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Original Research Article

A Retrospective study of contrast media related adverse drug reactions at tertiary hospital in South India

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ABSTRACT

Background: Adverse drug reaction not only occurs with curative, preventive and palliative drugs but also with diagnostic tools like radio contrast agents which are used for enhancement of images. Timely and incessant reporting of adverse drug reaction with various agents is necessary to reduce the incidence. The study aims to find out the trend of contrast media related adverse drug reactions from 2016 to 2021.

Materials and Methods: A retrospective observational study was conducted on adverse drug reactions reported to the adverse drug reaction monitoring centre at tertiary care hospital in South India. All the adverse drug reactions related to various contrast agents used in computed tomography and magnetic resonance imaging were recorded. Patients' demographic details, individual contrast agent, clinical manifestations of reactions, severity, causality were mentioned in descriptive statistics.

Results: A total of 218 (16%) adverse drug reaction were reported due to various contrast media including non-ionic iodinated and gadolinium-based agents. The incidence of adverse drug reactions with radio contrast agents varies between 0.23% - 0.35%. 89% of symptoms were itching and rashes. Using the WHO-UMC (Uppsala monitoring centre) causality assessment scale, 87% of adverse drug reactions were categorized as 'probable'.

Conclusion: Unavoidable and untoward reactions can happen in any patient with any contrast agent. With the introduction of newer agents for last six years reactions continue to occur in same proportion. There is no culprit agent, but being 'vigilante' on reactions and timely reporting is necessary.

1. Introduction

Contrast media (CM) are pharmacological agents frequently injected into the human body as part of various radiological investigations. With increase in number of patients undergoing computed tomography (CT) or magnetic resonance imaging (MRI), one should be aware of the various CM-related adverse events (AEs) and their management. The Haschek and Lindenthal, in 1896 recorded the use of contrast agents for the first time. They used elements like bismuth, lead, barium salts for the angiography of an amputated hand.[1] Discovery of iodine as a radio-opaque dye was serendipitous. The urine of patients treated for syphilis with iodine containing compounds were radio-opaque. Later strontium bromide and sodium iodide were introduced but, high toxicity of these agents limited them.[2] Triiodinated benzoic acid salts were introduced in 1950s with least toxic potential, but hyperosmolarity and ionic nature leads to hypotension, cardiac arrhythmias and fluid overload.[3] Now a days non-ionic iodine containing

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contrast agents are being used in CT procedures.

Gadolinium (Gd^{3+}) compounds are now commonly used in magnetic resonance imaging (MRI) procedures. Before the successful introduction of gadolinium ions, paramagnetic ion complexes of copper (Cu^{2+}), chromium (Cr^{3+}), iron (Fe^{3+}) and manganese (Mn^{2+}) were investigated. Weinmann et. al. German based research group noted the safety and effective T1 relaxivity with gadolinium compounds and led to the development of gadopentetate dimeglumine.[4] Pharmacokinetic properties of iodine and gadolinium follows a biphasic profile i.e.; they quickly diffuse into interstitial space from the plasma. Therefore, they have a short plasma half-life (2-30min) and longer interstitial half-life (1-2hours). Iodine contrast agents and gadolinium compounds are not metabolised and are excreted unchanged via glomerular filtration.[5]

Although safer radio contrast agents were now being widely used, the physicians and radiologists must be prepared for the adverse reactions ranging from mild immediate hypersensitivity reactions to anaphylaxis. These agents can not only alter normal physiology but can modulate immune response, and can interact with many diseases or drugs. Here comes the importance of pharmacovigilance which means being 'vigilante' on science and activities related to the detection, assessment and prevention of adverse effects related to drugs, vaccines, blood products etc.[6] A drug or vaccine is approved only after vigorous safety and efficacy evaluation during clinical trials, but side effects may emerge while being used by heterogenous group of people with concomitant comorbidities and on multiple drugs. Therefore, reporting an adverse drug reaction is a necessity to extend the adverse drug reaction profile and to ensure safety of the public. So, the present study is required to know the various contrast media (CM) related adverse drug reactions (CM-ADRs).

2. Materials and Methods

A retrospective observational study was conducted from August 2021 to December 2021 in the Department of Pharmacology, ADR monitoring centre in collaboration department of Radiology. Study was conducted in a 1300-bedded super-specialty tertiary care health centre with an attached medical college hospital in south India. This being an eminent institution receives a plenty of referrals from the state as well as from the surrounding states. Since October 2021, it has upgraded to Regional Training Centre under Indian Pharmacopeia Commission, Ghaziabad.

Study was initiated from the approval from institutional ethical committee. Permission to access the ADR data was obtained from Pharmacovigilance Program of India. All the ADR reported during the study period, from January 2016 to December 2021 was screened. Later all the Radiocontrast related adverse drug reactions which were spontaneously reported to the ADR monitoring centre was taken physical ADR reporting form. As this was a secondary data, patient informed consent was not necessary. Patient demographic details, history of clinical symptoms, history of past illnesses, contrast agent (brand name and batch number), route of administration, dose given, severity of ADR symptoms (based on Hartwig's Severity assessment scale), causality (based on WHO causality assessment scale) and reporter of this event etc were taken from the physical ADR forms and added into Microsoft excel version 2019.

Hartwig's severity scale graded the severity as mild, moderate and severe, based on clinical presentation and management. Mild-Level 1 includes no change in treatment. Mild-Level 2 includes withdrawal of suspected drug and no other treatment given for ADR. Moderate-Level 3 includes addition of specific treatment/ antidote for the suspected drug. Moderate-Level 4 includes any admission related to the suspected ADR. Severe-Level 5 is that one requires intensive care treatment. Severe-Level 6 and Severe-Level 7 are those causing permanent harm and indirectly/directly causing death of the patient respectively.

WHO causality assessment scales were used and categorised the ADRs accordingly. It was termed 'Certain' when all the criteria like – 1. Event or laboratory test abnormality, with plausible time relationship to drug intake, 2. Cannot be explained by disease or other drugs, 3. Response to withdrawal plausible (pharmacologically, pathologically), 4. Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon), 5. Rechallenge satisfactory, if necessary.

The ADR will be a 'probable', when following criteria are satisfied: 1. Event or laboratory test abnormality, with reasonable time relationship to drug intake, 2. Unlikely to be attributed to disease or other drugs, 3. Response to withdrawal clinically reasonable, 4. Rechallenge not required. ADR will be 'Possible', when these are satisfied: 1. Event or laboratory test abnormality, with reasonable time relationship to drug intake, 2. Could also be explained by disease or other drugs, 3. Information on drug withdrawal may be lacking or unclear. 'Unlikely': 1. Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). 2. Disease or other drugs provide plausible explanations. 'Conditional/Unclassified': 1. Event or laboratory test abnormality, 2. More data for proper assessment needed, or Additional data under examination. 'Un-assessable/Unclassifiable': 1. Report suggesting an adverse reaction, 2. Cannot be judged because information is insufficient or contradictory, 3. Data cannot be supplemented or verified.

The minimum sample size was calculated from earlier publication with 10% allowable error and 95% confidence was 64.[7] But the study has included all the contrast agents related ADRs reported during the study period. The

proportions were stated in descriptive statistics and strength of association was analysed using Pearson chi-square test methods using IBM SPSS Statistics 18.0 software (IBMCo., Armonk, NY).

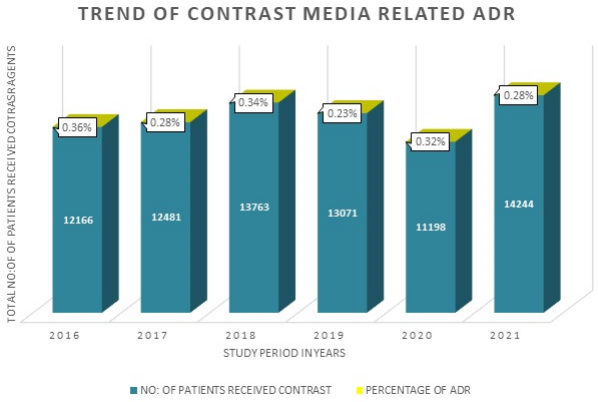

Fig. 1: Bar diagram showing the percentage of radio contrast induced ADRs

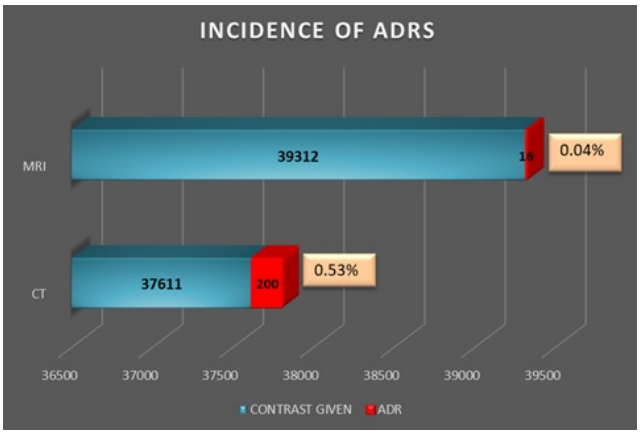

Fig. 2: Incidence of ADRs related to contrast agents used in CT and MRI

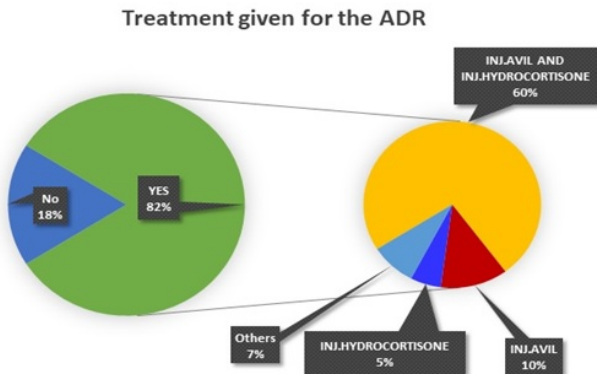

Fig. 3: Adverse drug reaction management

3. Results

We have screened a 1360 ADR forms and found out 218 (16%) were related to various contrast agents. Among the 218 ADR, 200 (91.8%) were due to various contrast agents used in CT procedures (Table 1). Gadolinium compound related ADR were seen in 16 (7.3%) of patients (Table 2). Fluorescein sodium which is contrast medium used during Fundus fluorescein angiography (FFA) has also reported ADR in 2 (0.9%) patients. 54.1% (n=218) were males and mean age of the patients was 48.6 years. Each year the Radiology department has approximately 10,000 and above procedures will be using various contrast agents for CT and MRI. The patients will be observed during and after the contrast administration for half an hour. Any symptoms onset during this period was considered as an adverse drug reaction due to the dye and therefore reported. Each year the incidence of ADR pertinent to CT and MRI contrast media varies between 0.23% - 0.35% (Figure 1).

During our study period, 37611 patients received iodinated radiocontrast agents for various CT procedures and of which 200 (0.53%) patients developed reactions (Figure 2). Patients received any of non-ionic iodinated radio contrast agent mentioned in Table 1. 39312 patients received gadolinium compounds for MRI investigations and adverse reactions were seen in 16 (0.04%) patients. Number of ADRs varies with each agent. The macrocyclic agent, Gadoterate meglumine related ADR was reported in one of the patients (Table 2).

Itching and rashes were reported in 89% (n=218) patients. The most common site was head and neck region (44%, n=193). 18.7% (n=193) patients had generalised urticaria and pruritus. Swelling around the eyes and lips were noted in 2.6% (n=193) patients (Table 3). 137 (62.8%, n=218) patients developed symptoms within the first few minutes and lasted for 2 hours. 74(33.9%, n=218) patients had symptoms lasted for 6 hours. Only 2(<1%, n=218) of them had severe symptoms and admitted for more than 24 hours.

Severity was graded according to the Hartwig et al scale for adverse drug reactions. Mild-Level 2 are those requires the withholding of suspected drug or otherwise changed. There was no treatment or antidote given for the suspected ADR. We had 39 (17.9%, n=218) ADRs categorizing as mild self-limiting. The suspected drug to be withheld, discontinued or otherwise changed and/or an antidote or symptomatic treatment was given without hospital admission was considered as Moderate-Level 3. So, in this study we had 169 (77.5%, n=218) reactions categorised under Level 3. Antihistamines with or without steroids were given for immediate cutaneous reactions. Other symptoms like nausea and vomiting were managed with intravenous proton pump inhibitors. We had 8 (3.7%, n=218) patients had breathlessness or gastrointestinal upset and/or giddiness along with hyper sensitivity reactions and were admitted

Table 1: Adverse drug reactions reported due to iodinated radio contrast agents in CT

Chemical structure	Radio contrast agent	Brand name	No of reported CM ADR (N=218)
Non-ionic	Iodixanol	Dimer / Iso-osmolar Visipaque (GE Healthcare, US)	11 (5.0%)
	Iohexol	Monomer / Low - osmolar Omnipaque (GE Healthcare, US)	106 (48.6%)
	Iopromide	Ultravist (Bayer Healthcare, US)	37 (17%)
	Iopamidol	K-scan (Trivitron Healthcare, India)	26 (11.9%)
	Iobitridol	Xenetix (Guerbet, France)	21 (9.6%)

CM ADR- Contrast Media Adverse Drug Reaction, GE Healthcare, US – General Electric Healthcare, United States

Table 2: Adverse drug reactions reported due to gadolinium compounds

Chemical structure		Brand name	No of reported CM ADR (N=218)
Linear	Gadodiamide	Non-ionic Omniscan (0.5mmol/mL) (GE Healthcare, US	7 (3.2%)
	Gadapentetate dimeglumine	Ionic Magnevist (0.5mmol/mL) (Bayer Healthcare, US)	7 (3.2%)
Macrocyclic	Gadoterate meglumine	Ionic Clariscan (0.5mmol/mL) (GE Healthcare, US)	1 (0.5%)

CM ADR- Contrast Media Adverse Drug Reaction, GE Healthcare, US – General Electric Healthcare, United States

Table 3: Clinical manifestations and organ system involvement of adverse drug reactions

Clinical manifestations	Organ system/ systems involved	No: of patients (percentage) N=218
Itching and/or rashes with or without swelling around eyes and/or around lips	Dermatological alone	193 (89%)
Itching and/or rashes, swelling around eyes and/or around lips with any gastrointestinal symptoms	Dermatological with GIT	9 (4%)
Any gastrointestinal symptoms (nausea/vomiting/abdominal pain/diarrhoea)	Gastro intestinal alone	5 (2%)
Breathlessness	Respiratory alone	4 (2%)
Shivering, palpitation, giddiness with or without any other symptoms	Cardiovascular/vascular with Dermatological, GIT and CNS	7 (3%)

GIT - Gastro intestinal system, CNS- Central nervous system

Table 4: Statistical analysis of severity of ADRs due to variousradio contrast agents and system involvement

Severity	Systems Involved For ADR					p value (p<0.05)
	Dermatological alone	Dermatological and GIT	GIT	Respiratory alone	CVS with dermatological, GIT and CNS	
Mild - Level 2	35	0	3	1	0	p = 0.000
Moderate - Level 3, Level 4	158	9	2	3	5	
Severe - Level 5	0	0	0	0	2	
Total	193	9	5	4	7	

GIT - Gastro intestinal system, CNS- Central nervous system, CVS- Cardiovascular System, ADR-Adverse Drug Reaction

for the same was classified under Moderate-Level 4. They were treated with antihistamines, steroids, bronchodilators, adrenaline, oxygen inhalation, antiemetics or proton pump inhibitors as necessary (Figure 3). Life threatening events or those requiring intensive care treatment was seen in 2 (0.9%, n=218) patients were categorised as Severe-Level 5. Out of 2 severe cases, one patient had cardiac arrest and managed in intensive care unit for 2 days. The other patient had immediate hypersensitivity reactions and within minutes developed breathlessness and swelling around lips. Injection adrenaline was given suspecting angioneurotic edema. Later the patient got admitted in intensive care unit (1 day) for further management. Both the patients got discharged after relieving symptoms. No deaths were reported during the study period.

In our study majority of the ADRs were moderate in severity with dermatological manifestations (hyper sensitivity reactions). We could also find statistical significance($p<0.000$) with the severity and clinical presentation (Table 4).

Causality was assessed following World Health Organisation Uppsala Monitoring Centre (WHO-UMC) causality assessment scale. According to WHO-UMC causality assessment, 87% were probable and 13% were possible. 96.3% ADRs were reported by the staff nurses in the ADR administration room, followed by clinical pharmacist - 3.2% and doctors - 0.5%.

4. Discussion

During our study period, a total of 1360 adverse drug reactions were reported to the adverse drug reaction monitoring centre (AMC). Out of these 218 (16%) adverse drugs reactions were related to various contrast agents used in CT, MRI and fundus fluorescein angiography (FFA) procedures. On an average 3 were reported per month and 36 were reported annually

The contrast related adverse drug reaction were highest among the age group 36 to 60 years (47.2%). Few studies also reported more ADRs in similar age group (between 30-50 years).[3,8] While Bhowmick et.al study on non-ionic contrast agents observed more adverse reactions in age <35 years.[9] In this study male gender shows a little higher percentage (54.1 %) of ADR. Similarly, male gender preponderance was noted in Dahara Patel et.al and Bhowmick et.al contrast related ADR studies.[8,9] In contrast to our findings female gender is predicted as risk factor in many studies[8,10] There were studies which showed equal incidence among both gender in development of hypersensitivity reactions to contrast media.[11] Kyungsoo Bae et.al also reported female gender, age less than 60 years, previous history of allergy and spring season as the risk factors for adverse drug reaction during contrast administration.[12] Therefore, gender is not a conclusive risk factor of CM-ADR. So, a thorough clinical history with screening for these risk factors will help in predicting the emergence of adverse reactions during contrast administration.

Non-ionic iodinated radio contrast agents are considered to be safest and the incidence was 0.53%. Similarly, Cochrane et. noted the incidence of low osmolar non-ionic agents varies between 0.2 to 0.7%.[13] More than 90% of the reported ADRs were because of the iodinated contrast agents which were widely used in various CT procedures.

In this study we observed iohexol reported highest percentage of ADRs (48.6%) followed by iopromide (17%) and iopamidol (11.9%). All of these agents are low-osmolality non-ionic monomers. Initially high osmolar contrast agents were used. But as they are hypertonic and produces non anaphylactoid adverse reactions due to fluid shifting, they were removed from use. Low osmolar contrast agents and iso osmolar contrast agents are now being used. Monomers were predicted safe comparative to older agents. But with the discovery of non-ionic dimers, the toxicity seems to greatly reduced.[5] In our study also, iodixanol (isosmolar non-ionic dimer) reported least number of ADRs. Comparative studies between monomer and dimer also noted nil ADRs with the later and considered as preferred agent in renally impaired patients.[3,14,15] Therefore we can conclude that the use of low osmolar non-ionic agents has least incidence (0.2% - 0.4%) of ADRs.

Majority of the reactions were mild to moderate in severity with itching and rashes. The symptoms were noted mainly on head and neck, upper limbs and upper trunk. Gastrointestinal symptoms were reported comparatively fewer in number. Our findings were similar to Kyung et.al. i.e., urticaria, pruritus and localised skin reactions were noted in majority of cases.[16] On the contrary, vomiting was the most common adverse reaction recorded by Chopra et.al.[3] Immediate hypersensitivity reaction mediated by immunoglobulin E, histamine, bradykinin and prostaglandins is responsible for this itching, rashes, swelling, nausea, vomiting and even dyspnoea.[17] According to WHO UMC causality assessment majority of the reactions were ‘Probable’ which was similar to Patel et.al, Kyung et.al, Chopra et.al and Nilay et.al findings in radio contrast related ADR studies.[3,8,11] In contrast, all the ADRs with non-ionic contrast agents by Bhowmick et.al was possible in nature but by Naranjo scale.[9]

Gadolinium compounds have better safety profile than iodinated agents with an incidence far less i.e., 1 in 10,000 to 40,000 injections.[18] Incidence of ADRs with various gadolinium-based agents was 0.04%. Adverse drug reaction does not significantly vary with the agents. All the reported adverse reaction was immediate hypersensitivity reactions. Itching and rashes over hands and upper part of the body were the most common reported reaction. The reactions were mild in nature and treated with injection hydrocortisone and injection pheniramine.

5. Limitation

Reactions which were observed during the first 30 min was studied; therefore, late onset reactions could not be analysed. Premedication history of patients could not be studied as the data was retrieved from ADR forms.

6. Conclusions

It's clear that the proportion of adverse drug reactions remains steady between 0.2% to 0.4%. Hence ADRs continue to develop during with newer and better contrast agents in Indian population. So, each administration requires a watchfulness and readiness to deal with mild to severe events. Most of the reactions were moderate in severity with cutaneous manifestations and lasted only for less than 2 hours. Severe hypersensitivity although rare but anticipated any time. Therefore, life savings medications should always be ready in each contrast administration. Any ADR even its mild should be encouraged to be reported to the adverse drug reaction monitoring centre.

7. Abbreviations

1. WHO UMC – World Health Organization Uppsala Monitoring Centre
2. AMC - Adverse Drug Reaction Monitoring Centre
3. CM - Contrast Media
4. AE – Adverse event
5. ADR - Adverse Drug Reaction
6. CM ADR - Contrast Media Adverse Drug Reaction
7. CT – Computed Tomography
8. MRI – Magnetic Resonance Imaging
9. FFA – Fundus Fluoresceine Angiography
10. GIT – Gastro Intestinal System
11. CNS – Central Nervous System
12. CVS – Cardiovascular System

8. Source of Funding

None.

9. Conflicts of Interest

None.

10. Acknowledgement

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