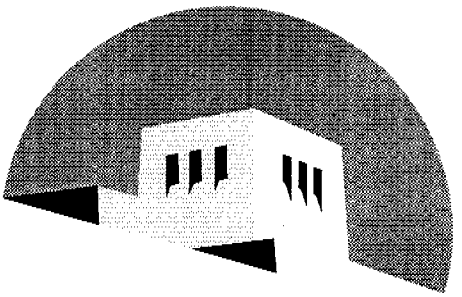

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Adverse Reactions to Radiopharmaceuticals

by:

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ADVERSE REACTIONS TO RADIOPHARMACEUTICALS

STATEMENT OF OBJECTIVES

The goal of this correspondence continuing education lesson is to increase the reader's ability to define and recognize adverse reactions to radiopharmaceuticals, which requires an understanding of the probability of causation. This lesson will also provide a reference relating individual radiopharmaceuticals to the adverse events to which they have been linked with various degrees of certainty.

On completion of this continuing education lesson, the reader should be able to:

1. define an adverse reaction to a radiopharmaceutical;
2. understand the problems of attributing causality;
3. identify the criteria for determining the probability that a clinical event occurring after administration of a radiopharmaceutical is due to that material;
4. recognize the very low adverse reaction rate from radiopharmaceuticals;
5. describe the problems with available reporting systems for adverse reactions;
6. discuss possible mechanisms of adverse reactions;
7. list the radiopharmaceuticals most and least likely to cause adverse reactions;
8. recognize the common symptoms and signs of adverse reactions;
9. treat adverse reactions to radiopharmaceuticals and adjunct medications.

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ADVERSE REACTIONS TO RADIOPHARMACEUTICALS

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INTRODUCTION

There are several reasons why adverse reactions to injected or ingested radiopharmaceuticals are quite uncommon. First, a very small mass of drug, usually a few milligrams or micrograms is administered. There are rarely more than one or two exposures to these radioactive drugs, so immunization is less likely to occur. Radiopharmaceuticals are employed, not for a pharmacologic action, but because a specific localization occurs due to a physiologic mechanism. They were not developed for a pharmacologic action so one is not anticipated.

DEFINITIONS

Food and Drug Administration

There are several definitions of an adverse reaction to a pharmaceutical. The United States Food and Drug Administration (FDA) prefers the term "adverse drug experience," which means "any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice, an adverse event occurring from drug overdose, whether accidental or intentional, an adverse reaction occurring from drug withdrawal, and any significant failure of expected pharmacologic action." [1] The issue of causality is avoided with this definition because of the phrase "whether or not considered drug related." With regard to reporting requirements, radiopharmaceutical manufacturers in the United States are bound by this definition.

According to the FDA "unexpected adverse drug experiences" are adverse drug experiences "not listed in the current labeling for the drug product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity." [1]

WORLD HEALTH ORGANIZATION (WHO)

The World Health Organization (WHO) has adopted the following definitions:

Side effect: "Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug." An example would be somnolence caused by an opiate administered for pain relief.

Adverse event: "Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relation with this treatment," e.g., hair loss during thyroxine replacement rherapy, which is only sometimes due to the hormone.

Signal: "Reported information on a possible causal relation between an adverse event and a drug, the relation being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information."

Adverse reaction: "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[2,3] Rash following penicillin is a not uncommon adverse reaction.

SOCIETY OF NUCLEAR MEDICINE (SNM)

The Pharmacopeia Committee of the Society of Nuclear Medicine (SNM) has suggested a definition where causality should be explored in each case of the association of radiopharmaceutical (or adjunct pharmaceutical) and symptom, sign, or laboratory data alterations. The following operational definition of an adverse reaction is proposed:

1. The reaction is a noxious and unintended clinical manifestation (signs, symptoms, laboratory data abnormalities) following the administration of a radiopharmaceutical or nonradioactive adjunct pharmaceutical.

2. The reaction is not one anticipated from the known pharmacologic action of the nonradioactive pharmaceutical.

3. The reaction is not the result of an overdose (which is a misadministration).

4. The reaction is not the result of injury caused by poor injection technique.

5. The reaction is not caused by a vasovagal response (slow pulse and low blood pressure).

6. The reaction is not due to deterministic effects of therapeutic radiation (e.g., myelosuppression).

7. The definition excludes altered biodistribution which causes no signs, symptoms or laboratory abnormalities.[4]

PREVALENCE OF REACTIONS

Some perspective on the safety of radiopharmaceuticals is provided by a comparison with the adverse reaction record of radiographic contrast media. The latter has been associated with reactions in 3.8-12.7% of administrations of ionic, and 0.6-3.1% of nonionic, contrast media.[5,6] The higher range comes from Japanese data[7] which have received some criticism for both possible information and selection bias.[8] Severe reactions* occur in 0.01-0.32% of injections,[(5,6)] and the fatality rate for all contrast media is about one per 75,000 (0.0013%).[8] [**Hypotensive shock, bronchospasm, pulmonary edema, respiratory or cardiac arrest, convulsions*[5].]

Another comparison provides some perspective as well. During hospitalization adverse drug reactions (virtually always involving nonradioactive therapeutic pharmaceuticals) have been noted in 1.5 to 35% of patients,[9] although one of the most careful such studies places the figure for drug related adverse events in the hospital at 0.7%, with 27.6% of these allegedly due to negligence.[10] These wide ranges of rates for adverse reactions reflect, in part, uncertainty in the definition of an adverse reaction. This is obviously a relevant issue in any analysis of radiopharmaceutical reactions.

In nuclear medicine the frequency of adverse reactions per 100,000 administrations has been estimated at 0.3,[11] 1 to 6,[12,13] 1.3,[14] 11 to 20,[15] and 33.[16] A prospective study coordinated by the Pharmacopeia Committee of the Society of Nuclear Medicine found a prevalence of 2.3 per 100,000 administrations.[4] Based on available data, adverse reactions following administration of contrast media is at least 200 times more likely, and perhaps thousands of times more likely, than that from a radiopharmaceutical.[4, 11-16]

The prevalence of adverse reactions may have decreased since early surveys in the 1970s. Among the reasons for this are improvement in manufacturing processes, the use of the *Limulus* amebocyte lysate (LAL) test which has raised the sensitivity of detection of Gram negative endotoxin, and the abandonment of both ferric hydroxide and human albumin microsphere radiopharmaceuticals which

had a relatively high frequency of adverse reactions.[12, 15, 17] Endotoxin injection into the cerebrospinal fluid may cause aseptic meningitis and only radiopharmaceuticals with a very low endotoxin content, approved by the USP, should be given intrathecally.

REPORTING SYSTEMS

Few adverse reactions to radiopharmaceuticals are ever reported, perhaps 10% or less. [15] Reasons for this unfortunate problem include ignorance of the reporting schemes, even though they are publicized by mailings to all American physicians. In a recent study of 3,000 randomly selected physicians, only 57% were aware of the FDA reporting system for any adverse drug reaction. While 418 physicians (14% of the total) had witnessed an adverse drug event in the prior year, only 21, or 5% of these, had reported the occurrence to the FDA. Other reasons for physician non-reporting include the time required to fill out a report; forms which are not readily available; considerable liability concerns; a belief that they (physicians) are too busy; lack of interest in reporting an event already documented in the literature; [18] the impossibility of recognizing a reaction if the patient leaves the nuclear medicine division before its occurrence and it is not reported; and confusion over the basic definition of an adverse reaction.[19]

The current U.S. reporting system for adverse reactions has evolved over more than two decades. Reports from the SNM Adverse Reactions Subcommittee, [11,12,17] in collaboration with the FDA and the United States Pharmacopeia (USP), began in 1972. Since 1986 the USP Drug Product Problem Reporting Program, in cooperation with SNM, has provided a form to be used for reporting adverse reactions (and also altered radiopharmaceutical biodistribution, a topic not covered in this lesson). A copy of this form is included as Figure 1. A copy of each completed report is also sent to the FDA, although this agency no longer funds the program. The USP also has a toll-free number for reporting adverse reactions: 800-822-8772.

Japan has had a reporting system for a number of years. The Joint Committee on Radiopharmaceuticals of the SNM-Europe initiated a system to monitor adverse drug effects and defective radiopharmaceuticals in 1979 and has reported the data collected on multiple occasions. [20-26,48] The successor group, the European Association of Nuclear Medicine, has continued the reporting mechanism.

While each of these professional societies records the number of reactions reported for a given time period, these are probably underestimates by a factor of 2-10. Furthermore, the denominator, or number of doses actually administered in the population surveyed by such reporting systems, has only been estimated. The Pharmacopeia Committee of the SNM (successor to the Adverse Reactions Subcommittee) initiated a study in 1989 in selected large U.S. hospitals requiring a monthly report on the number of adverse reactions to both radiopharmaceuticals and non-radioactive drugs used for pharmacologic intervention, as well as the total number of doses administered of each. The adverse reaction rate in this, the first prospective study on the subject with an accurate numerator and denominator, was 2.3 per 100,000 radiopharmaceuticals (95% confidence limits of 1.2-3.4 per 100,000). For nonradioactive drugs used in nuclear medicine for pharmacologic intervention, the risk of an adverse reaction was 5.9 per 100,000 , with 95% confidence limits of 0.1-11.7 per 100,000.[4]

MECHANISMS AND CLASSIFICATION OF ADVERSE REACTIONS

The very low prevalence of adverse reactions to radiopharmaceuticals has inhibited any comprehensive mechanistic study in animals or humans. The most obvious classification of adverse reactions, however, divides them into the frequent, dose dependent, Type A reactions due to the pharmacologic action of the drug, and Type B reactions, which are unexpected and unrelated to the known pharmacology of the drug.[27] Type B reactions describe most adverse responses to radiopharmaceuticals.

One frequently employed reporting system classifies the types of adverse reactions as follows:

1. vasomotor effects, e.g., hypotension;
2. anaphylactoid effects, e.g., nausea, rash, bronchospasm;[28]
3. pyrogen-type reactions, e.g., fever, headache.[29]

The obvious overlaps in this classification scheme diminish its usefulness. For example, both anaphylaxis and a vasovagal response to pain can cause hypotension. While there may be true allergy to some radiopharmaceuticals, the adverse reactions noted are usually at first exposure and therefore more likely anaphylactoid, i.e., direct release of mediators not related to antibody-antigen interaction.

Similarly, fever following administration of a radiopharmaceutical could represent infusion of an infectious agent or a pyrogen, or it could be caused by an allergic response.[29] True allergic reactions are often classified by their pathogenesis: 1) immunoglobulin E (IgE)-mediated hypersensitivity (including anaphylaxis); 2) cytotoxic antibody; 3) immune complex disease; and 4) delayed cell-mediated hypersensitivity.

Non-immunologic anaphylactic-like, or anaphylactoid,

Figure 1.

RADIO PHARMACEUTICALS

USP PRACTITIONERS' REPORTING NETWORK℠

An FDA MEDWATCH partner

The DPPR for Radiopharmaceuticals is presented in cooperation with The Society of Nuclear Medicine

RADIOPHARMACEUTICAL IDENTIFICATION

1. Name of radiopharmaceutical prepared agent _____

Manufacturer's name and address _____

_____

Central pharmacy name and address (if applicable) _____

_____

Radioactivity concentration _____ Assay date and time _____ Preparation time _____

Calibration date _____ Expiration date _____

2. Tc-99m generator ☐ Check here if not applicable

Brand name _____ Size _____ Ci Lot # _____

Calibration date and time _____ Date and time of current and last elution _____; _____ Exp. date _____

Amount and volume Tc-99m added to kit or given to patient _____

Manufacturer's name and address _____

Central pharmacy name and address (if applicable) _____

2a. Kit ☐ Check here if not applicable

Name of kit _____ Lot # _____ Volume diluted to _____ Expiration date _____

Kit heated ☐ No ☐ Yes duration _____

Manufacturer's name and address _____

Central pharmacy name and address (if applicable) _____

2b. Were manufacturer drug preparation methods strictly adhered to? ☐ Yes ☐ No ☐ Not applicable

2c. If non-radioactive drugs were used in association with radiopharmaceuticals, please list here _____

_____

PRODUCT ADMINISTERED TO PATIENT

☐ Yes, go to #3 ☐ No, go to #8

3. Problem noted or suspected

☐ Adverse reaction ☐ Other _____

☐ Altered biodistribution _____

☐ Product quality ☐ Patient physiology ☐ Concomitant drugs

4. Describe the problem (Please give time sequence of events, attach additional pages if necessary.)

4a. Was interpretation of image possible? ☐ Yes ☐ No ☐ Not applicable

5. Patient information

a. Patient initials _____ b. Suspected disease _____

c. Concurrent drugs, doses and frequency _____

d. Other disease states _____

6. Administration information

Activity administered _____ mCi / μCi (Circle one) Volume administered _____ mL Route of administration _____

Date and time of administration (indicate AM or PM) _____ Site of administration _____

Other patients received dose from same lot ☐ Yes ☐ No

Did they experience any reaction or altered biodistribution? ☐ Yes ☐ No

If yes, please file a report for each reaction. Number of patients _____

FILE ACCESS NUMBER:	DATE RECEIVED BY USP:

Figure 1. (cont'd)

7. Adverse reaction information

Date and time of reaction onset _____

☐ Recovered, no treatment necessary ☐ Died (date _____)
☐ Alive, with sequelae ☐ due to product
☐ Recovered, required treatment ☐ due to other cause
☐ unknown

Your interpretation of reaction cause

☐ Allergic
☐ Pyrogenic _____
☐ Pharmacologic effect _____
How classified (briefly) _____

8. Problem noted or suspected (check all that apply)

☐ Product identification incorrect ☐ Packaging compromised ☐ Compounding error
☐ Radiochemical impurity ☐ Radionuclide impurity ☐ Color/clarity/foreign matter
☐ pH high ☐ pH low ☐ Other_____ ☐ Particle size/number
☐ Heating period too long or short

9. Describe the problem

10. Test(s) if any (include ITLC data, particle size, etc.), performed to confirm problem

REPORTER IDENTIFICATION

11. Your name and title

11a. Name and address of institution

11b. Phone number, please indicate times you are available at workplace.

12. Please indicate to whom USP may voluntarily disclose your identity (check boxes that apply).

☐ Involved manufacturer(s) ☐ Society of Nuclear Medicine
☐ Food and Drug Administration (FDA) ☐ Other persons requesting a copy of this report

13. If requested, is sample of involved product available for examination?

☐ Yes ☐ No ☐ Sent to manufacturer

14. Signature and date

Evaluation by SNM Committee

Reviewer:

Return To:
USP Practitioners' Reporting Network℠
12601 Twinbrook Parkway
Rockville, Maryland 20852

OR

Call Toll Free Anytime
1-800-4-USP PRN
1-800-487-7776
(FAX 1-301-816-8532)

Electronic reporting forms are available. Please call 1-800-487-7776 for additional information and/or your free diskette.

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responses are caused by direct release of chemical mediators from mast cells unrelated to IgE binding. The putative mediators of these anaphylactic and anaphylactoid responses include histamine, prostaglandin D2, leukotrienes, complement (C4), platelet-activating factor, tryptase, chymase and heparin.[28,29] These can cause multiple syndromes, many of which are lsted in Table 1.

Table 1. Syndromes Caused by Mediators of Anaphylactic and Anaphylactoid Responses

Cutaneous erythema
Pruritus
Urticaria or angioedema
Mucous membrane pruritus
Swelling involving the eyes, nose, mouth, or larynx
Bronchoconstriction
Cardiovascular collapse from peripheral vasodilatation
Enhanced vascular permeability
Electrocardiographic abnormalities
Multiple gastrointestinal symptoms (nausea, vomiting, abdominal cramps and diarrhea)

All of these anaphylactoid syndromes have been associated with radiopharmaceuticals and appear to be more common in atopic patients and those with a history of reactions to other drugs.

There are other agents, including hyperosmolar radiocontrast media, and aspirin, which can also stimulate direct mediator release without IgE or complement involvement.[28] Other data suggest that contrast media do not release histamine solely by osmotic mechanisms.[30,31] Some drugs can directly trigger the complement cascade (again independent of IgE) which yields complement protein fragments C3a and C5a. Both these fragments cause direct release of mediators from mast cells and basophils.

Adverse reactions can be caused both by non-sterile products and from pyrogenic reactions to endotoxin. Sterility has not been a reported problem in the recent practice of nuclear medicine. However, experimentally, small inocula of *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* can all survive in nonradioactive radiopharmaceutical reagent kits with incubation times up to 5 days. In a radioactive vial *Pseudomonas* did not survive but *Bacillus subtilis* did.[32] This data logically leads to the conclusion that meaningful tests of sterility must take place shortly after radiopharmaceutical preparation, before extensive radioactive decay.

Endotoxin, a lipopolysaccharide derived from Gram negative bacterial cell walls, can lead to a febrile reaction by causing release of tumor necrosis factor, interleukin 1, interferons and other cytokines from monocytes/macrophages.[33,34] These promote the synthesis of E-series prostaglandins in the hypothalamus, and PGE_2 activates heat generating and conserving mechanisms.

Endotoxin, from cisternographic agents, has caused occasional meningeal reactions ,[34] and has been shown to be at least 1,000 times more potent in producing fever through the intrathecal than the intravenous route in three mammalian species.[29,35] With the sensitive *Limulus* amebocyte lysate test now widely used to detect endotoxin, pyrogen reactions have become quite uncommon.

The mechanisms of most adverse reactions cannot be investigated without promptly obtaining blood specimens to measure the levels of mediators listed above, and these are rarely available on an emergent basis. For bioethical reasons, rechallenge with these agents is uncommonly attempted, so research on the pathogenesis of adverse reactions from radiopharmaceuticals has been minimal.

In summary, adverse reactions can be caused by injection of infectious agents or endotoxins. They can also be anaphylactoid in nature. If one follows the not unreasonable convention of adding "other" as a fourth kind of adverse reaction,[3] one has a reasonably comprehensive, but not very heuristic, classification.

PROBABILITY OF CAUSATION

The problem of causality as, for example, between a drug under scrutiny and the patient's symptoms, signs, and laboratory tests, has challenged philosophers for centuries. Hume wrote that "all reasoning concerning matters of fact are founded on the relation of cause and effect, and that we can never infer the existence of one object from another, unless they be connected together, either mediately or immediately." Attribution of cause required "contiguity in time and place" and "priority in time" as requisite circumstances. A third requirement from Hume is that there be " a constant conjunction between the cause and effect. Every object like the cause produces always some object like the effect. Beyond these three circumstances of contiguity, priority and constant conjunction, I can discover nothing in this cause."[36] Since an adverse outcome of a radiopharmaceutical administration is rarely seen, the problem of imputability, of ascribing cause, is even more difficult.

More recently Hill[37] asked how we distinguish association from causation. The "strength" or prevalence of the association is first on Hill's list to help decide if there is a case for causation, but one should "not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight." Next to the strength of an association, Hill places the consistency of the observed association. It is helpful

if different observers have noted the association at different places and times, and under different circumstances. A third characteristic to help define causality suggested by Hill is the specificity of the association, i.e., the occurrence seen in a specific population, at a particular site, with a single type of reaction. A strong temporal relationship is a crucial fourth characteristic required to impute causality, as Hume had also noted. Other criteria Hill suggests are: a biologic gradient or dose-response curve (valid for the Type A response only); biological plausibility; coherence with generally known facts about the resultant reaction or disease; the presence of experimental evidence; and an analogy from similar responses to another drug.[37]

The analytic approaches of Hume and Hill to the problem of causality remind the investigator to develop criteria very carefully to suggest that an adverse reaction is due to a given pharmaceutical. The effect must follow the drug in a reasonable temporal association, but we will always lack consistency of the observed response, since adverse reactions to radiopharmaceuticals are very uncommon occurrences. Since we do not understand the precise mechanisms of many of these reactions, we cannot employ other criteria of Hill, e.g., biologic plausibility.

The strength of association, how likely an adverse effect is due to an administered radiopharmaceutical, is therefore a determination of certainty which almost never reaches 100% in nuclear medicine. There are confounding variables in such assessments. These include incomplete information; multiple drugs given at the same time; and a limited number of final common pathways of clinical response (including the disease under study). These considerations provide the background to several schema which have been suggested to evaluate a suspected cause and effect relationship between a radiopharmaceutical and some adverse reaction.

ALGORITHMIC APPROACHES

One of the first algorithms developed to determine the probability of causation was presented as a series of three decision tables that leads the investigation through the process of determining that an adverse drug reaction has actually occurred, by first excluding accidental poisoning, suicide attempt and non-compliance. Then, in the second table, one refines the chances of an adverse event by considering temporal relationships, the clinical state, and the response to dechallenge (discontinuing the drug) and rechallenge, to yield a spectrum of probabilities. The third table in this algorithm distinguishes the actual causes of the drug reaction. However, the described algorithm agreed with a consensus of three expert clinical pharmacologists only 71% of the time as to the probability of a reaction.[38]

Another algorithm has been described employing a semi-quantitative scoring system for each of six "major axes of decision strategy":

1. previous general experience with the drug;
2. alternative etiologic candidates;
3. timing of events;
4. drug levels and evidence of overdose;
5. dechallenge;
6 rechallenge.

Points assigned from each axis are added to give probability scores which translate into the chances of a reaction as definitive, probable, possible or unlikely. This system has the flexibility to be used with multiple drugs and drug interactions.[(39)] Subsequent data from the same group showed that three "non-experts" (who, in fact, developed the algorithm) agreed unanimously using their own guidelines, in only 67% of 30 cases. Two "experts," a clinical pharmacologist and clinical pharmacist "using implicit judgement" agreed in 47% of cases before the algorithm was used (often two to three levels of probability apart). Using the explicit judgment of the algorithm, agreement rose to 63%. In ten of eleven areas of disagreement the experts' difference was only one level of probability apart, rather than the two or three levels apart previously noted.[40] A somewhat similar approach, with a 23 item check list and quantitative weighting scores for the responses, has been described which produces causality levels described as not related, unlikely, possible, probable or definite.[41]

Cordova, Hladik and Rhodes offered an analysis of adverse reactions to radiopharmaceuticals, using the six axis algorithm described above.[39] Their data base included 277 cases of suspected reactions reported from 1976 through 1981 to the SNM. These were classified into one of the four categories (definite, 17%; probable, 40%; possible, 36%; unlikely, 7%) by unanimous consensus.

A Bayesian approach to imputation of causality has also been suggested using quantitative data culled from the literature for input to the estimate of probability.[43] These data, however, tend to have wide confidence intervals for the prevalence of drug reactions, so that precise numeric probabilities must be used with some caution.

A recent summary of the problem of attribution points out that in order to determine whether an association between a drug and an adverse effect is causal, one must exclude not only chance but also bias, confounding issues, and reverse cause, i.e., an effect of disease.[44]

A REVISED APPROACH TO ANALYZING CAUSALITY

The Pharmacopeia Committee of the SNM has recently

revised the approach to assigning probability of adverse reactions.[4] Among the problems raised by previous schema are the following:

1. For radiopharmaceuticals, the certainty of an adverse reaction can rarely be declared unequivocal or definite; the underlying disease for which the test has been ordered can cause unusual symptoms; the timing of the reaction may be delayed; and the reaction may never have been seen before.

2. The prevalence of adverse reactions is extremely low, so there is no vast experience with many reports of specific adverse reactions to radiopharmaceuticals.

3. Textbook lists of drug reactions do not prove that a genuine relationship exists.[37]

4. Any single adverse event not previously described must be registered if there is even a remote chance of a causal relationship. The probability of causation between radiopharmaceutical and the effect will clearly increase as more examples of the reaction are reported, but the first report must never be ignored.

5. An algorithm should exclude no possible adverse event which is even remotely related to a radiopharmaceutical, as long as this is so classified.

6. The clinical and laboratory features of most drug reactions are not unique.

7. Every radiopharmaceutical experience involves "dechallenge" since the radiotracer is administered only once.

8. Rechallenge may not produce the same reaction and could carry risk.

9. It is very difficult to be absolutely and unequivocally certain that an adverse reaction is or is not related to an administered radiopharmaceutical.

CATEGORIES FOR DETERMINING RELATIONSHIP OF REACTION TO RADIOPHARMACEUTICAL

The following definitions of probable causality have been suggested by the Pharmacopeia Committee of the SNM:[4]

Not related.

This category is applicable to those adverse experiences which, after careful medical consideration, are judged to be not related to the test material. Neither painful local sensation from drug infiltration nor hematoma at the injection site is considered an adverse reaction. An adverse experience may be considered not related if or when:

1. only a vasovagal response to a radiopharmaceutical is documented (low blood pressure and slow pulse);

or any three of the following are found:

2. it does not follow a reasonable time sequence from administration of the test material;

3. it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other materials administered to the patient;

4. it does not follow a known response pattern to the suspected test material;

5. it does not reappear or worsen when the test material is readministered .

Conditional, unlikely, or remote.

This category applies to those adverse experiences which, after careful medical consideration, cannot be placed in either "Possibly Related" or "Not Related" categories. This definition is to be used when the exclusion of radiopharmaceutical causality of a given clinical event seems plausible but the precise criteria in the "Not Related" category cannot be met. The event can also represent the first reported true side effect of a radiopharmaceutical, but since it would never have been reported before, the reaction would be registered in this category; it would be moved to the "probable" list at a later time if more reports of the same reaction occurred. An adverse experience may be considered conditional, remote, or unlikely if or when: (must have one of the following two criteria)

1. it follows a reasonable time sequence but does not follow a known response pattern to the test material administered,

OR

2. it does not follow a reasonable time sequence from administration of the test material but does follow a known response pattern to the suspected test material.

Possible.

This category applies to those adverse reactions for which, after careful medical consideration, the correlation with the radiopharmaceutical administration appears

possible if or when: (must have all three of the following criteria)

1. it follows a reasonable time sequence from the administration of the radiopharmaceutical;

AND

2. it follows a known response pattern to the suspected tracer;

AND

3. it could possibly have been produced by the patient's clinical state, environmental or toxic factors, or other diagnostic or therapeutic interventions (including other medications, contrast media, etc.) administered to the patient.

Probable.

This category applies to those adverse experiences which, after careful medical consideration, are believed with a high degree of certainty to be related to the radiopharmaceutical. An adverse experience may be considered probable if or when: (must have first two criteria plus numbers 3 or 4)

1. it follows a reasonable time sequence from administration of the tracer;

AND

2. it follows a known pattern of response to the suspected radiopharmaceutical material;

AND

3. it could not be reasonably explained solely by the known characteristics of the patient's clinical state, environmental or toxic factors, or other medications, contrast media, etc., administered to the patient;

OR

4. if rechallenge is medically necessary, the reaction recurs.

ADVERSE SIGNS AND SYMPTOMS FOLLOWING RADIOPHARMACEUTICAL ADMINISTRATION

The data in the following list of clinical findings which has been associated with (and probably caused by) radiopharmaceutical administration, has been obtained from the medical literature [19, 42,45,46] the registries kept by the SNM, European and Japanese Nuclear Medicine organizations, the USP,[47] manufacturers' package inserts (approved by the FDA), and a review of all unpublished adverse reactions reported to the USP from 1987 to mid-1993. Gastrointestinal, cutaneous, and cardiovascular responses comprise most adverse reactions.

The most common agents linked to adverse reactions over the past decade have included Tc-99m sulfur colloid, Tc-99m human albumin microspheres (no longer on the U.S. market) and Tc-99m medronate (MDP). Reviews of drug reactions dating from the late 1970s to the mid-1980s in the United Kingdom find Tc-99m diphosphonates/phosphates to account for 33-35% of all reactions and Tc-99m colloids 11-21%,[19, 46] Other authors using U.S. SNM data, note Tc-99m colloids to be the most prevalent cause of adverse reactions (24-26%) with Tc-99m MDP involved in 8-10%.[42,45] The inert gases, which have minimal absorption and no chemical reactivity *in vivo*, have not been associated with adverse reactions.

The adverse reactions (if any) to each radiopharmaceutical available in the United States in mid-1996 are listed below, alphabetically by radionuclide.[4] The time of onset may be as late as 24-36 hours following injection, especially with diphosphonates. One cannot distinguish which element of the solution injected from the radiopharmaceutical kit is directly causative. For example, a preservative, stabilizer, or suspending agent, rather than the radiopharmaceutical, could be causative. Microgram amounts of iodide, gallium or thallium alone are unlikely to cause symptoms. An etiologic evaluation of each sign or symptom is not possible, for reasons noted above, but the vast majority are believed to be anaphylactoid. The reactions listed have not been analyzed as to likelihood of causality, i.e., remote, possible, probable. This task requires use of the more recent algorithm as previously described . Details of the reactions which permit use of the algorithm have recently been published.[4] Following is a comprehensive list of adverse reactions associated with clinically-used radiopharmaceuticals:

^{57}Co-cyanocobalamin: none noted
^{51}Cr-sodium chromate: none noted
^{18}F-fluorodeoxyglucose: none noted
^{67}Ga-gallium citrate: nausea, vomiting, pruritus, diffuse rash, flushing, urticaria, facial swelling, dyspnea, bronchospasm, syncope, dizziness, tachycardia, salty taste
^{111}In-indium oxine labeled leukocytes: fever, diffuse rash, pruritus, urticaria
^{111}In-indium pentetate (DTPA): fever, nausea, vomiting, drowsiness, anorexia, headache, aseptic meningitis (all from the intrathecal route)
^{111}In-indium pentetreotide: fever, nausea, flushing, hypotension, bradycardia, hypoglycemia with insulinoma, dizziness, headache, diaphoresis, arthralgia.
^{111}In-satumomab pendetide: chills, fever, nausea, diarrhea, diffuse rash, flushing, pruritus, chest pain, hypertension, diaphoresis, hypotension, dizziness, headache, arthralgia, asthenia, confusion, anxiety, hypothermia
^{123}iobenguane (MIBG): none in diagnostic doses;
^{123}I-iodohippurate sodium: nausea, vomiting , urticaria, diffuse rash, pruritus , urticaria, diaphoresis, hypotension, syncope
^{123}I-iofetamine: chest pain, hypertension, dizziness
^{123}I-sodium iodide: nausea, vomiting, diffuse rash pruritus, urticaria, chest pain, tachypnea, tachycardia, headache, faintness
^{125}I-iodinated albumin: diffuse rash
^{125}I-iothalamate: none noted
^{131}I-iobenguane (MIBG): none in diagnostic doses; flushing, hypertension only in therapeutic doses injected rapidly
^{131}I-iodinated albumin: none noted for intravenous route;

intrathecally can cause aseptic meningitis

^{131}I-iodohippurate sodium: nausea, vomiting, urticaria, diaphoresis, hypotension, syncope, facial swelling, anaphylaxis

^{131}I-sodium iodide: nausea, vomiting, pruritus, urticaria, chest pain, tachycardia, headache

^{131}I-6-beta-iodomethyl-19-norcholesterol: nausea, vomiting, chest pain, hypertension, hypotension, headache, dyspnea, flushing, dizziness, facial swelling, abdominal pain, metallic taste

^{81m}Kr-krypton: none noted

^{13}N-ammonia: none noted

^{32}P-chromic phosphate: chills, fever, nausea, vomiting, chest pain, dyspnea, abdominal pain (some or most of these reported reactions may be due to the effusions for which chromic phosphate is administered)

^{32}P-sodium phosphate: nausea, vomiting, hypotension, diaphoresis (bone pain as flare response and myelosuppression, both from beta radiation, are not direct adverse drug effects but are due to absorbed radiation)

^{82}Rb-rubidium: none noted

^{89}Sr-strontium chloride: chills, fever (see parenthesis under ^{32}P-sodium phosphate)

^{99m}Tc-human serum albumin: chills, fever, flushing, diffuse rash, dyspnea, hypotension, tachycardia, vertigo, facial swelling

^{99m}Tc-albumin colloid: chills, nausea, abdominal cramps, hypotension, tachycardia, dyspnea, anaphylaxis

^{99m}Tc-bicisate hydrochloride: nausea, vomiting, diffuse rash, chest pain, respiratory arrest, seizures, syncope, vertigo, headache, cyanosis

^{99m}Tc-disofenin: none reported

^{99m}Tc-exametazime (HMPAO): fever, dyspnea, rash, hypertension, facial swelling, cyanosis, anaphylaxis, myoclonus (the last symptom could have been due to underlying neurologic disease)

^{99m}Tc-gluceptate: rash, urticaria, headache, nausea, vertigo, pruritus, flushing, diaphoresis, tachycardia, dyspnea, syncope

^{99m}Tc-lidofenin: chills, nausea

^{99m}Tc-macroaggregated albumin (MAA): fever, chills, nausea, erythema, flushing, urticaria, rash, pruritus, chest tightness, tachycardia, hypotension, syncope, dyspnea, wheezing, anaphylaxis, diaphoresis, asthenia, cyanosis, metallic taste

^{99m}Tc-mebrofenin: chills, nausea, pruritus, urticaria,

^{99m}Tc-medronate (MDP): headache, chills, fever, nausea, vomiting, rash, pruritus, urticaria, hypotension, anaphylaxis, weakness, dyspnea, vertigo, cardiac arrest

^{99m}Tc-mertiatide (MAG3): nausea, vomiting

^{99m}Tc-oxidronate (HDP): arthralgia, nausea, vomiting, erythema, faintness, diaphoresis

^{99m}Tc-pentetate (DTPA): nausea, chills, dyspnea, hypotension, syncope, hypertension, headache, rash, pruritus, urticaria, anaphylaxis, arthralgia

^{99m}Tc-pyrophosphate (PYP): chills, fever, nausea, vomiting, rash, flushing, pruritus, hypotension, dizziness

^{99m}Tc-sestamibi: rash, flushing, seizure, headache, metallic taste

^{99m}Tc-pertechnetate: chills, nausea, vomiting, rash, pruritus, urticaria, chest pain, hypotension, dizziness, headache, diaphoresis, anaphylaxis

^{99m}Tc-succimer (DMSA): fever, nausea, erythema, rash, flushing, syncope, abdominal pain

^{99m}Tc-sulfur colloid: fever, headache, nausea, vomiting, erythema, rash, flushing, pruritus, urticaria, bradycardia, tachycardia, chest pain, cardiac arrest, hypertension, cyanosis, diaphoresis, hypotension, dizziness, syncope, wheezing, anaphylaxis, seizure

^{99m}Tc-teboroxime: nausea, hypotension, facial swelling, metallic taste, pain at injection site

^{201}Tl-thallium chloride: rash, pruritus, hypotension

^{127}Xe-xenon: none noted

^{133}Xe-xenon: none noted

THERAPY OF ADVERSE REACTIONS

Most adverse reactions are mild and require little or no treatment. Mild cutaneous reactions generally respond well to oral or parenteral antihistamines. Severe anaphylaxis may require aqueous epinephrine, 0.3-0.5 mL of a 1:1,000 solution, subcutaneously or intramuscularly; this dose may be repeated every 15 minutes as needed to a total of three doses. For rapidly progressing and clinically severe anaphylactoid reactions, 3-5 mL of intravenous epinephrine (a 1:10,000 solution) should be considered. Epinephrine causes bronchodilatation, improves cardiac contractility, elevates blood pressure and decreases angioedema and urticaria. It also prevents further release of mediators of anaphylaxis. If there is a poor response to epinephrine, aminophylline may be employed to control bronchospasm. Antihistamines and corticosteroids do not provide immediate relief of symptoms but may reduce or prevent delayed manifestations of anaphylaxis. Severe anaphylaxis may also require assisted ventilation, maintenance of intravascular volume and further administration of inotropic agents.[9]

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REFERENCES

1. Code of Federal Regulations; Title 21, Part 310.305.

2. WHO Tech Report Ser. 1972; 498.

3. Delamothe T. Reporting adverse drug reactions. *Br Med J* 1992; 304:465.

4. Silberstein EB, Ryan J. Prevalence of adverse reactions in Nuclear Medicine. *J Nucl Med* 1996; 37:185-192.

5. Bush WH, Swanson DP. Acute reactions to intravascular contrast media: Type, risk factors, recognition and specific treatment. *Am J Roentgen* 1991; 157:1153-1161.

6. Wolf GL, Mishkir MM, Roux SG, et al. Comparison of the rates of adverse drug reactions: Ionic contrast agents, ionic contrast agents combined with steroids, and nonionic agents. *Invest Radiol* 1991; 26:404-410.

7. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media: A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990; 175:621-628.

8. Gertsman BB. Epidemiologic critique of the report on adverse reactions to ionic and nonionic media by the Japanese Committee on the Safety of Contrast Media. *Radiology* 1991; 178:787-790.

9. Savitsky ME. Recognizing hospital adverse drug reactions. *J Pharmacy Practice* 1989; 11:203-208.

10. Leape LL, Brennan TA, Laird NM, et al. The nature of adverse events in hospitalized patients. New *Eng J Med* 1991;324:377-384.

11. Atkins HL. Reported adverse reactions to radiopharmaceuticals remain low in 1984. *J Nucl Med* 1986;27:327.

12. Rhodes BA, Cordova MA. Adverse reactions to radiopharmaceuticals: Incidence in 1978 and associated symptoms. Report of the Adverse Reactions Subcommittee of the Society of Nuclear Medicine. *J Nucl Med* 1980;21:1107-1110.

13. Cordova MA, Rhodes BA, Atkins HL, et al. Adverse reactions to radiopharmaceuticals. *J Nucl Med* 1982; 23:550-551.

14. Subcommittee of the Safety Issue for the Radiopharmaceuticals, Medical Science and Pharmaceuticals Committee, Japan Radioisotope Association. Survey of the adverse reactions to radiopharmaceuticals in Japan. *Nuclear Medicine* 1979, 16:511-517.

15. Keeling DH, Sampson CB. Adverse reactions to radiopharmaceuticals. United Kingdom 1977-1983. *Br J Radiol* 1984:57:1091-1096.

16. Williams ES. Adverse reactions to radiopharmaceuticals: a preliminary survey in the United Kingdom. *Br J Radiol* 1974; 47:54-59.

17. Ford L, Shroff A, Benson W, et al. SNM Drug Problem Reporting System. *J Nucl Med* 1978; 19:116-117.

18. Rogers AS, Israel E, Smith CR, et al. Physician knowledge, attitudes and behavior related to reporting adverse drug events. *Arch Int Med* 1988; 148:1596-1600.

19. Sampson CB, Hesslewood S. Adverse reactions to and drug incompatabilities with radiopharmaceuticals. In: Theobold SR, editor. *Radiopharmaceuticals: Using Radioactive Compounds in Pharmaceutics and Medicine*. Chichester, U.K; Ellis Horwood Co., 1989:132-151.

20. The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine - Europe: First report on the system for "Reporting of Adverse Reactions and Drug Defects": 1980-1982. *Eur J Nucl Med* 1984; 9:45-49.

21. The The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine - Europe: European system for reporting of adverse reactions and drug defects: second report 1982-1983. *Eur J Nucl Med* 1984; 9:388-389.

22. European Nuclear Medicine Society Newsletter 7. *Eur J Nucl Med*; 1984; 9:47.

23. European Nuclear Medicine Society Newsletter 8. *Eur J Nucl Med*; 1984; 9:388.

24. European Nuclear Medicine Society Newsletter 9. *Eur J Nucl Med*; 1988; 13:487.

25. European Nuclear Medicine Society Newsletter 10. *Eur J Nucl Med* 1988; 13:491.

26. European Association of Nuclear Medicine Newsletter 4. *Eur J Nucl Med* 1988; 14, A9.

27. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. *Textbook of Adverse Drug Reactions*, 2nd ed. Oxford: Oxford University Press; 1981:11-34.

28. Bocher BS, Lichtenstein LM. Anaphylaxis. *New Eng J Med* 1991; 324:1785-1790.

29. Bennett IL, Petersdorf RG, Keene WR. Pathogenesis of fever: Evidence for direct cerebral action of bacterial endotoxins. *Trans Assoc Am Physicians* 1954; 70:64-73

30. Watkins J. Markers and mechanisms of anaphylactoid reactions. In: Allergic Reactions to Anaesthetics. Clinical and Basic Aspects. Monographs in Allergy, Karger, Basel, 1992; 30:108-129.

31. Baxter AB, Lazarus SC, Brasch RC. In vitro histamine release induced by magnetic resonance imaging and iodinated contrast media. *Invest Radiol* 1993; 28:308-312.

32. Brown S, Baker M. The sterility testing of dispensed radiopharmaceuticals. *Nucl Med Communic* 1986; 7:327-336.

33. Bone RC. The pathogenesis of sepsis. *Ann Intern Med* 1991; 115:457-469.

34. Cooper JF, Harbert JC. Endotoxin as a cause of aseptic meningitis after radionuclide cisternography. *J Nucl Med* 1975; 16:809-813.

35. Villablanca J, Myers RD. Fever produced by microinjection of typhoid vaccine into hypothalamus of cats. *Am J Physiol* 1965; 208:703-707.

36. Hume D. Abstract of a Treatise of Human Natur Cambridge, England. Cambridge University Press, 1740, reprinted 1938, pp. 11-25.

37. Hill AB. The environment and disease: Association or causation. *Proc Royal Soc Med* 1965; 58:295-300.

38. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clin Pharm Therapy 1977; 21:247-254.

39. Kramer MS, Leventhal JM, Hutchinson TA, et al. An algorithm for the operational assessment of adverse drug reactions. 1. Background, description, and instructions for use. *JAMA* 1979; 242:623-632.

40. Hutchinson TA, Leventhal JM, Kramer MS, et al. An algorithm for the operational assessment of adverse drug reactions. II Demonstration of reproducibility and validity. *JAMA* 1979; 242:633-638.

41. Venulet J, Ciucci AG, Berneker G-C. Updating of a method for causality assessment of adverse drug reactions. *Int J Clin Pharmacol Therapy Toxicol* 1986; 24:559-568.

42. Cordova MA, Hladik WB, Rhodes BA. Validation and characterization of adverse reactions to radiopharmaceuticals. *Noninvasive Med Imaging* 1984; 1:17-24.

43. Jones JK. Epidemiologic perspective of causality assessment for drug associated events. *Drug Inform J* 1986; 26:413-421.

44. Glynn JR. A question of attribution. *Lancet* 1993; 2:530-532.

45. Keeling, DH. Adverse reactions and untoward events associated with the use of radiopharmaceuticals. In: Sampson CB, editor: *Textbood of Radiopharmacy. Theory and Practice.* New York: Gordon and Beach, Inc; 1990.

46. Cordova MA. Adverse reactions associated with radiopharmaceuticals. In: Hladik WB, Saha GB, Study KT, editors. *Essentials of Nuclear Medicine Science.* Baltimore: Williams & Wilkins, 1987.

47. USP 23/NF18 The United States Pharmacopeia National Formulary, United States Pharmacopeial Convention Inc. Rockville, MD 1995

48. European system for reporting adverse reactions to and defects in radiopharmaceuticals: annual report 1994. Eur J Nucl Med 1995;22:BP29-BP33.

QUESTIONS:

1. Adverse reactions to radiopharmaceuticals are uncommon because of all but one of the following reasons: Which one is incorrect?

   a. They are non-antigenic.
   b. They are rarely given more than 1-2 times to a patient.
   c. The mass of drug given is low.
   d. The radiopharmaceutical has little or no pharmacologic action.

2. The FDA definition of an adverse drug experience includes all but one of the following elements. Which one is not considered with the FDA's definition?

   a. Failure of expected pharmaceutical action
   b. Adverse reaction from a drug overdose
   c. A drug misadministration
   d. Adverse event occurring from drug withdrawal

3. The Society of Nuclear Medicine definition of adverse reaction includes:

   a. the vasovagal response
   b. radiation myelosuppression
   c. rash occurring later than 24 hours after radiation administration
   d. tracer infiltration

4. Adverse reactions from radiopharmaceuticals have a higher prevalence than adverse reactions :

   a. in hospital patients.
   b. in outpatient administration of ionic contrast.
   c. in outpatient administration of nonionic contrast.
   d. none of the above.

5. The frequency of adverse reactions to radiopharmaceuticals is:

a. $2.3/10^6$
b. $2.3/10^5$
c. $2.3/10^4$
d. $2.3/10^3$

6. Adverse reaction prevalence has been decreasing over the last two decades in part because:

a. ferric hydroxide aggregates have replaced unstable Tc-99m macroaggregates in lung scanning.
b. the rabbit pyrogen test has become more sensitive in detecting endotoxin.
c. fewer radiotracers are in use now.
d. human albumin microspheres are no longer available.

7. Physician reporting of adverse reactions is less than it should be for all but one of the following reasons. Which one is incorrect?

a. ignorance of the reporting system
b. fear of malpractice suits and other liability concerns
c. lack of a concerned federal agency
d. uncertainty as to the definition of an adverse reaction

8. The Drug Product Problem Reporting Program is monitored by which federal agency?

a. NRC
b. FDA
c. OSHA
d. EPA

9. All of the following statements but one are true concerning Type B adverse reactions. Which one is false?

a. They are unanticipated responses to the drug.
b. They are due to the action of the drug on the immune system.
c. They are unrelated to the usual pharmacologic effects of the drug.
d. They are the more common type of adverse reaction from radiotracers.

10. Which one of the following is <u>not</u> a type of adverse reaction to radiotracers?

a. myelosuppressive effects
b. vasomotor effects
c. anaphylactoid effects
d. pyrogen-like effects

11. The pathogenesis of an allergic reaction to a radiotracer includes all but one of the following. Which one is incorrect?

a. delayed cell-mediated hypersensitivity
b. an anaphylactoid response
c. IgE mediated hypersensitivity
d. immune complex disease

12. Anaphylactoid responses occur when mediators are released from:

a. lymphocytes
b. macrophages
c. monocytes
d. mast cells

13. Anaphylactoid responses are mediated, at least in part, by:

a. leukotrienes
b. corticosteroids
c. somatostatin
d. immunoglobulin E

14. The syndromes of an anaphylactoid response rarely involve:

a. the kidney
b. the lung
c. the skin and mucous membranes
d. the gastrointestinal tract

15. Radiographic contrast media cause severe vasomotor reactions in part by:

a. IgE dependent mechanisms.
b. by direct venular toxicity.
c. osmotic mechanisms.
d. immune-complex formation.

16. Which one of the following statements about endotoxin is false?

a. It is a lipopolysaccharide.
b. It is found in the walls of Gram positive bacterial cell walls.
c. It is more toxic when given by the intrathecal route than intravascularly.
d. It is virtually synonymous with pyrogen.

17. Ascribing causality in analyzing an adverse drug reaction is difficult for all but one of the following reasons. Which one is incorrect?

a. The reaction may occur over 24 hours after the patient leaves the nuclear medicine division.
b. There are no specific diagnostic blood tests available.
c. The characteristic rash maybe quite evanescent and is rarely pruritic.
d. Reaction prevalence is quite low.

18. Ascribing causality for an adverse drug reaction is confounded by all but one of the following reasons. Which one does not confound the issue?

a. Rechallenge may not be ethically possible.
b. Dechallenge may not be ethically possible.
c. There are usually many potential etiologies.
d. The available algorithms have less than 80% predictive value.

19. An adverse reaction cannot be attributed to a specific radiopharmaceutical the patient has received if

a. a rash occurs longer than 36 hours following the dose.
b. the blood pressure and pulse both drop at the beginning of the injection.
c. dyspnea occurs longer than 30 minutes following injection.
d. the patient experiences emesis one hour after injection.

20. Which one of the following is not a synonym in describing the probability of a drug reaction in the Society of Nuclear Medicine classification?

a. possible
b. remote
c. unlikely
d. conditional

21. Which one of the following radiopharmaceuticals has been associated with adverse reaction?

a. xenon-133 as a gaseous inhalent
b. chromium-51 as chromate
c. iodine-131 as iodide
d. rubidium-82 as the cation

22. The most common agents linked to adverse reactions over the past decade include all but one of the following. Which one is not commonly associated with reactions?

a. Tc-99m sulfur colloid
b. Tc-99m mebrofenin
c. Tc-99m human albumin microspheres
d. Tc-99m methylene bisphosphonate

23. Which one of the following could not be responsible for an adverse reaction?

a. the preservative in the vial
b. the needle placed in the vial
c. the anti-oxidant in the vial
d. the suspending agent in the vial

24. A radiopharmaceutical used at two dosages (activities) with a clear dose-dependent adverse reaction probability is:

a. fluorodeoxyglucose
b. iodinated albumin
c. iodohippurate
d. iobenguane

25. Epinephrine has which one of the following effects?

a. bronchoconstriction
b. hypertensive
c. enhances capillary permeability
d. releases prostaglandins