

## Review of Adverse Reactions Associated with the Use of Common Diagnostic Radiopharmaceuticals

### Abstract

Radiopharmaceuticals are used in the diagnosis and management of various diseases. There are several reports of adverse reactions related to the use of radiopharmaceuticals, though it is not as common as conventional drugs. Adverse reactions related to radiopharmaceuticals have been not widely reported and documented. In this review, we have tried to summarize the adverse reactions associated with some of the commonly used radiopharmaceuticals.

**Keywords:** *Adverse drug reaction, adverse events, radionuclides, radiotracers, side effects*

### Introduction

Adverse drug reaction (ADR) is a common occurrence in clinical practice. It is responsible for significant morbidity, mortality, and the overall increase in patients' health-care expenditure.<sup>[1,2]</sup> ADR and the side effect are not the same. ADR is defined as "a response to a drug that is noxious and unintended, and which occurs at doses normally used in human beings for prophylaxis, diagnosis or therapy of disease or the modification of physiological function.<sup>[3]</sup>" Side effect of a drug is "any unintended effects occurring at the normal dose and related to that particular drug's pharmacological properties.<sup>[3]</sup>"

Radiopharmaceuticals (medicinal radio compounds) are medicinal formulations containing both radioactive component and the drug component.<sup>[4]</sup> They have become indispensable to the health-care system because of their broader application in diagnosis and therapy of various benign and malignant diseases.<sup>[5,6]</sup>

Unlike traditional drugs, adverse reactions with radiopharmaceuticals are relatively uncommon. A possible explanation could be that radiopharmaceuticals are distinct from conventional pharmaceutical agents. Usually, they do not exhibit pharmacological effects, dose-response relationships, and are administered in minute quantity for a limited number of times to patients.<sup>[7]</sup> The British Nuclear Medicine Society (BNMS) maintains

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an online database of adverse reactions to radiopharmaceuticals (ARRPs). The prevalence of ARRs reported in the BNMS database was very less, only 3.1 and 2.5 in 2013 and 2015, respectively, per 100,000 administrations of radiopharmaceuticals. Most of those reported reactions were trivial reactions such as skin rash, pruritus, and vomiting.<sup>[8]</sup> However, national pharmacovigilance database of France revealed 304 reports of ARRs between the years 1989 and 2013. Of those, 131 (43%) were classified as serious adverse events, which led to 12 deaths, 15 life-threatening complications, 89 patients required hospitalization, and 15 other serious conditions.<sup>[9]</sup> Similarly, there are instances when radiopharmaceutical agents such as Technetium-99m (<sup>99m</sup>Tc) Fanolesomab had to be withdrawn from use due to severe adverse reactions leading to life-threatening events and death.<sup>[10]</sup> Therefore, though the chance of an adverse reaction following the radiopharmaceutical agent's administration is less in comparison to conventional pharmaceutical agents, the possibility still exists. Hence, it is crucial to record any untoward occurrences associated with their use.

Our review article's content is based on a narrative literature review undertaken with the use of various scientific and pharmacovigilance databases. Our literature review focused mainly on the adverse reactions observed with some of the commonly used diagnostic radiopharmaceuticals [Table 1].

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## Adverse Reactions to Single-Photon-Emission Computed Tomography Radiopharmaceuticals

### Technetium-99m methyl diphosphonate

$^{99m}\text{Tc}$  methyl diphosphonate ( $^{99m}\text{Tc}$ -MDP) is a commonly used radiopharmaceutical for the bone scintigraphy. It is one of the common examples of radiopharmaceuticals that cause adverse effects. Erythema, nausea, vomiting, and malaise are typical adverse reactions associated with  $^{99m}\text{Tc}$ -MDP.<sup>[11-13]</sup>

There are also reports of other types of reactions associated with  $^{99m}\text{Tc}$  MDP. Garcia-Souto *et al.* had reported a skin reaction following the administration of  $^{99m}\text{Tc}$  diphosphonate. In a patient referred for a bone scan, hyperpigmented linear lesions appeared at the injection site in the forearm after the bone scan. The patient did not have any history of trauma. The patient also did not have any pain or itching. The patient informed that lesions had resolved spontaneously, leaving slight residual hyperpigmentation at medical consultation.<sup>[14]</sup>

Similarly, Balan *et al.* had reported an incidence of severe systemic reaction in a 42-year-old female suffering from breast carcinoma following the administration of  $^{99m}\text{Tc}$  MDP. After 24 h of  $^{99m}\text{Tc}$  MDP injection, the patient sensed uneasiness. Subsequently, an erythematous rash was developed on the trunk and around the eyes accompanied by puffiness. She also developed oliguria and jaundice. His postscan biochemical test was compared with that of pre-scan, and the findings were suggestive of abnormal liver and kidney function. The patient was managed with a regime of intravenous fluids and corticosteroids, and her renal and liver function became normal 15 and 21 days after the bone scan, respectively. Her skin manifestations resolved within 1 week.<sup>[15]</sup>

### Technetium-99m SestaMIBI

$^{99m}\text{Tc}$  SestaMIBI is commonly used for parathyroid scintigraphy and myocardial perfusion imaging. Many patients had developed adverse reactions following the administration of  $^{99m}\text{Tc}$ -SestaMIBI. The reported adverse reactions include vomiting, malaise, and some severe reactions such as generalized exfoliative dermatitis, angioedema, and erythema multiforme.<sup>[16,17]</sup> A case report by Thompson *et al.* describes an adverse reaction to  $^{99m}\text{Tc}$ -SestaMIBI 48 h after administration. The patient developed an erythematous papulovesicular rash on the trunk, arms, and scalp with target lesions suggestive of erythema multiforme. The patient had no history of drug allergy or any dermatological disorders.<sup>[18]</sup> There are reports of patients developing angioedema and anaphylaxis following injection of  $^{99m}\text{Tc}$ -SestaMIBI during nuclear stress testing for suspected coronary artery disease.<sup>[19,20]</sup>

### Technetium-99m sulfur colloid

$^{99m}\text{Tc}$ -sulfur colloid is a commonly used radiopharmaceutical for liver/spleen scintigraphy, lymphoscintigraphy, and gastric emptying scintigraphy. Some of the common adverse events reported with the use of  $^{99m}\text{Tc}$ -sulfur colloid were injection-site pain, fever, and mild hypersensitivity reaction. Rare serious adverse events were also reported with the administration of  $^{99m}\text{Tc}$ -sulfur colloid. One patient developed an anaphylactic reaction followed by renal failure and another patient experienced a loss of consciousness.<sup>[16,21]</sup>

### Technetium-99m nanocolloid

$^{99m}\text{Tc}$ -nanocolloid is used for sentinel node detection and bone marrow scintigraphy. It is used for bone marrow scintigraphy and lymphoscintigraphy. Adverse reaction to this radiopharmaceutical is uncommon. However, there are few reports of Type-I hypersensitivity reaction manifested as urticaria, generalized, erythema, and angioedema following administration of  $^{99m}\text{Tc}$ -nanocolloid.<sup>[22]</sup>

### Technetium-99m technegas

$^{99m}\text{Tc}$ -technegas is used for lung perfusion imaging. The adverse event associated with use of  $^{99m}\text{Tc}$ -technegas was low oxygen saturation. A study done in series of patients undergoing ventilation scintigraphy transient decrease in oxygen saturation was observed in 87% of patients. In preoxygenated patients, fall in oxygen saturation was less than those who were not preoxygenated.<sup>[23]</sup>

### Technetium-99m pertechnetate

$^{99m}\text{Tc}$ -pertechnetate is used as a radiopharmaceutical for various indications such as thyroid scintigraphy, testicular scintigraphy, and Meckel diverticulum scan. There are many reports of adverse events following the administration of pertechnetate. The most common were hypersensitivity, rash, and nausea.<sup>[16]</sup> Two serious adverse events were also recorded in which two patients lost consciousness following the injection of  $^{99m}\text{Tc}$  pertechnetate.<sup>[16]</sup>

### Diagnostic $^{123}\text{I}$ and $^{131}\text{I}$ labeled tracers

Radioactive iodine is used in nuclear medicine practice to evaluate thyroid disorder such as hyperthyroidism, hypothyroidism, thyroiditis, goiter, and thyroid cancer. The most common adverse events reported with radioactive iodine use were nausea, vomiting, and back pain. The use of sodium iodide  $^{131}\text{I}$  also sometimes causes hypersensitivity reactions.<sup>[24]</sup>

A few patients developed anaphylactic shocks and ventricular tachycardia following the administration of  $^{131}\text{I}$  nor-cholesterol.<sup>[25]</sup> Similarly, few cases of were also reported along with the use of other  $^{131}\text{I}$  preparations such as  $^{131}\text{I}$  iodohippurate.<sup>[16]</sup>

## Gallium-67 citrate

The use of gallium-67 ( $^{67}\text{Ga}$ ) citrate is not much after the widespread use of fluorodeoxyglucose (FDG) positron-emission tomography-computed tomography (PET-CT).  $^{67}\text{Ga}$ -citrate is used in the infection imaging, sarcoidosis diagnosis, and diagnosis of various malignancies such as Hodgkin's disease and lung cancer. Severe itching, erythema, and rash were observed in some patients following the administration of  $^{67}\text{Ga}$ . The rare occurrence of severe anaphylaxis reactions also has been reported in association with  $^{67}\text{Ga}$  use.

Schreuder *et al.* mentioned about 92 adverse events reported with  $^{67}\text{Ga}$ . Most of those were trivial events such as rash, pruritus, or fever. Only two patients had serious events: one developed bradycardia and another lost consciousness.<sup>[16,26,27]</sup>

## Adverse Events Associated with Positron-Emitting Tracers

### $^{18}\text{F}$ -fluorodeoxyglucose

$^{18}\text{F}$  FDG PET-CT plays a vital role in detecting diagnosis, staging, restaging, and treatment response evaluation in various malignancies. It is also useful in infectious condition, cause of fever of unknown origin, and in cardiology and neurology. The common adverse events reported were minor nonserious reactions such as rash, pruritus, and erythema.<sup>[28,29]</sup> However, Lee *et al.* had reported a case of anaphylactic reaction following the administration of FDG.<sup>[30]</sup> Silberstein had reported a case of adverse reaction where flushing of the face and trunk occurred a few minutes after the injection of FDG and resolved within 2 h of administration.<sup>[31]</sup>

### $^{18}\text{F}$ -fluciclovine

US-FDA has approved  $^{18}\text{F}$ -fluciclovine in 2016 to image patients with suspected prostate cancer recurrence following treatment. Adverse reactions with  $^{18}\text{F}$ -fluciclovine

is uncommon and observed in less than 1% of participants during clinical trials of  $^{18}\text{F}$ -fluciclovine.<sup>[32]</sup> The most common adverse reactions reported were dysgeusia and pain and erythema at the injection site.<sup>[33]</sup>

### $^{68}\text{Ga}$ -DOTATATE

Gallium-68 ( $^{68}\text{Ga}$ ) DOTATATE is a somatostatin receptor analog and a PET diagnostic agent for diagnosis, staging, and response to treatment evaluation of somatostatin receptor-expressing tumors. Adverse events have been reported in patients using this agent. Deppen *et al.* have recorded three events: tachycardia, increase in serum transaminase enzyme, and increase in blood glucose level in four patients after injection of  $^{68}\text{Ga}$ -DOTATATE in 78 patients. These events were observed only for a short period.<sup>[34]</sup>

### $^{68}\text{Ga}$ -DOTATOC

Four adverse events were reported in a study done to assess the safety and tolerability of  $^{68}\text{Ga}$ -DOTATOC in 20 patients with biopsy-proven Grade 1–2 gastroenteropancreatic neuroendocrine tumors and most of them were minor reactions such as rash and pruritus.<sup>[35,36]</sup>

## Conclusion

The prevalence of ARRs is relatively less frequent in comparison to conventional pharmaceutical agents. Most of the ARRs found in the public domain were cases reported long ago. There are very few cases reported in recent times which suggest that the frequency of reaction ARRs appears to be decreasing. The possible explanation could be due to improved quality control of radiopharmaceuticals in recent times. Another possible reason for the low frequency of adverse events in the public domain could be due to the under-reporting of associated adverse events. In general, under-reporting adverse events is a significant issue, whether with conventional pharmaceutical or radiopharmaceutical agents or medical devices.<sup>[3,37]</sup> Medical professionals have cited multiple reasons for this under-reporting of

**Table 1: Summary of adverse reactions and associated radiopharmaceuticals**

Radiopharmaceuticals	Adverse reactions
$^{99\text{m}}\text{Tc}$ MDP	Nausea, vomiting, malaise, hyperpigmented lesions, erythematous rash, systemic reactions <sup>[12-15]</sup>
$^{99\text{m}}\text{Tc}$ SestaMIBI	Vomiting, malaise, exfoliative dermatitis, angioedema, erythema multiform <sup>[17-20]</sup>
$^{99\text{m}}\text{Tc}$ sulphur colloid	Fever, hypersensitivity, injection site pain, anaphylactic reaction, renal failure, loss of consciousness <sup>[16,21]</sup>
$^{99\text{m}}\text{Tc}$ nanocolloid	Generalized erythema, urticaria, angioedema <sup>[22]</sup>
$^{99\text{m}}\text{Tc}$ Technegas	Low oxygen perfusion <sup>[23]</sup>
$^{99\text{m}}\text{Tc}$ Pertechnetate	Rash, nausea, loss of consciousness <sup>[16]</sup>
FDG	Rash, pruritus, erythema, flushing of the face and trunk, sarcoid reaction, anaphylactic reaction <sup>[28,31]</sup>
$^{18}\text{F}$ -Fluciclovine	Injection site pain, injection site erythema and dysgeusia <sup>[33]</sup>
$^{131}\text{I}$ -Sodium iodide	Nausea, vomiting, anaphylactic reaction <sup>[24,25]</sup>
$^{131}\text{I}$ -Nor cholesterol	Anaphylactic shocks and ventricular tachycardia <sup>[25]</sup>
$^{67}\text{Ga}$ -Citrate	Itching, erythema, rash, bradycardia, loss of consciousness <sup>[16,26,27]</sup>
$^{68}\text{Ga}$ -DOTATATE	Tachycardia, increased serum transaminase enzyme, and increased blood glucose <sup>[34]</sup>
$^{68}\text{Ga}$ -DOTATOC	Headache, nausea, dysgeusia, paresthesia <sup>[35,36]</sup>

FDG:  $^{18}\text{F}$ -Fluorodeoxyglucose,  $^{99\text{m}}\text{Tc}$  MDP:  $^{99\text{m}}\text{Tc}$  methyl diphosphonate

adverse events associated with drugs or devices. One of the common reasons is the lack of awareness about the importance of adverse reaction reporting and the existing pharmacovigilance program.

As most of the diagnostic radiopharmaceutical agents are administered only once, rechallenge and test is mostly not feasible. Hence, it is difficult to establish the cause-effect relationship of an adverse event associated with radiopharmaceuticals. This review found that majority of the adverse reaction reported with diagnostic radiopharmaceuticals agents are minor reactions and resolved without any major complications. We have also observed that the incidences of reported adverse reactions are very few in comparison to the dose administered in a total number of patients. Many of the reported events were published in the literature many years back when quality control of radiopharmaceutical preparation was a big issue. Since then, it has improved considerably.

Although adverse reactions following the administration of radiopharmaceuticals to patients are rare, most of the time, they are nonfatal. However, it is still important to regularly record and report any suspected adverse events associated with their use as it will help detect unknown adverse events and create a database for future reference. Further, this will enhance nuclear medicine physician's knowledge of these ARRs leading to better patient care.

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### Conflicts of interest

There are no conflicts of interest.

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