

A STUDY OF ADVERSE DRUG REACTIONS TO RADIOCONTRAST MEDIA IN A TERTIARY CARE TEACHING RURAL HOSPITAL

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DOI: 10.5455/ijmsph.2013.251020131

Received Date: 08.10.2013

Accepted Date: 25.01.2014

ABSTRACT

Background: Most common ADRs associated with radiocontrast media are rash, fever, nausea, vomiting and shivering. Rarely life threatening anaphylaxis and acute hypersensitivity reaction may also occur. Very few studies are carried out in India focusing on this aspect.

Aims & Objective: To study and report the Adverse Drug Reactions (ADR) caused by radio contrast media in a tertiary care teaching rural hospital.

Material and Methods: Two hundred and fifty seven patients from Radiology department were observed for occurrence of adverse drug events (ADEs) from 01 Jul 2012 to 31 Jul 2012. ADEs were either spontaneously reported or elucidated from personal interviews were analysed.

Results: Total 8 (3.11%) out of 257 patients who had undergone for ionic radio contrast dye investigation had a single event of ADR. Total occurrence rate of ADR is 3.11%. Most common ADR was rash followed by shivering, nausea, vomiting and fever with use of ionic contrast media. All Adverse Drug Reactions, according to WHO-UMC and Naranjo's scale were of "probable" category. All the ADRs were at level-3 according to Modified Hartwig and Siegel severity scale. All the ADRs according to Modified Schumock and Thornton criteria for Preventability of an ADR are of "not preventable" category. All the ADRs were of "Bizarre" type. All the patients were treated with antihistaminic and steroids.

Conclusion: It is recommended to use non-ionic contrast media instead of ionic media by all the health care professionals. Treatment with steroids and antihistaminic in patients who develop ADRs due to radiocontrast media can be effective.

Key-Words: Adverse Drug Reaction; Radiocontrast Media; Non-Ionic and Ionic Contrast Media; Radiology

Introduction

Radio contrast agents are a type of medical contrast medium used to improve the visibility of internal bodily structures in X-ray based imaging techniques such as computed tomography (CT) or radiography (commonly known as X-ray imaging). Radio contrast agents are typically iodine or barium containing compounds. Iodine contrast agents are used for various procedures like Angiography (arterial investigations), Venography (venous investigations), VCUG (voiding cystourethrography), HSG (hysterosalpinogram), IVU (intravenous urography) etc. The contrast highlights different tissue types, bringing out vessels, tumors, inflammation, cysts, etc., that might be missed if the dye was not administered for the scan for identifying stage of diseases and to follow progress.^[1]

Modern intravenous contrast agents are typically based on iodine. Iodine based contrast media are usually classified as ionic or organic (non-ionic). Both types are used most commonly in radiology, due to its relatively harmless interaction with the body and its solubility. Ionic agents were developed first and are still in widespread use depending on the requirements but they are associated

with more adverse events. The advantages of organic (non-ionic) compound over ionic compounds are reduced tonicity, decrease in hypersensitivity reactions, decrease in damage to Blood brain barrier (BBB), reduced chemical, neural and cardio toxicity. All intravascular iodinated contrast agents are based on a tri-iodinated benzene ring structure. They exist in High osmolar contrast media (HOCM), Low osmolar contrast media (LOCM) and Iso-osmolar contrast media (IOCM).^[2] The toxicity of contrast agents decreases as osmolality approaches that of serum. Most contrast enhanced examinations are now carried out using low or iso-osmolar iodinated contrast agents. A high osmolar contrast media is rarely preferred. These contrast agents are sold as clear colourless water solutions, the concentration is usually expressed as mg/ml.^[3]

Most common ADRs associated with radiocontrast media are rash, fever, nausea, vomiting and shivering. Rarely life threatening anaphylaxis & acute hypersensitivity reaction may also occur.^[4] Very few studies are carried out in India focusing on this aspect. Therefore the present study was carried out with the aim of studying the profile of ADRs due to radiocontrast media with body system affected and its causality, severity and preventability analysis.

Materials and Methods

A prospective observational study spread over one month from 1st July 2012 to 1st August 2012 was carried out in patients at department of Radiology of Dhiraj Hospital a 1250 bedded tertiary care teaching rural hospital, Sumandeep Vidyapeeth, Piparia, India. The study protocol was approved by Human Research Ethics Committee of the institute prior to commencement of study. Written informed consent was obtained from the patients before enrolling them for the study.

Criteria for Inclusion of Participants: Patients of either sex with age 18 years and above, who came to the outpatient department of radiology from 1st July to 1st August 2012, in whom Radio contrast dye was administered, were recruited in study. Those patients who suffered from an Adverse Drug Reaction (ADR) due to the radio contrast dye were included in the study.

Criteria for Exclusion of Participants: Patients unable to communicate i.e. patients on seriously ill patients requiring ICU admission or unwilling to participate were excluded from the study.

The study was conducted in outdoor patients meeting inclusion criteria. A time period of 1 month was spent in department of Radiology. All the ADRs either spontaneously reported or elucidated by researcher were reported and analysed. Case Record Form (CRF) was used for gathering information regarding description of ADR, system affected, the treatment required. The primary researcher was trained in identification and reporting and analysis of the adverse drug events. In case of conflict in analysis of the reports, the opinion of the treating physician was also obtained. The researchers were not the part of a treating team of the patient and were not involved in any therapeutic decisions related to the patients involved in the study.

Data were analyzed to find out the frequency of patients developing ADE during therapy, age and Sex distribution of reported ADEs, system wise distribution of reported ADEs, causality assessment by both WHO-UMC scale^[5] and Naranjo's probability score^[6], severity of ADEs using scale of Hartwig and Siegle^[7] and preventability of ADEs using criteria of Schumock and Thornton modified by Lau^[8] et al, 2003.

Statistical Analysis: All data were analyzed using Graphpad Prism version 5.0. Data were represented as actual frequencies, percentage and mean. Chi square test

was used for comparison and p value less than 0.05 was considered as significant.

Results

Out of 257 patients included in the study, 160 (62.26%) were male patients and 97 (37.74%) were female. Out of these 257 patients, 8 (3.11%) had developed one or other ADRs. However, further analysis showed that out of 160 male patients, 04 (2.5%) patients developed ADR and out of the 97 female patients, 04 (4.12%) patients developed adverse drug reactions (p= 0.7218). Thus, gender of the patient was not significantly associated with development of ADRs. (Table 1)

Majority of patients (50%) who developed ADRs were age group of 41-50 years followed by in age group of 31-40 years (25%). Age group of the patient was not significantly associated with sex of patients (p= 0.6) (Table-2).

Table-1: Association of the gender of patients and development of ADR

Gender	Patients with ADR N (%)	Patients without ADR N (%)	Total N (%)
Male	4 (2.5)	156 (97.5)	160 (100)
Female	4 (4.12)	93 (95.88)	97 (100)
Total	8 (3.12)	249 (96.88)	257 (100)

Chi square test, p= 0.7218

Table-2: Association of the age of patients and development of ADR

Age in years	Patients who developed ADR N (%)	Total number of patients N (%)
18-20	00	22 (8.56)
21-30	1 (12.5)	52 (20.23)
31-40	2 (25)	46 (17.89)
41-50	4 (50)	101 (39.3)
51-60	1 (12.5)	36 (14)
Total	8 (100)	257 (100)

Chi square test, p= 0.6

Table-3: Patient's presentation of adverse drug reactions

Chief Complain	Male	Female	Total
Fever, chills	1	1	2
Epigastric pain	0	1	1
Shivering	1	2	3
Rash	0	3	3
Vertigo	1	0	1
Nausea, vomiting	2	1	3

The main presentation of ADRs was in the form of fever, chills, epigastric pain, shivering, rash, vertigo and nausea among all eight adverse drug reaction cases as shown in table-3. Out of 8 patients who developed ADRs, 7 (87.5%) patients were given ionic radiocontrast media and only 1 (12.5%) patient was given non-ionic contrast media. Causality assessment was performed by using both WHO-UMC method and Naranjo's scale and all the 8 ADRs were of 'probable' category. Severity of ADRs were assessed by using modified Hartwig and Siegel severity scale and it showed that all the ADRs were of level 3 requiring administration of the antidote or other drugs for treatment. All 8 reactions were of type B (Bizarre) of

Adverse Drug Reactions. In all the cases, the ADRs did not last for more than one day. Analyzing preventability of ADRs using modified Schumock and Thornton criteria, all the reactions were of 'not preventable' category.

Discussion

The National Pharmacovigilance Program (NPP) which was launched by CDSCO in 2004^[9] had made possible spontaneous reporting and documentation of the Adverse Drug Reactions (ADRs). Since then, ADRs have gained utmost importance all over the world and are part of pharmacovigilance activity. ADRs were claimed to be the 4th leading cause of death in USA.^[10]

The present study was carried out in the outpatient unit of radiology department focusing on patients who developed an Adverse Drug Reactions (ADR) due to the radiocontrast media. All the reported ADRs were due to ionic contrast media with prevalence of 3.11%. To best of our knowledge, no study from India has reported the prevalence of ADRs due to radio contrast media. In the study by Katayama et al^[11] had shown prevalence of adverse reaction with ionic contrast media was 12.66% in comparison with use of non-ionic contrast media which was reduced to 3.13%. This suggests low rate of ADRs in our population. The reason for this difference could be inclusion of small number of patients in the study, genetic makeup or different geographical distribution among population. Same author also reported that that nonionic contrast media significantly reduce the frequency of severe and potentially life-threatening ADRs to contrast media at all levels of risk and are most effective means of increasing the safety to the use of contrast media.^[11]

In this study, adverse drug reactions developed more, though statistically not significant, in patients of fourth decade of life. Study carried out at American society of emergency radiology by Namasivayam S. et al^[12] has reported that acute adverse reactions due to radio contrast media are more frequent in persons between 20 and 50 years of age and are less frequent above 50 years. However, one patient who had developed ADR was above the age of 50 years in this study, which is quite unusual. Another study by Shehadi WH et al had shown that incidence of ADR due to radiocontrast media are higher in third and fourth decade of life.^[13] However, one patient developing ADR was above the age of 50 years in this study which is quite unusual.

In this study, male and female had equal incidence of development of an adverse drug reactions. Several studies

showed that there was no significant gender difference in development of an ADR due to radio contrast media.^[13]

The pathogenesis of general adverse reactions to contrast media is not well-defined and is likely to be multifactorial. They were thought to be allergic in origin by many health care professionals but there is no such conclusive evidence that adverse reactions to contrast media are allergic as antibodies to contrast media.^[14]

Adverse reactions to intravenous iodinated contrast media are broadly classified into general (fever, rash, nausea, vomiting etc.) and organ-specific adverse effects such as nephrotoxicity, cardiovascular, pulmonary, and neurotoxicity. All the patients in present study had developed general reaction and none had organ specific toxicity. The general adverse reactions are further sub classified into acute and delayed reactions. Acute reaction usually occurs within 1 hour of administration of an offending agent while delayed adverse reaction usually occurs in 1 hour to 1 week after contrast injection, which is predominantly a skin reaction.^[15] In present study all the patients had developed reaction within 1 hour of contrast administration, thus classified as acute general reaction.

Acute general adverse reactions are summarized into mild, moderate and severe reactions. Mild reactions are of short duration, self-limiting, and generally do not require specific treatment. However, moderate and severe reactions represent serious degrees of reactions that need immediate management.^[15]

In this study, prevalence of rash among the patients was highest followed by nausea, vomiting and shivering. These symptoms were graded as mild ADR according to one of the study in USA by Namasivayam et al.^[12]

Causality assessment of the reported ADRs was carried out by using both WHO-UMC criteria and Naranjo's scale which revealed that the reactions were "probable" in nature. Thus, the results of causality assessment are coinciding by both the scales in the study. However, causality assessment was quite obvious because only a single drug was administered at the time and no re-challenge was carried out due to ethical issues and considering patient safety.

We observed that all 8 patients who developed ADR were at level 3 of scale by Hartwig and Siegle scale, meaning that they required management of ADR. All the ADRs were well managed with corticosteroids and anti histaminics. All the patients recovered after giving the medication. A study by

Kelly et al^[16] concluded that pretreatment with corticosteroid and anti histaminics 30 minutes to 1 hour before the administration of radiocontrast media reduces the risk of ADRs to ionic contrast in high risk patients.

On analysing preventability of ADRs, all ADRs were "Non Preventable" in nature. Prevention is always better than cure. It would be advisable to prevent the ADR rather than curing it after it is developed. Past history of such allergy should be asked before taking patient for radiocontrast administration. This would entirely change the scenario of the development of ADRs due to radiocontrast media. Contrast materials as such are safe drugs, most of the reactions are mild in nature while serious allergic reactions are rare, therefore radiology departments should be well-equipped to deal with them.^[17]

At the end, it will be prudent to say that the pharmacovigilance activity is still in infancy in India. There is still less reporting of ADR to appropriate authority in India. Therefore, there is a need to inform treating doctors about the importance of looking for ADRs following pharmacotherapy and recording them scrupulously. This practice will prove to be very valuable in making drug therapy safe and rational.

This study is probably the initial step of reporting ADRs due to radiocontrast media from Gujarat. It entirely highlights various aspects related to ADRs like the time of onset, management of patients, causality, and severity and at last preventability assessment. However the limitations of the study are relatively small sample size, short duration, lack of follow up. Despite the above limitations, the present study clearly showed that it was possible to carry out studies on adverse drug reactions and their monitoring if there is willingness and determination on the part of investigator and support from the health care professionals is available. However, further studies are required to elaborate various aspects of ADRs due radiocontrast media.

Conclusion

Radiocontrast media are routinely used nowadays in day to day practice for diagnostic and interventional procedures. Use of iodine containing media is prone to development of

ADRs, more with ionic ones as compared to the non-ionic media. At last, monitoring and attention towards patients who are at high risk could reduce the impact of ADR and quality of care.

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Cite this article as: Modi NB, Vaidya K, Dudhia S, Shah RB, Date SK. A study of adverse drug reactions to radiocontrast media in a tertiary care teaching rural hospital. *Int J Med Sci Public Health* 2014;3:133-136.

Source of Support: Nil

Conflict of interest: None declared