had bronchospasm. Three of these 11 had asthma, and three others were receiving β -adrenergic blockers. With the exception of a 56-year-old asthmatic man who had a bronchospastic reaction, all others with severe anaphylactoid reactions were female patients (OR = 21.77, 95% CI = 3.13 – 435.12, *p* < 0.0005). A major and life-threatening reaction occurred in only one patient: a 61-year-old woman with angina pectoris undergoing computed tomography of the abdomen to rule out pancreatic carcinoma in whom tongue swelling, throat constriction, and hypotension (blood pressure = 50/0 mm Hg) developed. She required resuscitation with subcutaneous epinephrine; intravenous fluids, diphenhydramine, methylprednisolone; and subsequent hospitalization.

DISCUSSION

Although female predominance has been reported in several series of anaphylaxis cases,⁹⁻¹¹ no

TABLE I. Distribution and risk of anaphylactoid reaction according to gender by severity of reaction

Type of anaphylactoid reaction	Females (%)	Males (%)	OR	CI	p Value
None	2549 (98)	2642 (99.2)	1		
Mild	12 (0.46)	8 (0.30)	1.55	0.59–4.16	0.33
Moderate	18 (0.69)	13 (0.49)	1.44	0.67–3.11	0.32
Severe	21 (0.81)	1 (0.04)	21.77	3.13–435.12	<0.0005

definite precedent has been established for greater risk of anaphylactoid reactions caused by radiographic contrast media on the basis of gender.^{1,3} Our report demonstrates that female and male patients undergo computed tomography procedures in equal numbers but that female patients are at greater risk for anaphylactoid and severe anaphylactoid reactions. In a recently published survey of contrast media reactions in Japan, which included more than 337,000 contrast media exposures,¹² and in two prior multicenter surveillance studies,^{13,14} one of which included more than 112,000 contrast media exposures,¹⁴ greater risk for contrast media reaction among female patients was not found. However, cases with anaphylactoid reaction were not considered independently of other types of adverse reactions in these studies. Kalimo et al.,¹⁵ in the only previous study in which anaphylactoid reactions caused by intravenous contrast infusion were specifically evaluated for gender, reported statistically significant risk among female patients. In the context of these previous reports, our data imply that gender risk for anaphylactoid reaction caused by intravenous contrast infusion: (1) appears to be specific for anaphylactoid vis-a-vis hemodynamic, vasovagal, or other types of adverse reaction; and (2) is unlikely to be a reflection of gender bias in recording adverse reactions. The latter interpretation is also supported by the preponderance of women with severe anaphylactoid reactions, the manifestations of which are more overt and less subject to reporting bias.

Our findings indicate the actual risk for severe anaphylactoid reaction associated with female gender is most likely to be increased 21.77 times, but that with 95% certainty lies within a range of 3.13 to 435.12. The wide confidence limits observed reflect the small number of cases of severe anaphylactoid reactions available for analysis. Studies with larger numbers of reactors will be required to achieve a more precise estimate of this statistically and clinically significant risk. Although the risk estimate is unstable, even if a value at the lower

boundary of this range were true, this would still be regarded as clinically significant because it indicates that an increase of more than threefold for severe reaction associated with female gender exists. Moreover, because of the high prevalence of "exposure" (the proportion of patients receiving contrast media who are female is approximately 50%), the public health significance of this risk may be considerable. Statistically significant risk for mild and moderate anaphylactoid reaction was not found in our study. However, the point estimates indicate that an increase in risk of 55% and 44%, respectively, for female patients exists. The upper end of the CIs for each (4.16 and 3.11) is at a level that is clinically significant. Therefore these data do not permit a definitive determination as to whether gender risk also includes mild or moderate anaphylactoid reactions.

Whether gender risk observed in this study truly reflects risk among female patients or is a marker for another factor cannot be determined from our data. Although other confounders are possible, gender risk for anaphylactoid reaction may reflect the smaller average body size of women. In the United States the median weight for men aged 18 to 74 years is approximately 170 pounds, but the median weight for women in this age group is between 130 and 140 pounds.¹⁶ These data indicate that 50% of men, but only 17% of women, weigh 170 pounds or more. That a relatively higher per-kilogram contrast media exposure may pose greater risk is consistent with findings of Ansell et al.,¹³ who reported a significant association between dose of contrast medium and severe and fatal reactions. More frequent adverse reactions with increasing dose of medium per body weight was also observed by Ochsner and Calonje¹⁷ in an earlier study analyzing adequacy of roentgenographic opacification and risk for adverse reaction associated with performance of intravenous urography. These authors proposed an "ideal dose-weight relationship" to optimize efficiency and safety of intravenous contrast media infusion. Over the past 2 decades, the dose of contrast media

administered during radiology procedures has increased. As reviewed by Thrall,¹⁸ the influence that these greater volumes of contrast media may have on frequency of untoward reactions has not been studied in a systematic fashion. Administration of 150 ml (282 mg of iodine per milliliter) now occurs routinely during computed tomography, whereas contrast enhancement described in the series by Ansell et al.¹³ in 1980 consisted of only 70 ml (containing 300 mg of iodine per milliliter). Dosage of contrast media was not significantly associated with risk for serious or anaphylactoid reactions in a number of previous reports¹²; however, a cluster of reactors who received small amounts of contrast media, and in whom an infusion was aborted with onset of an untoward reaction, was typically encountered in such studies.¹³ More recent evidence indicates that smaller coronary artery size is disadvantageous for outcomes among women undergoing myocardial revascularization.¹⁹ Similarly, it is conceivable that reduced vascular size may predispose women to greater endothelial disruption resulting from intravenous contrast media infusion^{1, 3, 20} and promote greater risk for anaphylactoid reaction. An alternative interpretation of our data, that larger body size confers a protective advantage for men receiving intravenous contrast media infusion, merits consideration and further investigation.

Because only one case of hypotension occurred in our study, greater risk for major and life-threatening anaphylactoid reaction on the basis of gender cannot be evaluated from these data. This investigation focused on anaphylactoid reactions caused by infusion of intravenous contrast media; therefore, these findings cannot be applied to risk for anaphylactoid reaction from intraarterial contrast media infusion. Because only patients receiving conventional contrast agents were studied, whether gender risk also extends to lower osmolality contrast media or whether these newer agents can influence such risk cannot be determined from our data. Catamenial exacerbation of asthmatic and anaphylactic potential may exist^{21, 22}; however, we are unable to assess the potential importance of this factor. Frequency of asthma, β -blocker exposure, cardiovascular disorders, or other (putative) conditions associated with increased risk for anaphylactoid reactions^{3, 7, 18} was not tabulated among all persons receiving contrast media in our study. Because we are unable to determine the prevalence of such conditions among our consecutive sample of patients undergoing computed tomography procedures with contrast media, we cannot

exclude the influence of these factors on female gender as an independent risk factor for anaphylactoid and serious anaphylactoid reaction caused by contrast media infusion.

In conclusion, our findings demonstrate greater risk for anaphylactoid and severe anaphylactoid reaction caused by intravenous infusion of conventional contrast media in association with female gender. Further studies are indicated to identify mechanisms to explain this risk. The implications of these findings for cost-effective use of lower osmolality contrast media need to be determined.

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