SPECIAL ARTICLE

Adverse reactions to radiopharmaceuticals
Reacciones adversas a radiofármacos

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Resumen
El Real Decreto Legislativo 1/2015, de 24 de julio, consideró los radiofármacos como medicamentos sometidos a la legislación vigente en esta materia. Los radiofármacos, una vez preparados en las unidades de radiofarmacia, son administrados a un paciente para observar las alteraciones o su distribución anormal. A diferencia de los fármacos convencionales, los radiofármacos raramente provocan reacciones adversas; sin embargo, cuando ocurren, suelen causar alarma tanto al paciente como al personal sanitario, además son administrados a los pacientes una sola vez o un número limitado de veces. La mayoría de las reacciones adversas a radiofármacos son leves y requieren tratamiento mínimo o no lo requieren. Dichas reacciones, aunque raras, pueden ocurrir, e incluyen reacciones de sensibilidad con síntomas sistémicos. En general, las reacciones adversas a radiofármacos más comunes son: náusea, disnea, broncoespasmo, disminución de la tensión arterial, picor, rubor, urticaria, resfriado, tos, bradicardia, calambres musculares y mareo. La incidencia de reacciones adversas a radiofármacos comunicadas es baja. El objetivo de esta revisión es describir las reacciones adversas a radiofármacos publicadas más comunes y sus características, administrados con fines diagnósticos o terapéuticos.

KEYWORDS
Radiopharmaceuticals; Adverse effects; Pharmacovigilance.

PALABRAS CLAVE
Radiofármacos; Reacciones adversas; Farmacovigilancia.
Introduction

The Spanish Royal Legislative Decree 1/2015 of July 24 approved the revised text of the Law on guarantees and the rational use of medicines and medical devices. Article 48 addresses radiopharmaceuticals and defines them as any product that, when prepared for use for therapeutic or diagnostic purposes, contains one or more radionuclides (radioactive isotopes).

Radiopharmaceuticals can be used for two purposes: as diagnostic agents (those containing an isotope that emits photons or a radiation) or as therapeutic agents (whose isotope emits α or β particles). Radiopharmaceuticals have to be produced under special conditions that involve radiation protection and aseptic preparation. Working with radiopharmaceuticals is potentially dangerous and the level of risk depends on the type of radiation emitted and the half-life of the isotope used. In medical practice, these agents are used to diagnose and treat a large number of diseases. Radiopharmaceuticals are typically applied in oncology, cardiology, and neurology.

Radiopharmaceuticals are prepared via the reaction of a radionuclide with a precursor or binder in compliance with standards for the extemporaneous preparation of radiopharmaceuticals. Most of the radionuclides used have a short half-life and so they are prepared in situ before administration to patients. Following their preparation in Radiopharmacy Departments, radiopharmaceuticals are administered to patients to observe or quantitate biochemical or physiological processes and thus alterations or abnormal distribution in the body depending on the pathology.

Most radiopharmaceuticals are used in very small quantities and have no pharmacological effect, although adverse reactions (ARs) may occur. Adverse reactions to radiopharmaceuticals (ARRs) are considered to be rare.

On the other hand, adverse events caused by radioactivity can take years to develop and may occur not only in patients but also in exposed workers.

Spanish Order SCO/2733/2007 established that one of the objectives of Radiopharmacy Specialists is to participate in pharmacovigilance (PV) programs.

The aim of the present article is to review the scientific literature on the most significant ARs to diagnostic or therapeutic radiopharmaceuticals as well as their characteristics.

Adverse reactions to radiopharmaceuticals

Unlike conventional drugs, radiopharmaceuticals rarely cause ARs, but when they do occur, they often cause alarm to patients and health care staff. Radiopharmaceuticals are relatively safe, not only because small amounts are injected or ingested, typically in the order of micrograms or less, but also because they are typically administered only once or a limited number of times. In fact, 88% of patients attending a nuclear medicine service (NMS) typically receive a single dose of radiopharmaceutical.

Adverse drug reactions are an unintended response to doses prescribed for humans. An AR may predict risk for future administrations or warrant prevention or targeted treatment, changes in dosage, or withdrawal of the drug. Aronson et al. classified ARs into two types: predictable, dose-dependent, based on the pharmacology of the drug (type A or intrinsic); and unpredictable, not dose dependent, unrelated to the pharmacology of the drug and often immunologically mediated (type B or idiosyncratic). Classification also takes into account the time course of their appearance and severity, as well as the patient’s gender and pathology, which confer susceptibility. Adverse drug reactions are a relevant cause of iatrogenic disease and have many forms of clinical presentation. Although estimations of the incidence of ARs vary, they cause morbidity and mortality and involve significant costs to the health care system. Most ARs are mild and require minimal or no treatment.

Some authors have suggested that therapeutic radiopharmaceuticals could theoretically produce type I hypersensitivity reactions (anaphylactic) following exposure to an antigen. In humans, type I reactions are mediated by immunoglobulin IgE antibodies and are influenced by helper and suppressor T cells. Type I reactions involve a decrease in cyclic adenosine monophosphate (cAMP) that initiates the release of histamine and other substances. These changes manifest in patients as itching, hives, erythema, asthma, and bronchospasm. The musculature of the gastrointestinal tract may also be affected, leading to vomiting and diarrhea.

Radiopharmaceuticals can also cause other types of hypersensitivity reactions, such as type II antibody-dependent (cytotoxic) reactions, in which the target antigens are surface compounds of both normal and altered cells. Type III hypersensitivity reactions are mediated by immune complexes that are deposited in the tissues where the acute inflammatory reaction is initiated. In this type of reaction, complement activation and accumulation of polymorphonuclear leukocytes occur. Finally, type IV hypersensitivity reactions are cell-mediated rather than antibody-mediated and involve two types of reactions: delayed hypersensitivity and cell-mediated cytotoxicity.

The reactions are not usually dose-related unless they are due to overdosage or medication errors involving the radiopharmaceutical, such as extravasation. Grosset et al. noted that 643 ARs were reported out of 1,180 safety evaluable patients. The number of patients with at least 1 ADR was 261 (22%). The number of patients with at least 1 ARR leading to discontinuation from the study was 14 (1%), leading to death was 5 (< 1%), and considered a serious ADR was 44 (4%). The following ARs were considered to be causally related to the radiopharmaceutical: headache (11%), nausea (< 1%), vertigo, dry mouth, hunger, injection site hyperemia, dizziness, paraesthesia, balance disorder, and dysgeusia. Hollopene is a well-tolerated radiopharmaceutical that has no causal relationship with serious ARs.

Description of published adverse reactions to radiopharmaceuticals

We now provide a description of the most relevant published ARs to the radiopharmaceuticals most frequently used in nuclear medicine. We classify radiopharmaceuticals according to the Anatomical Therapeutic Chemical (ATC) classification system, in which radiopharmaceuticals are included in subgroup V09 (diagnostic radiopharmaceuticals) and subgroup V10 (therapeutic radiopharmaceuticals).

Diagnostic radiopharmaceuticals (ATC Group V09)

1. Central Nervous System (V09A)

[99mTc]Tc-Hippuran. The literature has described several reactions associated with the administration of this medicinal product. The most common effect is rash, pain at the injection site, pruritus, and erythema. In a safety analysis, Grosset et al. noted that 643 ARs were reported out of 1,180 safety evaluable patients. The number of patients with at least 1 ADR was 261 (22%). The number of patients with at least 1 ARR leading to discontinuation from the study was 14 (1%), leading to death was 5 (< 1%), and considered a serious ADR was 44 (4%). The following ARs were considered to be causally related to the radiopharmaceutical: headache (11%), nausea (< 1%), vertigo, dry mouth, hunger, injection site hyperemia, dizziness, paraesthesia, balance disorder, and dysgeusia.

2. Skeletal system (ATC Group V09B)

These compounds are grouped under the name “diphosphonates” due to their basic chemical structure, all of which are labelled with technetium. These compounds include [99mTc]Tc-oxodronate ([99mTc]Tc-HDP), [99mTc]Tc-medronate ([99mTc]Tc-MDP, and [99mTc]Tc-DPD (disopyropyl diphosphonate) and are characterised by their involvement in more ARs than other radiopharmaceuticals. One reason for this may be because they have been the most widely used radiopharmaceuticals in nuclear medicine for many years. The most frequent ARs associated with this group are erythematous maculopapular rashes, dermographism, vertigo, nausea, pruritus, hypotension, fever, and nasal congestion.

The most commonly reported ARs of [99mTc]Tc-HDP are rash, oedema, and pruritus. There are also reports of respiratory arrest, loss of consciousness after injection, angioedema and anaphylactic shock, allergic dermatitis, acute generalised pustulosis, and gastrointestinal disorders.

Pérez Iruela et al. reported an ADR after re-exposure with [99mTc]Tc-HDP in a 43-year-old female patient who had attended a NMS for a bone scan, where she was administered a dose of 740 MBq of [99mTc]Tc-HDP. The patient had no previous history of drug or food allergy. Seven months later, she underwent a new gammagraphic study to follow up her disease. She was administered a new dose of 740 MBq of [99mTc]Tc-HDP, which triggered the ADR in the form of a neck rash accompanied by pruritus, headache, and a
tingling sensation on the scalp, nose, and upper lip. She promptly reported these symptoms to the medical staff of the department.

Santos-Oliveira et al.27 reported an ARR that occurred when a patient underwent a bone scan with [99mTc]-Tc-MDP. Within 48 hours of administration, she developed a scratchy sore throat, intense pruritus, and an erythematous rash which persisted for 3 to 4 days. After 10 months, she underwent another bone scan with the same radiopharmaceutical, and after 48 hours she developed a sore throat and a macular-papular rash with pruritus and erythema. Over the passage of a few hours, other symptoms appeared, such as conjunctivitis and hyperemic ulcerated pharynx. Finally, she was given a diagnosis of erythema multiforme due to exposure to the radiopharmaceutical.

The development of a skin rash with [99mTc]-Tc-MDP is the most common allergic reaction reported for this radiopharmaceutical28,29,30. It is also the most widely used diphosphonate in nuclear medicine and accounts for the majority of ARs28,29,30. The most common symptoms following an AR to [99mTc]-Tc-MDP are dermatographism, pruritus, malaise, vertigo, and pruritus.

3. Renal system (ATC Group V09C)

[99mTc]-Tc-Pentetate (diethylenetriaminepentacetate acid, [99mTc]-Tc-DTPA). Cases of paralysis after intrathecal injection have been described. Thus, the Radiopharmacy Committee of the European Association of Nuclear Medicine issued a notice to manufacturers requesting them to specify the prohibition of intrathecal use in the SPC31. In fact, in Europe, this type of severe reaction has been associated with the administration of [99mTc]-Tc-DTPA due to the erroneous formulation of the drug. Almost all of its formulations used for renal studies contain a mixture of the calcium and sodium salt of DTPA and must be administered intravenously. However, a manufacturing labora

tory52,53 issued a notice in 2014 to manufacturers requesting them to specify the prohibition of intrathecal use in the SPC51. Animal studies52 have shown that trisodium salt is able to cause

calcium and magnesium from the cerebrospinal fluid when administered intrathecally, thus depleting ions from the cerebrospinal fluid, which was the cause of paralysis in these 2 patients51,53. This radiopharmaceutical is only authorized for intravenous, oral, and inhalation administration51 and not for intrathecal administration. Thus, the 2 patients experienced a medication error that led to a severe ARR.

4. Haptic and reticuloendothelial system (ATC Group V09D)

[99mTc]-Tc-albumin nanocolloid. This compound is used in liscintigraphy for sentinel lymph node detection in pre-surgery scans for specific tumours21. Hives has been described as the most common AR to albumin colloids20,21,22,23. Cotrina-Morony et al.23 performed the intradermal administration of 74 MBq of [99mTc]-Tc-albumin nanocolloid in the periareolar region in a patient undergoing surgical excision of a sentinel lymph node. After 10 minutes, the patient developed an allergic reaction with macular lesions and intense itching on the palms of the hands, forearms, arms, and anterior chest region, which subsided spontaneously within a few minutes. The patient had no previous history of sensitivity to human albumin. The macular lesions and intense pruritus subsided spontaneously without the administration of steroids or antihistamines.

This radiopharmaceutical is also used for scintigraphic studies of the liver, spleen, and bone marrow23. ARs associated with these scans include pallor, flushing, hypotension, bronchospasm, and dyspnoea24,25.

5. Respiratory system (ATC Group V09E)

[99mTc]-Tc-NAA (macroaggregated albumin). The most frequently described ARs associated with this compound26,27,28,29,30,31 are hypersensitivity, dyspnoea, dizziness, rash, and vomiting. Other ARs include angioedema, cardiac arrest, bradycardia, and respiratory arrest. Three deaths have also been reported26. Of these, two patients had a history of pulmonary hypertension and one had a history of advanced pulmonary vascular disease. The ARs were probably caused by the number and size of the particles26.

In patients with normal pulmonary vascular beds, the administered dose of [99mTc]-Tc-NAA would be 0.1 mg to 4 mg with a particle size of 10 m to 50 m, which would produce an occlusion of 0.1% of the cross-sectional area of the pulmonary vascular bed26. When a patient has a disease involving a reduced number of pulmonary capillaries, blocking part

of the remaining capillaries can lead to respiratory stress. Because of size differences between particles, larger particles will occlude larger vessels, which involves extra care in patients with pulmonary hypertension or other diffuse pulmonary pathologies. In these cases, the dose to be administered should be appropriately calculated according to the number of particles and slowly administered intravenously26.

6. Tumour detection (ATC Group V09I)

[99mTc]-Fluorodeoxyglucose ([99mTc]-FDG). Recently, [99mTc]-FDG Position Emission Tomography (PET) scans have begun to play an important role in the assessment of chemotherapy response and in the detection of primary tumours and metastatic lesions in many tumours. The most commonly described ARs are rash, pruritus, and erythema24, anaphylactic reaction, angioedema, exfoliative dermatitis, seizures, sweating, nausea, vomiting, and diarrhoea25, and two cases of cardiac arrest resulting in death26. The first reported AR to this compound was provided by Silverstein28. This author described the symptomatology as flushing of the face and trunk that appeared minutes after administration and lasted less than 2 hours. In addition to the cutaneous ARR mentioned above, other authors29 have described angioedema, exfoliative dermatitis, hyperhidrosis, local reactions, dysgeusia, and convulsions. Two deaths associated with its use have also been reported26. Rocha et al.30 described an ARR to [99mTc]-FDG in a patient undergoing PET scanning that showed tracer accumulation in the tumour and a mediastinal nodule. Biopsy of the nodule showed a sarcoïd reaction and no pathological tumour cells were found. The altered biodistribution of the radiopharmaceutical was reported as an ARR.

7. Other diagnostic radiopharmaceuticals (ATC Group V09X)

[18F]-Norcholesterol. This radiopharmaceutical has been on the market for more than 30 years28 and its management is well known. It is a nonepinephrine analogue used for adrenal scintigraphic imaging studies in primary aldosteronism and pheochromocytoma. Published ARs suggest the involvement of the adrenergic nervous system, given that some of the ARs resemble pheochromocytoma symptoms28: increased blood pressure, tachycardia, dyspnoea, sweating, etc.). It often produces mild ARs, the most common being nausea, back pain, and flushing28. Other reports include cases of anaphylactic shock 15 minutes after injection, verticullar tachycardia, and one case of an atypical anaphylactic reaction29,30. Kazerooni et al.30 described an ARR that required treatment in a 21-year-old patient with a history of ARs to multiple procedures. The patient developed nausea and dizziness at the end of a slow injection of 74 MBq [18F]-Norcholesterol. This was accompanied by flushing, headache, shortness of breath, and back pain, loss of consciousness for 10 to 20 seconds, tachycardia, and hypertension. After receiving oral diphenhydramine, her symptoms disappeared within 1 hour and her vital signs stabilised. According to the authors30, other patients received injections of the same batch number without experiencing ARs.

Spyridonidis et al.30 assessed the efficacy of [18F]-Norcholesterol in a study that reported two cases of AR. In the first case, a 73-year-old woman underwent a [18F]-Norcholesterol scan to diagnose an inci
dentoma. The patient had received premedication for the scan with oral potassium iodate 24 hours before tracer injection, as indicated in the Summary of Product Characteristics (SPC)31. As soon as the tracer infusion started, she developed flushing, chest tightness, increased blood pressure (160/90 mmHg) — although the patient had no history of hypertension — and severe lower back pain at the level of the kidneys. The radiopharmaceutical infusion was discontinued, and hydrocortisone and antihistamine were administered. The patient was transferred to the Emergency Department, but clinical examination showed no significant findings. After a few hours of observation, she was discharged in good clinical condition.

The second case30 occurred in a 57-year-old woman with an inci
dentoma. She had also received premedication with oral potassium iodate. Within 9 to 10 minutes after the end of the slow tracer infusion, she developed chest discomfort and lower back pain. The symptoms were not as intense as in the previous case. The lower back pain lasted for about 20 minutes. She did not require any rescue medication. The patient was discharged from the Emergency Department half an hour
later. The authors commented that it did not appear to be a pure ana-
phylactic reaction24. They also noted that in the first case there was an
increase in blood pressure, which is not very common in anaphylaxis
and unexplained back pain, whereas in the second case the characteris-
tic feature was chest tightness (not associated with bronchospasm). The
reported chest tightness, lower back pain, and flushing are described in
the SPC of the drug22. These specific symptoms have been attribu-
ted to [131I]Norcholesterol as well as others, such as nausea, vomiting,
erythema, respiratory reaction, dyspnoea, tachycardia, dizziness, head-
dache, diarrhoea, facial swelling, abdominal pain, metallic taste, and
tongue insensitivity22.

According to some authors25, there is a significantly higher incidence of
ARRs to [131I]Norcholesterol than to other radiopharmaceuticals more com-
monly used in nuclear medicine.

Therapeutic radiopharmaceuticals (ATC Group V10)

1. Anti-inflammatory agents (ATC Group V10A)

Radiosynovectomy in arthritis and synovitis using [99mTc]Yttrium citrate
and [99mTc]ReRhenium sulphide is associated with very moderate ARs, which
are limited to transient aggravation of pain in a few patients and, very rarely,
radioanercrosis26. Hung et al.27 published a case of severe skin ulceration
due to [99mTc]Yrtrim chloride therapy which, after 1 hour of administration,
was accidentally deposited in the perivascular tissue of the forearm, which
necessitated a 2-centimetre surgical excision of the ulcerated area.

2. Iodine (131I) compounds (ATC Group V10XA)

[131I]-Iobenguane (MIBG, metaiodobenzylguanidine). At low doses this
compound is used for diagnosis, whereas at high doses it is administered
for therapy. Several cases of ARs have been published28,29. A Japanese
survey of reported ARs was conducted between 2000 and 200130. A
notable case occurred in a 35-year-old man who presented at a routine
medical check-up with hypertension and increased adrenaline secretion.
He had no history of allergic reactions. A diagnostic dose of 20 MBq
[131I]-MIBG was administered to detect the presence of a possible phe-
ochromocytoma. Within 18 hours of administration, the patient developed
a symmetrical erythematous macular papular rash on both sides of the chest
walls, elbows, neck, and face, suggestive of erythema multiforme due to
an ARR. Intravenous injection and oral administration of hydrocortisone and
olopatadine drastically reduced the rash within 1 day, and oral adminis-
tration of loratadine completely resolved it 13 days after symptom onset.
Based on the sequence of events and the symptomatology, diagnosis was an
allergic reaction to [131I]-MIBG.

Intravenous injections of [131I]-MIBG contain excipients such as acetic
acid, sodium acetate, and sodium chloride. There have been reports of
hypersensitivity to the ethanol metabolite, acetic acid, sodium acetate and
sodium chloride, although this response is extremely rare. If a patient has a
history of this type of reaction to these substances further allergic reactions
may be expected31.

[131I]-Na. This radiopharmaceutical does not usually cause ARs in itself
because it is an iodised salt. However, its formulation as a hard gelatin
capsule may contain some excipients (sodium thiosulphate pentahydrate,
disodium phosphate dihydrate, sodium hydroxide) that can cause reac-
tions32. Most of the ARs to this radiopharmaceutical are caused by the
beta radiation of the isotope at high doses33. Jané-Soler et al.34 published
an AR to this radiopharmaceutical after ablative treatment with a therapeu-
tic dose of 5550 MBq [131I]-Na in a woman who had undergone surgery
for papillary thyroid carcinoma following the administration of recombi-
nant TSH. Six days after administration, the patient began to experience
difficulty swallowing and oropharyngeal and oesophageal pain accom-
panied by erythema and ulcerative lesions at these levels, suggestive of
oropharyngeal and oesophageal mucositis. She was treated with cor-
ticosteroids and antifungals and the symptoms resolved 3 months after
therapy. They noted that the symptoms indicated a mucosal response to the
high level of radiation received, given that [131I]-Na has a tendency to
accumulate in the salivary glands and subsequently can be secreted into
the oral cavity and pharynx, thus reaching the oesophagus by swallowing.

Table 1 summarises other ARs published in the scientific literature.

Incidence and prevalence of adverse reactions
to radiopharmaceuticals

Cordova et al.35 reported that between 1976 and 1979 the rate of
ARRs was in the range of 1 to 6 per 100 000 administrations. Keeling et
al.36 estimated that only 10% of possible ARs are reported, although these
would include the most significant events. There is also continuing uncer-
tainty regarding difficulties in demonstrating causal relationships between
the administration of radiopharmaceuticals and observed effects37. In the
US, the incidence of ARRs is about 2.3 per 100 000 administrations38. The
number of ARs has been decreasing mainly due to the improved formulation
and manufacturing of radiopharmaceuticals.

In 1997, Hesselwood, Keeling, and the Radiopharmacy Committee of
the European Society of Nuclear Medicine39 conducted a prevalence
study, which analysed all adverse events using an algorithm established by
Silberstein et al.40. Out of a total of 71,046 radiopharmaceutical administra-
tions, 18 ARs were reported, 5 of which were considered to be vasovagal
in nature. Of the remaining thirteen, 8 ARs were categorised as possible
or probable. Thus, the prevalence of the 18 included cases was 25 events
(95% confidence interval [95%CI]: 13-27) per 100,000 administrations.
When the 5 cases described as vasovagal reactions were excluded, pre-
valence was 18.2% (95%CI: 8.28) per 100,000 administrations. When only
the possible or probable ARs were included, prevalence fell to 11 events
(95%CI: 3.3-19.2) per 100,000 administrations. The authors34 suggested
that obtaining medical care staff experience issues when reporting ARs, partly
due to lack of time to complete the forms and the type of AR not being recognised
by the NVMS staff. There are also problems related to forming causal rela-
tionships between ARs and the administration of radiopharmaceuticals35,36,
the appearance of symptoms when the patient is outside the hospital or
clinical centre39, and the knowledge that the radiopharmaceutical may be
the cause of the AR40. The latter aspect is probably the most significant, and
it may be the case that many transient reactions that do not have sequelae
or do not require medical intervention are not considered as notifications
to be assessed34.

The study by Hesselwood et al.39 found a slightly higher prevalence than
that obtained in the USA, they reported 25 events per 100,000 administra-
tions, which is close to the upper value of 33 per 100,000 administrations
reported by Silberstein40. If ARs are restricted to those classified as possible
or probable, a lower prevalence is inevitable40.

Silberstein published a study40 on the prevalence of ARs between
2007 and 2011 as a continuation of the previous study39. Eleven institutions
finally participated in the study and submitted data from 2007 to 2011.
Of the 1,010,977 diagnostic studies reported, 20.5% were PET studies
and 79.5% were Single-Photon Emission Computed Tomography (SPECT). A
total of 13,200 therapeutic procedures were performed (1.3% of the total).
The percentage of therapeutic procedures per year ranged from 1.2% to
1.5% of the total. This study found an incidence of ARs equal to that of the
previous study (2.3/100,000 administrations).

Recently, Schreuder et al.41 published a review of 2,447 ARRs. A total
of 84.4% of the reported adverse events were associated with diagnostic
radiopharmaceuticals. The most common ARRs were “skin and subcuta-
aneous tissue disorders” (26.6%), and “general disorders and administration
site conditions” (24.4%). Other adverse events were related to “gastroin-
testinal disorders” (9.8%), “nervous system disorders” (8.5%), and “immune
system disorders” (7%).

Conclusions

Although the prevalence of ARs to radiopharmaceuticals is very low,
such reactions can be severe. These ARs should be better documented and
communicated to all health care staff.

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Conflict of interest

The authors have no conflicts of interest to declare.
<table>
<thead>
<tr>
<th>PET RADIOPHARMACEUTICALS</th>
<th>Adverse reaction</th>
<th>Diagnostic use</th>
<th>Reference</th>
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<tbody>
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<td>[^{18}F]FDG</td>
<td>Erythema, flushing, hypertension, tachycardia, angioedema, exfoliative dermatitis, convulsions, hyperhidrosis, dysgeusia</td>
<td>Diagnosis, assessment, and staging of various tumors</td>
<td>6, 9, 10, 19, 27</td>
</tr>
<tr>
<td>[^{68}Ga]Ga-DOTANOC</td>
<td>Maculopapular rash</td>
<td>Diagnosis of neuroendocrine tumors</td>
<td>27</td>
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<td>READY-TO-USE RADIOPHARMACEUTICALS</td>
<td></td>
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<tr>
<td>[^{67}Ga]Ga-citrate</td>
<td>Nausea, vomiting, erythema, flushing, diffuse rash, pruritus, urticaria, respiratory reaction, tachycardia, syncope, dizziness, facial swelling, metallic taste, salty taste</td>
<td>Bone infection or inflammation, non-Hodgkin lymphoma, sarcoidosis</td>
<td>6, 10, 20</td>
</tr>
<tr>
<td>[^{111}In]In-oxine</td>
<td>Fever, diffuse rash, pruritus, urticaria</td>
<td>Cell labeling (leukocytes and platelets)</td>
<td>10</td>
</tr>
<tr>
<td>[^{111}In]In-DTPA (diethylentetriaminepentaoctacetic acid)</td>
<td>Fever, nausea, vomiting, erythema, flushing, pruritus, urticaria, cardiac arrest, hypertension, headache, aseptic meningitis, neck stiffness, Kernig's signs, Brudzinski's signs, one death at 20 minutes post-injection</td>
<td>Radionuclide cisternography</td>
<td>6, 10</td>
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<tr>
<td>[^{111}In]pentetreotide</td>
<td>Fever, nausea, erythema, flushing, hypotension, bradycardia, dizziness, vertigo, headache, diaphoresis, arthralgia and anemia</td>
<td>Neuroendocrine tumors</td>
<td>10</td>
</tr>
<tr>
<td>[^{123}I]Iobenzylguanidine (MIBG; metiodobenzylguanidine)</td>
<td>Fever, nausea, erythema, flushing, hypertension, respiratory reaction, syncope, weakness, dizziness, lightheadedness, vertigo, tachypnea, chest pain, abdominal pain, dementia, headache, depression, facial pain, epistaxis, sweating</td>
<td>Pheochromocytoma and neuroblastoma</td>
<td>6, 10, 18</td>
</tr>
<tr>
<td>[^{123}I]InNa</td>
<td>Nausea, vomiting, skin rash, pruritus, urticaria, hypotension</td>
<td>Thyroid disease</td>
<td>6, 10</td>
</tr>
<tr>
<td>[^{131}I]Inocholesterol (6-beta-iodomethyl-18-norcholesterol)</td>
<td>Fever, nausea, vomiting, erythema, flushing, chest pain, chest tightness and heaviness, hypertension, respiratory reaction, tachycardia, dizziness, headache, diaphoresis, facial swelling, abdominal pain, metallic taste, numb tongue, dyspnea, anaphylactic reaction, low back pain, chest tightness, tongue insensitivity</td>
<td>Adrenal gland disorders, primary aldosteronism, diagnosis of pheochromocytoma</td>
<td>6, 10, 20, 29, 30, 31</td>
</tr>
<tr>
<td>[^{75}Se]Tauroselcholic acid</td>
<td>Anaphylactic reactions, nausea, indigestion, dizziness, pain, burning sensation</td>
<td>Assessment of bile acid malabsorption and determination of bile acid loss</td>
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<tr>
<td>[^{123}I]Ioflupane</td>
<td>Rash, injection site pain, pruritus, skin erythema, headache, nausea, vertigo, dry mouth, increased appetite, paresthesia, dysgeusia</td>
<td>Differential diagnostic study of Parkinson's disease and Parkinsonism</td>
<td>6, 18</td>
</tr>
<tr>
<td>[^{201}Tl]TlCl₂</td>
<td>Skin rash, erythema, mild anaphylaxis, bradycardia</td>
<td>Myocardial scintigraphy for coronary perfusion study, scintigraphic study of muscle perfusion, parathyroid scintigraphy, visualization of thallium-uptaking tumors</td>
<td>6, 20</td>
</tr>
<tr>
<td>TECHNETIUM RADIOPHARMACEUTICALS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[^{99m}Tc]Tc-HMPAO (hexamethylene-propylene-aminooxime)</td>
<td>Fever, erythema, flushing, diffuse rash, hypertension, hypotension, respiratory reaction, seizures, diaphoresis, cyanosis, anaphylaxis, facial swelling, abdominal pain</td>
<td>Brain scintigraphy, use in leukocyte labeling</td>
<td>10</td>
</tr>
<tr>
<td>[^{99m}Tc]Tc-human albumin colloids</td>
<td>Chills, nausea, erythema, flushing, diffuse rash, pruritus, hypertension, hypotension, respiratory reaction, tachycardia, dizziness, lightheadedness, vertigo, diaphoresis, anaphylaxis, abdominal pain, myelosuppression, dyspnea, bronchospasm, pallor</td>
<td>Lymphoscintigraphy, sentinel lymph node detection scintigraphy (subcutaneous administration), hepatosplenic scintigraphy, venogramography</td>
<td>6, 10, 16, 20, 25</td>
</tr>
<tr>
<td>[^{99m}Tc]Tc-arcitumomab</td>
<td>Transient eosinophilia, nausea, bursitis, urticaria, pruritus, headache, nausea, fever, seizure, HAMA production by patient in reinjections</td>
<td>Scintigraphy of osteoarticular inflammatory/infectious processes by binding to the CD20 lymphocyte receptor</td>
<td>10</td>
</tr>
</tbody>
</table>
### Table 1 (cont.). Adverse reactions to the most commonly used radiopharmaceuticals in radiopharmacy

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Adverse reaction</th>
<th>Diagnostic use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIAGNOSTIC RADIOPHARMACEUTICALS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-MAA} \ (\text{human albumin macroaggregates})]</td>
<td>Chills, nausea, erythema, flushing, diffuse rash, pruritus, urticaria, cardiac arrest, chest pain, chest heaviness, hypertension, hypotension, respiratory reaction with arrest, tachycardia, syncope or weakness, diaphoresis, cyanosis, anaphylaxis, metallic taste, dyspnea, throat tightness, numbness of arm, paroxysmia</td>
<td>Lung perfusion scintigraphy</td>
<td>6, 10, 14, 20</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-Mebrofenin}]</td>
<td>Urticaria, maculopapular rash</td>
<td>Biliary tract scan</td>
<td>10, 61</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-MDP \ (medronate)}]</td>
<td>Chills, fever, nausea, vomiting, erythema, flushing, diffuse rash, pruritus, urticaria, cardiac arrest, chest pain, chest heaviness, hypertension, hypotension, respiratory reaction, tachycardia, convulsions, syncope, dizziness, vertigo, headache, diaphoresis, anaphylaxis, abdominal pain, metallic taste, anesthesia, pain or burning sensation at injection site, photophobia, death secondary to cardiac arrhythmia</td>
<td>Bone scan</td>
<td>6, 10, 13, 19, 20, 22</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-HDP \ (oxidronate)}]</td>
<td>Nausea, vomiting, erythema, flushing, diffuse rash, pruritus, chest pain, heaviness, heartburn, convulsions, diaphoresis, facial swelling, respiratory arrest, loss of consciousness, angioedema, anaphylactic shock</td>
<td>Bone scan</td>
<td>6, 10, 15, 19, 20, 22</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-DTPA \ (diethylenetriaminepentaacetic acid)}]</td>
<td>Chills, nausea, vomiting, erythema, flushing, diffuse rash, pruritus, urticaria, hypertension, hypotension, respiratory reaction, tachycardia, syncope, headache, cyanosis, anaphylaxis, arthralgia, pain, burning at injection site, coughing, wheezing</td>
<td>Renogram, glomerular filtration rate studies, gastro-esophageal reflux scintigraphy</td>
<td>6, 10, 20</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-MIBI \ (methoxyisobutylisonitrile)}]</td>
<td>Nausea, erythema, flushing, diffuse rash, pruritus, seizures, headache, metallic taste (dysgeusia), tingling, vomiting</td>
<td>Myocardial perfusion scintigraphy, parathyroid scintigraphy</td>
<td>6, 10, 20, 62</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{NaTcO}_4]</td>
<td>Chills, nausea, vomiting, diffuse rash, pruritus, urticaria, chest pain, chest heaviness, hypertension, dizziness, vertigo, headache, diaphoresis, anaphylaxis, arrhythmias, vasodilatation, facial edema</td>
<td>Thyroid scintigraphy, salivary gland scintigraphy, Meckel’s diverticulum localization scintigraphy, scintigraphic localization of occult gastrointestinal bleeding, radionuclide ventriculography studies</td>
<td>6, 22, 42</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Succinic acid \ (DMSA: Dimercaptosuccinic acid)}]</td>
<td>Nausea, erythema, flushing, syncope, abdominal pain, headache, dizziness</td>
<td>Renal scintigraphy</td>
<td>6, 20, 22</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Sulfur colloid}]</td>
<td>Chills, fever, nausea, vomiting, erythema, flushing, rash, pruritus, urticaria, cardiac arrest, chest pain, chest tightness, hypertension, hypotension, respiratory stress, tachycardia, Bradycardia, convulsions, syncope, dizziness, vertigo, headache, diaphoresis, cyanosis, anaphylaxis, arthralgia, pain and burning sensation at injection site, wheezing, dyspnea, asphyxia, sneezing, lachrymation, paresthesia, weakness</td>
<td>Sentinel node scintigraphy, hepatosplenic scintigraphy, venography</td>
<td>6, 22</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{Tc-tetrofosmin}]</td>
<td>Angina, hypertension, prolonged QT, vomiting, abdominal pain, hypotension, dyspnea, metallic taste, burning sensation in mouth, unusual odor, mild leukocytosis</td>
<td>Myocardial perfusion scintigraphy</td>
<td>6, 20, 22</td>
</tr>
<tr>
<td>[\text{[^{99m}\text{Tc}]}\text{mercaptoacetyl triglycine (MAG3: mercaptodiglycine)}]</td>
<td>Nausea, dizziness, vomiting, rash</td>
<td>Radioisotope renography</td>
<td>6, 22</td>
</tr>
<tr>
<td><strong>THERAPEUTIC RADIOPHARMACEUTICALS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>[\text{[^{131}I]}\text{Iobenguane \ (MIBG; metaiodobenzylguanidine)}]</td>
<td>Erythema, flushing, diaphoresis, metallic taste, tingling in arms and face, maculopapular erythematous rash, erythema</td>
<td>Treatment of neuroblastoma and pheochromocytoma</td>
<td>6, 20, 22, 34</td>
</tr>
<tr>
<td>[\text{[^{131}I]}\text{Na}]</td>
<td>Chills, nausea, vomiting, pruritus, urticaria, chest pain, chest tightness and heaviness, tachycardia, headache, dizziness, mucusitis, ulcers</td>
<td>Thyroid cancer, hyperthyroidism (dose-dependent)</td>
<td>22, 36</td>
</tr>
</tbody>
</table>
Table 1 (cont.). Adverse reactions to the most commonly used radiopharmaceuticals in radiopharmacy

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<tr>
<td>[111In]Lixidronam (Quadramet&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Myelosuppression, bone pain due to the flare phenomenon</td>
<td>Treatment of metastatic bone pain from prostate cancer</td>
<td>22, 33</td>
</tr>
<tr>
<td>[90Y]YCl&lt;sub&gt;3&lt;/sub&gt; (Metasticon&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Chills, fever, myelosuppression, bone pain due to the flare phenomenon</td>
<td>Treatment of metastatic bone pain from prostate cancer</td>
<td>22, 33</td>
</tr>
<tr>
<td>[123I]TcCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Fever, erythema, flushing, diffuse rash, pruritus, hypotension</td>
<td>Myocardial viability scintigraphy, scintigraphic localization of brain tumours</td>
<td>22</td>
</tr>
<tr>
<td>[164Y]YI&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Severe ulceration</td>
<td>Radiopharmaceutical labeling</td>
<td>30, 33</td>
</tr>
<tr>
<td>[177Lu]PSMA</td>
<td>Fatigue, muscle stiffness, dry mouth, anaphylactic reaction</td>
<td>In clinical trials for the treatment of metastatic castration-resistant prostate cancer</td>
<td>43, 66</td>
</tr>
<tr>
<td>[18F]Fibritomomabixueten (Zevalin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Hematologic toxicity, infections</td>
<td>Treatment of relapsed or refractory CD20+ follicular B-cell non-Hodgkin’s lymphoma</td>
<td>32, 44</td>
</tr>
</tbody>
</table>
| [131I]I-

tc-exametazine-leukocytes | Dyspnea with myoclonus | Infection/inflammation scintigraphy | 6, 22 |

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Adverse reactions to radiopharmaceuticals


