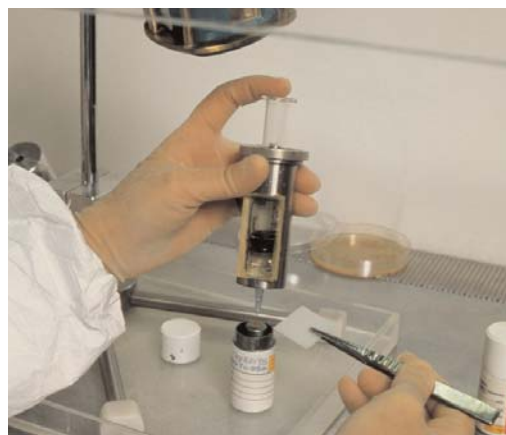


# Radiopharmacy

## — problems encountered with the products

By Neil G. Hartman, PhD

Radiopharmaceuticals, like all drugs, have the potential to cause harm. This article reviews the adverse effects, interactions and product defects associated with radiopharmaceutical agents



Preparation of an injectable technetium-99m radiopharmaceutical for gamma scintigraphy

**R**adiopharmaceuticals are drugs with a radioisotope attached. They are used, attached to low amounts of radioactivity, as diagnostic agents in nuclear medicine and molecular imaging. They are also used, attached to greater amounts of radioactivity, as therapeutic agents in patients with cancer and hyperthyroidism.

Radiopharmaceuticals are similar to magnetic resonance, ultrasound and radiographic contrast media (ie, gadopentetic acid, iohexol, perflorinated) in as much as a certain volume of agent is administered (mostly intravenously, but also via other routes) in order to enhance the visualisation or localisation of a specific organ or physiological system of the body. Unlike other contrast media, radiopharmaceuticals also contain a certain amount of radioactivity (either for visualisation or *in vitro* quantification), and it is this which ultimately makes the localisation of the radiopharmaceutical possible (with a gamma camera, whole-body counter, positron emission tomography or with other *in vitro* counting techniques).

### Radiation dose

The radiopharmaceuticals currently used in nuclear medicine emit either gamma rays, beta particles (charged positively or negatively), or both. Alpha particle-emitting

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radiopharmaceuticals are rarely used in nuclear medicine. In current pharmacopoeias, there is typically little mention of pharmacological adverse events, since they are not regarded as significant in comparison with the risk presented by the radionuclidic part of the radiopharmaceutical. Textbooks mention mostly untoward effects caused by radiation (external or internal) such as genetic damage, leucopenia, anaemia, inflammation of the skin, etc.<sup>1</sup>

When a radiopharmaceutical is administered, the non-radioactive moiety directs the radiopharmaceutical to specific organs, and those target organs might receive a higher dose, and could be at risk of tissue damage due to radiation. Under diagnostic conditions, when small quantities of radiopharmaceuticals are used, this does not pose a significant risk. When used in a therapeutic application, the aim is for the target organ to experience cell damage so as to ablate or reduce the cancer cells.

The acute effects of radiation only occur after whole-body exposures in excess of 1 to 2 gray (Gy).<sup>2</sup> (One Gy is equal to one joule of energy being absorbed in 1kg of tissue). The whole body dose received after the injection of a technetium-99m (<sup>99m</sup>Tc) radiopharmaceutical is in the order of 1.2 to 5.4mGy/gigabecquerel (GBq).<sup>1</sup> (One Bq is the unit of radioactivity and is defined as one disintegration per second.) For example, for a thyroid uptake scan, the radiopharmaceuticals of choice are either <sup>99m</sup>Tc pertechnetate or iodine-123 (sodium iodide). The typical patient dose of the former is 80MBq. For

ablation thyroid therapy, however, one would administer up to 8,000 or 9,000 MBq of iodine-131 (<sup>131</sup>I-sodium iodide) to a patient. The whole-body doses and target organ doses are listed in Panel 1 (p306).

From Panel 1 it is evident that the diagnostic thyroid dose, for example, is a fraction of the 1 to 2Gy that could result in acute radiation damage. Even the whole-body dose for a sizeable thyroid ablation dose with <sup>131</sup>I is only 0.142Gy, and thus quite a bit less than the whole body dose at which haematopoietic or gastrointestinal symptoms would occur.

Yttrium-90 ibritumomab tiuxetan (Zevalin) is administered to treat patients with refractory or relapsed CD20<sup>+</sup> follicular B-cell non-Hodgkin's lymphoma, and the typical dose is 15MBq/kg up to a maximum dose of 1,200MBq. The effective total-body dose<sup>4</sup> after the administration of 1,200MBq is 0.5mGy/MBq, or 600mGy in total. The summary of product characteristics (SmPC) specifies that "due to the exposure to ionising radiation derived from the radiolabel, a risk of mutagenic and carcinogenic effects has to be taken into account". The author is not aware of any reported adverse event in this regard to date.

Diagnostic quantities of radiopharmaceuticals lead to a small effective dose. (The effective dose is a quantification of the harmful effects of radiation on the body, taking into account the probability of stochastic effects [a radiation-induced health effect, the probability of occurrence of which is greater for a higher radiation dose and the severity of which is independent of dose].)<sup>5</sup> Examples of

effective doses for commonly used radiopharmaceuticals are listed in Panel 2.<sup>6</sup>

### Adverse events

For “regular” therapeutic pharmaceuticals, adverse events are nearly always caused by the presence of larger quantities of active ingredients. Most radiopharmaceuticals contain only sub-pharmacological quantities of active ingredients in a solution (most frequently) which might contain other excipients. A typical radiopharmaceutical vial might therefore contain a few milligrams of the drug, a stabiliser such as p-aminobenzoate, l-cysteine hydrochloride

or Poloxamer 188, and/or a reducing agent such as stannous chloride or stannous fluoride. Any allergic reaction that might occur would be ascribed to any of these components. It is rare to see a pyrogen-type reaction, since all radiopharmaceuticals are prepared within barrier units (pharmaceutical isolators or laminar flow cabinets).

The occurrence or reporting (by patients or nuclear medicine professionals) of side effects after radiopharmaceutical injections remains rare, and the incidence is far less than one in 5,000. In 2004, 59 adverse events or defective products were reported in the UK,<sup>7</sup> and of these 23 would qualify as clinical adverse events. Most adverse events can easily

### Panel 1: Radiation doses received from radiopharmaceuticals<sup>3</sup>

Target organ(s)	Total dose of radioactivity (mGy)	
	Technetium-99m pertechnetate (0.08GBq)	Iodine-131 sodium iodide (0.74GBq, assuming 25% thyroid uptake)
Whole body	0.240	1.42x10 <sup>2</sup>
Thyroid	2.808	2.59x10 <sup>5</sup>
Upper large intestine	2.592	
Liver		95.978

mGy means milligray. GBq means gigabecquerel

### Panel 2: Effective doses of radiopharmaceuticals<sup>6</sup>

Radionuclide	Radiopharmaceutical	Effective adult dose (mSv) per normal dose of radiopharmaceutical (MBq)
Fluorine-18	2-Fluoro-2-deoxy-d-glucose	7.03mSv/370MBq
Chromium-51	Chromium EDTA	0.004mSv/2MBq
Technetium-99m	Technetium DMSA	0.66mSv/75MBq
Technetium-99m	Technetium DTPA	0.98mSv/200MBq
Technetium-99m	Technetium HIDA	1.275mSv/75MBq
Technetium-99m	Technetium MAG3	0.7mSv/100MBq
Technetium-99m	Technetium macroaggregated albumin	1.1mSv/100MBq
Technetium-99m	Technetium MIBI	9.0mSv/1,000MBq*
Indium-111	Indium octreotide	10.8mSv/200MBq
Indium-111	Indium-labelled white cells (leucocytes)	5.76 mSv/16 MBq
Yttrium-90	Yttrium ibritumomab tiuxetan	600.0mSv/1,200 MBq <sup>5</sup>

mSv means millisieverts. The unit sievert can be used interchangeably with gray for the purposes of this article. MBq means megabecquerel. The doses are the diagnostic reference levels used for adult patients at Addenbrooke’s Hospital. Acronyms are defined in the box below. \*This refers to the combined dose of the stress and rest elements of a cardiology study

#### Acronyms of compounds used in radiopharmacy

<b>BIDA</b>	Parabutyl iminodiacetic acid	<b>HMPAO</b>	Hexamethylpropylene amine oxime
<b>DMSA</b>	Dimercaptosuccinic acid	<b>HSA</b>	Human serum albumin
<b>DTPA</b>	Diethylenetriamine-pentaacetic acid	<b>MAA</b>	Macroaggregates of albumin
<b>EDTA</b>	Ethylenediamine tetraacetic acid	<b>MAG3</b>	Mercaptoacetylglycylglycylglycine
<b>HIDA</b>	2,6 Dimethylacetanilido-iminodiacetic acid	<b>MDP</b>	Methylene diphosphonate
<b>HIG</b>	Human immunoglobulin	<b>MIBG</b>	Meta-iodobenzylguanidine
		<b>MIBI</b>	Methoxy-isobutyl isonitrile



be treated with antihistamines. The most common adverse events reported during this period were non-specific rashes, malaise, swollen injection site, oedema, tachycardia, dizziness, diarrhoea, breathing difficulties, and rarely short periods of tremor, partial loss of visual field, hypertension and nausea.

The SmPCs include a wider list of suggested adverse events, and they are listed (not an exhaustive list) in Panel 3 on p308 (it has to be stressed that these are rare occurrences).

There is a national mechanism in the UK to report all adverse events caused by radiopharmaceuticals (and product defects). When an event occurs, it can be reported either via the British Society of Nuclear Medicine website ([www.bnms.org.uk](http://www.bnms.org.uk)) or via the UK Radiopharmaceutical Group website ([www.ukrg.org.uk](http://www.ukrg.org.uk)). Once the details have been entered, the information is sent directly to a UK database where all information is tabulated, and the Medicines and Healthcare products Regulatory Agency is informed when necessary (depending on the type of adverse event or defect).

## Interactions

It is known that various factors can alter the biodistribution of a radiopharmaceutical. Several categories of altered biodistribution occur, and include altered pharmacokinetics (away from the target organ), enhanced uptake of a radiopharmaceutical in a specific organ or a reduced uptake. An altered biodistribution could make a diagnosis difficult, or in some cases be the cause of a wrong diagnostic decision. This can result in the need for a repeat scan, which causes unnecessary exposure to radiation.

A general list of drug-related altered biodistributions, taken mainly from the respective SmPCs, is presented in Panel 4 (p309).<sup>3</sup> The list is not exhaustive.

## Product defects

Most radiopharmaceuticals are prepared (reconstituted) only a few hours before use. Product defects do occur but are identified by stringent quality control procedures before patient use. A product is not used in patients unless it meets a pre-determined list of safety standards. Quality control is carried out after each preparation or assembly. Radionuclidic precursors are generally obtained either from generators or in-house cyclotrons (a particle accelerator in which charged particles are accelerated while being confined by a magnetic field). Otherwise, they are purchased as long-lived radionuclides.

The generator-produced radionuclide (ie, <sup>99m</sup>Tc, krypton-81m, rubidium-82, gallium-68) supply could be interrupted by generator defects, and this forms more than 50 per cent of product concerns reported. Defects can involve malfunctions of aspects related to the column, filters, tubing or shielding.

## Panel 3: Adverse effects of radiopharmaceuticals

Radiopharmaceutical	Possible adverse events
Technetium-99m BIDA	None reported
Technetium-99m DMSA	Occasional allergic reactions
Technetium-99m DTPA	Occasional vasomotor effects, rare urticarial-type reactions
Technetium-99m HIG	None reported
Technetium-99m HMPAO	Rare mild hypersensitivity, ie, urticarial erythematous rash, possible anaphylactic reaction after injection of white cells labelled with technetium-99m HMPAO
Technetium-99m MAA	Hypersensitivity (also local reactions), chest pain and collapse
Technetium-99m MAG3	Anaphylactoid reactions
Technetium-99m MDP	None reported
Technetium-99m MIBI	Metallic/bitter taste, transient headache, flushing and non-itching rash, oedema, dyspepsia, dry mouth, dyspnoea, hypotension
Technetium-99m tin colloid	Vasomotor problems, malaise, bradycardia, angio-oedema, rare cutaneous reactions
Technetium-99m nanocolloid	Occasional hypersensitivity and local allergic reactions
Technetium-99m tetrofosmin	Body warmth, vomiting, headache, dizziness, transient metallic taste, disturbance of smell, isolated cases of anaphylactic reaction or severe allergic reaction
Stannous agent (non-radioactive)	Rash, itching, skin irritation, rare hypotension, nausea, vomiting, malaise, oedema
Iodine-123 ioflupane (DaTSCAN)	Headache, vertigo, increased appetite
Iodine-123 MIBG	Rare blushes, urticaria, nausea, cold chills; and when administered too fast, palpitations, dyspnoea, transient hypertension, stomach cramps
Iodine-125 HSA	Fever, dizziness, nausea, vomiting, tachycardia, hypotension, urticaria
Iodine-131 sodium iodide	Hypothyroidism, hypoparathyroidism, radiation thyroiditis, oedema of thyroid that can lead to asphyxiation, leukaemia, carcinoma of the thyroid <sup>1</sup>
Chromium-51 EDTA	Mild allergic reactions
Gallium-67 gallium citrate	Anaphylactoid reactions, flushing, cutaneous erythema, pruritus, urticaria
Indium-111 DTPA	Lumbar/occipital puncture causes mild headaches and signs of meningeal irritation
Indium-111 octreotide	Specific effects have not been observed, but symptoms observed are suggestive of vasovagal reactions or of anaphylactoid drug effects
Selenium-75 SeHCAT capsules	None reported
Cobalt-57 cyanocobalamin capsules	None reported

Acronyms defined in box on p306

Cyclotron target/gas/current insufficiencies can also lead to reduced or no yields. There are numerous reasons for cyclotron problems, and even when the radionuclide has been produced with a significant yield, the subsequent synthesis could be interrupted because of difficulties in one of the many synthetic steps.

## Conclusion

Hospital pharmacists should be aware of the possibility of the, albeit rare, adverse effects from radiopharmaceuticals. The medicines of patients who will be receiving a radiopharmaceutical should be assessed to establish if there are any potential drug interactions.

## References

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## Panel 4: Potential interactions between drugs and radiopharmaceuticals

Radiopharmaceutical (RP)	Drug	Effect of the interaction
Technetium-99m phosphonates	Chemotherapeutic agents, dextrose, iron Melphalan Corticosteroids Meperidine Aluminium ion	Increases renal activity of RP Increases bone activity of RP Decreases bone activity of RP Causes soft tissue uptake of RP Increases liver activity of RP
Technetium-99m BIDA	Opiates, barbiturates	Increases intrabiliary pressure and increases gall bladder activity of RP
Technetium-99m DMSA	Nicotinic acid Cholecystokinin Atropine, somatostatin Ammonium chloride Sodium bicarbonate Mannitol Captopril	Decreases hepatic uptake and bile excretion of RP Increases gall bladder emptying of RP Decreases gall bladder emptying of RP Decreases renal uptake and increase hepatic uptake of RP Decreases renal uptake of RP Decreases uptake of RP Decreases renal uptake of RP in affected kidney of patients with unilateral renal artery stenosis
Technetium-99m DTPA	None reported	
Technetium-99m HIG	None reported	
Technetium-99m HMPAO	None reported	
Technetium-99m MAA	Chemotherapeutic agents, heparin, bronchodilators Diamorphine, nitrofurantoin, bisulfan, bleomycin, methysergide Magnesium sulphate	Possible effect on efficacy of the drug Possible side effects from the drug Causes pharmaceutical interactions
Technetium-99m MAG3	None reported	
Technetium-99m MIBI	None reported	
Technetium-99m tin colloid	Chemotherapeutic agents, oral contraceptives, tetracyclines	Alters biodistribution patterns of RP
Technetium-99m nanocolloid	Iodinated contrast media	May interfere with lymphatic scanning
Technetium-99m tetrofosmin	Beta-blockers Calcium antagonists Nitrates	Could lead to false negative results Could lead to false negative results Could lead to false negative results
Chromium-51 EDTA	None reported	
Iodine-123 ioflupane (DaTSCAN)	Amphetamines, benzatropine, cocaine, mazindol, sertraline, methylphenidate, phentermine Levodopa	Most medicines that bind to the dopamine transporter with high affinity can affect RP studies No interaction, so drug can be continued
Iodine-123 MIBG	Nifedipine	Prolonged MIBG retention in neural crest tumours
Iodine-125 HSA	Reserpine, labetalol, tricyclic antidepressants, sympathomimetics	Causes reduced uptake of RP
Iodine-131 (sodium iodide)	Amiodarone, propylthiouracil, thiopentone, thyroxine sodium, liothyronine, carbimazole, expectorants, perchlorate, vitamins, lithium, phenylbutazone, salicylates, antihistamines, steroids, sodium nitroprusside, penicillins, benzodiazepines, intravenous contrast media, oral cholecystographic agents, sulphonamides, sodium sulphobromophthalein, anticoagulants	Many agents affect the uptake of radioiodine and should be stopped before administration of RP
Gallium-67 citrate	Prior iron dextran Post iron dextran Prior desferrioxamine Post desferrioxamine Cytotoxics, immunosuppressants, contrast media, metoclopramide, reserpine, methyldopa, oral contraceptives	Decreases uptake of RP Increases uptake of RP Decreases uptake of RP Increases uptake of RP Distribution of RP affected by drug
Indium-111 DTPA	None reported	
Indium-111 octreotide	None reported	
Selenium-75 SeHCAT capsules	None reported	
Cobalt-57 cyanocobalamin	Aminoglycoside antibiotics, cytostatics, neuroleptics, anti-epileptics, biguanides, cholestyramine, EDTA, potassium-sparing diuretics, alcohol	The use of these drugs affects the result of the imaging, so they should be discontinued up to 10 days before administration of RP

Acronyms defined in box on p306

## Corrections

The third sentence of the last paragraph in the second column (p305) should have read: “The whole body dose received after the injection of a technetium-99m (<sup>99m</sup>Tc) radiopharmaceutical is in the order of 1.2 to 5.4mGy.”

In Panel 1 (p306), the total dose of radioactivity (mGy) for the whole body entry should have read 1.12 mGy for 80 MBq injected Tc-99m pertechnetate, and  $1.78 \times 10^4$  mGy (35% thyroid uptake) for 740 MBq I-131 sodium iodide injected. The reference for these figures is: Valentin DJ. Biokinetic models, absorbed doses, and effective doses for individual radiopharmaceuticals. *Annals of the ICRP* 1998;28(3):116-118.