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Research Article

A study on adverse drug reactions to non-ionic contrast medium in an Indian population: a 1-year experience

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ABSTRACT

Background: To the best of our understanding, very few studies focusing on the adverse drug reaction (ADR) profile of non-ionic contrast medium (NICM) has been carried out until date among the Indian population. Hence, this study was planned. We sincerely believe that the knowledge gathered from this study can improve safer usage of these agents among the patients of Indian origin. The objective was to evaluate the incidence and severity of ADRs of non-ionic radio contrast media (CM) used in tertiary care hospital in Eastern India.
Methods: For the duration of 1-year from July 2011 to July 2012, we prospectively recorded all the ADRs associated with the administration of NICM (iohexol and ioversol) in 3708 patients of Indian origin undergoing computed tomography scan at the hospital. The average median age, weight, dose used; types of ADRs, concomitant medication, final diagnosis, reasons for use were recorded and analyzed with appropriate statistical tools. Causality assessment was performed using Naranjo scale.
Results: Eleven of 3708 patients who received either ioversol or iohexol developed ADRs (i.e. 0.3% of patients). The most common ADR was rigor. The incidences of mild, moderate and severe reactions were 55%, 36% and 9%, respectively. Average median age, weight, and dose used were 35 years, 66 kg and 70 ml, respectively. All the ADRs were early (occurred within 1 hr of CM administration). Due to logical constraints, the follow-up of these patients was not possible and hence late ADRs were not captured. The common concomitant medication used was pantoprazole (63.63% of patients). The difference in the incidence of ADRs by age distribution (Group 1 - Iohexol, Group 2 - Ioversol) and weight distribution was not statistically significant ($p=0.75$ and $p=0.18$, respectively). Causality analysis revealed that all the ADRs were possible (Score of 4). Interestingly, the incidence of reactions was noted to be higher in patients with a history of gastro intestinal disorders (45.45%).
Conclusions: This pilot study reveals that adverse reactions to NICM are rare and severe reactions are less common among the patients of Indian origin. However, a larger multicentric study across the country should be carried out to understand the safety profile of these CM better among the Indian population.

Keywords: Adverse drug reaction, Non-ionic contrast medium, Indian population, Pharmacovigilance

INTRODUCTION

Non-ionic contrast medium (NICM) is currently amongst the most commonly used drugs in radiodiagnosis. Modern iodinated NICM are safe, adverse drug reactions (ADRs) exist but they are uncommon. It was first introduced in 1950s, it has now become the standard in diagnostic imaging due to its high level of safety and tolerability and is currently the most commonly used drug in radiological imaging.[1] No drug is absolutely safe, and radio contrast agents are not exceptions. The existence of adverse acute reactions has long been well established in the literature in large scale prospective studies.[2,3] Imaging modality using contrast media (CM) is increasing. Adverse reactions to CM range from a mild inconvenience, such as nausea, vomiting, flushing, and pruritus, to life-threatening hypotension, anaphylactoid reaction, Stevens–Johnson syndrome, and toxic epidermal necrolysis.[4,5]

The adverse reactions occurring after CM administration may be divided into three different types: allergic and non-allergic hypersensitivity reactions, toxic reactions and events unrelated to CM exposure.[6] The CM may be divided into higher osmolar, ionic agent and lower osmolar, non-ionic agent. The former dissociate into ions when dissolved in water and are contained in an iodinated benzene ring.[7] As a result, ionic agents have a higher osmolarity than blood, and the latter is less likely to cause an adverse reaction. Hence, the use of NICM is increasing despite its higher cost.

To the best of our knowledge, the safety profile of NICM has not been investigated in India, therefore we conducted this study to understand the safety profile of these CM and improve their safe usage in the Indian population.

METHODS

A prospective, unicentric study was conducted in a tertiary care hospital in Kolkata in Eastern India.

Study protocol was duly approved by the Institutional Ethics Committee of the hospital.

Written informed consent was taken from all the patient included in the study.

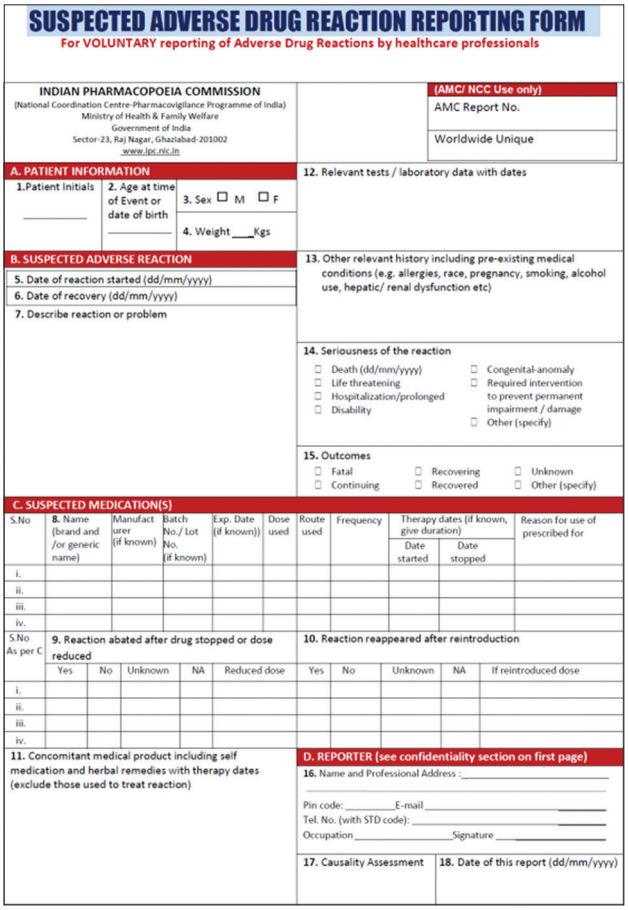
The study included all patients in the radiology department who received either ioversol or iohexol for diagnostic procedures, except in those who were considered high risk by the consultant radiologist and had a previous history of ADRs.

The hospital nursing staffs posted at the radiology department was trained by the consultant clinical pharmacologist to report ADRs associated with usage of NICM in the radiology department in the prescribed form of suspected ADR reporting form developed by the Indian Pharmacopoeia Commission of India, National Coordinator Centre - Pharmacovigilance Programme of India, Ministry of Health and Family Welfare, Government of India,[8] as shown in Figure 1. Dedicated training was conducted every month for 6 months prior to study initiation by the clinical pharmacologist, in which the methodology for capturing suspected ADRs was discussed. The radiologist of the hospital helped in detecting the case of ADR, which was then captured by the nursing staff and reported to the clinical pharmacology department where the causality assessment was performed. The prescribed form requested information for the sex, age, date of reaction started and date of recovery, name of CM, dose used, route used, duration of therapy, reason for use, seriousness of the reaction, outcome. Once reported, these forms were sent to the clinical pharmacology unit where the causality assessment was done with Naranjo Scale.[9]

We collected the data that were reported from July 2011 to July 2012 and were analyzed with appropriate statistical tools.

RESULTS

From Table 1, between July 2011 and July 2012, we got 11 cases of ADR reports. In these reports, seven patients were male, and four patients were female. Average median age was 35 years. In 2011, iohexol was used as NICM and in 2012, ioversol was used. The results were graphically represented in Figures 2 and 3. Average median used dose was 70 ml and route of dose was intravenous (IV) and oral.



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
www.ipc.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique

A. PATIENT INFORMATION
1.Patient Initials | 2. Age at time of Event or date of birth | 3. Sex ☐ M ☐ F | 4. Weight ___Kgs

12. Relevant tests / laboratory data with dates

B. SUSPECTED ADVERSE REACTION
5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction
☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to prevent permanent impairment / damage
☐ Hospitalization/prolonged ☐ Other (specify)
☐ Disability

15. Outcomes
☐ Fatal ☐ Recovering ☐ Unknown
☐ Continuing ☐ Recovered ☐ Other (specify)

C. SUSPECTED MEDICATION(S)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known))	Dose used	Route used	Frequency	Therapy dates (if known, give duration) Date started	Date stopped	Reason for use of prescribed for
i.										
ii.										
iii.										
iv.										

S.No As per C	9. Reaction abated after drug stopped or dose reduced: Yes	No	Unknown	NA	Reduced dose	10. Reaction reappeared after reintroduction: Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. REPORTER (see confidentiality section on first page)
16. Name and Professional Address : _____
Pin code: _____ E-mail _____
Tel. No. (with STD code): _____
Occupation _____ Signature _____

17. Causality Assessment | 18. Date of this report (dd/mm/yyyy)

Figure 1: Suspected adverse drug reaction reporting form of Central Drugs Standard Control Organisation.

Table 1: NICM adverse reaction reporting summary.

Reaction date	Sex	Age (years)	Average median±IQR age (years)	Weight (kg)	Average median±IQR Wt (kg)	CM	Dose used	Average median±IQR dose used (ml)	Route used
11.07.2011	M	42	35±23	55	66±14.333	Iohexol	80 ml	70±32.500	IV
20.07.2011	M	25		70		Iohexol	75 ml		IV
13.11.2011	F	45		70		Iohexol	70 ml		IV
19.11.2011	M	25		51		Iohexol	70 ml		IV
23.11.2011	M	32		73		Iohexol	70 ml		IV
02.02.2012	M	70		65		Ioversol	70 ml 30 ml		IV Oral
17.02.2012	F	50		69.7		Ioversol	80 ml 40 ml		IV Oral
25.02.2012	F	25		59		Ioversol	80 ml 40 ml		IV Oral
09.03.2012	F	73		66		Ioversol	40 ml		Oral
19.07.2012	M	35		52		Ioversol	70 ml		IV
28.07.2012	M	33		73		Ioversol	70 ml 50 ml		IV Oral

IV: Intrevanous, NICM: Non-ionic contrast medium, IQR: Inter quartile range, CM: Contrast media

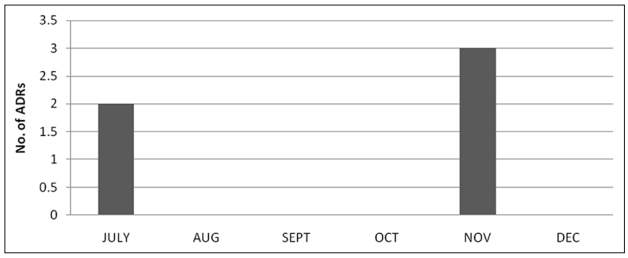


Figure 2: Number of adverse drug reactions reported in 2011.

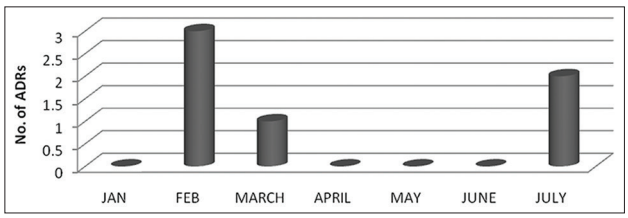


Figure 3: Number of adverse drug reactions reported in 2012.

In our study, the rigors were self-limiting, requiring no medical interventional support, except in one case. Hence, they were classified as mild reactions. Moderate and severe reactions represent serious degrees of reactions that need immediate medical management,[10] which was missing in our case.

Totally 11 patients out of 3708 patients of Indian origin showed ADRs. Table 2 gives the overall incidence of ADRs as well as the incidence of reactions classified according to the severity. Symptomatic treatment without medical intervention was given in the majority of patients who suffered ADRs. Rigor was managed by providing blankets

Table 2: Incidence of adverse reaction to radio CM.

Reaction	Number (n=11)	Incidence (%)
Total	11	0.3
Mild	6	55
Moderate	4	36
Severe	1	9

CM: Contrast media

and warming the patient; no medical treatment was required. Hence, they were categorized as mild rigors, except in one case (case 6 of Table 3) where severe rigor was managed by injections of anti-histamines (phenergan) and steroids. Vomiting was controlled by giving ondansetron injection and breathing difficulty was managed in ER by providing oxygen supplementation.

The incidence of reactions according to age is given in Table 4. The difference in the incidence of ADRs by age distribution (Group 1 - Iohexol, Group 2 - Ioversol) was not statistically significant (p=0.75).

The difference in the incidence of ADRs by weight distribution (Group 1 - Iohexol, Group 2 - Ioversol) given in Table 5 was not statistically significant (p=0.18).

The difference in the incidence of ADRs by weight distribution given in Table 6 (Group 1 - Male, Group 2 - Female) was not statistically significant (p=0.48).

Table 3 gives the details of ADRs experienced.

Causality assessment was done for each adverse reaction report with Naranjo Scale as shown in Table 7. All of the

Table 3: Details of ADRs.

ADRs	Class of ADR	Type of ADR	Reason for use	Average number of concomitant medication	Final diagnosis
Fever, rigor	Moderate	Early	Renal angiography	3.64	Renal donor
Fever, rigor	Moderate	Early	Kidney, ureter, bladder CECT		Hemorrhagic left renal cyst, acute viral hepatitis a, uncomplicated cholesterosis GB
Rigor	Mild	Early	Upper abdomen CECT		Acute pancreatitis
Rigor	Mild	Early	Whole abdomen CECT		Fecal discharge through the abdominal drain in the RIF
Rigor	Mild	Early	Whole abdomen CECT		Infective diarrhea, diabetes mellitus
Severe rigor	Severe	Early	CT scan of chest and upper abdomen		Pneumonia With diabetes mellitus
Rigor	Mild	Early	CT scan of whole abdomen		Type II diabetes mellitus, hypertension, diabetic nephropathy, hypothyroidism, left kidney upper pole abscess
Rigor	Mild	Early	CT scan of whole abdomen		Hyper eosinophilia due to anaphylactic reaction with CM, hepasplenomegaly, enteral gastritis, hypocholemia
Rigor and vomiting	Moderate	Early	Brain plain with contrast		CVA
Rigor	Mild	Early	CT of renal angiography		Renal donor
Rigor and mild breathing difficulty	Moderate	Early	CT scan of whole abdomen		Non ulcer dyspepsia, fatty liver

ADR: Adverse drug reaction, CT: Computed tomography, CECT: Contrast enhanced CT, GB: Gall bladder, RIF: Right iliac fossa, CVA: Cerebral vascular accident, CM: Contrast medium

Table 4: Incidence of adverse reactions by age distribution.

Age (years)	Iohexol	Ioversol	Total incidence	p value
25-34	3	2	5	0.75
35-44	1	1	2	
45-54	1	1	2	
>55	0	2	2	

Table 5: Incidence of adverse reactions by weight distribution (Group 1 - iohexol, Group 2 - ioversol).

Weight (kg)	Iohexol	Ioversol	Total incidence	p value
51-60	2	2	4	0.18
61-70	2	3	5	
>70	1	1	2	

11 (male - 7, female - 4) cases scored 4, which signify they all are possible adverse reactions.

Table 6: Incidence of ADRs by weight distribution (Group 1 - male, Group 2 - female).

Weight (kg)	Male	Female	Total incidence	p value
25-34	4	1	5	0.48
35-44	2	0	2	
45-54	0	2	2	
>55	1	1	2	

ADRs: Adverse drug reactions

In our study, male patients (63.63%) were found to be more prone to adverse reactions than the female patients (36.36%). Patients of age group 25-34 (5 out of 11) faced more adverse reactions than the others. The average median dose of 70 ml of CM was responsible for the reactions. The evaluation of the final diagnosis revealed gastro intestinal (GI) disorders as the most common clinical diagnosis among the patients experiencing ADRs. Most of these patients with GI disorders experiencing ADRs were administered IV CM. Hence, the authors feel that patients with a history of GI disorders are more prone to develop ADRs with these agents.

Table 7: Causality assessment.

Patient no.	Naranjo scale score	Classification
1	4	Possible
2	4	Possible
3	4	Possible
4	4	Possible
5	4	Possible
6	4	Possible
7	4	Possible
8	4	Possible
9	4	Possible
10	4	Possible
11	4	Possible

As rechallenge was not possible on ethical grounds, these associations can be concluded as risk factors and radiologists should be careful while administering these agents among such patient population.

DISCUSSION

In our study, a total of 3708 administrations of NICM were studied, of which only 11 cases of ADRs were reported (0.3% reaction rate).We observed more adverse reactions in the age range of 25-34 years (5 out of 11) and reaction rate is higher for male patients as compared to the female (4 female and 7 male). The incidence of mild, moderate and severe reactions was 54.54%, 36.36% and 9.09% respectively. Our observed reaction rate is comparable with previously reported by Wang et al.,[11] where they got 0.6% of reaction rate on Michigan population. Breathing difficulty and rigors were also observed in their report. 418 (77%) of the contrast reactions were classified as mild, 116 (21%) as moderate and 11 (2%) as severe. In our study, we also found that those patients with predisposing factors such as diabetes mellitus are at an increased risk for developing adverse reactions. In a study conducted in Brighams and Women Hospital by Mortelé et al, in 2005, adverse events were observed in 211 patients (0.7% reaction rate). Women ($p>0.001$) and outpatients ($p>0.001$) had statistically significant higher incidence of adverse events.[12] In a study conducted at St. Mary's Hospital by Jung et al., in 2012, adverse reactions were noted in 62 cases out of total 47,338 cases, 50 cases (80.7%) were categorized as cutaneous adverse reactions (CARs). Among them, there were 24 male and 26 female patients. There was no significant difference between the sexes and CARs occurred in all age groups. The highest occurrence was in the age range of 50-59 years. CARs included urticaria (78%), angioedema (10%), macula popular rash (8%), erythema (2%), and pruritus without rash (2%). Immediate reactions were 92% (46 cases) where late reactions were 8% (4 cases).[13] A study of UCLA School of Medicine, Los Angeles, in 2002, reported the reaction rate to be 6-8% when only ionic CM was used. With the selective use of contrast material, the adverse reaction rate was 0.6% and 0.7% respectively for ionic and non-ionic agents. The rate was decreased to 0.2% with the universal use of non-ionic agents. More than 90% of adverse reactions were allergic.[14] Adverse events were noted in 306 cases of total 13,552 cases in 2007 in a study by Kim et al. The incidence of adverse reactions was 2.3%, and severe reactions were 0.04%. The incidence of immediate reaction was 2.0% and late reactions were 0.3%. Symptoms of immediate and late reactions were nausea/vomiting (22.2%), erythema/pruritus/urticaria (74.2%), angioedema (2.0%) and hypotension (1.6%).[15] In contrast to some published reports, we observed no relationship between the incidence of adverse events and the dose of iodine administered.[16] Cochran et al. speculated that contrast dose might play a role in the incidence of reactions, because 70% of severe reactions occurred in patients receiving higher iodine doses for computed tomography (CT) angiography. However, Cochran et al. were unaware of the exact number of CT examinations performed using a higher contrast dose; therefore, this speculation may be based on a statistical quirk. Our results are also supported by the fact that most of the events are allergic reactions that are not dose-dependent.

In a recent study conducted by Gharekhanloo and Torabian in Iran on new non-ionic contrast agents,[17] mostly mild skin reactions, nausea and vomiting were observed which could be resolved simply. In our study also most reactions were mild in nature (54.54%).

In another recent study conducted on 29,962 patients in an Australian tertiary hospital to examine the incidence of immediate hypersensitivity reactions to IV non-ionic iodinated contrast agents by Ho et al.,[18] there was a relatively low incidence of 0.16% immediate hypersensitivity reactions to non-ionic contrast CT. 70% of the patients had a mild reaction, 23% moderate and 7% severe. It was found that the incidence of immediate hypersensitivity reactions in contrast CT is low and mostly mild, which is comparable to our findings.

CONCLUSION

This pilot work indicates that the use of NICM for radio diagnosis in the patients of Indian origin is safe. There were some limitations in our study, which includes monitoring of ADRs regulated by time limit, because we studied ADRs reported only in patients in the radiology outpatient department. This requires a larger study to assess the long-term outcomes among the patients of Indian origin.

Another limiting factor was the unicentric nature of the study, so larger prospective multicentric study across the country should be carried out in association with radiologists to understand the safety profile of these CM and improve their safe usage in the Indian population. To conclude, adverse reactions to NICM are rare and severe reactions are less common among the Indian population. Most patients recover from their reactions without any long term treatment.

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Ethical approval: Study protocol was duly approved by the Institutional Ethics Committee of the hospital

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