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Original Article

An analysis of adverse drug reactions to radiographic contrast media reported during a 3 year period in a tertiary care hospital in south india

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Abstract

Aim : The aim of this study was to analyse the nature and incidence of adverse drug reactions to radiographic contrast media (ionic and non ionic) reported during a 3 year period in a tertiary care hospital in South India.

Methods : Adverse Drug Reactions (ADRs) to radiographic contrast media (ionic and non ionic) reported during a 3 year period to the pharmacovigilance centre, JIPMER, Pondicherry were retrospectively analysed for demographic profile, frequency, severity, causality and the temporal relationship of contrast administration to the occurrence of ADR.

Results : A total of 99 ADRs were spontaneously reported from 63 patients. It included 38 (60.3%) males and 25 (39.7%) females. The most common ADRs were nausea 26 (26.5%), vomiting 33 (33.7%) and rashes 30 (30.6%). As per Naranjo's algorithm and WHO causality assessment, all reactions were 'probable'. According to the Hartwig severity scale, 60 reactions were mild (60.6%), 34 (34.3%) were moderate and 5 (5.1%) were severe. There was no fatality reported. Adverse events required treatment in 38 (60.3%) patients. Most of the reactions (n=48, 76.2%) occurred immediately after contrast administration. Five (7.9%) reactions occurred during contrast administration and 10 (15.9%) reactions occurred within the next 30 minutes after contrast administration. Among the ADRs reported, the proportion of mild reactions were significantly higher in patients who received ionic contrast (n=42) than those who received non-ionic contrast (n=21) ($p<0.05$).

Conclusion : The common adverse reactions to contrast were nausea, vomiting and rashes. Most of the reactions occur immediately after administration of contrast and are of milder severity.

Introduction

Adverse drug reactions (ADRs) to intravascular contrast media are a cause of concern during radiographic and cardiac procedures involving administration of these agents. Radiographic opacity by these water soluble contrast agents is provided by iodine. In order to deliver large quantities of iodine into the vascular tree, they have been formulated with organic compounds that decrease the toxicity of the whole molecule.

Iodinated contrast media can be classified chemically

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into four categories (1): a) Ionic monomers – salts of sodium and meglumine. They dissociate in solution to produce a cation and anion and hence are hypertonic. eg. Diatrizoate; b) Non ionic monomers – as they are non-ionic they do not dissociate in solution, hence have less than half of the osmolality of ionic monomers. Eg. Iohexol, Iopamidol, Iopromide c) Ionic dimers d) Non ionic dimers. Eg. Iodixanol

Ionic monomers and dimers have an osmolality of 1500-1700 and 560 mosmols/kg of water respectively. Non ionic monomers and dimers have an osmolality of 600-700 and 300 mosmols/kg of water respectively. The osmolality of non ionic dimers is similar to physiological osmolality of blood (300 mosmols/kg of water). Hence non ionic dimers are considered as iso-osmolar contrast media (2).

In one study done in 2005 in USA, using non ionic contrast, the incidence of adverse drug events was found to be 0.7% (3). Another multicentre study that was done on outpatients and inpatients in 738 study centres in 21 countries in Europe and Asia using non ionic contrast in 2012 showed the incidence of severe ADR to be 0.02% (4).

To the best of our knowledge, no study has been done to study the characteristics of adverse drug reactions to radiographic contrast media in India. This study was undertaken to analyse the nature of ADRs to radiographic contrast media in South India.

Methods

The study was conducted using ADR reports received by Pharmacovigilance centre, JIPMER, Pondicherry. Personnel in the hospital were requested personally and through awareness programmes to report any adverse drug reaction to radiographic contrast media in the Adverse Drug Event Reporting Form provided by Central Drugs Standard Control Organisation, Ministry of Health and Family Welfare, Government of India. ADR drop boxes with ADR reporting forms were kept in vantage locations in the hospital. Health care professionals were asked to fill in details of any adverse drug reaction that occurred in the forms and drop it in the box. The filled forms were periodically collected by the members of the pharmacovigilance team. Besides they were provided phone numbers through which they can also report the adverse drug reaction directly to the pharmacovigilance centre and a member of the pharmacovigilance team would fill up the form from the details collected. Data on the demographic profile of the patient, description of the adverse drug event, details of the contrast media used, indication for which it was used, outcome of the event were collected in the form.

All the ADRs that were reported following intravascular administration of radiographic contrast media to patients during a 3 year period from July 2005 to June 2008 were analysed to study the nature of the adverse drug reactions. The adverse drug reactions (ADR) reported to ionic and non ionic contrast media were analysed for demographic profile of patients; type of contrast used (ionic or non ionic); frequency, severity and causality of ADRs. The temporal relationship of time of administration of contrast media to the occurrence of ADR (event occurred during, immediately after or within the next 30 minutes after administration of contrast media) was analysed. WHO causality assessment scale (5) and Naranjo's algorithm (6) were used to assess the causality and Modified Hartwig and Siegel scale (7) was applied to assess the severity of the reported adverse reactions.

Statistical analysis was done using SPSS for windows (version 17). Chi-square or Fischer exact test was used to check for differences in severity between groups of patients who received ionic and non ionic contrast. $p<0.05$ was considered as statistically significant.

Results

During July 2005 to June 2008, 18535 patients received contrast media (15858 patients received ionic contrast media and 2677 patients received non-ionic contrast media)

A total of 99 ADRs were obtained from reports of 63 patients who developed adverse drug reactions. Of

these 63 patients, 42 patients were given ionic contrast (Diatrizoate) and 21 patients were given non-ionic contrast (Iohexol, Iopamidol and Iopromide).

Among those who were reported to have developed ADRs, 38 (60.3%) were males and 25 (39.7%) were females. The mean age±SD of the people who developed ADRs was 42.60±14.14 years. The age of patients ranged from 8 years to 73 years. The mean age±SD of patients who received ionic contrast was 40.71±13.72 (95% CI 36.4 to 44.9 years) and the mean age of patients who received non ionic contrast was 43.52±19.83 (95% CI 34.5 to 52.5 years).

As per Naranjo's algorithm, all the reactions were found to be probable in causality. Pre existing risk factors were provided in the reporting form in 13 patients. Of these, 12 (57.1%) patients who had developed ADR with non ionic contrast had a pre existing risk factor, while one patient (2.38%) who had developed an ADR with ionic contrast had pre existing risk factor. Of the 63 patients, contrast media was used for the purpose of taking CT scan or IVP in 51 patients and for the purpose of coronary angiogram in 12 patients.

Comparison of the frequency of different adverse drug events between ionic and non ionic contrast is provided in Table I. The severity of the adverse drug events is compared between ionic and non ionic contrast in Table II. As per Hartwig and Siegel severity scale, among the 42 patients who received ionic contrast, 22 (52.4%) people had mild reactions, 20 (47.6%) patients had moderate or severe reactions. Among the 21 patients who received non ionic contrast, one patient (4.8%) patient had mild reaction and 20 (95.2%) patients had moderate or severe reaction. Among the ADRs reported, the proportion of mild reactions compared to moderate or severe reactions were significantly higher in patients who received ionic contrast (n=42) than those who received non-ionic contrast (n=21) ($p<0.05$). The number of adverse drug reactions totally to both ionic and non ionic contrast was 60 (60.6%) mild reactions, 34 (34.3%) moderate reactions and 5 (5.1%) severe reactions. One patient who was given non ionic contrast developed renal failure but he had pre existing diabetes and coronary artery disease.

The incidence of mild, moderate and severe reactions in our study in ionic and non ionic contrast was

TABLE I: Comparison of frequency of adverse drug events between ionic and non-ionic contrast medium.

ADR	*Ionic (%)*	*Non ionic (%)*	*Total (100%)*
Nausea or vomiting	47 (69.1%)	12 (38.7%)	59 (59.6%)
Urticaria	14 (20.6%)	16 (51.6%)	30 (30.3%)
Sneezing	1 (1.47%)	0	1 (1%)
Facial swelling	1 (1.47%)	0	1 (1%)
Thrombophlebitis	1 (1.47%)	0	1 (1%)
Hypotension	0	2 (6.45%)	2 (2%)
Tightness of chest	1 (1.47%)	0	1 (1%)
Renal failure	0	1 (3.23%)	1 (1%)
Bronchospasm	1 (1.47%)	0	1 (1%)
Cardiopulmonary arrest	2 (2.9%)	0	2 (2%)
Total	68 (100%)	31 (100%)	99 (100%)

TABLE II: Severity of adverse drug events reported with ionic and non ionic contrast.

Hartwig and Siegel scale	*Total*		*Number of adverse drug events*			
			Ionic contrast		*Non ionic contrast*	
	Number of events	*Number of patients*	*Number of events*	*Number of patients*	*Number of events*	*Number of patients*
Mild	60 (60.6%)	25 (39.7%)	48 (69.6%)	23 (54.8%)	12 (40%)	2 (9.5%)
Moderate	34 (34.3%)	33 (52.4%)	16 (23.2%)	15 (35.7%)	18 (60%)	18[#] (85.7%)
Severe	5 (5.1%)	5 (7.9%)	4 (5.9%)	4 (9.5%)	1 (3.2%)	1 (4.8%)
Total	99 (100%)	63 (100%)	68 (100%)	42 (100%)	31 (100%)	21 (100%)

[#]Of these 18 patients, 8 patients had both mild and moderate reactions.

TABLE III: Incidence of reactions.

Hartwig and Siegel scale	*Overall incidence*	*Incidence of reactions*		*Wolf et al (1991)(12)*	
		Ionic	*Non ionic*	*Ionic*	*Non ionic*
Mild	0.14%	0.15%	0.08%	2.8%	0.44%
Moderate	0.18%	0.01%	0.67%	1.2%	0.135%
Severe	0.03%	0.03%	0.04%	0.3%	0.011%
Overall incidence	0.34%	0.26%	0.78%		

TABLE IV: Time of reaction in relation to administration of contrast media.

	Total number of patients	*Number of patients*	
		Ionic	*Non ionic*
During administration of contrast	5 (7.9%)	5 (11.9%)	0
Immediately after administration of contrast	48 (76.2%)	34 (81%)	14 (66.67%)
Within 1 hour of administration of contrast	10 (15.9%)	3 (7.1%)	7 (33.33%)
	63 (100%)	42 (100%)	21 (100%)

compared with the study done by Wolf et al. (Table III). When the temporal relationship between the onset of ADR and administration of contrast agent was analysed, it was found that most of the reactions (76.2%) occurred immediately after contrast administration (Table IV). Ten reactions (15.9%) occurred within the next 30 minutes after administration of contrast.

Discussion

In a report from the Japanese Committee on the safety of contrast media published in 1990, the overall incidence of reactions from ionic contrast was found to be 12.66% and to non ionic contrast was found to be 3.13% (8). In a study done in Boston in 2005, the incidence of reactions to non ionic contrast in patients undergoing CT was 0.7% (3). The incidence of adverse drug reactions in our study was 0.34%. Among patients who received non ionic contrast, the incidence was 0.78% (1 in 100 patients) and among patients who received ionic contrast, the incidence was 0.26% (1 in 350 patients). The overall incidence of reactions reported in our study is less than that reported in other studies. It could be because the method that was followed in our study to collect data was spontaneous reporting in which underreporting is a known drawback.

Previous studies have shown that minor symptoms such as nausea, vomiting or sneezing are less common with non-ionic contrast (9-12) (Table III). In a study done in 1988, the incidence of sneezing was 0% with iohexol and 2.2% with metrizoate. The incidence of nausea was 0.8% with iohexol, 15.8% with metrizoate. The incidence of vomiting was 1.2% with iohexol and 9.7% with metrizoate (10). Among the ADRs reported to us, the proportion of mild reactions compared to moderate or severe reactions were significantly higher in patients who received ionic contrast (n=42) than those who received non-ionic contrast (n=21) ($p<0.05$).

Renal failure had been reported in one patient with pre-existing diabetes and coronary artery disease who received ionic contrast. Studies have shown that the risk of nephropathy in patients with no pre existing risk factors is the same with ionic and non ionic contrast (13). However in patients with dehydration, pre-existing renal failure or diabetes the risk may be higher and non ionic contrast may be preferred in such patients (14).

In another study, the risk of contrast induced kidney injury was found to be the same in patients receiving iopromide (LOCM) and iodixanol (iso osmolar contrast media), even in patients with diabetes and when high volume of contrast is given (>500 ml), provided sufficient hydration is maintained (15). The main factor in pathophysiology of contrast induced nephropathy is due to reduction in renal perfusion

caused by direct effect of contrast media on the kidney (16). Hence maintaining sufficient hydration is necessary for patients at risk of contrast induced nephropathy.

The amount by which the use of non ionic contrast decreases the risk of nephropathy in patients with pre existing risk factors is yet to be determined. Drugs such as N - acetylcysteine, theophylline are being studied to see their effect in reducing the risk of contrast induced nephropathy (17). There is insufficient evidence to support the use of prophylactic administration of N-acetylcysteine in patients having a high risk of contrast induced nephropathy.

There have been reports of coronary vasospasm following contrast media administration (18-20). This might be the pathophysiology behind the symptoms of tightness of chest in one patient who received ionic contrast.

Anaphylactoid reactions can occur with both ionic and non ionic contrast. The risk of fatal reactions is the same with ionic and non ionic contrast media (21). In our study two patients developed cardiopulmonary arrest, one patient developed bronchospasm and one patient developed tightness of chest. Clinical opinion is divided regarding the use of premedication to prevent severe reactions to contrast media in high risk patients (22, 23).

Skin tests may be able to detect this hypersensitivity. Studies are being done to explore the use of skin tests for the selection of the appropriate contrast medium for the patient. The sensitivity and specificity are yet to be determined (24).

In our study, most reactions (n=53) occurred during or immediately after giving contrast. Ten reactions occurred within 30 minutes of giving contrast. Seven patients developed skin reactions and vomiting 15 minutes after giving contrast. They were all given non ionic contrast and had pre existing coronary artery disease. The other three patients did not have any pre existing medical conditions and were all given ionic contrast. Of these, one patient developed skin reaction 10 minutes after giving contrast, another patient developed bronchospasm 20 minutes after giving contrast and another patient developed vomiting and tightness of chest 30 minutes after giving contrast.

As per the standards issued by the Royal College of Radiologists, patients must remain in the department for at least 15 minutes after the contrast injection. In patients at increased risk of reaction this should be increased to 30 minutes (25).

Conclusion

The present study shows that nausea, vomiting and rashes are the most commonly observed ADRs associated with contrast media. Majority reactions observed were mild to moderate in severity. Most of the reactions occur immediately after the administration of contrast. More number of ADRs of mild nature was observed in patients receiving ionic contrast media.

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