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ORIGINAL RESEARCH ARTICLE

Adverse Reactions to Contrast Media: An Analysis of Spontaneous Reports in the Database of the Pharmacovigilance Programme of India

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Abstract

Background Contrast media are used widely to improve medical imaging. Like all other pharmaceuticals, these agents are not completely devoid of risk, and continuous monitoring of adverse reactions with these agents is important. Spontaneous reporting is the simplest method for understanding the safety profile of pharmaceutical products after their approval.

Objective Our objective was to identify the pattern and characteristics of adverse reactions attributed to contrast media in the Indian population reported to the National Coordination Centre for the Pharmacovigilance Programme of India (NCC-PvPI).

Methods Individual case safety reports (ICSRs) attributed to contrast media submitted spontaneously to the NCC-PvPI were extracted from the database for July 2010 to September 2013. We analysed these reports for information related to reporter's professional category, patient's age and sex, reporter's diagnosis of the reaction, seriousness of the reaction, type of contrast media exposure, system organ class (SOC) affected (as described in World Health Organization Adverse Reaction Terminology [WHO-ART]) and outcome.

Results Of the total 59,915 ICSRs in the database, 415 (0.7 %) were suspected adverse reactions to contrast media; 44 reports were serious, including three fatal cases. The most affected SOCs were skin and appendage disorders, body as a whole–general disorders, gastrointestinal system disorders and respiratory system disorders. Hypersensitivity reactions were reported in the majority of ICSRs. The contrast media with the highest number of reports were iohexol (40.7 %), iomeprol (17.8 %), iopamidol (12 %) and diatrizoate (12 %).

Conclusions Most of the reactions to contrast media were allergic-like, and no previously unrecognised adverse reactions were observed in the Indian population. Further data and increased awareness among healthcare professionals is required to signal and prevent the consequences of adverse reactions attributed to contrast media.

Key Points

Intensive monitoring of cardiac function is important while administrating contrast media

The paediatric population requires attention for serious contrast media adverse reactions

A greater proportion of reactions to low osmolar contrast media were hypersensitivity reactions compared with high osmolar and gadolinium-based contrast media

1 Background

Contrast media are used widely to improve medical imaging. Like all other pharmaceuticals, these agents are not completely devoid of risk. Contrast media-induced adverse reactions can be categorized into hypersensitivity (allergic-like) and physiologic (toxic) reactions. Hypersensitivity reactions can be further divided into acute (immediate) and delayed

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hypersensitivity reactions. An immediate (within 1 h of administration) hypersensitivity reaction can range from urticaria and angioedema to laryngeal oedema, hypotension and even death. Delayed hypersensitivity reactions to contrast media occur from 1 h to 1 week after administration and have mostly cutaneous manifestations. Toxic reactions are related to specific molecular attributes and represent a physiologic response to contrast media. [1–3]. Adverse reactions to contrast media are an important clinical problem and range from a mild inconvenience to life-threatening emergency or potentially fatal complications. Therefore, special attention is required to monitor these reactions. To safe-guard public health and assure medicine safety in India, the Ministry of Health and Family Welfare, Government of India, launched a nationwide Pharmacovigilance Programme of India (PvPI) in July 2010, with the All India Institute of Medical Sciences (AIIMS), New Delhi, as its National Coordination Centre (NCC). The NCC was shifted to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, in April 2011; it is responsible for monitoring adverse drug reactions (ADRs) observed in the Indian population and making recommendations to the Central Drug Standard Control Organisation (CDSCO) for regulatory interventions. There are 150 adverse drug monitoring centres (AMCs) under the PvPI throughout India. Each AMC sends individual case safety reports (ICSRs) received spontaneously at their centres to the NCC. Anyone in India can report ADR information to NCC. The reports from consumers and non-healthcare professionals are first validated by the healthcare professional and only after this validation will it be entered in the database. The NCC also participates in the World Health Organization (WHO) Programme for International Drug Monitoring and collects data through VigiFlow Software (a web-based ICSR management system) provided by the Uppsala Monitoring Centre, Sweden. The drugs in VigiFlow are codified according to anatomical therapeutic chemical (ATC) classification [4], while adverse reactions and system organ classes (SOCs) are codified according to the WHO adverse reaction terminology (WHO-ART) [5]. The NCC database contains ICSRs for a wide range of pharmaceutical products, including drugs, vaccines, blood products and contrast media. To our knowledge, only one study has been conducted in India to determine the epidemiological characteristics and clinical presentation of adverse reactions with contrast media specific to the Indian population [6]. Hence, the present study analysed the pattern and characteristics of adverse reactions with contrast media recently observed in the Indian population.

2 Methods

All the ICSRs received by the NCC-PvPI from July 2010 to September 2013 were selected. The ICSRs involving contrast media as either a suspected or concomitant medication were searched by their ATC code (ATC code for contrast media: V08) and extracted from the NCC database for this period. The extracted reports were examined for the following information: reporter's professional category; patient's age and sex; reporter's diagnosis or description of the reaction; type of contrast media exposure, including indication, duration of treatment and dosage; SOC affected; outcome; causality assessment; and, where recorded, concomitant therapies. We manually searched for duplicate reports by first cross-checking patient's initials, age, sex and source of the report. If all these details were found to be the same, the reports were further investigated for other information, such as reaction term and suspected contrast media; the duplicate reports were then excluded. Adverse reactions were also classified as 'serious' or 'not serious' events in accordance with the International Conference on Harmonization E2D guidelines [7]. According to these criteria, serious reactions include those that are fatal, life-threatening, disabling or incapacitating, causing or prolonging hospitalisation, causing congenital abnormalities or medically important on the basis of clinical judgement. The WHO causality assessment tool was used in the reported ICSRs to establish the relationship between the suspect drug and suspected adverse reaction [8]. Outcomes were evaluated with respect to four different categories: patient recovered, patient recovering, patient not recovered and death at the time of reporting. Depending on the reaction features in each case report, the contrast media ADRs were classified into hypersensitivity and physiologic contrast media reactions. Hypersensitivity reactions were further classified into acute reactions (which occurred within 1 h after contrast media administration) and delayed reactions (which become apparent more than 1 h after contrast media exposure) [1–3, 9]. We used the anaphylactic reaction classification by Ring and Behrendt [10] to assess the acute reactions according to four grades of severity of clinical symptoms. Delayed reactions were classified as mild, moderate or severe, as suggested by Thomsen and Morcos [11].

3 Results

A total of 59,915 ICSRs were received from July 2010 to September 2013, of which 415 (0.7 %) were for contrast media. No duplicates were detected. All these reports had contrast media as the suspect medication, and no single report with a contrast medium as a concomitant drug was observed. The 415 ICSRs included 441 adverse reaction terms. Serious adverse reactions to contrast media accounted for 11 % of the total cases (44 of 415). Indications reported for contrast media administration were computerized tomography (31), urography (five), coronary angiography (four) and magnetic resonance imaging (one). In the remaining reports, the indication was not specified.

Dosage information was available for 93 % of reports and in all cases doses were within the recommended ranges in the summary of product characteristics.

The only source of contrast media reports received at the NCC was the AMCs under the PvPI, and all these reports were filled by physicians. Analysing by outcome, 357 cases experienced complete recovery, 12 cases were still recovering, one patient had not recovered and three patients had fatal outcomes at the time of reporting; outcome was missing in the remaining reports. After applying the WHO criteria for causality assessment, the adverse reactions were classified as 'certainly' and 'probably or possibly' related to contrast media in 9,281 and 151 cases, respectively. However, it should be noted that few reports listed concomitant medicines, and other reports may or may not have concomitant medicines. In our data for concomitant drug, 'none' represents that information was not provided.

3.1 Characteristics of Patients

In the 413 reports in which sex was recorded, 230 patients were males and 183 females. (sex was not indicated in the report for two patients). The mean age of these patients was 43.9 (standard deviation [SD] ± 15) years, and median age was 45 years. Figure 1 shows the age distribution of the patients.

Subgroup analysis of the case reports showed the same pattern of adverse events related to age when considering 10-year intervals although there was a slight predominance of patients aged between 50 and 59 years (24 %).

With regard to the seriousness of the adverse reactions, no sex difference was observed (female: male ratio 1.1:1). However, a higher proportion of paediatric patients (0–11 years) were affected by serious adverse reactions compared with other age groups (Table 1).

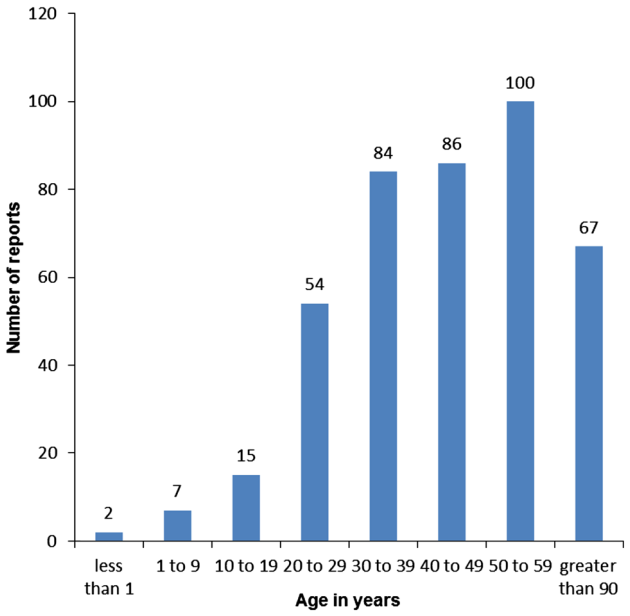

Fig. 1 Age wise distribution of reports

Table 1 Percentage of serious adverse reaction reports with contrast media according to sex and age distribution

	Serious adverse reactions reports	Total contrast media reports	% Serious
Total reports	44	415	11
Sex			
Males	23	230	10
Females	21	183	11
Age (years)			
0–11 (paediatric)	4	11	36
12–18 (adolescent)	0	10	0
19–60 (adults)	34	327	10
≥60 (elderly)	6	67	9

Table 2 Percentage of contrast media adverse reaction reports according to system organ class affected from July 2010 to September 2013

System organ class	No. of reports	% of reports
Skin and appendages disorders	285	68.7
Body as a whole—general disorders	64	15.4
Gastrointestinal system disorders	48	11.6
Respiratory system disorders	15	3.6
Central and peripheral nervous system disorders	8	1.9
Heart rate and rhythm disorders	6	1.4
Cardiovascular disorders, general	5	1.2
Urinary system disorders	5	1.2
Application site disorders	1	0.2
Platelet, bleeding and clotting disorders	1	0.2
Special senses other, disorders	1	0.2
Vascular (extracardiac) disorders	1	0.2
White cell and reticuloendothelial system disorders	1	0.2

3.2 Types of Adverse Reactions by System Organ Class

The 415 reports included 441 different adverse reactions (Table 2). The most frequently reported reactions were rash, urticaria, allergic reaction, vomiting, pruritus, rash purpuric, rigors, nausea and anaphylactic reaction. The SOCs most affected were skin and appendages (285), body as a whole (64), gastrointestinal system (48) and respiratory system (15).

3.3 Hypersensitivity and Physiologic Contrast Media Reactions

Of the ICSRs, 351 were associated with hypersensitivity reactions and the remaining 64 were classified as physiologic

Table 3 Fatal adverse reaction reports associated with contrast media

Parameter	Case 1	Case 2	Case 3
Contrast media	Iodixanol	Iopamidol	Iomeprol
Age	9 months	50 years	74 years
Sex	Male	Male	Male
Adverse reaction	Death	Cardiac arrest	Cardiac arrest
Death cause	Cardiac arrest	Cardiac arrest	Cardiac arrest
Indication for contrast media	Brain MRI	Abdomen CT scan	CT angiography
Concomitant drugs	None	Pancuronium bromide 2 mg	None
Co-morbid conditions	Hepatomegaly	Patient had no cardiac problem	Patient had a pacemaker

CT computed tomography, *MRI* magnetic resonance imaging

reactions. For hypersensitivity reactions, 234 (66.7 %) reports were associated with acute hypersensitivity, four (1.1 %) with delayed hypersensitivity; the remaining 113 (32.2 %) reports did not mention the time taken for the reaction to occur. The symptoms of hypersensitivity reactions were predominantly rash, urticaria and pruritus and principally involved the skin. No sex difference was observed among these reports. On the basis of the Ring and Behrendt classification of anaphylactic reactions, the severity scoring of immediate hypersensitivity reactions was 'grade I' in 223 cases, 'grade II' in two cases, 'grade III' in five cases and 'grade IV' in four cases. As per the Thomsen and Morcos classification, all four cases of delayed hypersensitivity reactions were mild.

The physiologic contrast media reactions mainly involved the gastrointestinal system (with symptoms such as nausea, vomiting, loss of taste and dry mouth), the central and peripheral nervous system (dizziness) and the cardiovascular system (hypertension).

3.4 Serious Contrast Media Reactions

Using the criteria defined in the "Methods", 44 reactions were classified as serious; three patients died (Table 3); ten experienced life-threatening events (Table 4) and 19 were hospitalised. The remaining 12 were considered serious, as they were considered to be medically important conditions.

3.5 Contrast Agents Reported

The NCC database contains reports for low- and high-osmolality iodinated contrast media, gadolinium-based contrast media and iodized oil contrast media. Table 5 shows their distribution and Table 6 shows the proportion of hypersensitivity, serious, fatal and life-threatening reactions among these categories of contrast media. The contrast agents iohexol (40.7 %), iomeprol (17.8 %), iopamidol (12 %) and diatrizoate (12 %) had the greatest number of reports.

A greater proportion of reports for low-osmolar contrast media (LOCM) were for hypersensitivity reactions. Conversely, a greater proportion of reports for high-osmolar contrast media (HOCM) and gadolinium-based contrast media were physiologic, and reports for these agents were also more often serious, although all the fatalities were associated with LOCM.

4 Discussion

Contrast media are among the most commonly used diagnostic agents. Present-day radiologic imaging would be lacking without these agents. Although contrast agents are widely used, with safe outcomes and little or no side effects, adverse reactions nonetheless occur. Therefore, there is a need to collect information on the adverse events following administration of contrast media. The data represented in the present study were all collected via a spontaneous reporting system. It is therefore important to consider that variations in reporting with age, sex and type of contrast medium may reflect prescribing patterns rather than a difference between groups in their likelihood of developing an adverse reaction. Nevertheless there are some similarities with data from larger studies.

In our study, a small number of adverse reactions due to contrast media have been reported to NCC-PvPI as compared with available epidemiological data [12–15]. In a large prospective study in Japan, Katayama et al. [12] reported that the incidence of severe and life-threatening reactions was higher after intravascular administration of ionic HOCM than non-ionic LOCM. However, no difference was observed in the incidence of fatal reactions to both types of contrast media, with only one fatality in each group of over 160,000 patients [12]. Analysis of safety reports received by the US FDA from 1990 to 1994, together with manufacturer's exposure data, showed similar observations when comparing HOCM with non-ionic LOCM with respect to severe reactions (37.4 vs. 10.6 per million exposures) [13]. Furthermore, the reporting rate for fatal reactions was higher with HOCM than with LOCM (3.9 vs. 2.1 per million exposures) [13]. As a percentage of total reports, renal failure was reported more often with

Table 4 Life-threatening adverse reaction reports associated with contrast media

Case	Contrast media	Age (years)	Sex	Adverse reaction	Concomitant drugs	Outcome
1	Diatrizoate sodium	60	Male	Bronchospasm	None	Unknown
2	Diatrizoate sodium	60	Male	Bronchospasm	None	Unknown
3	Diatrizoate sodium	45	Male	Nephropathy tubular	None	Recovered
4	Iohexol	47	Female	Allergic reaction	None	Recovered
5	Iohexol	33	Female	Allergic reaction	None	Recovered
6	Iohexol	56	Male	Hypersensitivity	None	Recovered
7	Iopamidol	39	Male	Anaphylaxis	None	Recovered
8	Iopamidol	45	Female	Anaphylactic shock	None	Recovered
9	Iopamidol	34	Male	Anaphylactic shock	None	Recovered
10	Gadolinium	2.5	Female	Laryngospasm	None	Recovered

Table 5 Individual contrast media involved in adverse reactions

Type of contrast media	Agent	No. of reports	Percentage of all contrast media reports
Iodinated contrast agent			
High osmolality, ionic	Diatrizoate	50	12.0
	Iothalmate	1	0.2
Low osmolality, ionic	Ioxaglate	6	1.4
Low osmolality, non-ionic	Iobitridol	33	7.9
	Iodixanol	11	2.6
	Iohexol	169	40.7
	Iomeprol	74	17.8
	Ioversol	3	0.7
	Iopromide	5	1.2
	Iopamidol	50	12.0
Iodized oil-based contrast agent	Iodized oil	1	0.2
Gadolinium-based contrast agent			
Ionic	Gadopentetate	3	0.7
	Gadoterate	3	0.7
	Gadolinium	2	0.4
Non-ionic	Gadodiamide	4	0.9

LOCM (2.3 %) than with HOCM (0.6 %) and usually occurred in cardiac patients, as was the case in the one report of a serious renal reaction in our study [13]. Interestingly, when HOCM were compared with ioxaglate (an ionic LOCM), the incidence of severe reactions was almost the same and the incidence of fatal reactions was lower [13]. However, one cohort study of over 90,000 patients found that mild and moderate reactions occurred more often with HOCM than with LOCM, and no significant difference in the number of severe reactions was reported, although those with LOCM were more likely to be physiologic [14]. Two fatal cases were reported with non-ionic and no fatal cases reported for ionic media in this study (difference not significant) [14]. The study noted that the overall rate of adverse reactions fell as the range of contrast agents increased to allow selective use. Although these studies were published one and two decades ago, the contrast media used were largely similar to those in our study. However, caution must be taken, as these studies compare the incidence of reactions and our analysis shows the proportion of reports in the NCC database. Nonetheless, a pattern or type of adverse reaction to contrast media can still be compared. Our study shows a higher proportion of serious and life-threatening reactions with HOCM than with LOCM, which is similar to the first two studies mentioned above. In our study, the proportion of serious and life-threatening reactions with gadolinium-based contrast media was similar to that with HOCM and lower than with LOCM. Since gadolinium-based contrast media are chemically different from HOCM and LOCM, a separate investigation is important for the future. Three fatal cases are recorded in the NCC database, for which non-ionic LOCM was the suspect drug; no fatal

Table 6 Proportion of hypersensitivity, serious, fatal and life-threatening reaction reports in the database for different categories of contrast media

Contrast media	Hypersensitivity reaction		Serious reaction		Fatal reaction		Life-threatening reaction	
	No. of reports	Proportion of reports	No. of reports	Proportion of reports	No. of reports	Proportion of reports	No. of reports	Proportion of reports
HOCM	25	49.02	8	15.69	0	0	3	5.88
LOCM ionic	5	83.33	0	0	0	0	0	0
LOCM non-ionic	314	90.75	34	9.83	3	0.87	6	1.73
Gadolinium based	7	58.33	2	16.67	0	0	1	8.33

HOCM high-osmolar contrast media, *LOCM* low-osmolar contrast media

cases were reported with HOCM and gadolinium-based contrast media. The number of fatalities is very small, so this observation may just reflect greater usage of non-ionic LOCM, and comparison with exposure data would be useful. In line with published literature, most of the reactions associated with contrast media reported to the NCC were hypersensitivity reactions occurring unpredictably [11–15]. The exact mechanism of these reactions is unclear but literature suggests release of vasoactive substances such as histamine and serotonin and the activation of a physiologic cascade and, eventually, the complement system. In some cases, an immunoglobulin E (IgE)-mediated mechanism is also responsible, especially with severe immediate hypersensitivity reactions. Most of the contrast media-induced non-immediate skin eruptions appear to be T-cell-mediated allergic reactions [3, 9, 16–18]. The clinical manifestations of allergic-like reactions are skin rash, itching, pruritus, dermatitis, facial or laryngeal oedema, bronchospasm, dyspnoea, pulmonary oedema, hypotension, life-threatening arrhythmias, cardiac arrest and death [3, 19, 20]. In our database, anaphylactic manifestations (hypersensitivity reactions) occur in a higher proportion of reported reactions, with non-ionic LOCM as compared with HOCM, which is not in line with the other epidemiological and spontaneous reporting studies [13, 15, 21]. In addition to this, dyspnoea is reported to occur with approximately equal incidence for the two classes of contrast media but less commonly with ioxaglate [13], but no such difference was observed in our data. For gadolinium-based contrast media, the proportion of anaphylactic reactions is lower than with LOCM but higher than with HOCM.

The NCC database contains a small number of reports associated with non-anaphylactic or toxic reactions to contrast media. These reactions are believed to result from a disturbance of homeostasis and mostly affect the cardiovascular, urinary, gastrointestinal and nervous systems [16]. The toxic reactions mainly reported were nausea, vomiting, abdominal pain, taste loss, dizziness and hypertension. Iodinated contrast media are known to be toxic to the kidneys and kidney function. The exact pathophysiology is not clear, but factors that have been suggested include renal hemodynamic changes (vasoconstriction), and direct tubular toxicity [9, 16]. The NCC received two reports of nephropathy after contrast media administration (one each for diatrizoate and iohexol). Further data and investigations are required to draw conclusions on contrast media-induced nephrotoxicity occurring in India. In our database of 59,915 ICSRs, the number of adverse reaction reports for males exceeds that for females and so it is possible that the predominance of male reports for contrast media is due to a reporting pattern rather than a real difference in risk. Some studies have shown that females are at greater risk of developing severe anaphylactic reactions [22, 23]. According to the Japanese report by Katayama et al. [12] and an Italian report by Cutroneo et al. [15], no significance difference regarding acute reactions between men and women exposed to contrast media has been observed. In particular, females were shown to be at risk for delayed reactions [17]. No such difference in the number of reports for these types of reactions was found in the NCC database, and data on total exposure to contrast media are required to evaluate such a difference. The impact of sex on fatality is not well studied, but the US FDA database showed that male patient deaths exceeded those of females by a ratio of 1:2 [13]. All three of the fatal reports in the NCC database were associated with males, and no such ratio could be evaluated. However, it is important to note that for all three fatalities, cardiac arrest was the cause of death, and only one patient had a previous cardiac complication.

Studies have shown that elderly patients are more prone to serious reactions with contrast media [6, 15, 24]. Other studies have shown that the incidence of reactions due to contrast media is relatively high in the third and fourth decades of life [6, 12, 25]. In the NCC database, we found a prominence of age group 50–59 years for overall reported reactions with contrast media, followed by similar numbers of reports for age groups 30–39 and 40–49 years. When considering serious reactions to contrast media, paediatric patients are prominent in the percentage of serious reports to total reports. The numbers are small, but this group clearly need to be closely monitored for risk factors.

Race could also be a predisposing factor for contrast media-induced adverse reactions. Incidence of contrast reactions amongst patients of Indian origin and patients of Mediterranean origin in the UK was significantly higher than that in the indigenous White population [26]. On other hand, Shehadi and Toniolo [25] found a similar incidence of reactions in all countries. An Indian study found the incidence of contrast media-induced mild reactions in Indians to be high compared with studies conducted on White populations in the Western world; the incidence of moderate and severe reactions was no higher [6]. There is no clear explanation for the racial differences in the incidence of contrast reactions. Other important risk factors for serious reactions to contrast media are previous history of contrast media reactions, asthma and specific allergies.

Spontaneous reporting databases contain heterogeneous data from a range of sources, and analysis of the databases is constrained by under-reporting, biased reporting and lack of denominator data. Nevertheless, not only can the databases signal previously unrecognised adverse reactions but they can also alert us to serious known reactions. From our analysis, it is clear that paediatric case reports need to be closely monitored. In addition, our reports of serious and fatal reactions suggest that it would be useful to ascertain whether radiology centres throughout India give prophylaxis to patients at increased risk for contrast media allergic reactions and take measures to reduce the risk of arrhythmias, as there was nothing in the reports to indicate whether such measures had been taken.

5 Conclusion

The characteristics of adverse reactions for all contrast media in the Indian population are similar to those reported in other counties. The paediatric population requires attention for serious contrast media adverse reactions. The impact of sex and aging on these reactions needs further evaluation. Most of the reactions in the NCC database due to contrast media were allergic-like, and no previously unknown reactions were observed. Hypersensitivity was reported in a greater proportion of LOCM reports compared with the other contrast media groups. The fatal reports emphasise the need for intensive monitoring of cardiac function when administering contrast media. Further, more robust data are required to draft guidelines on use and selection of contrast media specific to patients in the Indian population. Radiological contrast media are frequently used and are safe for most patients. Increased awareness among healthcare professionals is also required to signal and prevent, where possible, the consequences of adverse reactions induced by contrast media.

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