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Original Research Article

A study of adverse drug reactions to iodinated contrast agents in tertiary care teaching hospital

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ABSTRACT

Background: Contrast agents have long been used for the imaging of anatomic boundaries and to explore normal and abnormal findings in X-ray based imaging technique. These agents are not completely devoid of risk. Adverse effects from administration of contrast media vary from minor physiological disturbance to rare life threatening situation.
Methods: A cross-sectional retrospective observational study over one-year duration from 1st August 2015 to 31st July 2016 was conducted at radiology department of a Pandit Deendayal Upadhyay Government Medical College and Teaching hospital, Rajkot, Gujarat. Adverse drug reactions were analyzed to study the nature of reactions caused by iodinated contrast agents. The temporal relationship of time of administration of contrast agents to the occurrence of adverse reaction was analyzed and classified as immediate or delayed type of reaction.
Results: Out of 868 patients that were analysed 15 out of 497 male patients and 11 out of 371 female patients developed adverse reaction. Age range of patients that developed reactions was 20-55 years. Most common adverse drug reaction occurred in our study was nausea and vomiting which was treated by parenteral Ondansetron. All the reactions were found to be 'probable' in causality as per WHO causality assessment scale and Naranjo's algorithm.
Conclusions: Physicians performing diagnostic or therapeutic procedures with contrast agents must be aware of the risk, preventability and treatment so that reactions can be prevented. Sensitization of physicians is required to increase reporting of adverse drug reactions occurred due to radiocontrast agents.

Keywords: Adverse drug reaction, Iodinated radiocontrast agents, Intravascular iodine

INTRODUCTION

Contrast agents have long been used for the imaging of anatomic boundaries and to explore normal and abnormal physiologic findings in X-ray based imaging technique such as computed tomography (CT) or radiography. Intravascular iodine plays key role in attenuation of X-ray.[1] Iodinated contrast media is used for various procedures like arteriography, venography, voiding cystourethrography (VCUG), Hysterosalpingography (HSG), intravenous pyelography (IVP), etc.[1]

Iodinated contrast media was first used in a clinical setting with development of sodium iodine since the 1920s. In the 1950s, iodinated contrast media based on tri- iodobenzoic acid ring and in the 1970s, non-ionic contrast media and dimeric iodinated contrast media were developed. They differ in three significant ways: iodine atom to particle ratio, osmolality, viscosity.[2,3] According to osmolality, they are classified as high osmolar, low osmolar and iso-osmolar contrast agents. They have different clinical use and toxicity profile. For example, charged ionic species tend to disrupt electric potential of cell membrane, accounting for increased toxicity.[1]

Like all other pharmaceuticals, these radiocontrast agents are not completely devoid of risk. Adverse side effects from the administration of contrast media vary from minor physiological disturbance to rare severe life threatening situation.[4] Because of the documented low incidence of adverse events, intravenous injection of contrast media may be exempted from the need for informed consent. Hence, the present study was planned to know the nature and analyze causality, severity, preventability, treatment of adverse drug reactions caused by radiocontrast media.

METHODS

A cross-sectional retrospective observational study spread over one-year duration from 1st August 2015 to 31st July 2016 was done. The study was conducted at radiology department of Pandit Deendayal Upadhyay Medical College and Teaching hospital, Rajkot, Gujarat. The study protocol was assessed and approved by Institutional Ethics Committee of the same hospital. All the study data were collected from physician records of radiology department. Patients irrespective of age and sex who received IV iodinated contrast agents, were included in the study. Adverse drug reactions were recorded in modified adverse drug reaction form, from central drug standard control organization (CDSCO). The Adverse drug reactions with inadequate data were excluded from the study.

Adverse drug reactions were analyzed to study the nature of adverse drug reactions caused by iodinated contrast agents. Adverse drug reactions were also analyzed to know the type of iodinated contrast agent used (ionic or non-ionic), indications for which it was used, treatment given to the patient, the outcome of the patient, severity, and causality of the adverse drug reaction. The temporal relationship of time of administration of iodinated contrast agents to the occurrence of adverse drug reaction was also analyzed, according to which adverse drug reactions could be classified as immediate or delayed type of reaction. Causality assessment was done by WHO causality assessment scale, and Naranjo's algorithm.[5,6] Modified Hartwig and Siegel scale was used to assess the severity of adverse drug reactions.[7,8] Schumock and Thornton scale was used to assess the preventability of the ADEs.[9]

Statistical analysis was done by using Microsoft excel 2013. Chi-square test was used for comparison between ionic and non-ionic iodinated contrast agents induced adverse drug reactions and $p<0.05$ was considered.

RESULTS

In our study, 868 patients received iodinated contrast agents for the imaging procedure. Ionic contrast agent used in our study was diatrizoate sodium and meglumine dye and non-ionic contrast agent was isohexol. Ionic contrast agent was given to 424 patients, out of which 331 were males and 93 were females and non-ionic contrast agent was given to 444 patients, out of which 166 were males and 278 were females. It was found that out of 497 male patients, 15 (3.02%) developed adverse drug reactions and out of 371 female patients, 11 (2.96%) developed adverse drug reactions ($p=0.96$). Thus, total 26 adverse drug reactions were reported, in which 21were caused by ionic contrast agent and 5 were caused by non-ionic contrast agent ($p=0.0037$) (Table 1).

Table 1: Comparison between gender and radio contrast agent induced adverse drug reactions.

Gender	Ionic dye induced ADRs	Non-ionic dye induced ADRs	Total
	N (%)	N (%)	N (%)
Male	15 (100)	0	15 (100)
Female	6 (54.55)	5 (45.45)	11 (100)
Total	21 (80.77)	5 (19.23)	26 (100)

Table 2: Comparison between ionic and non-ionic contrast agent induced adverse drug reactions.

Radio contrast agent	Number of patients with ADRs	Number of patients without ADRs	Total
Ionic	15	409	424
Non-ionic	11	433	444
Total	26	842	868

Table 3: Incidence of adverse drug reactions due to radio contrast agents.

Radio contrast agents	Number of patients	Incidence of adverse drug reactions (%)
Diatrizoate sodium and meglumine dye	424	0.049
Isohexol	444	0.011
Total	868	0.029

Table 4: Number of adverse drug reactions developed in different age group.

Age group (in years)	Male with ADRs	Female with ADRs	Total
20-30	1	1	2
31-40	7	1	8
41-50	5	9	14
51-60	2	0	2
Total	15	11	26

Table 5: Different types of adverse drug reactions reported by ionic and non-ionic contrast agents.

Reaction	ADRs due to ionic contrast agent	ADRs due to non-ionic contrast agent	Total
	N (%)	**N (%)**	**N (%)**
Nausea and vomiting	9 (34.62)	3 (11.54)	12 (46.15)
Rashes	3 (11.54)	0	3 (11.54)
Facial flushing and allergic reaction	2 (7.69)	0	2 (7.69)
Local urticaria	2 (7.69)	1 (3.85)	3 (11.54)
Local swelling	4 (15.84)	1 (3.85)	5 (19.23)
Convulsion /shivering	1 (3.85)	0	1 (3.85)
Total	21 (80.77)	5 (19.23)	26 (100)

Table 6: Assessment scales used in evaluation of outcomes.

Causality assessment scale			Severity scale	Preventability scale
Scale	WHO causality scale (%)	Naranjo's algorithm (%)	Modified Hartwieg and Siegel scale (%)	Shumock and Thornton preventability (%)
Probable	26 (100%)	26 (100%)	18-level 3(69%) 8-level 4 (type A) (31%)	Not preventable 26 (100%)

Comparison of ionic and non-ionic contrast agent induced adverse drug reactions is shown in Table 2 (p=0.36). Incidence of adverse drug reactions due to ionic and nonionic contrast agents is shown in Table 3.

The mean age±SD of patients who developed adverse drug reaction was 50.71±11.85 years. The mean age±SD of patients receiving ionic contrast agent was 40.48±7.28 years and the mean age±SD of patients receiving non-ionic contrast agent was 45±2.28 years. Age range of patients developed adverse drug reactions was from 20 years to 55 years. Majority of adverse drug reactions were seen in age group of 41-50 years (Table 4).

Table 5 shows different types of adverse drug reactions caused by ionic and non-ionic contrast agents. Most common adverse drug reaction occurred in our study was nausea and vomiting which was treated by injection ondansetron. Other reactions like local swelling, urticaria and allergic reactions were reported which was treated by injection hydrocortisone, injection pheniramine maleate and injection dexamethasone. One patient developed convulsion which was treated by tablet sodium valproate.

Table 6, describes that all the adverse drug reactions were found to be 'probable' in causality as per WHO causality assessment scale and Naranjo's algorithm. Severity assessment was done by Modified Hartwig and Siegel severity scale and it showed that 18 adverse drug reactions were of level 3 and 8 adverse drug reactions were of level 4 (type-a). All the adverse drug reactions were 'not preventable' type, according to Schumock and Thornton preventability scale. Here all the adverse drug reactions were of immediate type because they occurred within an hour of administration of iodinated contrast agent.

DISCUSSION

The first large, multicentre, prospective study in 1975, which estimated the incidence of contrast reaction at approximately 5%.[10] Recent estimates of all adverse reactions to iodinated contrast media range from 1 to 12% with severe reactions comprising only 0.01 to 0.2% of total reaction.[11,12] The incidence of adverse reactions is more common after the use of high-osmolarity agents: approximately 15% with a high-osmolarity agent vs only 3% with a low-osmolarity iodinated contrast agents.[13] In our study incidence of adverse drug reactions was 0.029%. The incidence of the ionic radiocontrast agent (diatrizoate sodium and meglumine, ionic monomeric, high osmolality agent) induced adverse drug reactions were 0.049% and non-ionic radiocontrast agent (Isohexol, non-ionic monomeric, low osmolality agent) induced adverse drug reactions was 0.011%.

Association of gender with development of adverse drug reactions was statistically not significant. But comparison of gender and radio contrast agents induced adverse drug reaction reported that male had more adverse drug reactions due to ionic radio contrast agent than female. It may be because more number of males are exposed to ionic radiocontrast.

A study done by Namasivayma et al had shown that adverse drug reactions due to radiocontrast agents are more frequent in between 20 to 50 years of age and are less frequent above 50 year of age.[14] In our study, adverse drug reactions occurred in the age range between 20 years to 55 years and only 2 adverse drug reactions seen in patients above 50 years of age. More adverse drug reactions occurred in the age group of 41 to 50 years.

Adverse drug reactions caused by radiocontrast media are broadly classified as general and organ-specific. General adverse drug reactions are further sub-classified into an acute type which usually occurs within one hour of administration of radiocontrast agent and delayed type which usually occurs in one hour to one week after radiocontrast agent administration.[15,16] In our study, all reactions caused due to iodinated radiocontrast agents were general except one which was organ specific type (neurotoxicity) of reaction. All general reactions occurred within one hour of administration of the radiocontrast agent. So, known as an acute general reaction.

In the present study, most common adverse drug reaction was nausea and vomiting, more due to an ionic radiocontrast agent than non-ionic radiocontrast agent and followed by local swelling, rashes, facial swelling and allergic reaction. Which was comparable with a study done by Oowaki, which showed that nausea and vomiting are more common with the high osmolarity ionic monomeric agents.[17]

Pathogenesis of nausea, vomiting, rashes, allergic reaction, urticaria were attributed to the release of histamine, prostaglandin, bradykinins, immunoglobulin E and other mediators.[18,19] Development of local swelling could be explained by two different mechanisms first due to release of various mediators and another due to extravasation of dye at site of injection which is supported by American College of Radiology Manual on Contrast Media.[4]

Causality assessment of reported adverse drug reactions was carried out by using WHO-UMC criteria which revealed that the reactions were probable in nature. It is quite obvious because only single drug administered at the time and no challenge was carried out because of ethical issues and considering patient safety.[5] Severity assessment was done by modified Hartwig and Siegel severity scale and it showed that 18 adverse drug reactions were of level 3 which requires specific antidote or other treatment and no increase in length of hospital stay and 8 adverse drug reactions were of level 4 (a) which increases length of hospital stay by at least one day.[7,8]

On the basis of preventability issue, all ADRs due to radiocontrast dye were 'Non-preventable' in nature because it was spontaneous reporting of adverse drug reaction where detail history about the previous risk of drug or dye was lacking.

CONCLUSION

Physicians performing diagnostic or therapeutic procedures with contrast agents must be aware of the risk, preventability and treatment so that reactions can be prevented. Sensitization of physicians is required to increase reporting of adverse drug reactions occurred due to radiocontrast agents.

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REFERENCES

1. Pasternak JJ, Williamson EE. Clinical Pharmacology uses, and adverse reaction of iodinated contrast agents: a primer for the non-radiologist. Mayo Clin Proc. 2012;87(4):390-402.
2. Morcos SK, Thomsen HS. Adverse reactions to iodinated contrast media. Eur Radiol 2001;11(7):1267-75.
3. Singh J, Daftary A, Iodinated contrast media and their adverse reactions. J Nucl Med Technol. 2008;36(2):69-74.
4. ACR Manual on contrast Media, Version 10.1, 2015. Available at: http://www.acr.org/-/media/37D84428BF1D4E1B9A3A2918DA9E27A3.pdf. Accessed on 3 June 2019.
5. The use of WHO-UMC system for standardized case causality assessment. Available at: http://www.WHO-UMC.org/graphic/24734.pdf. Accessed on 3 June 2019.
6. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
7. Hartwig SC, Siegle J, Schineider PJ. Preventability & severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49:2229-32.
8. Note on clinical pharmacology. Available at URL:http://edusanjalpharmacology.blogspot.in/2012/

12/severity-asssessment-of-adrs.html. Accessed on 3 June 2019.
9. Raut AL, Patel P, Patel C, Pawar A. Preventability, Predictability and Seriousness of Adverse Drug Reactions amongst Medicine Inpatient in Teaching Hospital: A prospective observational study. IJPCS. 2012;1(3):1293-9.
10. Shehadi WH. Adverse reactions to intravascularly administered contrast media. A comprehensive study based on a prospective survey. Am J Roentgenol Radium Ther Nucl Med. 1975;124(1):145-52.
11. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and non-ionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology. 1990;175(3):621-8.
12. Bush WH, Swanson DP. Acute reactions to intravascular contrast media: types, risk factors, recognition and specific treatment. AJR Am J Roentgenol. 1991;157(6):1153-61.
13. Dickinson MC, Kam PC. Intravascular iodinated contrast media and the anaesthetist. Anaesthesia. 2008;63(6):626-34.
14. Namasivayam S, Kalra Mk, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: a primer for radiologists. Emerg Radiol. 2006;12(5):210-5.
15. Edwards IR, Aronson JK. Adverse reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255-9.
16. Modi N, Vaidya K, Dudhia S, Shah R, Date S. A study of adverse drug reactions to radiocontrast media in a tertiary care teaching rural hospital. Int J Med Sci Public Health. 2014;3(2):133-6.
17. Oowaki K, Saigusa H, Ojiri H, Ariizumi M, Yamagisi J, Fukuda K, et al. Relationship between oral food intake and nausea caused by intravenous injection of iodinated contrast material. Nihon lgaka Hoshasen Gakkai Zasshi. 1994;54(6):476-9.
18. Bottinor W, Polkampally P, Jovin I. Adverse reactions to iodinated contrast media. Int J Angiol. 2013;22:149-54.
19. Almen T. The etiology of contrast medium reactions. Invest Radiol. 1994;29(Suppl1):S37-S45.

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