Original Article

Adverse events associated with the use of radiopharmaceuticals: A prospective study from a tertiary care institute

Kanhaiyalal Agrawal, Bikash Ranjan Meher[1], Abhinav Baranwal, Navneet Kumar

Departments of Nuclear Medicine and [1]Pharmacology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Abstract

Introduction: Radiopharmaceuticals (RPs) are used in the diagnosis and management of various cancer and noncancerous conditions. Like those of conventional drugs, the use of RPs may also be associated with the development of various adverse events (AEs). The information obtained from patients about these AEs may empower medical professionals to identify, evaluate, and manage them more efficiently to ensure the safe use of RPs.

Objective: The objective of our study was to assess the type, timing, and frequency of the reported AEs associated with the use of RPs and to establish their causal association as well as to evaluate the outcome of these AEs from the perspective of patients.

Methods: This study was a prospective cohort study conducted on 315 patients who underwent nuclear medicine examination in a tertiary care center for various indications. Relevant data were collected from the participants regarding suspected AEs associated with the use of various RPs. The collected data were objectively analyzed and assessed.

Results: Of 315 patients, 39 (12.3%) developed 59 AEs. All the reported AEs were mild in nature and neither required hospitalization nor caused death of any participants. 37.2% of the reported AEs occurred within 1 h of administration of the RPs and spontaneously resolved within a few hours. Of these 59 AEs, 10 had causal associations (possible or probable) with RPs and were considered adverse drug reaction (ADR). The incidence of ADR in our study was 2.2%.

Conclusion: RPs can cause ADRs though it is less in comparison to conventional drugs. We expect that our study will increase the awareness of AEs associated with the use of RPs among patients and health-care professionals and encourage its reporting.

Keywords: Adverse drug reactions, radionuclides, radiopharmaceuticals, radiotracers

Address for correspondence: Dr. Bikash Ranjan Meher, Department of Pharmacology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.
E-mail: pharm_bikash@aiimsbhubaneswar.edu.in
Received: 20-05-24, **Revised:** 28-06-24, **Accepted:** 03-07-24, **Published:** 10-09-24.

INTRODUCTION

Adverse drug reaction (ADR) is a harmful and unintended response in human beings resulting from the use of drugs for prophylaxis, diagnosis, or treatment of diseases.[1] ADR causes significant morbidity and mortality in patients and increases the overall health-care expenditure.[2-4] Adverse

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.picr_89_24

How to cite this article: Agrawal K, Meher BR, Baranwal A, Kumar N. Adverse events associated with the use of radiopharmaceuticals: A prospective study from a tertiary care institute. Perspect Clin Res 2025;16:87-91.

event (AE) is defined as any untoward occurrence after exposure to a drug irrespective of whether the drug is suspected to be the cause.[5] Radiopharmaceuticals (RPs) are medicinal formulations consisting of both radioactive component and the drug component.[6] They have become an integral component of the health-care delivery system due to the increasing application of nuclear medicine in the diagnosis and treatment of many malignant and nonmalignant conditions. The incidence of AEs associated with RPs is less in comparison to conventional drugs. This could be due to its use in minimal dose for various interventions.[7] However, the possibility of ADRs or AEs to RPs cannot be completely ruled out. There are reports of ADRs associated with the use of RPs like technetium (Tc)-99m methyl diphosphonate (99mTc-MDP), Tc-99m Sesta MIBI (99mTc SestaMIBI), and Iodine-123(I-123).[8-12] These are all either individual case reports reported by clinicians or data obtained from database maintained by different national pharmacovigilance (PV) centers. Voluntary reporting by medical professionals is one of the common methods of reporting ADRs and AEs; however, underreporting is its main drawback.[13] In many countries apart from health-care professionals, patients themselves can report any suspected ADRs or AEs to the ADR monitoring centers. To the best of our knowledge, no study has been conducted in India regarding the reporting of AEs following the administration of RPs. Hence, we conducted this prospective study in patients undergoing nuclear medicine procedures on AEs associated with RPs.

METHODS

Study site

The study was carried out in All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India, which is a tertiary care institute of national importance and an approximately 1000-bedded hospital.

Study design and study population

Our study was a prospective study carried out in patients who underwent nuclear medicine examination at the Nuclear Medicine Department of AIIMS, Bhubaneswar, and who were administered RPs either for diagnostic or therapeutic purposes.

Ethical issue

The study was initiated after obtaining approval from the institutional ethics committee (T/IM-NF/Pharm/21/102). Patients who were scheduled for a nuclear medicine examination and who provided written informed consent were included in the study. The participants were informed about the objectives of the study as well as explained about the contents of the questionnaire.

Study tool and data collection

A study tool was designed to gather relevant information from the patients. The study tool was designed by the combined effort of all investigators following similar kind of previous studies.[14,15] It contained questions about the demographic details of patients, their current complaints, current diagnosis, comorbid conditions, past history of nuclear medicine examination, past history of drug allergy, dose, and routes of administration of the administered RPs. The content validity of the questionnaire was carried out by experts to assess the relevance, clarity, and simplicity of the questions. Then, the study tools were pretested in 30 patients to assess the appropriateness, relevance, and comprehensibility of the questions. Then, the modified questionnaire was used for data collection. The data were collected regarding any suspected AEs following the administration of RP immediately, within 24 h, and between 2nd and 7th days. Information regarding AEs immediately after administration of RP was collected by face-to-face interviews, whereas AEs within 24 h were collected on the next day and AEs between the 2nd and 7th day were collected on the 7th day through telephonic conversation. Causality assessment is an important part of PV, which essentially means finding the causal association between suspected AEs and administered drugs. As there is no specific method to assess the causal relationship between suspected ADRs and RPs, we adapted the algorithm used by Silberstein and Ryan and the methods described by Schreuder *et al*. to categorize the probability of causation.[14,15] According to Silberstein *et al*., there are four categories of causal association, namely, not related, unlikely, possible, or probable.[15] This categorization is slightly different from the WHO-UMC Causality Assessment Scale, which is a widely used method for the evaluation of causal association in the case of conventional drugs, and is classified into six categories, namely, certain, probable, possible, unlikely, unclassified, and unclassifiable.[16]

Statistical analysis

All the data were entered into the Microsoft Excel sheet. Categorical data were represented in proportions. The difference between the groups was assessed using the Chi-square test. A sample size of 139 was required to produce a 95% confidence interval of 0.05 precision, assuming that the prevalence of AEs associated with RPs was 10%.[14]

RESULTS

Of the 315 patients, 185 (58.7%) were male and 130 (41.7%) were female. In our study, 234 (74.2%) patients

had not undergone any nuclear medicine examination previously, whereas 81 (25.7%) had undergone some nuclear medicine examination before. Twenty-nine (9.2%) participants had a history of drug allergy [Table 1]. The majority of patients (n = 301, 95.5%) were administered RPs for diagnostic purposes, whereas only 14 (4.5%) patients received RPs for therapeutic reasons. Tc99-MDP (n = 122, 38.7%) was the most commonly administered RP in our study. The other three commonly used RPs in our study were Technetium-99m ethylene dicysteine (Tc99m-EC) (n = 45, 19.4%), I-131 (n = 36, 11.4%), and technetium-99m - dimercaptosuccinic acid (Tc99-DMSA) (n = 25, 8.01%), whereas Technetium(99m) hepatobiliary iminodiacetic acid (Tc99m-HIDA) (n = 1) and Sm-153 ethylene diamine tetramethylene phosphonate (EDTMP) (n = 1) were the least commonly used RPs [Table 2]. Of 315 patients, 39 (12.3%) patients reported 59 AEs, with an average of 1.5 AEs per patient. Of 59 AEs, 53 (89.9%) were reported with diagnostic RP and 6 (10.1%) were reported with therapeutic RP. Among the diagnostic RPs, the maximum number of AE (n = 18, 30.5%) was reported with Tc99-MDP. Twenty-two (37.2%) AEs were reported immediately after the administration of RP, whereas the rest were reported between 1 and 24 h and none were reported beyond 24 h [Table 3]. The most commonly reported AEs were giddiness, headache, dyspnea, and vomiting [Table 4]. All AEs resolved spontaneously or by symptomatic treatment and did not require any hospitalization. None of the AEs were serious in nature. Causality assessment revealed that among the suspected and reported AEs, 48 belonged to the "not related category," 7 belonged to the "possible," and 3 belonged to the "probable" category. These 10 AEs were considered ADRs, which occurred in 7 (2.2%) out of 315 patients. In our study, we did not find any association of gender (P = 0.08), RP types (diagnostic or therapeutic) (P = 0.20), comorbidity (P = 0.70), past history of nuclear medicine examination (P = 0.44), and past drug allergy (P = 0.40) with reported AEs [Table 1].

Table 1: Characteristics of the patients included in the study (n=315)

Category	Total (n=315)	Reported AEs	Did not report AEs	*P*
Gender				
Male	185	18	167	0.08
Female	130	21	109	
RPs				
Diagnostic	301	36	266	0.20
Therapeutic	14	3	10	
Comorbidity				
Yes	79	9	70	0.70
No	236	30	206	
Past history of nuclear medicine examination				
Yes	81	12	69	0.44
No	234	27	207	
Past history of drug allergy				
Yes	29	5	24	0.40
No	286	34	252	

AEs=Adverse events, RPs=Radiopharmaceuticals

DISCUSSION

Although Schreuder *et al.* had conducted a study about the prevalence of AEs associated with the use of various RPs, our study is the first study conducted in India about the same. Though, reporting of any suspected AEs is not mandatory for any healthcare professionals in India, it is better to report to safeguard the health of patients and promote safe use of medicines. Global collaboration and cooperation and initiation of PV have substantially increased the reporting of suspected adverse drug events

Table 2: Frequency of adverse events to radiopharmaceuticals as reported by patients

Diagnostic/ therapeutic	RP	Number of patients	AEs			
			Probable	Possible	Unlikely	Not related
Diagnostic	Tc99-MDP	122	0	3	0	15
	FDG	23	0	0	0	3
	Tc99m-DTPA	21	0	0	0	4
	Tc99-DMSA	25	0	0	0	9
	Tc99m-EC	45	0	2	0	4
	Tc99m-MIBI	21	0	0	0	0
	I-131	23	2	0	0	4
	Tc99m-mebrofenin	7	1	1	0	5
	Tc99-SC	4	0	0	0	0
	Tc99m-HIDA	1	0	0	0	0
	99mTcO4-	2	0	0	0	0
	Sulfur colloid	6	0	0	0	0
	RBC labeled Tc 99m	1	0	0	0	0
Therapeutic	I-131	13	0	1	1	4
	Sm-153 EDTMP	1	0	0	0	0
-		315	3	7	1	48

AEs=Adverse events, MDP=Methyl diphosphonate, RP=Radiopharmaceutical, RBC=Red blood cell, FDG=Flurodeoxyglucose, DTPA=Diethylenetriaminepentaacetic acid, DMSA=Dimercapto succinic acid, MIBI=Myocardial perfusion imaging, EC=Ethylene dicysteine, HIDA=Hepatobiliary iminodiacetic acid, EDTMP=Ethylenediaminetetramethylene phosphonic acid

in the last few years. PV program has helped a great deal in increasing the reporting ADRs in India. The use of RPs worldwide including India has increased manifolds in recent times; however, there are not much studies undertaken to evaluate whether the use of RPs for therapeutic or diagnostic purposes in malignant or nonmalignant conditions could lead to any untoward AEs like that of conventional drugs.[6] Causality assessment is an important part of PV, which essentially means finding the causal association between suspected AEs and administered drugs. In our study, we adapted the algorithm followed by Silberstein *et al*. to categorize the probability of causation.[15] Causality assessment of all the reported AEs in our study has shown that 81% of the suspected AEs were not related to the administration of RP and could have happened due to the medical illness of patients or concomitant medical conditions or for some unknown reasons. This fear factor may sometimes lead to nonspecific symptoms. The most reported AEs in this study were mild in nature, did not require any medical consultation or hospitalization, and resolved spontaneously. None of the AEs caused any disability or death. Many patients had general complaints such as headache, giddiness, pruritus, or swelling at the administration site. This type of finding was also recorded by Schreuder *et al*. in their study,[14] where they found that the frequency of ADRs associated with RPs as reported by patients was 2.8%. None of the patients developed any serious ADRs and none of them required hospitalization due to ADRs in our study. One of the earliest studies regarding the prevalence of AEs due to the use of RPs was conducted by Silberstein and Ryan[15] It was a prospective multicenter study, in which they analyzed 783,524 radiopharmaceutical doses and found 18 suspected events. Similarly, few other reviews also reported a low prevalence of AE among RP users. Matsuda et al. had conducted a survey for examining the association between RPs and AEs to RPs from 1975 and 2017 in Japan. They found that 1099 adverse reactions were reported from 46,645,580 RP administrations, hence a prevalence of 2.4 adverse reactions per 100,000 administrations.[17] Kennedy-Dixon *et al*. conducted a study to evaluate RP-associated ADRs reported to the British Nuclear Medicine Society (BNMS) from 2007 to 2016 and observed that the prevalence of adverse reactions to RPs reported in the BNMS database remained low, with a frequency of 3.1 reports per 100,000 administrations in 2013 and 2.5 per 100,000 administrations in 2015.[18] Evaluation of RP-related adverse reactions reported to the French Pharmacovigilance Database between 1989 and 2013 by Laroche *et al*. identified 304 reports. Out of 304 ADRs, 43% were classified as serious.[19]

Table 3: Frequency of adverse events to radiopharmaceuticals at different time points

	At 0 h	1–24 h	2–7 days
Tc99-MDP	8	10	0
FDG	3	0	0
Tc99m-DTPA	2	2	0
Tc99-DMSA	1	8	0
Tc99m-EC	2	4	0
I-131	5	7	0
Tc99m-mebrofenin	1	6	0

MDP=Methyl diphosphonate, FDG=Flurodeoxyglucose, DTPA=Diethylenetriaminepentaacetic acid, DMSA=Dimercapto succinic acid, EC=Ethylene dicysteine

The relatively smaller number of AEs in all the studies compared to our study can be explained by the fact that in those times, PV practice in general and nuclear medicine in particular were nascent or nonexistent. Due to the lack of awareness of PV among health-care professionals, underreporting of AE was very common. However,RPs drug development has rapidly expanded in last few years and their use has increased in patient care. Similarly, PV program has also expanded and consequently suspected AEs reporting has also increased in last decade. This might be the reason for reporting a greater number of suspected AEs in this study as well as study conducted by Silberstein et al compared to study conducted by Mastuda *et al*.[15,17] The inherent strengths of our study are that apart from studying the frequency and type of AEs, we studied the outcome of these AEs from the perspective of patients. We believe that this study will provide insight and contribute to the area of PV and safe use of RPs, in which not much research has been performed.

CONCLUSION

We studied the AEs associated with the use of RPs and found that the incidence of the reported ADRs to RPs was 2.2%, which is less than conventional drugs

Table 4: Overview of adverse drug reaction

RPs	Total number of patients	Types of ADRs	Total number of ADRs
Tc99-MDP	2	Pruritus, discomfort, headache	3
Tc99m-EC	1	Giddiness, dyspnea	2
Tc99m-mebrofenin	2	Pain, dizziness	2
I-131	2	Dysgeusia, headache, swelling of the neck	3
-	7		10

RPs=Radiopharmaceuticals, ADRs=Adverse drug reactions, MDP=Methyl diphosphonate, EC=Ethylene dicysteine

where it is found to be between 5% and 10%.[1] Most of the ADRs and AEs were mild in nature and resolved spontaneously. This study will hopefully increase the awareness of AEs associated with the use of RPs among patients and health-care professionals and facilitate their reporting.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond) 2016;16:481-5.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 1998;279:1200-5.
3. Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993;27:832-40.
4. Rodríguez-Monguió R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. Pharmacoeconomics 2003;21:623-50.
5. Adverse Event. Available from: https://www.ema.europa.eu/en/glossary/adverse-event. [Last accessed on 2023 Dec 15].
6. Meher BR, Agrawal K, Padhy BM. The global perspective of pharmacovigilance in nuclear medicine practice. Indian J Nucl Med 2018;33:269-72.
7. Hesslewood SR, Keeling DH. Frequency of adverse reactions to radiopharmaceuticals in Europe. Eur J Nucl Med 1997;24:1179-82.
8. Balan KK, Choudhary AK, Balan A, Wishart G. Severe systemic reaction to (99m) Tc-methylene diphosphonate: A case report. J Nucl Med Technol 2003;31:76-8.
9. Doukaki S, Aricò M, Bongiorno MR. Erythroderma related to the administration of 99mTc-sestamibi: The first report. J Nucl Cardiol 2010;17:520-2.
10. Makaryus JN, Makaryus AN, Azer V, Diamond JA. Angioedema after injection of Tc-99m sestamibi tracer during adenosine nuclear stress testing. J Nucl Cardiol 2008;15:e26-7.
11. Schreuder N, Koopman D, Jager PL, Kosterink JG, van Puijenbroek E. Adverse events of diagnostic radiopharmaceuticals: A systematic review. Semin Nucl Med 2019;49:382-410.
12. Meher BR, Agrawal K, Gnanasegaran G. Review of adverse reactions associated with the use of common diagnostic radiopharmaceuticals. Indian J Nucl Med 2021;36:163-7.
13. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: A systematic review. Drug Saf 2006;29:385-96.
14. Schreuder N, Jacobs NA, Jager PL, Kosterink JG, van Puijenbroek EP. Patient-reported adverse events of radiopharmaceuticals: A prospective study of 1002 patients. Drug Saf 2021;44:211-22.
15. Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med 1996;37:185-92.
16. The Use of the WHO-UMC System for Standardised case Causality Assessment. Available from: https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf. [Last accessed on 2023 Dec 18].
17. Matsuda H, Uehara T, Okazawa H, Mizumura S, Yokoyama K, Yoshimura M, *et al*. Full report on a survey of adverse reactions to radiopharmaceuticals from 1975 to 2017 in Japan. Ann Nucl Med 2020;34:299-304.
18. Kennedy-Dixon TG, Gossell-Williams M, Cooper M, Trabelsi M, Vinjamuri S. Evaluation of radiopharmaceutical adverse reaction reports to the British Nuclear Medicine Society from 2007 to 2016. J Nucl Med 2017;58:2010-2.
19. Laroche ML, Quelven I, Mazère J, Merle L. Adverse reactions to radiopharmaceuticals in France: Analysis of the national pharmacovigilance database. Ann Pharmacother 2015;49:39-47.