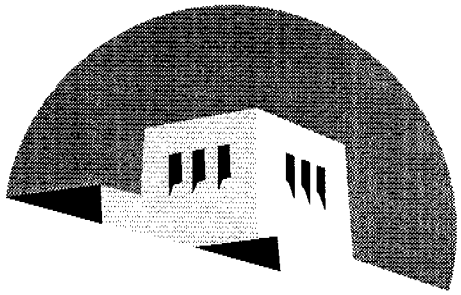

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Correspondence Continuing Education Courses for Nuclear Pharmacists and Nuclear Medicine Professionals

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Drug-Radiopharmaceutical Interactions: A Review of the Concept and an Update of Selected Literature (1990-1995)

by:

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DRUG INTERACTIONS INVOLVING RADIOPHARMACEUTICALS: A REVIEW OF THE CONCEPT AND AN UPDATE OF SELECTED LITERATURE (1990-1995)

STATEMENT OF OBJECTIVES

The purpose of this continuing education lesson is to comprehensively review the concept of drug-radiopharmaceutical interactions, and to illustrate this concept by using examples from recent primary literature sources. Aspects including mechanism, significance, prediction, and documentation of such interactions will be discussed.

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

1. discuss how radiopharmaceuticals are used to achieve positive patient care outcomes.
2. define the term "drug-radiopharmaceutical interactions."
3. explain how medication and contrast agents can interfere with the biokinetics of radiopharmaceuticals.
4. explain how drug-radiopharmaceutical interactions can impact patient care outcomes.
5. describe how to document drug-radiopharmaceutical interactions.
6. discuss factors that should be considered when attempting to predict the occurrence of a drug-radiopharmaceutical interaction.
7,. describe the process by which interactions that are detrimental in nature when first reported, may evolve into a useful technique for monitoring some aspect of drug therapy.
8. discuss the details of several recently-reported drug-radiopharmaceutical interactions, including the mechanism and significance of such interactions.

COURSE OUTLINE

I. THE ROLE OF RADIOPHARMACEUTICALS IN ACHIEVING POSITIVE PATIENT CARE OUTCOMES

II. DEFINITION OF A DRUG-RADIOPHARMACEUTICAL INTERACTION

III. GROSS MECHANISMS OF DRUG EFFECTS ON RADIOPHARMACEUTICALS

IV. DOCUMENTATION OF DRUG-RADIOPHARMACEUTICAL INTERACTIONS

V. PREDICTION OF DRUG-RADIOPHARMACEUTICAL INTERACTIONS

VI. EVOLUTION OF AN "INTERFERING" INTERACTION INTO A "USEFUL" INTERACTION

VII. EXAMPLES FROM RECENT LITERATURE

- A. Bone scintigraphy
- B. Imaging with ^{99m}Tc red blood cells
- C. Myocardial perfusion scintigraphy
- D. Thyroid uptake/imaging
- E. Neuroreceptor imaging
- F. Imaging with radiolabeled leukocytes
- G. ^{67}Ga scintigraphy
- H. Liver/spleen scintigraphy
- I. Pulmonary ventilation/perfusion scintigraphy

VIII. SUMMARY

DRUG INTERACTIONS WITH RADIOPHARMACEUTICALS: A REVIEW OF THE CONCEPT AND AN UPDATE OF SELECTED LITERATURE (1990-1995)

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THE ROLE OF RADIOPHARMACEUTICALS IN ACHIEVING POSITIVE PATIENT CARE OUTCOMES

The desired goal of medical intervention is to achieve an optimum therapeutic outcome in order to improve patient status. There are many elements required to achieve an optimum therapeutic outcome, but undoubtedly one of the major determinants is the quality of the therapeutic plan upon which it was predicated. The establishment and maintenance of an effective therapeutic plan hinges upon (a) proper evaluation of pertinent diagnostic information and (b) monitoring of appropriate parameters to obtain necessary feedback on the effectiveness of the plan. The use of radiopharmaceuticals can contribute significant information that may assist in the development or modification of the therapeutic plan. This is due to the fact that the biodistribution patterns of specific radiopharmaceuticals are representative of the function of various biological/organ systems of the human body. Therefore, the status of a particular system can be evaluated by monitoring the distribution of an appropriately-selected radiopharmaceutical. However, in order to avoid confusion in the interpretation of nuclear medicine study results, one must be aware of all factors that are capable

of effecting changes in radiopharmaceutical distribution, either directly (through interaction with the radiopharmaceutical itself) or indirectly (through modification of these biological/organ systems).

DEFINITION OF A DRUG-RADIOPHARMACEUTICAL INTERACTION

It is generally accepted that a variety of factors other than pathology can alter the "normal" biodistribution of radiopharmaceuticals. One such factor is drug therapy. A drug-induced modification in the biologic distribution of a radiopharmaceutical, that results in potential interference or confusion when interpreting data from the corresponding nuclear medicine procedure, is commonly referred to as a drug-radiopharmaceutical interaction. An interaction such as this is the consequence of a drug's effect on the kinetics of a radiopharmaceutical.

Although drug interactions involving two therapeutic medications are mechanistically similar to those involving a drug and a radiopharmaceutical, the outcome of each interaction is quite different. In the case of therapeutic drug-drug interactions, often Drug 1 will alter the way the body acts on Drug 2 (e.g., Drug 1 may affect the metabolism of Drug 2), thus ultimately modifying the action of Drug 2 at its target. Alternatively, Drug 1 may alter the body in such a way as to change the sensitivity or responsiveness of the target tissues to Drug 2. In yet another case, Drug 1 may physically alter Drug 2 (e.g., Drug 1 may chemically inactivate Drug 2), again changing the activity of Drug 2 at its site of action. This discussion underscores the fact that, whenever two therapeutic drugs are involved in an interaction, Drug 1 exerts influence on Drug 2, either directly or indirectly, to alter the pharmacologic effect of Drug 2. This is not the case, however, when Drug 2 is a radiopharmaceutical, due to the fact that radiopharmaceuticals, by definition, exert no pharmacologic effect. Rather, the action of Drug 1 on the radiopharmaceutical is manifested as altered kinetics of the radiopharmaceutical resulting in an unexpected biodistribution pattern.

Following the administration of a radiopharmaceutical, patients are imaged to determine the biodistribution pattern of the radiopharmaceutical. This pattern is determined by the kinetics of the radiopharmaceutical. Because radiotracer kinetics are dynamic, each image can only reflect an instantaneous biodistribution pattern -- much like each single frame of a motion picture. As a result, it may be necessary to obtain multiple images to observe biodistribution changes over time. Since diagnostic decisions are made based on analysis of these images, any changes in the biodistribution of a radiopharmaceutical due to external factors, such as drug therapy, will ultimately affect patient management. Thus, due consideration must be given to drugs which may affect radiopharmaceutical kinetics.

GROSS MECHANISMS OF DRUG EFFECTS ON RADIOPHARMACEUTICALS

Broadly speaking, diagnostic interference due to drug-radiopharmaceutical interactions may be clinically manifested in one of two ways.[1]

(1) A radiopharmaceutical biodistribution pattern may mimic a pattern normally visualized with a naturally occurring disease process.

Example: Bone scans performed in patients three to six months following initiation of therapy with leuprolide acetate for breast, prostatic, or lung cancer have exhibited (a) a transient increase in radiotracer intensity at sites of bone metastases and/or (b) the appearance of "new" lesions. This scintigraphic "flare" may represent either osteoblastic activity suggestive of a positive response to therapy or it may be a manifestation of hyperemia secondary to an inflammatory response at the sites of skeletal tumor destruction.[2] Of significance, however, is the fact that this finding should not be confused with scan results that are suggestive of progressive disease. The scintigraphic flare effect has also been observed on the bone scans of patients receiving paclitaxel[3] and other chemotherapy agents[4,5].

(2) A radiopharmaceutical biodistribution

pattern may diminish or mask the ability to identify a naturally occurring disease process by interfering with the interpretation of scintiscans.

Example: A well-known, but problematic drug interaction that ultimately affects radiopharmaceutical distribution involves the use of methylxanthines (i.e., products containing theophylline, caffeine, etc.) prior to performing a dipyridamole-enhanced myocardial perfusion study.[6] Dipyridamole induces vasodilation by causing an increase in endogenous plasma adenosine levels, and any antagonist to adenosine diminishes the response to dipyridamole. Since methylxanthines are competitive antagonists of adenosine receptors, extreme care must be taken to assure that these interfering medications have been discontinued for a sufficient length of time before initiating the study. Otherwise, the full effect of dipyridamole may not be realized, possibly resulting in a false negative myocardial perfusion study. [An exception to this rule appears to occur when using the medication pentoxifylline (Trental®), which is a methylxanthine derivative indicated for therapy of intermittent claudication. A study performed in dogs showed that, following administration of dipyridamole, theophylline significantly lowered peak coronary blood flow, but pentoxifylline did not decrease dipyridamole-induced hyperemia even a high doses.[7]]

As mentioned previously, these phenomena are due to drug effects on radiopharmaceutical kinetics. In this regard, there are several specific mechanisms by which drugs can induce altered kinetics. A number of authors have suggested ways to classify these mechanisms.[8-12] By incorporating the ideas offered by these authors with certain additional information, the following classifications are proposed to distinguish the various types of mechanisms by which interactions occur.

Pharmacologic

A pharmacologic mechanism of interaction occurs when any one of several expected pharmacodynamic actions of a drug affect a physiologic system, subsequently causing a secondary disturbance in the *in vivo* handling (kinetics) of a radiopharmaceutical by that same system.

Example: Labetalol, along with many other drugs which affect noradrenaline activity at the post-synaptic neuron, have been reported to alter the biodistribution of radiolabeled metaiodobenzylguanidine (MIBG).[13-16] This antihypertensive medication, through its pharmacologic action, interferes with the uptake of MIBG in sympathomedullary tissues and tumors (pheochromocytomas) by inhibiting the specific neuronal catecholamine uptake mechanism (uptake 1) and by depleting storage vesicle contents.[16] Therefore, in order to prevent the occurrence of a false negative study, labetalol should be discontinued for at least 72 hours prior to undertaking scintigraphy with radioiodinated MIBG.

Toxicologic

A toxicologic mechanism of interaction occurs when an overextension of one of the expected pharmacologic effects of a drug, or an adverse reaction to that drug (or to a contrast agent), results in a disease process which affects the kinetics of the radiopharmaceutical.

Example: Drug-induced liver dysfunction, such as that reportedly associated with nicotinic acid (niacin) therapy, can result in altered biodistributions of radiopharmaceuticals which rely on hepatic mechanisms for localization. One such altered biodistribution was encountered in a patient who displayed negligible hepatic extraction of a radiolabeled iminodiacetic acid compound while

on high-dose nicotinic acid therapy.[18] Several weeks following discontinuation of the drug, a normal hepatobiliary scan was obtained suggesting that reversible cholestasis[19] was responsible for the previous false positive results. This condition was likely due to parenchymal cell injury, portal fibrosis, cholangitis, and/or lymphatic infiltration around the bile ducts, any or all of which this drug is known to cause.[20]

Pharmacokinetic

A pharmacokinetic mechanism of interaction occurs when the *in vivo* handling of a radiopharmaceutical is altered by competition between a therapeutic medication (or contrast agent) and a radiopharmaceutical for receptor binding sites or metabolic/elimination pathways.

Example: A good example of this phenomenon is the interaction between etidronate disodium (the drug) and ^{99m}Tc diphosphonate bone imaging agents (the radiopharmaceutical).[21-26] Etidronate, which is also a diphosphonate compound, apparently saturates skeletal binding sites which are shared by both the drug and the radiopharmaceutical. Because of its much higher concentration, etidronate competitively blocks much of the uptake of the radiopharmaceutical into both normal and diseased bone. This results in a scintiscan that demonstrates a poor target-to-background ratio, manifested by diminished radiotracer localization in bone and, in some patients, increased soft tissue activity. In cases where the concentration of the radiotracer in bone lesions is dramatically reduced, this inter-action may lead to false negative study results. When bone scintigraphy is used to monitor therapy with etidronate for Paget's disease, hypercalcemia (associated with malignancy), heterotopic ossification, or osteoporosis, decreased bone uptake of radiotracer may be incorrectly interpreted as being indicative of clinical improvement. [Note: In contrast to the previously-mentioned reports, Pecherstorfer et al.[27] found that three weeks of intravenous clodronate (dichloromethylene diphosphonate) therapy did not impair the sensitivity of ^{99m}Tc medronate bone scintigraphy in detecting skeletal lesions in patients with metastatic breast cancer.

Physicochemical

This mechanism of interaction results from a direct physicochemical attraction or interaction between a therapeutic medication (or contrast agent) and a radiopharmaceutical (e.g., transchelation, or redox reaction), or indirectly from a drug-induced change in the *in vivo* environment in which the radiopharmaceutical exists (e.g., alterations in blood or organ pH). Any of these events could result in altered radiopharmaceutical kinetics.

Example: A moderate increase in liver and spleen uptake of ^{99m}Tc medronate was observed on the scintigram of a patient who was administered iohexol, a lower osmolality contrast agent, for a computed tomography study just after the radiopharmaceutical was injected[28]. Iohexol may have caused this phenomenon by inducing the formation of a radiocolloid or, alternatively, by facilitating hepatic localization of the radiotracer due to its alkaline pH. Regardless of the mechanism, similar scintigraphic findings have been attributed to ischemic hepatopathy, hepatic necrosis, amyloidosis, thalassemia, faulty radiopharmaceutical preparation, and concomitant drug therapy.[28] In light of this, caution must be taken in interpreting a study showing this pattern of distribution.

DOCUMENTATION OF DRUG-RADIOPHARMACEUTICAL INTERACTIONS

Over the past twenty years quite a number and variety of drug-radiopharmaceutical interactions have been reported in the medical literature. Not too surprisingly, these reports have varied widely in their overall quality and in the manner that authors have provided evidence to document the occurrence of specific interactions. Publications have included single- and multiple-patient case reports, retrospective analyses of large groups of patients, prospective controlled clinical studies, as well as research using animal models. As with any other type of scientific literature, caution must be taken when analyzing/interpreting reports of drug-radiopharmaceutical interactions, and when extrapolating data from them for use in one's own clinical practice.

In the United States, the only formal mechanism for reporting drug-radiopharmaceutical interactions, other than through publication in the medical or pharmacy literature, is the Drug Product Problem Reporting Program (DPPRP) for Radiopharmaceuticals, which is jointly sponsored by the United States Pharmacopeial Convention and the Society of Nuclear Medicine. Historically, this nationwide reporting system has been used principally for reporting adverse reactions and product quality problems. Unfortunately, most health professionals associated with nuclear medicine are either unfamiliar with this program or are unaware that the program can be used to document drug-radiopharmaceutical interactions. The problem stems from the fact that, until recently, the program has not been specifically promoted for this purpose. The form used to report problems associated with radiopharmaceuticals (see Figure 1) clearly asks the reporter to categorize the encountered clinical problem as either (a) an adverse reaction, (b) an altered biodistribution, or (c) other (e.g., product defect, compounding error, etc.). Even though the form also provides space to list the patient's medications, many individuals who report problems apparently believe that this information is most relevant only when documenting adverse reactions (i.e., that the information is being used to rule out the possibility that one of the medications may have caused the adverse reaction rather than the radiopharmaceutical). Since 1989, when the form last underwent major revision, virtually all of the reports of altered radiopharmaceutical biodistribution have been related to radiopharmaceutical formulation problems; there have been very few, if any, reports of suspected drug-induced altered biodistribution. Nevertheless, the form itself is designed appropriately (as a result of recent minor modifications) for collecting information on drug-radiopharmaceutical interactions, and it simply needs to be more widely publicized as a mechanism for reporting this type of problem.

PREDICTION OF DRUG-RADIOPHARMACEUTICAL INTERACTIONS

It would be extremely desirable to be able to predict the likelihood that a specific interaction will occur in a particular patient, based on the presence or absence of certain variables. Unfortunately, with a few possible exceptions, there is insufficient information available to make this type of determination with any certainty; details concerning the critical/compulsory prerequisite conditions necessary for specific interactions to occur are lacking in the literature.

It is much too simplistic to assume that Undesirable Interaction X will always ensue just because Radiopharmaceutical Y is administered to a patient who is receiving Medication Z. Rather, in most cases, it is likely that certain other requirements must be satisfied before the interaction will develop. In some instances certain co-factors must be present for an interaction to occur. Further, these co-factors must exist in appropriate concentrations, locations, and/or at the appropriate times in order for an interaction to occur. Parameters such as the following should be considered:

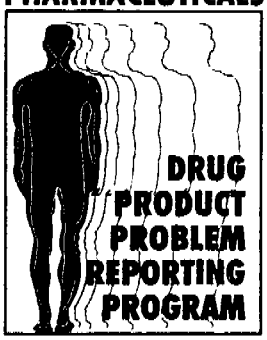
(1) What is a minimum concentration of the drug required in the serum or in a specific organ system to initiate the interaction? What dosage range of the drug will typically result in this concentration? What patient attributes can affect the kinetics of the drug?

(2) What is the duration of the drug's effect (on radiopharmaceutical kinetics) once it has been discontinued?

(3) What physiologic/pathophysiologic conditions and/or co-factors are required to facilitate or augment the drug's effect on

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
☐ Radiochemical impurity ☐ Radionuclide impurity
☐ pH high ☐ pH low ☐ Other_____
☐ Compounding error
☐ Color/clarity/foreign matter
☐ 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
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Electronic reporting forms are available. Please call 1-800-487-7776 for additional information and/or your free diskette.

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the kinetics of the administered radiopharmaceutical? (e.g., Will the interaction occur only if the pH of the blood is abnormally low, or only if the serum calcium level is abnormally high, or only if the patient is dehydrated?, etc., etc.)

This list of considerations is by no means complete, but it illustrates the points that (1) on occasion, several clinical parameters, or co-factors, may be required to be present and "in sync" before an interaction will take place and (2) each patient must be evaluated on a case by case basis to determine if the necessary conditions exist to allow an interaction to happen. The absence of any one essential condition may explain why Interaction X is not evident in some patients who are taking Medication Z and subsequently receive Radiopharmaceutical Y. Because of this complexity, it is essential that clinicians (1) possess the proper body of knowledge necessary to identify drug interactions, (2) integrate their knowledge of previous drug-radiopharmaceutical interactions with each patient's clinical presentation, and (3) apply some measure of clinical judgement in order to accurately predict the likelihood of interactions occurring in the presence of previously-identified risk factors.

Therefore, to improve patient care, it seems a reasonable goal to screen patients in this manner to allow for proper adjustments and/or interventions in patient care to be made. However, this can only be accomplished by putting forth a much greater effort to document the frequency with which interactions occur and the conditions under which they may be encountered.

CLINICAL IMPACT OF DRUG-RADIOPHARMACEUTICAL INTERACTIONS

Of concern to many nuclear medicine and nuclear pharmacy practitioners is the question of the true significance of drug-radiopharmaceutical interactions. Strictly speaking, the importance of any particular drug-radiopharmaceutical interaction depends on the extent to which the interaction interferes with patient management. Obviously the only interactions involving diagnostic radiopharmaceuticals of any consequence are those that are manifested during the time of image acquisition. To date, no study results have been published to help us estimate the potential effect these interactions may have on patient care. However, this topic can be discussed on a theoretical basis. As might be expected, not all drug-radiopharmaceutical interactions adversely affect diagnostic outcomes to the same degree. For example, (as mentioned previously) some interactions may precipitate radiopharmaceutical biodistribution patterns that either mask or mimic a spontaneously-occurring disease process, and thus have the potential to seriously compromise the utility and/or accuracy of the nuclear medicine study. In less extreme cases, an interaction may produce unusual or unanticipated findings on the associated scintiscan. These findings do not necessarily result in misdiagnoses, but they may lead to requests for additional diagnostic testing in order to confirm or rule out confounding initial impressions, thus increasing healthcare costs and patient inconvenience. In both instances, the interaction leads to an undesirable outcome, but the former example may have more serious clinical consequences than the latter.

The first test to assess significance, then, is to answer the questions, (1) How is the interaction manifested on the scintiscan?, and (2) Could the observed pattern of radiopharmaceutical distribution readily be attributed to (or confused with) influences other than drug therapy? Of course, if the answer to the second question is "yes" or even "maybe," then we must assume that the interaction has some potential significance. In its purest sense, significance should be an intrinsic quality of an interaction. However, on a practical level, familiarity with the spectrum of parameters associated with an interaction plays an important role in determining how a physician will deal with that interaction should it arise. In this regard, beyond the "inherent" effect of a drug on radiopharmaceutical kinetics and biodistribution, there are two other closely-related factors that may influence the significance of a particular interaction. The following questions (and associated discussion) address these:

(1) Is the physician aware that Medication Z can affect the biodistribution of Radiopharmaceutical Y under the appropriate conditions?

(2) Is the physician aware that (a) the patient being examined with Radiopharmaceutical Y is actually on a drug regimen which includes Medication Z, and (b) the neces-

sary conditions are present in the patient to allow the kinetics of Radiopharmaceutical Y to be altered by some pharmacologic, toxicologic, physicochemical, or pharmacokinetic property of Medication Z?

If the answer to both questions is "yes," then the interaction is not likely to hamper the physician's ability to appropriately interpret the results of the nuclear medicine study under consideration. However, if the answer to either question is "no," then there is a real possibility that the interaction may result in some degree of confusion. It obviously does little good to be knowledgeable about drug-radiopharmaceutical interactions if patients' medication histories are not readily accessible for use in assessing the probability that an interaction could occur (or has occurred). Likewise, it does little good to be aware of the medications a patient is receiving if one does not understand how these drugs may affect the outcome of the study. [Certainly if a previously unreported interaction is encountered, the discussion above does not apply; investigative and logical reasoning processes will be required to define the parameters of the interaction.]

EVOLUTION OF AN "INTERFERING" INTERACTION INTO A "USEFUL" INTERACTION

Not infrequently, an interaction that was initially considered to interfere with scan interpretation has been found to be useful as an interventional or monitoring tool. Use of two examples may best illustrate this point:

Example: It is not uncommon for a patient with acute abdominal pain to be given morphine (or one of its analogues) and then sent to nuclear medicine to determine if hepatobiliary disease may be the cause of the symptoms. The effect of the drug on the radiotracer study is to delay passage of the administered radiopharmaceutical into the small bowel, resulting in a pattern of distribution on the scintiscan which mimics common bile obstruction.[29,30] This pattern is due to a constriction of the sphincter of Oddi and an increase in intrabiliary pressure induced by the opiate-type analgesics. Of course, if one is not aware that these drugs can produce this biodistribution pattern (or if it is not known that the patient has received the drug therapy), it is possible that the scintiscan could be misinterpreted. However, several nuclear medicine clinicians have used the knowledge that these drugs effect a "back pressure" within the hepatobiliary system to develop a useful interventional technique[31]. These authors have suggested the use of morphine to promote patency of the cystic duct prior to initiation of hepatobiliary scintigraphy, particularly in patients being evaluated for acute cholecystitis. The use of the drug in this manner apparently helps to prevent the occurrence of false positive studies.

Example: Nitrofurantoin is known to induce a pneumonitis which can cause characteristic changes on Ga-67 citrate scans as well as pulmonary ventilation/perfusion studies.[32] On the one hand, these changes in radiopharmaceutical biodistribution could be attributed to causes other than nitrofurantoin if the physician interpreting the scintiscan is unaware that the drug can induce these changes or if he/she is unaware that the patient is receiving this medication. On the other hand, these nuclear medicine studies, particularly Ga-67, may be useful for prospectively monitoring the adverse pulmonary effects of nitrofurantoin.

EXAMPLES FROM RECENT LITERATURE

The following is a synopsis of selected literature pertaining to drug-radiopharmaceutical interactions which was published between 1990 and 1995. Some of the interactions mentioned in

the following discussion have been previously reported (prior to 1990), but these current citations are included here to sustained our awareness, encourage our surveillance, and reinforce the fact that there are certain interactions that must be reckoned with.

For the most part, this summary is arranged according to the type of nuclear medicine procedure affected by the interaction. [Note that many of the examples used in the previous sections of this lesson are also from recent literature.]

Bone scintigraphy

Calcium gluconate. An oral solution of calcium gluconate was the apparent cause of intense accumulation of ^{99m}Tc oxidronate in the gastrointestinal tract of a 52- year old woman who was taking this medication on the advice of her dentist. Since there were no problems with the quality of the radiopharmaceutical, this pattern of localization can likely be attributed to uptake of radiotracer by gastrointestinal surface cells to which the calcium had become associated.[33]

Isotretinoin. This drug is a Vitamin A congener used for a wide variety of dermatologic disorders. Gastric mucosal calcification is a side effect of isotretinoin that has previously been reported in animals. Franco et al.[34] present the first clinical report of this phenomenon as a case study in which a 6-year old child demonstrated increased gastric uptake of a bone imaging radiotracer during therapy (26 months) with isotretinoin.

Radioiodinated contrast media. Aquino and Villanueva-Meyer[35] report a case in which anterior chest wall activity was observed on a bone scan. This unusual biodistribution pattern was related to extravasation of iothalamate meglumine into the right anterior chest wall from a central catheter. The radiographic contrast agent had been injected prior to initiation of radionuclide bone imaging, in order to obtain a computed tomography scan of the chest.

(See also the discussion on page 5 concerning liver and spleen uptake of 99mTc medronate following iohexol injection.)

Iron dextran. Retention of radioactivity in the blood pool has been noted in patients who receive iron dextran therapy and subsequently undergo bone scintigraphy.[36,37] In these same patients, increased uptake of the ^{99m}Tc diphosphonate compound is also frequently observed in the liver, spleen, and kidneys, with variable effects on bone localization. It is speculated that the technetium-99m may have become bound to the iron dextran circulating in the blood. This hypothesis is at least partially based on the fact that unlabeled (nonradioactive) iron dextran remains in the blood for a period of time post injection, and then is gradually cleared by the reticuloendothelial system; in both of the reported cases, the kinetic profile of (what appears to be) radiolabeled iron was nearly identical to that expected from the unlabeled iron. The increased kidney activity may also be due to some form of technetium-iron complex formed *in vivo*.

Iron colloid. Bone scans performed on two patients receiving intravenous iron colloid therapy revealed marked radioactivity in the liver.[38] An *in vivo* labeling of the iron colloid with Tc-99m probably occurred in these patients, resulting in the unusual hepatic uptake of radiotracer.

Calcium carbonate-containing antacids. The milk-alkali syndrome is a disease characterized by hypercalcemia, alkalosis, and renal impairment. It is commonly induced by the ingestion of large quantities of calcium and absorbable alkali (e.g., OTC calcium carbonate antacids and milk), usually for symptoms of dyspepsia. Results of bone scanning in a patient with this disorder demonstrated increased radiotracer uptake in the long bones and calvarium.[39] This pattern of localization is similar to that seen in patients with hyperparathyroidism and humeral hypercalcemia, although enhanced osteoneogenesis is not a documented feature of the milk-alkali syndrome as it is with most other disorders that result in augmented uptake of ^{99m}Tc diphosphonates.

Phenytoin. Splenic localization of ^{99m}Tc medronate was observed in a patient with pancytopenia.[40] The patient was taking phenytoin, a drug known to induce this disorder. Following discontinuation of phenytoin and initiation of

corticosteroid therapy, a repeat bone scan showed considerably less uptake in the spleen compared to the previous study. The specific mechanism for this altered biodistribution pattern is not known.

Hormonal therapy and chemotherapy. (See discussion on page 3 concerning the scintigraphic flare effect.)

Etidronate. (See discussion on page 5 concerning diminished uptake of bone imaging agents following etidronate therapy.)

Imaging with ^{99m}Tc red blood cells

Heparin/doxorubicin. In a study which examined multiple medications as possible causes of diminished labeling efficiency of ^{99m}Tc red blood cells (RBC), it was found that only heparin and doxorubicin had a significant impact on lowering the radiochemical purity of *in vivo* labeled ^{99m}Tc erythrocytes.[41] However, when the UltraTag® RBC reagent kit was used , no drug interference was noted. Although the reason for this finding is not known, it is possible that the amount of stannous ion involved in the labeling process may influence the outcome [i.e., there is more stannous ion (per milliliter of whole blood) used in the UltraTag® RBC kit compared to that used in the *in vivo* labeling method.]

Cyclosporine. At least three groups of investigators have looked at the effect of cyclosporine on RBC labeling with Tc-99m using *in vitro* methods.[42-44] Interference from cyclosporine was noted when the Brookhaven/Cadema kit was used, but no such problem was observed when the UltraTag® RBC kit or a stannous pyrophosphate *in vitro* kit was used to radiolabel the RBCs. Gleue et al.[44] speculated that the greater quantity of stannous ion included in the latter two methods may be the likely factor responsible for preventing cyclosporine interference.

Dipyridamole. It is not uncommon for dipyridamole-enhanced ^{201}Tl thallous chloride myocardial perfusion studies to be to be performed immediately before radionuclide ventriculography. Hicks et al.[45] evaluated the theory that dipyridamole may have a detrimental effect on labeling efficiency of ^{99m}Tc RBCs. These authors compared post-dipyridamole labeling yields to those obtained pre-stress, post-exercise, and post-aminophylline recovery. The results indicate that dipyridamole does not significantly compromise either the *in vitro* or modified *in vitro* methods of labeling RBCs with Tc-99m.

Myocardial perfusion scintigraphy

Caffeine. In eight patients referred for clinically-indicated evaluation of myocardial perfusion, the antagonistic effects of caffeine on adenosine receptors demonstrated a negative effect on the diagnostic results of dipyridamole-^{201}Tl myocardial imaging. Caffeine infusion significantly attenuated the dipyridamole-induced fall in blood pressure and the accompanied increase in heart rate. In six of eight patients, this effect was responsible for false-negative dipyridamole-^{201}Tl myocardial tests.[6]

In another study of 86 patients, the serum caffeine level following 24 hours of caffeine abstention was correlated with observed maximum pulse and blood pressure changes. Blood samples were drawn prior to the initiation of either dipyridamole or adenosine. Results were correlated with maximum pulse and blood pressure changes measured during and immediately after the stress agent infusion, and thallium imaging findings. Detectable caffeine levels were found in 34 patients (40%), ranging from 0.1 to 5.0 mg/L. Five patients (6%) demonstrated serum caffeine levels >1.0 mg/L 24 hours after abstention. There was no significant difference in mean systolic blood pressure decrease or mean pulse increase between patients with caffeine levels >1.0 mg/L and those with lower (0.1 to 0.9 mg/L) or no detectable caffeine levels. Redistribution of thallium imaging was also identified with a similar frequency in these three groups (2/5, 40%; 8/29, 28%; 22/52, 42% respectively). This study suggests that 24 hour caffeine abstention is sufficient for most patients undergoing pharmacologic stress imaging, but a longer period of abstention might be necessary in a small number of individuals. Moreover, some patients are definitely likely to have caffeine levels high enough to interfere with vasodilator stress-thallium myocardial perfusion imaging after only 6-12

hours of abstention.[46]

Granulocyte stimulating factor (GCSF). A recent case report details the abnormal uptake of ^{201}Tl-chloride in the bone marrow in an AIDS patient with Kaposi's sarcoma who received chemotherapy and subsequently developed severe leukopenia that was treated with GCSF. Thallium, which is distributed in proportion to Na-ATPase activity (metabolism), likely accrued within the bone marrow in response to the pharmacologic effects of GCSF on that organ. However, the site of suspected tumor was negative for thallium uptake.[47]

Beta blockers. In 12 patients with coronary artery disease the effect of beta blockers on ^{201}Tl SPECT myocardial perfusion imaging was evaluated. Each patient was studied on placebo and after a two week treatment of equivalent dosages of either propranolol (40mg QID) or betaxolol (20mg QD). Maximal exercise heart rate and blood pressure were reduced and exercise time was increased with beta blockers. Estimated stress defect size decreased from 47 $\pm$ 36.3 gm during placebo treatment to 32 $\pm$ 27.1 gm during beta blocker therapy (-32%; $p<0.01$). All patients demonstrated stress defects during placebo treatment and each had redistribution defects consistent with residual scarring. During beta blocker therapy, 2 of 12 patients (17%) had normal stress-redistribution studies and only five had redistribution defects. The authors concluded that beta blockade can reduce exercise and redistribution ^{201}Tl SPECT defect size significantly while simultaneously increasing exercise time and reducing angina. Moreover, ^{201}Tl SPECT imaging may be useful in defining the reduction in ischemia produced by some cardiac drugs.[48]

Phenytoin. A 70 year-old man on phenytoin for control of a seizure disorder was evaluated by simultaneous exercise echocardiography and ^{201}Tl myocardial scintigraphy. Both imaging modalities revealed infero-posterior disease. The patient's phenytoin was discontinued by the neurologist before a repeat ^{210}Tl myocardial scintigraphy. This again demonstrated inferior wall ischemia in a pattern not significantly different from the initial study. From this case, the authors concluded that, despite data from animal research demonstrating as much as a 38% decrease in myocardial ^{210}Tl uptake in rats receiving phenytoin, this drug had no clinically apparent effect on the uptake and distribution of the radiotracer in this patient.[49]

Thyroid uptake/imaging

Iodinated contrast media. Radiopaque contrast media (CM) have been reported to alter the function of the thyroid in a variety of ways, dependent upon the baseline function of the gland prior to exposure. The levels of contaminant iodide are thought to play a role in the short-term inhibition of radioiodine (RAI) uptake via the Wolff-Chaikoff effect.[50] Jaffiol et al.[50] demonstrated that thyroid hormone levels were only minimally decreased and TSH levels were unchanged following intravenous CM indicating that hormonal feedback inhibition is probably not responsible for depressed RAI uptake. It is suggested that CM have an inhibitory effect on the iodine pump mechanism.[51] One study evaluated the levels of contaminant, free iodide and iodine, in several commercially available ionic and nonionic CM. There was no free iodine in any of the CM tested. However, there was considerable variation in free iodide levels ranging from 1.38 μg/mL to 20.84 μg/mL among the CM tested, although no significant differences between ionic and nonionic CM were found.[52] Nuclear medicine thyroid imaging is affected by CM, resulting in virtual nonvisualization of the thyroid gland and showing prominent activity localized within the salivary gland(s).[53] Shih et al.[53] present information on two patients with recent contrast radiographic procedures who underwent ^{99m}Tc pertechnetate imaging that demonstrated photopenic lesions, one a thyroid cyst and the other an abscess. No normal thyroid was visualized. Intravenous CM affect thyroid localization of ^{99m}Tc pertechnetate or RAI for 4-8 weeks.[54,55] Therefore, thyroid imaging is normally delayed for a 1-2 month interval following a CM aided radiographic procedure. If precision as to the exact uptake is not critical, ^{99m}Tc pertechnetate thyroid imaging may follow a CM aided procedure with no interval. Thyroid uptake of ^{99m}Tc pertechnetate is lower (1-5% of administered dose) than that of RAI, resulting in high soft-tissue

background. In the two cases described above, suppression of thyroid uptake secondary to CM resulted in enhancement of existing soft tissue background and, hence, delineation of a photopenic lesion. Therefore, despite this interaction, in patients who have received a recent administration of CM, ^{99m}Tc pertechnetate thyroid imaging can show a cystic lesion.

Hyperthyroidism has also been reported following administration of intravenous CM. Iodine loading from CM is a recognized precipitant of thyrotoxicosis, particularly in patients with long standing multinodular goiter in whom autoregulation of thyroid hormone production is absent. In the case reported, a 76 year-old man presented with biochemical evidence of thyrotoxicosis several weeks after a staging CT study which employed an iodinated radiographic contrast agent. This patient was subsequently treated with a therapeutic dose of RAI (55 mCi). The patient had no complications from this therapy and was biochemically euthyroid by eight weeks after treatment.[56] The development of thyrotoxicosis after the administration of iodine is known as the Jod-Basedow phenomenon.[51]

Methimazole. A report of thyroid scintigrams of two women (aged 48 and 58) with previously diagnosed Plummer's disease showed unusual RAI accumulation during treatment with methimazole (MMI). Before MMI therapy the images revealed most of the RAI uptake confined to the nodules of the patients with minimal uptake in the non-nodular portions of the thyroid. Following initiation of MMI therapy, scintigrams performed at three and eight months revealed that the hot nodules had become hypofunctional and that the surrounding tissues had normal RAI accumulation. These findings indicate that the nodules in Plummer's disease continue to concentrate MMI selectively compared with normal surrounding thyroid tissue during therapy.[57] If images obtained from the second study were considered independent of the initial study, it would likely cause the clinician to misinterpret these cold nodules as suggestive of some pathology other than Plummer's disease.

Neuroreceptor imaging

Cardioactive medications. Hugeut et al.[58] report an *in vitro* human blood platelet model for evaluating the inhibitory effects on noradrenaline transport systems which may block the uptake of metaiodobenzylguanidine (MIBG). MIBG, an analog of noradrenaline, is used to explore the functional integrity of sympathetic nerve endings in the human heart. Labetalol and propranolol inhibited ^{125}I-MIBG uptake, while all other drugs tested including other beta blockers, calcium channel blockers, digoxin, and amiodarone had no effect even at doses exceeding predicted plasma levels of patients receiving these drugs. The labetalol dose inhibiting 50% of the ^{125}I-MIBG was lower than the plasma concentrations of this drug in treated patents, whereas the propranolol dose was higher than is normally encountered at therapeutic doses. The authors concluded that this *in vitro* study of these drugs is predictive of their effect on myocardial uptake of ^{123}I-MIBG in treated patients provided that plasma concentration is considered.[58]

Spironolactone. A case report illustrates the interference of spironolactone in a patient who underwent ^{131}I-6β-iodomethylnorcholesterol (NP-59).[59] It has been reported previously that spironolactone withdrawal is recommended 4-6 weeks prior to NP-59 scintigraphy.[60] In the patient presented, 10 days of spironolactone therapy was thought to be insufficient to cause interference; however, the drug appeared to have increased right adrenal NP-59 uptake sufficiently to give a misleading pattern of bilateral early adrenal visualization in a patient with unilateral (left) adenoma. This, and other reports, illustrate the need for meticulous attention to detail in searching for and excluding potential pharmacologic interference in neuroreceptor imaging.

Imaging with radiolabeled leukocytes

Antibiotics. In an effort to detect vascular graft infection, ^{111}In leukocyte imaging was performed in 23 patients with synthetic vascular grafts who had received prior antibiotic therapy.[61] When the imaging results were correlated with surgical, clinical and/or autopsy findings, the outcome was 10 true-positive, 11 true-negative, 2 false-positive, and no false-negative scans, for an overall

sensitivity of 100% and a specificity of 85%. Although this study involved a small number of patients, the results appear to indicate that antibiotic therapy does not adversely affect the ability of ^{111}In leukocytes to detect synthetic vascular graft infection.

Chemotherapy. As mentioned previously in this lesson, drug-induced pneumonitis can be detected by a variety of nuclear medicine studies. Palestro et al.[62] recently reported three cases involving diffuse lung uptake of ^{111}In leukocytes associated with chemotherapy-induced pneumonitis. Although several disorders have been linked with this pattern of radioleukocyte distribution, drug-induced pulmonary inflammatory disease should be considered in the differential diagnosis when a diffuse pattern of radioleukocyte localization is observed in the lungs.

Anitbiotics/chemotherapy. Two recent case reports document the absence of bone marrow uptake of ^{111}In-leukocytes with normal bone marrow localization of ^{99m}Tc-sulfur colloid in the same patients.[63,64] This discordant and unusual pattern of distribution was attributed to drug therapy. In one case, colitis secondary to antibiotic therapy probably caused the rapid migration of leukocytes to the site of inflammation and away from the normal reticuloendothelial clearance pathway.[63] In the other case, a variable cytotoxic effect on the reticuloendothial function secondary to chemotherapy may have been responsible for the discordant marrow uptake.[64]

^{67}Gallium scintigraphy

Amiodarone. An unusual doughnut shaped localization pattern was noted on a ^{67}Ga scintiscan, suggestive of a cavitary lung lesion. It was later recognized that this scintigraphic pattern was caused by amiodarone-induced pneumonitis, although this specific distribution pattern had not been previously reported.[65]

Chemotherapy. Burns and Schiffman[66] report a case of an 18 year-old woman with Hodgkin's disease of the mediastinum and lung parenchyma. A pretreatment gallium scan showed increased uptake in the mediastinum which correlated with other imaging studies performed. Following chemotherapy, this lesion was not detectable by the same imaging modalities. However, four months later, a repeat gallium scan again demonstrated uptake in the mediastinal and hilar regions showing a retrosternal mass. Biopsy of the mass was performed which revealed normal thymus tissue. Thymic enlargement following chemotherapy for Hodgkin's disease should be considered in young adults when interpreting gallium scans performed in these patients.[66]

Aluminum/desferoxamine. A 66 year-old hemodialysis patient was admitted to the hospital with profound lethargy. Medications on admission included aluminum hydroxide. The patient's serum aluminum level was significantly elevated, prompting treatment with desferoxamine, a potent, non-specific chelator of metal ions. The patient subsequently developed an effusion of the left knee, and a gallium scan was ordered to evaluate for occult infection. The resultant images showed minimal organ localization of the ^{67}Ga and diffuse activity throughout the entire body. It is proposed that aluminum ions occupied potential gallium binding sites on transferrin molecules while desferoxamine complexed directly with gallium in the serum thus preventing normal distribution and uptake into the suspected lesion.[67]

Gadopentetate. An 11 year-old patient was injected with gadopentetate four hours prior to the administration of gallium. The resultant images obtained 96 hours post injection revealed a biodistribution pattern of gallium which mimicked a bone scan. It is suspected that gadolinium has a strong carrier-like effect on ^{67}Ga citrate, resulting in increased bone uptake and elimination.[68]

Chemotherapy. Dambro et al.[69] report the case of a man presenting with a high-grade lymphoma. Images obtained 48 hours following injection of radiogallium demonstrated three distinct sites of uptake located within the neck and thorax. This patient subsequently received chemotherapy consisting of cytoxan, vincristine, and prednisone intravenously 27 hours after radiogallium administration. Images obtained 120 hours post ^{67}Ga-citrate injection showed markedly reduced tracer

uptake at all three sites. Research has shown that 24 hours is ample time for the radiogallium to become locked within the cytoplasm,[70] and normally Ga-67 already in the lesions should not have been affected. Therefore, the authors suggest that the most probable explanation is chemotherapy-induced destruction of the lymphomatous cells. This case illustrates that, whenever possible, Ga-67 imaging should be completed before starting chemotherapy so that the influence of these medications does not complicate interpretation.[69]

Liver/spleen scintigraphy

Niacin A potential interaction of niacin and ^{99m}Tc-sulfur colloid resulting in pulmonary uptake of the radiotracer was reported. Speculation as to the exact mechanism for this apparent altered biodistribution was made, but no clear explanation for this phenomenon was offered. Suggested rationale include hepatotoxic and RES mediated mechanisms.[71]

Pulmonary ventilation/perfusion scintigraphy

(See discussion on page 10 concerning nitrofurantoin induced pneumonitis.)

SUMMARY

Numerous medications can alter the distribution of radiopharmaceuticals. A knowledge of how these various drugs affect the outcome of nuclear medicine studies and an increased awareness of each patient's clinical presentation will help to enhance the physician's and pharmacist's ability to correctly interpret these diagnostic tests to achieve optimal patient outcomes.

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QUESTIONS

1. The general mechanism by which a drug interacts with a radiopharmaceutical is by altering the ...

   a. pharmacologic effect of the radiopharmaceutical.
   b. sensitivity of he receptor site to the radiopharmaceutical.
   c. kinetics/biodistribution of the radiopharmaceutical.
   d. ability of the radiopharmaceutical to emit photons effectively.

2. Broadly speaking, diagnostic interference resulting from drug-radiopharmaceutical interactions may be manifested in which of the following ways?

   a. as a radiopharmaceutical biodistribution pattern that results in the release of conversion electrons

b. as a radiopharmaceutical biodistribution pattern that mimics a pattern normally visualized with a natural occurring disease
c. as a radiopharmaceutical biodistribution pattern that diminishes or masks the ability to identify a naturally occurring disease process
d. answers (b) and (c)

3. Labetalol alters the biodistribution of radiolabeled MIBG by ...

a. inhibiting the specific neuronal uptake mechanism for MIBG and by depleting storage vesicle contents.
b. increasing endogenous levels of pseudoephedrine which block MIBG uptake.
c. destroying sympathetic nerve endings through free radical formation.
d. inducing metabolism of MIBG in the liver.

4. The visualization of certain manifestations of drug-induced disease on nuclear medicine scintiscans would be mechanistically considered as which of the following types of drug-radiopharmaceutical interactions?

a. pharmacologic
b. toxicologic
c. pharmacokinetic
d. physicochemical

5. Which of the following medications is most likely to saturate binding sites for ^{99m}Tc diphosphonate bone imaging agents?

a. diazepam
b. etidronate
c. cisapride
d. acetazolamide

6. In the United States, the only official reporting system for altered biodistributions caused by drug-radiopharmaceutical interactions is coordinated through which of the following organizations?

a. American Pharmaceutical Association
b. American Society of Health-System Pharmacists
c. Food and Drug Administration
d. United States Pharmacopeial Convention

7. Which of the following statements is most likely to be true?

a. A particular drug-radiopharmaceutical interaction will occur in every patient who receives the two agents concomitantly.
b. Discontinuation of a drug immediately prior to administration of a radiopharmaceutical will almost always prevent a potential interaction.
c. A particular drug-radiopharmaceutical interaction will occur regardless of the concentration of the drug in body compartments.
d. With many drug-radiopharmaceutical interactions, it is likely that certain compulsory co-factors or conditions must be present in a patient in order for the interaction to be manifested.

8. Drug-radiopharmaceutical interactions become most significant when they ...

a. interfere with patient care.
b. occur in 2-3 patients.
c. occur without anyone realizing it.
d. involve medications used for coronary artery disease.

9. Drug-radiopharmaceutical interactions may be manifested as ...

a. frank diagnostic interference.
b. unusual or unanticipated (but not necessarily interfering) findings on the scintiscan.
c. a normal scintiscan.
d. answers (a) and (b).

10. The effect of morphine on the kinetics of ^{99m}Tc hepatobiliary imaging agents is an example of an interaction that is ...

a. only documented in animals.
b. life-threatening.
c. potentially interfering ***or*** useful for interventional purposes.
d. seen only in patients under 35 years old.

11. Isotretinoin therapy has been reported to cause ^{99m}Tc bone imaging agents to localize in which of the following organs?

a. lungs
b. stomach
c. kidneys
d. liver

12. Which of the following medications has on several occasions been reported to induce decreased skeletal uptake and increased blood pool activity following the administration of ^{99m}Tc diphosphonates?

a. iron dextran
b. desferoxamine
c. amoxicillin
d. verapamil

13. Hormonal therapy and chemotherapy can sometimes cause a transient increase in ^{99m}Tc diphosphonate concentration in bony lesions indicating an improvement in the patient's condition. This phenomenon is known as ...

a. organ iron syndrome
b. the hot potato sign
c. scintigraphic flare
d. contiguous skull sign

14. Cyclosporine has been reported to interfere with the labeling efficiency of ^{99m}Tc red blood cells when which of the following *in-vitro* labeling methods is used?

a. UltraTag®RBC kit
b. Brookhaven/Cadema kit
c. stannous chloride (pyrophosphate)
d. Interference has been reported with all three methods.

15. Which of the following statements is true concerning dipyridamole's effect on the radiochemical purity of ^{99m}Tc red blood cells labeled via the *in-vitro* or modified *in-vitro* methods?

a. Dipyridamole has no significant effect on labeling efficiency.
b. Dipyridamole almost always decreases labeling efficiency.
c. Dipyridamole almost always increases labeling efficiency.
d. Dipyridamole decreases labeling efficiency only if aminophylline recovery is used.

16. Caffeine has been shown to cause false-negative dipyridamole-^{201}Tl myocardial perfusion imaging. Following 24 hours of caffeine abstention what percent of patients are likely to have serum caffeine levels capable of causing this interference?

a. > 75%
b. 25-50%
c. 10-20%
d. <10%

17. The concomitant administration of beta-blockers during myocardial perfusion imaging has been correlated with all of the following ***except***...
a. decreased elevation in heart rate
b. decreased exercise defect size
c. decreased elevation in blood pressure
d. increased redistribution defect size

18. Levels of contaminant iodide found in radiopaque contrast media are thought to play an important role in the inhibition of radioiodine. How are levels of thyroid stimulating hormone affected by free iodide from contrast media?

a. increased
b. decreased
c. unchanged
d. early decrease, followed by long term increase

19. In patients treated with methimazole whose subsequent thyroid scintigrams demonstrate cold-nodules, to what mechanism of interference discussed in this review is this pattern most likely attributable?

a. Wolff-Chaikoff effect
b. Jaffiol Effect
c. Jod-Basedow phenomenon
d. Plummer's disease

20. Which of the following drugs has demonstrated *in vitro* inhibition of MIBG uptake at doses lower than those predicted plasma levels of patients receiving this drug?

a. propranolol
b. digoxin
c. labetalol
d. amiodarone

21. Diffuse lung uptake of radioleukocytes can be attributed to...

a. drug-induced pneumonitis
b. aspiration pneumonia
c. iodinated contrast media
d. bacterial abscess formation

22. Early scintigrams suggestive of ulcerative colitis have been obtained following ^{111}In-leukocyte imaging in patients with absent ^{99m}Tc-sulfur colloid bone marrow distributions. A likely cause of this phenomenon is...

a. poor leukocyte labeling.
b. transchelation of ^{111}In to plasma proteins.
c. antibiotic therapy.
d. NSAID therapy

23. ^{67}Ga scintigraphy which demonstrates minimal organ localization and diffuse whole body activity could be attributed to which of the following?

a. significantly elevated serum aluminum
b. hyperalbuminemia
c. radiation therapy
d. hemodialysis

24. A patient who recently received gadopentetate was imaged 96 hours after ^{67}Ga citrate injection. The resultant scintigrams appeared to mimic a bone scan possibly due to...

a. ingestion of vitamin supplements
b. the carrier effects of gadolinium
c. the Wolff-Chaikoff effect
d. hyperemic bone syndrome

25. When assessing the probability of a drug-radiopharmaceutical interaction having affected a scintiphoto, which of the following are most important to consider?

a. pharmacology and kinetics of the drug(s)
b. pathophysiology of disease state(s)
c. disease prevalence
d. all of the above

FURTHER READINGS (REVIEW ARTICLES AND CHAPTERS) [Note that some reviews are listed in the Reference section above (Refs 1,9,10, 11,12.]

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