Review Article

NUCLEAR MEDICINE-INDUCED ALLERGIC REACTIONS

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ABSTRACT

Immunologic reactions to radiopharmaceuticals are usually mild and transient and require little or no medical treatment. As the usage of radiopharmaceuticals has increased, the reported adverse reactions remain comparatively few in number. Although the low reported numbers demonstrate that radiopharmaceuticals are safe and the pharmaceutical amount used in the formulation is small, it is worrisome that there is no single system for reporting adverse events associated with radiopharmaceuticals. The most commonly described allergic reactions still remain ^{99m}Tc-labelled diphosphonates, colloids and albumin. The likelihood of a reaction to PET radiopharmaceutical administration is low due to the chemical used being too small to induce a physiologic effect.

Reports on allergic reactions to therapeutic radiopharmaceuticals are rare. Although the advent of adverse events from the administration of this therapy may occur due to the deterministic effects of these radiopharmaceuticals, this is usually related to the amount of radiation administered rather than the pharmaceutical effects.

The advancement in technology has catapulted imaging into a new era allowing for hybrid imaging with SPECT/CT or MRI and PET/CT or MRI. This brings with it further risks for adverse events which have been associated with these radiological modalities and necessitates a discussion of allergic reactions from iodinated contrast media as well as gadolinium contrast.

As there is no alternative to the use of radiopharmaceuticals for nuclear medicine and the added benefit of a diagnostic radiology in one-sitting for certain cases, it is important to document and report on these few adverse reactions in order to improve the imaging methodology and possible prophylactic measures.

INTRODUCTION

Radiopharmaceuticals used in nuclear medicine are radioactive compounds containing the combination of a radionuclide and a pharmaceutical. These compounds may be administered intravenously, intrathecally or orally. They are used in the diagnosis and therapeutic treatment of human diseases and thus undergo meticulous quality assurance to ensure sterility, non-pyrogenecity and to ensure safe administration to humans.[1,2] The radiopharmaceuticals are usually used in tracer quantities. Thus, significantly unlike conventional drugs, there is no dose-response relationship for radiopharmaceuticals. Even when a radiopharmaceutical is used for therapeutic purposes, the effect achieved is not a pharmacologic consequence but a consequence of radioactivity. The tissue damage that may result from therapeutic radiopharmaceutical administration is commonly related to the high radiation rather than the pharmaceutical, however, this is usually targeted therapy and causes minimal damage to non-targeted (i.e. non-tumoral) tissue.[1,2]

Adverse drug reactions are defined by the WHO as "a response to a medicine which is noxious and unintended and which occurs at doses normally used in man".[3] This is a general statement indicating any untoward event that may occur from administration of a drug during its normal use and includes various reactions such as side effects, toxic effects, anaphylactic reactions, altered biodistribution, drug interactions and any other undesirable effects that may occur. The main cause of adverse drug reactions from

radiopharmaceuticals is from the pharmaceutical carrying the radiation and the kit components, not the radiation itself. Although special problems with radiopharmaceuticals might be the radiation effects, these are more properly categorised as problems associated with overdosage.[4]

Early reports of adverse reactions to nuclear medicine date back to 1972, reporting a total incidence of 1 in 9979 over a period of 4 years from 1967 to 1970.[5] In a meta-analysis performed by Salvatore et al. they reported a prevalence rate for adverse reactions to radiopharmaceuticals ranging from 0-11 cases per 100,000 administrations.[6] Silberstein reported a prevalence rate of 2.1 per 100,000 with no hospitalisations or deaths reported during the period from 2007 to 2011.[7]

The reporting of adverse drug reactions to radiopharmaceuticals has been found to be lacking despite pharmacovigilance by various regulations in different countries. There is no single system for reporting adverse events associated with radiopharmaceuticals. Different countries have different systems. Underreporting is a recognised problem; for example, annual reports about the South African or European Association of Nuclear Medicine database have not been published in recent years. In addition, adverse events may be described in scientific articles without being entered into a database.

Salvatori et al. postulate the reasons for this low prevalence rate and lack of reporting of events to be due to the fact that trace amounts of material are used in the formulation of radiopharmaceuticals and administered in small amounts as microdoses, resulting in mild and transient events requiring little or no therapy. Furthermore, the physician's anxiety of potential litigation, belief that interest in this information is low, the time it takes to complete the forms needed and the lack of availability of these forms, as well as the inability of the physician to recognise the event, may be additive to this problem.[6]

We describe adverse reactions due to immunological reactions to diagnostic and therapeutic radiopharmaceuticals as well as to contrast media used in hybrid imaging with PET or SPECT/CT or MRI.

IMMUNOLOGICAL REACTIONS

Allergic reactions are immune mediated, generally triggered by lymphocytes. Gell and Coombs[8] first categorised allergic reactions as class I through IV, based on distinct pathologic mechanisms. This system still serves as a basic framework but has evolved into additional subcategories and more thorough explanations, as knowledge of immunology has continued to progress. Regardless of the classification or precise mechanism, the pathogenesis of allergic reactions centres on the synthesis and release of chemical mediators.[8,9]

Type I (immediate or anaphylactic) reaction is mediated largely by antibodies of the IgE group of immunoglobulins (present on the surface of the mast cells and circulating basophils) and triggers release of pharmacological mediators, in particular histamine, but the number of recognised mediators continues to grow. Clinically, type I reactions are recognisable by urticarial and angioedema, rhinitis, bronchoconstriction and anaphylactic shock.[8,9]

The challenge of recognising the allergic reactions to radiopharmaceuticals may be due to the issue that many patients are already referred on various other drugs which may cause drug interactions or which may cause the allergic reaction. Recognising type I hypersensitivity reactions may also be a challenge, as some patients may not complain. This is especially true in delayed reactions that may be self-limiting.[2]

Type II (cytotoxic/membrane) reactions are those in which IgG and IgM antibodies react with cell-surface or tissue antigens to produce mostly autoimmune and haematological problems. While important in general medicine as causes of thrombocytopenia and haemolytic anaemia's, this form has not been encountered with radiopharmaceuticals. This should be separated from radiation induced thrombocytopenia which can be frequently seen in targeted radionuclide therapy.[8,9]

Type III (immune complex) reactions are usually due to IgG, IgM and IgA antibodies reacting with antigen in tissue where complement is activated and causes immune complex formation and deposition that result in local tissue damage. Although often called serum sickness from its original cause and description, it is an important form of reaction seen with radiopharmaceuticals, manifesting itself as low-grade fever, urticaria and maculopapular skin rashes, and late polyarthralgia.[8,9]

Type IV (cell-mediated or delayed hypersensitivity) reaction mediated by sensitised T-lymphocytes has not been noted with radiopharmaceuticals.

IMMUNOLOGICAL REACTIONS TO TECHNETIUM RADIOPHARMACEUTICALS

Adverse reactions to radiopharmaceuticals are comparatively few in number. Various estimates quote an incident rate of 1 to 6 reactions per 100,000 injections. The very low numbers of reported adverse effects probably reflect the tiny amounts of material which are used in the formulation of radiopharmaceuticals.[2]

Skeleton scanning agent diphosphonates are the most commonly reported radiopharmaceuticals that cause adverse effects. Most figures quote 1 in 800 for the bone-seeking radiopharmaceutical methylene diphosphonate (^{99m}Tc-MDP).

TABLE I: ADVERSE REACTIONS TO RADIOPHARMACEUTICALS[13]

RADIOPHARMACEUTICAL	TRADE NAME	SIDE EFFECTS, COMMENTS AND OTHER REACTIONS
^{57}Co-cyanocobalamin	Rubratope-57, Dicopac kit	None
^{51}Cr-sodium chromate	Chromitope	Erythema, flushing, hypertension, tachycardia and diaphoresis
^{18}F-fludeoxyglucose, FDG, Fluorodeoxyglucose		None
^{67}Ga-gallium citrate	Neoscan	Nausea, vomiting, erythema, flushing, diffuse rash, pruritus, hives/urticaria, respiratory reaction, tachycardia, syncope or faintness, dizziness, vertigo, facial swelling, metallic taste, dyspnoea, salty taste
^{111}In-capromab pendetide	ProstaScint	Increase in bilirubin, hypotension, hypertension, injection site reactions elevated liver enzymes (could be due to tumour), pruritus, fever, rash headache, myalgia, asthenia, burning sensation in thigh, shortness of breath, alterations of taste, production of HAMA by the recipient
^{111}In-indium oxyquinoline, Oxine		Fever, diffuse rash, pruritus and hives/urticarial
^{111}Inpentetate DTPA	MPI-DTPA	Fever, nausea, vomiting, erythema, flushing, pruritus, hives/urticaria, cardiac arrest, hypertension, headache, aseptic meningitis; one death 20 min post injection
^{111}In-pentetreotide	Octreoscan	Fever, nausea, erythema, flushing, hypotension, bradycardia, dizziness, vertigo, headache, diaphoresis, arthralgia and asthenia, one case anaemia
^{111}In-satumomab pendetide	OncoScint CR/OV	Chills, fever, nausea, erythema, flushing, diffuse rash, pruritus, chest pain, tightness or heaviness, hypertension, hypotension, dizziness, vertigo, headache, diaphoresis, arthralgia and asthenia, confusion, diarrhoea, hypothermia, bradycardia, vasodilatation, angioedema, production of HAMA by the recipient
^{123}I-iobenguane metaiodobenzylguanidine, MIBG		Nausea, erythema, flushing, hypertension, respiratory reaction, syncope or faintness, dizziness and vertigo, tachypnoea
^{123}I-iodohippurate sodium	Nephroflow, Nephropure	Nausea, diffuse rash, pruritus, hives/urticaria and hypotension
^{123}I-sodium iodide		Nausea, vomiting, diffuse rash, pruritus, hives/urticaria, chest pain, tightness or heaviness, respiratory reaction, tachycardia, syncope or faintness and headache, tachypnoea, parosmia
^{125}I-iodinated albumin (IHSA, iodinated human serum albumin)		Diffuse rash
^{125}I-sodium iothalamate	Glofil	None
^{131}I-iobenguane metaiodobenzylguanidine, MIBG		Erythema, flushing, diaphoresis and metallic taste, tingling of arms and face
^{131}I-iodinated albumin	RISA, Radioinated serum, Megatope	None
^{131}I-iodohippurate	Hipputope, Hippuran	Nausea, vomiting, pruritus hives/urticaria, hypertension, respiratory reaction, tachycardia, syncope or faintness, diaphoresis, anaphylaxis, facial swelling, dyspnoea, “cold sweat”, pallor, amarosis fugax
^{131}I-sodium iodide	Iodotope	Chills, nausea, vomiting, pruritus, hives/urticaria, chest pain, tightness or heaviness, tachycardia, headache, dizziness
^{131}I-6-beta iodomethyl-18-NOR cholesterol	NP-59	Nausea, vomiting, erythema, flushing, chest pain, tightness or heaviness, hypertension, respiratory reaction, tachycardia, dizziness, headaches, diaphoresis, facial swelling, abdominal pain, metallic taste, frozen tongue, dyspnoea
^{81m}Kr-krypton		None
^{13}N-ammonia		None
^{32}P-chromic phosphate suspension	Phosphocol	Chills, fever, nausea, vomiting, chest pain, tightness or heaviness, respiratory reaction, abdominal pain, dyspnoea, sore throat, cough, pleuritis, myelosuppression

^{32}P-sodium phosphate		Myelosuppression, bone pain from the flare phenomenon
^{82}Rb-rubinium		None
^{153}Sm lexidronam	Quadramet	Myelosuppression, bone pain from the flare phenomenon
^{89}Sr-strontium chloried	Metastron	Chills, fever, myelosuppression, bone pain from the flare phenomenon
^{99m}Tc-albumin colloid	Microlite	Chills, nausea, erythema, flushing, diffuse rash, pruritus, hypertension, hypotension, respiratory reaction, tachycardia, dizziness, vertigo, diaphoresis, anaphylaxis, abdominal pain, myelosuppression (injectate also included MDP and soluble albumin for cases with anaphylaxis)
^{99m}Tc-albumin (HSA, human serum, albumin)		Chills, fever, erythema, flushing, diffuse rash, hypotension, tachycardia, dizziness, vertigo, facial swelling, tachypnoea, malaise, dyspnoea
^{99m}Tc-arcitumomab	CEA-Scan	Transient eosinophilia, nausea, bursitis, urticaria, pruritus, headache, nausea, fever, one grand mal seizure, HAMA production by the recipient
^{99m}Tc-bicisate dihydrochloride (ethyl cysteinate dimer, ECD)	Neurolite	Nausea, diffuse rash, chest pain, tightness or heaviness, respiratory reaction, seizures, syncope or faintness, vertigo, headache, cyanosis and athenia, neurologic adverse events may have been related to underlying disease, including hallucinations, parosmia, also cardiac failure, respiratory arrest
^{99m}Tc-disofenin	Hepatolite	None
^{99m}Tc-exametazine (hexamethylpylene amine oxine, HMPAO)	Ceretec	Fever, erythema, flushing, diffuse rash, hypertension, hypotension, respiratory reaction, seizures, diaphoresis, cyanosis, anaphylaxis, facial swelling, abdominal pain, dyspnoea with myoclonus
^{99m}Tc-lidofenin	Technescan HIDA	Chills, nausea
^{99m}Tc-macroaggregated albumin (MAA)	AN-MAA, Macrotec, MPI-MAA, Pulmolite, Technescan MAA	Chills, nausea, erythema, flushing, diffuse rash, pruritus, hives/urticaria, cardiac arrest, chest pain, tightness or heaviness, hypertension, hypotension, respiratory reaction, tachycardia, syncope or faintness, diaphoresis, cyanosis, anaphylaxis, metallic taste, dyspnoea; throat tightness; arm numbness, parosmia
^{99m}Tc-mebrofenin	Choletec	Hives/urticaria
^{99m}Tc-medronate (MDP, methylene diphosphonate)	Osteolite, Technescan, MDP, AN-MDP, MPI-MDP	Chills, fever, nausea, vomiting, erythema, flushing, diffuse rash, pruritus, hives/urticaria, cardiac arrest, chest pain, tightness or heaviness, hypertension, hypotension, respiratory reaction, tachycardia, seizures, syncope or faintness, vertigo, headache, diaphoresis, anaphylaxis, abdominal pain/burning at injection site, photophobia, one death secondary to cardiac arrhythmia
^{99m}Tc-mertiatide (MAG3, mercaptoacetyl-glyclyglyclyglycine)	Technescan MAG3	Nausea, vomiting, erythema, flushing, syncope or faintness, sore, thick throat
^{99m}Tc-oxidronate (HDP, hydroxymethylene diphosphonate)	Osteoscan-HDP	Nausea, vomiting, erythema, flushing, diffuse rash, pruritus, chest pain, tightness or heaviness, heartburn, seizures, diaphoresis, facial swelling
^{99m}Tc-pentetate (DTPA, diethylenetriaminepetaacetic acid)	Technescan, DTPA, AN DTPA, MPI-DTPA, Techniplex	Chills, nausea, erythema, flushing, diffuse rash, pruritus, hives/urticaria, hypertension, hypotension, respiratory reaction, tachycardia, syncope or faintness, headache, cyanosis, anaphylaxis, arthralgia, pain, burning at injection site, cough, wheezing, trisodium salt can cause neurologic signs if given inthrathecally
^{99m}Tc-pyrophosphate (PYP) and Sodium Pyrophosphate)	Pyrolite, Technescan PYP, Phosphotec, MPI, Pyrophosphate, AN Pyrotec, Ultratag	Chills, fever, nausea, vomiting, erythema, flushing, diffuse rash, pruritus, hives/urticaria, chest pain, tightness or heaviness, hypotension, respiratory reaction, syncope or faintness, dizziness, vertigo, pain/burning at injection site, tinnitus
^{99m}Tc-sestamibi	Cardiolite, Mirluma	Nausea, erythema, flushing, diffuse rash, pruritus, seizures, headache, metallic taste, tingling
^{99m}Tc-sodium pertechnetate	Minitec, UltratecKow	Chills, nausea, vomiting, diffuse rash, pruritus, hives/urticaria, chest pain, tightness or heaviness, hypertension, dizziness, vertigo, headache, diaphoresis, anaphylaxis
^{99m}Tc-succimer (DMSA, dimercaptosuccinic acid)	MPI-DMSA, Nephroscint	Nausea, erythema, flushing, syncope or faintness, abdominal pain
^{99m}Tc-sulfur colloid	AN-Sulfur Colloid, TechneColl, TsSC, Tesuloid	Chills, fever, nausea, vomiting, erythema, flushing, diffuse rash, pruritus, hives/urticaria, cardiac arrest, chest pain, tightness or heaviness, hypertension, hypotension, respiratory reaction, tachycardia, bradycardia, seizures, syncope or faintness, dizziness, vertigo, headache, diaphoresis, cyanosis, anaphylaxis, arthralgia, pain/burning at injection site, wheezing, dyspnoea, choking, sneezing, itchy throat, parasthesia, weakness

Erythema, nausea, vomiting and malaise are some of the typical diphosphonate reactions and may start 2-3 hours after the injection. Respiratory or circulatory collapse and loss of consciousness are some of these adverse reactions.[2,10,11]

The other commonly described allergic reactions to ^{99m}Tc-labelled pharmaceuticals include the colloids and albumin. In this regard, a relatively higher figure of 1 in 400 for the lung perfusion imaging agent macroaggregated albumin (^{99m}Tc-MAA) has been reported. These aggregates accumulate and form microemboli in the small pulmonary capillaries. They are considered safe due to the ease at which they are fragmented and biodegraded, however, poor technique during the labelling process may result in substances, e.g. ferric chloride, remaining in the suspension and causing an anaphylactic reaction. Cardiac or cerebral reactions from the MAA particles that reach the circulation are also a possible consequence.[4]

Typical colloid reactions include pallor, nausea, flush and pulse changes. The colloids are used for liver and spleen scintigraphy.[2,10,12] Immunological reactions from colloids are most likely due to the stabilisers used in their preparation. Gelatin, human serum albumin or dextran used in these agents may be antigenic, with high molecular weight dextrans being more antigenic than the low molecular weight dextrans.[4]

Allergic reactions to other ^{99m}Tc radiopharmaceuticals are similarly very rarely reported as a cause for these adverse drug reactions (Table I).[13]

Adverse reactions to radiopharmaceuticals are usually mild and transient and require little or no medical treatment.

IMMUNOLOGICAL REACTIONS TO OTHER RADIOPHARMACEUTICALS

The likelihood of a reaction to other radiopharmaceutical administration, as with technetium, is also low. Due to the small number of studies conducted in comparison to technetium, most of the reports are single case studies.

IODINE-131 METAIODOBENZYLGUANIDINE (131I MIBG)

Ishibashi et al. reported an allergic reaction eighteen hours after intravenous administration of 131I MIBG, wherein a patient developed a rash and itching of his face and chest with erythematous maculopapular eruptions suggesting erythema multiforme. This allergic reaction responded to treatment of these lesions with prednisone and an antihistamine.[14]

ORTHOIODOHIPPURATE (125- AND 131I-HIPPURAN)

A case of a potentially fatal anaphylactic reaction to orthoiodohippurate, an iodine-125 or 131 labelled radiopharmaceutical occasionally used in renal scintigraphy, was reported seven minutes after administration of the radiopharmaceutical. The patient became acutely ill with flushing, nausea, abdominal pain, itching, dyspnoea, tachycardia and clouded consciousness. This allergic reaction responded to adrenaline and corticosteroids.[15]

THALLIUM-201

Allergic reactions such as erythema and vasovagal reactions have been reported with the use of Thallium-201.[11]

GALLIUM-67 CITRATE

Due to its composition, Ga-67 citrate has been reported to cause anaphylactic reactions. These reactions are usually mild resulting in cutaneous erythema, pruritis, urticaria and flushing. The prevalence of this event is reported to be 1 to 5 per 100,000 administrations.[11]

IMMUNOLOGICAL REACTIONS TO PET RADIOPHARMACEUTICALS

The use and availability of PET imaging and the number and variety of PET radiopharmaceuticals available has resulted in a significant increase in the use of this modality.

Hybrid imaging using PET/CT or PET/MRI implies a need for the use of contrast agents which may lead to an increase in allergic reactions being reported in nuclear medicine. This requires that staff be able to manage these allergic reactions as they occur and guidelines be readily available to the staff working in the nuclear medicine department. These reactions can vary from minor to major events as described in the discussion of contrast agents. Reported allergic reactions to PET radiopharmaceuticals, however, still remain low and have not increased despite the increase in the use of the modality and the number of PET radiopharmaceuticals available.[7,16]

Codreanu et al. reported an allergic reaction on two occasions following intravenous administration of 18F-FDG to a 59 year old male referred with a history of squamous cell carcinoma of the right pyriform sinus. The patient underwent a non-contrasted PET/CT scan. Following radiopharmaceutical administration, the patient presented with body rash, itching, with pruritic red papules on the face, trunk and extremities. These symptoms resolved following management by the dermatologist. All other possible causes for the patient's presentation were excluded. Preparation of future scans with premedication with prednisone resulted in the absence of this reaction.[17]

IMMUNOLOGICAL REACTIONS TO THERAPEUTIC RADIOPHARMACEUTICALS

Reports on allergic reactions to therapeutic radiopharmaceuticals are rare. Although the advent of adverse events from the administration of this therapy may occur due to the deterministic effects of these radiopharmaceuticals, this is usually related to the amount of radiation administered rather than the pharmaceutical effects.

IMMUNOLOGICAL REACTIONS TO IODINATED AND GADOLINIUM-BASED CONTRAST MEDIA

Intravascular contrast media used for clinical diagnostic imaging include iodinated and gadolinium-based contrast media.

Iodinated contrast media is increasingly used in diagnostic imaging and the incidence of adverse reactions is more common after the use of high osmolar agents. Thus, low osmolar contrast agents are now frequently used, and the incidence of adverse reactions is approximately 3%.

There are four major classes of iodinated contrast media, ionic monomer, ionic dimer, non-ionic monomer and non-ionic dimer. The various intravascular contrast agents vary in their toxicity depending on the viscosity, osmolarity, and immunogenicity. Contrast media have been categorised as being high osmolar (HOCM), low-osmolar (LOCM) and iso-osmolar (IOCM). Low-osmolar agents are preferred as osmolarity is related to some of the adverse reactions. The charged ionic contrast media tend to disrupt the electric potential of cell membranes, accounting for their increased toxicity and need to be administered in high concentrations that are hyperosmolar (approximate osmolarity 1500-2000 mOsm/L) compared with blood (approximate osmolarity 280-290 mOsm/L). Low-osmolar agents are thus preferred with osmolarities in the range of 290-860 mOsm/L. Low-osmolar agents include ionic dimers and non-ionic monomers, non-ionic dimers are iso-osmolar with blood.[18] The causes of most adverse reactions to intravascular contrast reactions are multifactorial and are probably due to a combination of direct chemotoxicity, the ionic state (i.e. ionic vs. non-ionic), or the osmolarity of the injected intravascular contrast agent.[18]

These adverse reactions may be classified as idiosyncratic (anaphylactic) or allergic-like as they do not involve antibody formation, and are not dose dependent and non-idiosyncratic (dose related).

The pathogenesis of such adverse reactions probably involves direct cellular effects, enzyme induction and activation of the complement, fibrinolytic, kinin and other systems.[19]

Reactions to contrast agents can be acute or delayed (Table II). Idiosyncratic reactions can be regarded as mild, moderate or severe. The majority of acute, non-renal, adverse reactions are considered to be idiosyncratic and may occur within 20 minutes of contrast administration. Mild reactions include nausea, vomiting, flushing and urticaria. Moderate reactions may include marked vomiting, urticaria, bronchospasm, facial and laryngeal oedema and vasovagal attacks. Severe contrast reactions include hypovolaemic shock, cardiac arrest, pulmonary oedema and convulsions.

Delayed contrast reactions can occur between 60 minutes to one week after contrast administration, and may present with skin reactions.[20]

Non-idiosyncratic reactions may include bradycardia, hypotension, vasovagal reactions, neuropathy, cardiovascular reactions and non-specific sensation of warmth, a metallic taste in the mouth, syncope and seizures.

Gadolinium based contrast agents are used for MRI and are associated with a varying degree of risk for nephrogenic systemic fibrosis, depending on the low or high risk gadolinium based contrast being used, and particularly in patients with renal impairment (Table II).

MANAGEMENT

The majority of radiopharmaceutical hypersensitivity reactions require little or no treatment. There are currently no documented treatment protocols for the management of hypersensitivity reactions secondary to radiopharmaceuticals. General guidelines on the management of hypersensitivity reactions may thus serve as a guideline for these events. Once the anaphylactic reaction is recognised, it is imperative to ensure a patent airway, breathing and circulation. The level of consciousness, cardiovascular system, gastrointestinal and skin changes must be assessed and managed. First-line treatment with adrenalin is recommended. In severe anaphylaxis, which is rare in nuclear medicine, the airway must be secured and oxygen and intravenous fluid therapy administered. Further diphenhydramine, an H1 antihistamine, can be used as second line to adrenalin. An inhaled β-agonist may be given in cases of bronchospasm. Treatment with glucocorticosteroids is not considered to be helpful in the acute phase but can help prevent recurrent and protracted anaphylaxis.[6] Mild and persistent allergic reactions may be treated symptomatically and antihistamines such as promethazine may be given.[21]

Reactions to intravascular contrast may be prevented by identifying high risk patients and attempting to minimise the risk by following preventive measures or using alternative investigations.

Special consideration should be given to high risk patients, particularly patients with asthma, previous contrast reaction, renal impairment and diabetes mellitus, including those on metformin treatment (which has been implicated due to accumulation of lactic acid). Further consideration should include pregnancy, where contrast administration should be avoided, except in emergency situations. Iodinated contrast should not be administered in hyperthyroid patients. Oncology patients on interleukin-2 may develop a delayed skin reaction.[20]

Preventative measures for iodinated contrast agents may include steroid preparations. Premedication is considered in high risk patients where the administration of contrast is unavoidable.

TABLE II: SUMMARY OF ADVERSE REACTIONS TO IODINATED CONTRAST AGENTS

DEFINITION	SIGNS AND SYMPTOMS	RISK FACTORS	PREVENTIVE MEASURES	TREATMENT
ACUTE REACTION				
Occurs within 1 hour of receiving an iodinated contrast agent. Usually mediated by osmotic or chemotoxicity. Severe reactions are usually anaphylactic or anaphylactoid.	Can be variable in presentation and severity. Common signs and symptoms: • Nausea, vomiting; • Pain on injection; • Hemodynamic changes; • Vagal reaction (bradycardia and hypotension); • Arrhythmia; • Anaphylaxis or anaphylactoid reaction; • Rash (pruritic urticaria); • Angioedema; • Flushing/rash; • Bronchospasm; • Cardiovascular collapse.	Patients with a history of: • Asthma; • Prior reaction to contrast; • Atopy; • Greater risk with ionic monomers.	Consider alternate imagining with technique that does not require iodinated contrast agent use. Avoid use of ionic monomers, if possible. Pre-treatment with corticosteroids with or without antihistamines may reduce the incidence of, but not prevent, severe reactions.	Symptomatic treatment for mild reactions: • Anti-emetics for nausea and vomiting; • Corticosteroids and antihistamines for rash and pruritus; • Intravenous fluids and pressors for hypotension; • Atropine for a vagal reaction. For severe reactions: • Ensure a patent airway and ensure oxygen delivery; • Adrenalin, 0.2-0.5 mg IM every 5-15 min, or administered IV and doses titrated to effect; • Corticosteroids.
DELAYED REACTION				
Occurs between 1 hour and 1 week after receiving an iodinated contrast agent. Cutaneous reactions are typically a T-cell–mediated type IV hypersensitivity reaction. Other symptoms may be due to chemotoxicity.	Can be variable in presentation and severity but are generally less severe than acute reaction. Common signs and symptoms: • Rash and pruritus most common; • Severe skin reactions (eg. Stevens Johnson reactions can occur but are very rare); • Nausea; • Vomiting; • Diarrhoea; • Hypotension (rare).	Patients with a history of: • Prior reaction to contrast; • Those being treated with interleukin 2; • Greatest risk with nonionic dimers; • Risk may be increased with sun exposure.	Consider alternate imagining with technique that does not require iodinated contrast agent use. Avoid use of non-ionic dimers if possible. Pre-treatment with corticosteroids can be helpful to lessen the severity.	Symptomatic treatment: • Anti-emetics for nausea and vomiting; • Corticosteroids and antihistamines for rash and pruritus; • Intravenous fluids and pressors for hypotension.
CONTRAST-INDUCED NEPHROPATHY				
Exact cause is unknown but can be attributed to: • Contrast agent-induced vasoconstriction; • Increased renal tubular flow causing decreased filtration via tubuloglomerular feedback; • Direct renal epithelial toxicity; • Increased free radial formation.	A >25% increase in baseline serum creatinine in a patient within 3 days after receiving an iodinated contrast agent.	• Pre-existing renal dysfunction; • Dehydration; • Increased age; • Diabetes mellitus; • Hypertension; • Poor renal perfusion; • Congestive heart failure; • Myocardial infarction; • Hemodynamic instability; • Concurrent use of renotoxic drugs; • Aminoglycosides; • ACE inhibitors; • Use of a high-osmolality contrast agent; • High volumes of contrast agent.	Consider alternate imagining with technique that does not require iodinated contrast agent use. Avoid use of ionic monomers, if possible. Minimise volume of contrast used. Treat dehydration. Prophylactic hydration with 0.9% sodium chloride or an equiosmolar solution of sodium bicarbonate. Consider *N*-acetylcysteine. Avoid forced diuresis with furosemide or mannitol. Avoid the concurrent administration of renotoxic drugs, if possible.	Given the generally benign course, patients are usually observed. Continue to: • Avoid dehydration; • Avoid concurrent administration of renotoxic drugs; • Consider hemodialysis and consultation with a nephrologist.

ACE = angiotensin-converting enzyme inhibitor; IM = intramuscular; IV = intravenous.

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Oral premedication with prednisone 50 mg per os at 13 hours, 7 hours and again at 1 hour prior to procedure. If the patient cannot take oral medication then 200 mg intravenous hydrocortisone at 13 hours, 7 hours and again at 1 hour prior to procedure may be administered. In an emergency situation 200 mg hydrocortisone may be given 1 hour prior to procedure.

Nausea and vomiting require supportive and symptomatic treatment. If urticaria is severe, antihistamines may be given orally or intravenously. For bronchospasm, oxygen by mask, beta-2 agonist metered dose inhaler and adrenaline if necessary, (1:1000, 0.1-0.3 ml intramuscularly) may be administered. If there is laryngeal oedema, oxygen by mask, and adrenalin (1:1000, 0.5 ml) should be given intramuscularly.

For hypotension, elevate the legs, administer oxygen, and administer intravenous fluids rapidly, preferably normal saline or Ringer's solution. If non-responsive, adrenalin (1:1000, 0.5 ml) should be given intramuscularly.

With vasovagal reactions (bradycardia and hypotension) it may be useful to elevate the patient's legs and to give oxygen and atropine (0.6-1.0 mg) intravenously as well as intravenous fluids.

In the case of a generalised anaphylactoid reaction, call the resuscitation team and continue with oxygen, suction, adrenalin (1:1000, 0,5 ml (0.5 mg)) intramuscularly, and an H1 blocker such as diphenhydramine (25-50 mg) intravenously.

CONCLUSION

With the increasing use of nuclear medicine procedures for both diagnostic and therapeutic administration, radiopharmaceutical-induced allergic reactions, although rare, may occur and must be known by the nuclear medicine staff to ensure early diagnosis and treatment.

The inclusion of MRI and CT for hybrid imaging necessitates that nuclear medicine staff are also cognisant of the possibility of allergic reactions from iodinated contrast media as well as gadolinium contrast and be vigilant to their possibility.

Treatment protocols for the management of allergic reactions should be set in place to reduce morbidity and possible extreme life-threatening circumstances. Prophylactic measures, in known allergies with premedications, can be taken prior to exposing the patients. Documentation and reporting of these adverse drug events to the respective national authorities and the manufacturer is important for pharmacovigilance and awareness of possible outcomes when administering these radiopharmaceuticals.

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