LETTERS TO THE EDITOR

The Descent of Nuclear Medicine

Bravo for Marshall Brucer and Henry Wagner to their articles on the past and future of nuclear medicine in the June edition of the *Journal*. These were so good that, for the first time, I read the *Journal* through from front to back instead of the usual back to front. But I was surprised to see Brucer date the beginning of nuclear medicine to 1815 and Prout's observations on the uric acid content of a boa constrictor's stool. I've been thinking all along that it started with Geoffrey Chaucer (1340?–1400) and Alexander Pope (1688–1744). Pope made the first reference to scintigraphy in "An Essay on Man." Readers will all recognize his famous lines:

"Know then thyself, presume not God to scan
The proper study of mankind is man."

Marshall Brucer could hardly have put it better himself.

And Chaucer must get credit for the first reference to in vitro nuclear medicine, which he made in his poem "Troilus and Cressida." Translated into modern English it goes as follows:

"For my affairs have come to such a pass
That I perceive that Fortune is my foe,
And all who up and down this wide world go
Must take whatever Fortune shall decree,
For as she will, she plays with bound and free."

I'd say that's an unequivocal reference to radioimmunoassay—and 550 years before Berson and Yalow.

And how heartening it was to read Wagner's inspiring article on the future of nuclear medicine and see his graph, which showed a steady decline in the death rate in a university hospital from 1962 to 1972. I could not help noting that in the year when I gave up practicing internal medicine in a university hospital in favor of nuclear medicine, the death rate took the sharpest dive recorded. Readers may draw whatever conclusion they wish from this observation. I know the one I'll choose. Makes a fellow kind of proud.

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Guidelines for the Clinical Evaluation of Radiopharmaceutical Drugs

I. INTRODUCTION

"General Considerations for the Clinical Evaluation of Drugs" should be reviewed before reading this guideline. It contains suggestions that are applicable to investigational drug studies for most classes of drugs and helps to eliminate repetitious material in each of the specific guidelines.

Investigational studies of radiopharmaceutical drug products (RDP's) should be carefully designed to provide the scientific evidence that will substantiate their safety and efficacy for proposed diagnostic or therapeutic indications. These investigations should be conducted so that safety and efficacy are demonstrated with minimum exposure of patients to unnecessary radiation.

Much of the information in this guideline is applicable to the clinical investigation of both diagnostic and therapeutic RDP's. However, the major emphasis in Sections I–III is on the requirements for diagnostic RDP's, whereas the information in Section IV considers the special requirements for therapeutic RDP's.

The evaluation of diagnostic RDP's will differ from that of most therapeutic drugs in several ways because of certain special characteristics:

1. Since diagnostic RDP's do not usually elicit a pharmacologic response, evaluation of safety often requires less detailed study of pharmacologic toxicity and is primarily related to adequate estimation of radiation absorbed dose.
2. A diagnostic RDP is considered to be effective if its use results in information leading to a decision concerning the presence or absence of disease or abnormality. It is recognized that with some diagnostic agents it may not be possible to specify the nature of the disease or abnormality.
3. The diagnostic value of a radiopharmaceutical is a function of its biodistribution and the character of the radiations emitted. The degree to which the biodistribution is altered by disease or abnormalities is of particular importance. Thus, the investigation should demonstrate the normal biodistribution, the pathologically altered distribution, and how the altered distribution is determined in patients—e.g., through imaging studies, in vivo uptake studies, or by in vitro tests.

II. PRECLINICAL STUDIES

Sufficient preclinical animal data, manufacturing information, and quality control information to establish reasonable safety must be available before the administration of a RDP to human subjects. Characterization and quantification of the radiochemical and radionuclidic purity of the radiopharmaceutical are important preliminaries to the evaluation of radiation dosimetry, in order to determine any trace radiocontaminants (including daughter products) and altered chemical forms that might significantly influence biodistribution and radiation absorbed dose.

Preclinical studies will generally include both biodistribution studies and animal toxicity studies.

These data may be obtained from experiments performed by the investigator, the published literature, or other valid sources, provided that the sponsor can demonstrate that the data are applicable to the substance under consideration (i.e., dosage form, route of administration, etc.).

A. Radiation Dosimetry

Preclinical (animal) studies are required to determine the biologic distribution, translocation, and the route and extent of excretion of the RDP. This information is essential for meaningful dosimetry calculations. Dosimetry calculations on these animal data should be determined before initiating human studies. In general, it is desirable to assay for the concentration of the RDP at selected time intervals in all major organs and tissues so that the organs (tissues) receiving the highest radiation absorbed doses can be identified. With a diagnostic RDP used for imaging purposes, the organ (tissue) receiving the highest radiation absorbed

dose is often, but not always, the same as the organ (tissue) of primary interest that is to be imaged. For example, in liver imaging with radiocolloids, the liver is generally both the organ receiving the highest radiation absorbed dose and the organ of primary interest, whereas in bone imaging with Tc-99m-labeled phosphate compounds the skeleton is the organ of primary interest, while the bladder is usually the organ receiving the highest absorbed dose.

B. Animal Toxicity Studies

It is recognized that only trace chemical quantities of radionuclides are used in most radiopharmaceutical procedures and that for diagnostic RDP's the absolute amount of the radioactive element generally is well below those levels expected to produce pharmacologic and/or toxic effects. Thus, the chemical toxicity of the other components of the RDP may be of greater importance than the toxicity of the radionuclide itself—e.g., in the case of In-111-tagged bleomycin, the toxicity of the bleomycin may be more significant than that of the indium.

In special circumstances, no animal toxicity studies will be required when the radiopharmaceutical is a tracer quantity of a normal body constituent (e.g., radiosodium). Under these circumstances, it is the responsibility of the sponsor to provide data showing that toxicity studies are not required for the specific formulation to be used clinically.

Part of the toxicology testing may be performed using the nonradioactive form of the drug substance if the radiation dose to the test animals interferes with the test results or if such tests create an unnecessary radiation hazard.

1. Acute toxicity testing will generally require studies in at least two animal species:

a. To determine the acute LD_{50} of the stable form of the RDP; or

b. To demonstrate that no acute toxicity would be expected from doses of the clinical dosage form of the RDP that are several orders of magnitude higher on a dose-per-kilogram basis than those proposed for human use, using the intended clinical route of administration.

2. Subacute toxicity testing (2–3 wk) usually should be performed in two animal species, a rodent and a nonrodent, at several dose levels providing adequate margins of safety relative to the equivalent maximum clinical dose. Where feasible, dosages should be selected so that the highest level can be expected to produce some toxicity and the lowest level can be expected to produce minimal or no toxicity. The clinical dosage form of the radiopharmaceutical should be administered daily for 2–3 wk by the route to be employed clinically. Hematologic and biochemical evaluations and gross pathologic and histologic examinations of the organs of primary interest, and of the organs receiving the highest radiation absorbed doses, should be performed. Some portions of this evaluation may be omitted if factual evidence can be provided to substantiate that it is unnecessary.

3. Chronic toxicity studies are usually not required, since RDP's (especially diagnostic products) are administered only once or infrequently to most patients.

4. Evaluation of carcinogenic potential of the chemical substance is generally not necessary; however, it may be necessary if the parent compound is structurally related to a known carcinogen.

5. Evaluation of ophthalmologic toxicity is generally not required. However, it should be noted that there is increasing concern for possible ophthalmologic toxicity of all drugs. Therefore, during biodistribution studies of a radiopharmaceutical, evaluation of the distribution to the eye may provide useful information concerning potential ophthalmologic toxicity and may serve as a guideline to the necessity for performing additional preclinical and clinical ophthalmologic toxicity studies.

6. Reproduction-teratology studies are generally not necessary but may be required in some specific instances.

III. CLINICAL STUDIES

A. Investigators for studies involving patients should be physicians or clinical pharmacologists qualified by training and experience in the evaluation of new RDP's.

B. When informed consent is obtained, a statement that the patient will receive radiation exposure as a part of the study must be included as part of the consent form.

C. Phase I Studies*

Initial studies in man (Phase I) should demonstrate normal biodistribution, the organs receiving the maximum concentration of the RDP, the clearance half-time, the routes of excretion, and optimum imaging or sampling times.

1. Population

A small number of normal or diseased subjects is usually sufficient; they may be either hospitalized patients or outpatients who can be adequately monitored. The extent of the use of normal subjects generally should be limited to that number necessary to obtain normal biodistribution and metabolic data. The criteria for determining normality or the presence of a given disease should be established prospectively.

Children and pregnant or lactating females are excluded from Phase I.

In some cases, patients with selected diseases may be the only appropriate subjects for study in Phase I trials. Diseased patients may also be appropriately studied to evaluate distribution and excretion in those cases in which these parameters are significantly altered by the disease process. (Absorbed radiation may be increased or decreased by changes in distribution and excretion.)

2. Dose

Determination of the optimal dose range for a diagnostic RDP may include the following considerations:

a. The radiation absorbed dose should be kept as low as practicable.

b. An adequate number of usable particles or photons should be available to ensure statistically meaningful images or counting results with the instrumentation likely to be employed clinically.

c. Imaging time per view (or sample counting time) must be kept within reasonable limits—e.g., to prevent image degradation due to patient motion.

3. Clinical Laboratory Tests

To permit an initial evaluation of the safety of the radiopharmaceutical, appropriate laboratory tests are needed. Suggested laboratory tests to help define medically significant abnormalities are: hematologic profile (including platelet estimate), BUN (or creatinine), fasting blood sugar (or 2-hr postprandial blood sugar), liver enzymes, bilirubin, and urinalysis. EKG and other tests should be done if appropriate. Such tests should be done both before and after the use of the RDP.

4. Drug Distribution

Data are required on blood clearance, urinary (and, if appropriate, fecal) excretion, and in some cases, the results of dynamic quantitative external organ imaging, to provide a more accurate basis of dosimetry calculations. With radionuclides having a long physical half-life, serial whole-body counting data may be valuable.

D. Phase II and Phase III Studies

1. General Considerations

Phase II studies should be designed to extend the evaluation of the RDP in a limited number of patients to provide further evidence of safety and the initial evidence of diagnostic or therapeutic efficacy.

Phase III studies involve the study of sufficient numbers of patients by two or more investigators to establish safety and efficacy and directions for use for the particular dosage form of the RDP for each proposed indication. Phase III studies will ordinarily require less extensive laboratory testing than is required in Phase II. In those cases where cross-over studies initially were deemed appropriate, they may be discontinued when the RDP under investigation is shown to be equivalent or superior to established diagnostic procedures. It is important that both the objectives and the study population be carefully defined in advance so that adequately controlled studies are performed.

2. Protocols

All of the following points should be determined and included in the protocol before the study is initiated in order to minimize bias and to promote the acquisition of reliable data which can then be analyzed satisfactorily:

a. The objectives should be clearly stated.

Example: To demonstrate the safety and efficacy of gallium-67 as an aid in the diagnosis of lymphoma, Hodgkin's disease, and bronchogenic carcinoma.

b. Rationale for the study.

Example: Gallium-67 has been observed to selectively concentrate in these neoplasms, and thus may offer a suitable noninvasive diagnostic technique.

c. The criteria by which efficacy will be evaluated

Example: Comparison with radiographic findings, with other RDP's, etc.

d. A clear statement should be made regarding the hypotheses to be tested, the Type I† and Type II† statistical error and the incidence of false-positive and false-negative decisions that will be tolerated.

e. Experimental Design

1. Patient Population

The criteria for admitting patients to the study must be specified to ensure that the patients in the study will provide an appropriate sample of the population for whom the RDP is intended. If it is anticipated that the RDP will have an important use in children, they should be included in Phase III studies.

Example: Source from which the patients are drawn; number (sample size); age; sex; height; weight; medical history; physical findings; laboratory findings; initial diagnostic impression etc.

The criteria for excluding subjects must be specified. *Examples:* Concurrent diseases that may interfere; concomitant medications that may interfere.

2. Type of Experimental Controls

a. Description of and the rationale for the particular study design selected—e.g., cross-over, parallel, historical reference, single-blind, double-blind, etc. It should be noted that historical controls and single-blind studies are the least desirable of experimental controls. If either of these methods are chosen, adequate evidence must be presented to support the necessity or validity of such a choice.

b. Relevant categorization of patients included in the study.

c. If patients are to be subdivided or stratified into groups for comparative purposes, the groups should be comparable to each other regarding age, sex, severity of condition, concomitant therapy, etc.

d. Description of types of instrumentation and techniques used—e.g., instrument make, model, interval between dose injection and imaging, use of image enhancement, etc.

e. If data from multiple investigators are to be combined for statistical analysis, special attention should be directed towards assuring compatibility of protocols, instrumentation, population characteristics, etc., between the several studies. Such pooling of data from a multiclinic study will not be allowed unless evidence of close clinical monitoring by the sponsor is presented.

3. Dosage Regimen

Specify for each patient the lot number, dose (in millicuries, etc.), the volume of RDP administered, and the route of administration.

a. Specify the duration of the study as a whole.

b. Specify the interval between administration of the RDP and imaging or study in each patient. In the case of a diagnostic procedure a single dose is commonly used; however, if any of the subjects will receive more than one dose the number of doses and the interval between studies should be specified.

4. Efficacy Considerations

The criteria by which efficacy is to be evaluated should be stated in the protocol prospectively—e.g., correlations of imaging findings with other specific diagnostic modalities.

5. Radiation Dosimetry

Projected human radiation dosimetry calculations should be shown for the primary organ(s) of concern, the organ receiving the highest absorbed radiation dose, the critical organs (whole body, active blood-forming organs, lens of the eye, gonads), and any other organs with significant radiation exposure from the RDP (e.g., bladder).

These calculations should include equations based on the highest dose of the radionuclide to be administered.

The actual equation(s) used for the dosimetry calculations should be given in full. The system set forth by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine or the system set forth by the International Commission on Radiological Protection for the calculation of radiation absorbed dose are the recommended methods of calculation. All underlying assumptions concerning distribution and effective half-lives should be documented. In general, biologic distribution studies for the radiopharmaceutical should be sufficiently complete to account for as much of the administered dose as possible.

6. Case Report Forms

A well-designed case report form will facilitate tabulation and evaluation of results. A proper case report form for each patient would include:

a. Identification of the study, preferably by sequential numerical code and investigator's name; designation of Phase I, II, or III; the date(s) on which the RDP was administered, observations made, scans performed, lab tests obtained, etc.

b. Subject information: age, sex, height, weight, medical findings, diagnostic impression.

c. Reason(s) for doing the study—e.g., to obtain initial diagnosis, to obtain additional diagnostic data, to evaluate therapy, etc.

d. Dose, volume administered, route of administration, time interval over which the RDP will be administered.

e. Technical information: drug manufacturer or source. Name of radionuclide—e.g., 131-I-19-iodocholesterol, Tc-99m sulfur colloid drug; lot number; dose-to-imaging time

interval; instrument(s) used; types of view obtained; information density image-enhancement, etc.

f. For diagnostic imaging procedures a description of all normal and abnormal image findings, including an evaluation of image quality (with reasons, if unacceptable), and interpreter's conclusions.

g. Correlation of image findings with other diagnostic modalities—e.g., radiographs, blood chemistries, biopsies, clinical course, autopsy findings, other nuclear medicine procedures, etc.

h. Overall evaluation of utility in each patient—e.g., "diagnostic," "confirmatory of prior data," "resulted in alteration of therapeutic plan," "resulted in misdiagnosis due to false-positive (or false-negative) result," etc.

i. Adverse reactions—subjective and objective. Include any changes in physical findings, laboratory data, etc. Also, information regarding product defects should be noted, such as size of aggregates, drug deposits in wrong organ (tissue), etc.

E. Considerations in Evaluation, Summarization, and Presentation of Completed Studies

1. Plan for evaluation of the data. In evaluating and comparing diagnostic products the statistical methods for assessing the accuracy and reliability of the diagnostic RDP should be presented in detail. In most cases the objectives of the studies will include the assessment of the sensitivity, specificity, and misclassification rates of RDP's. From a statistical viewpoint these terms are defined as:

Sensitivity—the ability of a test to give a positive finding when the subject tested truly has the disease under study.

Specificity—the ability of a test to give a negative finding when the person tested is free of the disease under study.

Misclassification rates—the frequency of false-negatives and false-positives, which is a function of sensitivity and specificity. Suitable statistical methods should be employed that may assist in the study design—e.g., whether reliability, accuracy, or false-positives/negatives are a function of investigator technique, differences in instrumentation, dosage, etc. In particular, the plan for evaluation should include the allowable statistical risks (Type I and Type II errors) and the precision with which the false-positive, false-negative, and misclassification rates will be estimated.

2. Plan for summarization and presentation of data and findings. In keeping with the study objectives, the summary findings should be presented in sufficient detail to allow judgments to be made concerning whether findings are consistent across relevant subgroups, and the extent to which safety and efficacy of the RDP under study are demonstrated. Such presentation should at least contain:

a. For each study, a separate tabulation of the data and laboratory findings, so that it may be analyzed independently of the other studies.

b. If applicable, a rationale and justification for combining findings from more than one investigator.

c. Displays of findings by relevant subgroups (i.e., sex, severity of condition, dose, imaging equipment, time of test) and by those factors that the protocol designated as being controlled.

d. Displays of all clinical and laboratory findings obtained before and after the RDP is administered and an appropriate statistical evaluation of the changes of the pre- and postadministration findings.

e. A detailed explanation and documentation of the methods of statistical analysis used in the study, along with the appropriate conclusions derived from the analysis.

f. A well-organized presentation of all the pertinent data upon which the statistical analyses and summaries were based.

IV. SPECIAL CONSIDERATIONS FOR THERAPEUTIC RADIOPHARMACEUTIC DRUG PRODUCTS

The section on therapeutic RDP's has been omitted in this publication to save space. This information may be obtained as a part of the HEW Publication No. 77-3044 from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, at a cost of $.90.

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FOOTNOTES

* Section III, D, 2 contains guidelines for Phase II and Phase III protocols; much of the material therein will apply also to Phase I studies.

† Type I and Type II errors are terms used in the statistical theory of hypothesis testing. A Type I error is defined as the probability of rejecting the null hypothesis when it is true. A Type II error is the probability of accepting the null hypothesis when it is false. A statistician may be consulted for a more detailed explanation and for assistance in planning of study sample sizes.

Tc-99m Phytate as an Imaging Agent for Lymph Nodes

We read with misgiving the article by Alavi et al. (*1*), noting particularly some contradictory statements. Technetium-99m stannous phytate, the agent that the authors have termed a "unique radiotracer for lymph node imaging," would appear to be uniquely unsuitable for lymph node imaging in view of their own introductory statements indicating high extranodal concentration in liver, spleen, kidneys, and bladder, requiring the additional qualification that "the agent appears suitable for lymph node imaging in areas where the extranodal concentration does not interfere." The poor target-to-background ratio inherent in Tc-99m stannous phytate for lymphoscintigraphy should have induced the authors to restrain their enthusiasm and more carefully review alternate agents.

We have compared the lymphatic uptake and dynamics of Tc-99m stannous phytate and of Tc-99m antimony sulphide colloid, the agent we consider optimum for interstitial lymphoscintigraphy. Following dorsal pedal injection in rabbits and subcostal injection in patients, respectively, the lymphatic images are consistently superior with Tc-99m antimony colloid. The stannous phytate agent yielded inconsistent, poor quality images and showed generally decreased lymph node uptake.

Alavi et al. comment on the small particle size of Tc-99m stannous phytate, but we question whether they actually measured the particle size of this preparation. By electron microscopic analysis, we have determined the particle size distribution of Tc-99m antimony colloid to be log normal, with an optimum between 8–12 nm (*2*). With combined electron microscopic analysis and centrifugation, we found only 8–10% Tc-99m stannous phytate is colloidal in nature, and these particles were approximately 8 nm in size. It is likely that when calcium complexes with phytate in vivo, the resulting colloid may be an aggregate of a rather large