Prevalence of Adverse Reactions to Positron Emitting Radiopharmaceuticals in Nuclear Medicine

Edward B. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine
Eugene L. Saenger Radioisotope Laboratory, Division of Nuclear Medicine, Department of Radiology, University of Cincinnati Hospital, Cincinnati, Ohio

This study was undertaken to determine the prevalence of adverse reactions to positron emitting radiopharmaceuticals as well as to nonradioactive drugs used in interventional nuclear medicine during PET studies. **Methods:** A prospective 4-yr study was performed with 22 collaborating institutions using a questionnaire, which indicated for each month of the study the number of PET procedures performed, the number of adverse reactions to PET radiopharmaceuticals as well as the number of adverse reactions to interventional nonradioactive pharmaceuticals used for PET. **Results:** A total of 33,925 radiopharmaceutical doses were recorded in a retrospective examination of records by the 22 participating institutions. In addition, the total prospective number of administered doses recorded by the participants was 47,876, for a total number of positron emitting radiopharmaceutical administrations of 81,801. No adverse reactions were found from any PET radiopharmaceutical dose. There were no deaths or hospitalizations caused by nonradioactive interventional pharmaceuticals used adjunctive to PET studies. **Conclusion:** PET radiopharmaceuticals have an extraordinary safety record with no adverse reactions reported in over 80,000 administered doses in this study.

Key Words: adverse reactions; radiopharmaceuticals; PET

J Nucl Med 1998; 39:2190–2192

The use of PET in cardiology, oncology and neurology is undisputed, with new applications appearing monthly. Reimbursement and regulatory issues have slowed the dissemination of PET, although recent U.S. Food and Drug Administration (FDA) reform legislation may make the production of PET radiopharmaceuticals less onerous.

There is the theoretical potential for safety problems, not only from on site synthesis of radiotracers from multiple agents but also because of the difficulty of performing sterility and pyrogenicity tests preinjection. Since we believe it is the responsibility of the users of PET radiopharmaceuticals to demonstrate the safety of our techniques, the Pharmacopeia Committee of the Society of Nuclear Medicine (SNM) undertook a 4-yr prospective study of adverse reactions to PET radiopharmaceuticals.

MATERIALS AND METHODS

Twenty-two of approximately 65 PET facilities across the U.S. volunteered to collaborate on both a retrospective and prospective study of adverse reactions to PET. These are listed in the acknowledgments at the end of the article.

There are several definitions of an adverse reaction to a radiopharmaceutical. The U.S. FDA prefers the term "adverse drug experience," which means "any adverse event associated with 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 U.S. 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 include an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity" (*1*).

In comparison, the World Health Organization has adopted the following definitions:

1. Side effect: "Any unintended effect of a radiopharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug."
2. 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."
3. 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."
4. 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*)

Given the unique nature of radiopharmaceutical administration, and building on these concepts, the Pharmacopeia Committee of the SNM has used a definition where causality should be explored in each case of the association of a radiopharmaceutical (or an adjunct pharmaceutical) with changes of symptoms, signs or laboratory data (*3*):

1. The reaction is a noxious and unintended clinical manifestation (signs, symptoms and laboratory data abnormalities) after the administration of a radiopharmaceutical or nonradioactive adjunct pharmaceutical.
2. The reaction is not 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 a poor injection technique.

Received Apr. 3, 1998; accepted Apr. 12, 1998.
For correspondence or reprints contact: Edward B. Silberstein, MD, University of Cincinnati Medical Center, 234 Goodman St., P.O. Box 670577, Cincinnati, OH 45267-0577.

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*).

A reporting form was developed that was received monthly from each of the collaborating PET facilities to provide prospective reporting of adverse reactions both to PET radiopharmaceuticals and to interventional drugs used with PET. The latter were reported only if hospitalization or death resulted from the interventional nonradioactive pharmaceutical.

The following definitions of probable causality have been used 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 appear 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.

Not to be reported were reactions from:

1. Overdose (this is a misadministration).
2. Vasovagal response.
3. Injury from poor injection technique.
4. Deterministic effects from therapy with unsealed sources (e.g., myelosuppression from a therapeutic agent).

RESULTS

The 22 PET centers provided prospective monthly data concerning adverse reaction to radiopharmaceuticals and adjunctive interventional nonradioactive pharmaceuticals from 1994 to 1997. A few centers had not completed the 1997 reporting cycle at the time of this publication. These centers also reviewed all previous records of every prior dose administered to look for reported reactions.

Retrospective data from the opening of these centers revealed 33,925 radiopharmaceutical dosages without an adverse reaction. The total prospective number of administered dosages recorded by the participants for 1994 to 1997 was 47,876. The total number of administered doses of PET radiopharmaceuticals studied for adverse reactions was, therefore, 81,801.

In no case did an adverse reaction occur (95% confidence limits: $0–3.7 \times 10^{-5}$). In addition, 3265 nonradioactive interventional drugs were given with no serious adverse reactions, i.e., hospitalization or death (95% confidence limits: $0–9.2 \times 10^{-4}$).

DISCUSSION

This article provides a denominator to, and confidence limits around, the remarkable absence of adverse reactions to PET radiopharmaceuticals, primarily ^{18}F-fluorodeoxyglucose but also $^{11}C\text{-}CO_2$, ^{11}C-methionine, $^{13}N\text{-}NH_3$ and $^{15}O\text{-}H_2O$.

Previously, 95% confidence limits have been established for adverse reactions to non-PET radiopharmaceuticals in a prospective study by this Pharmacopeia Committee, as $1.2–3.4/10^5$ (*4*) and for nonradioactive interventional drugs (primarily dipyridamole, adenosine and acetazolamide) used in nuclear medicine procedures as $0.1–11.7/10^5$.

The safety of PET radiotracers has been known to the nuclear medicine community for many years. PET radiotracers administered in microgram amounts are usually: labeled molecules found normally in the body; close analogs to molecules normally appearing in the body's metabolic processes; or molecules binding to receptors at a far lower concentration than

receptor-binding drugs with pharmacologic actions. Adverse reactions from very small amounts of labeled molecules used as radiotracers for physiologic processes would, therefore, be anticipated to be rare. In fact, none have been seen.

These data indicate not only the extraordinary safety of PET radiopharmaceuticals but also that regulation of radiopharmaceutical safety should assume a qualitatively different form than is required for therapeutic nonradioactive pharmaceuticals that (a) are given in doses in the range of many milligrams; (b) have expected pharmacologic effects and side effects; and (c) are given for periods of days, weeks or months.

CONCLUSION

The conclusions of this study are as follows:

1. Adverse reactions from PET radiotracers and concurrently used pharmacologic interventions have been studied retrospectively and prospectively by 22 of the approximately 70 functioning PET centers in the U.S. with none observed.
2. One can be 95% confident that the probability of an adverse reaction from the positron-emitting radiopharmaceuticals studied is, at most, 3.7 per 10^5 doses from combined studies involving 81,801 injected doses in which no adverse reactions were ever observed.
3. For nonradioactive pharmacologic interventions in PET the chance of causing death or hospitalization, with 95% confidence is, at most, 9.2 per 10^4 injections.
4. This safety record indicates that regulation of radiotracer safety requires a somewhat different approach to that for nonradioactive drugs used for therapeutic purposes, to which some adverse reactions are inevitable.

ACKNOWLEDGMENTS

The collaboration of the following PET centers is gratefully acknowledged:

Bowman Gray School of Medicine, Winston-Salem
Case Western Reserve-University Hospital, Cleveland
Children's Hospital of Michigan, Detroit
Christ Hospital, Cincinnati
Duke University, Durham
Emory University Hospital, Atlanta
John Hopkins Hospital, Baltimore
Kettering Hospital, Dayton
Mallinckrodt Institute, St. Louis
Massachusetts General Hospital, Boston
National Institutes of Health, Bethesda
Newport Diagnostic Center, Newport Beach
St. Joseph's Hospital, Phoenix
St. Louis University, St. Louis
University of California, Los Angeles
University of Iowa, Iowa City
University of Michigan, Ann Arbor
University of Pennsylvania, Philadelphia
University of Tennessee, Knoxville
University of Washington, Seattle
Vanderbilt University, Nashville
William Beaumont Hospital, Royal Oak

REFERENCES

1. U.S. Code of Federal Regulations. Title 21, part 310.305.
2. Delamothe T. Reporting adverse drug reactions. *Br Med J* 1992;304:465.
3. Silberstein EB, Ryan J. Prevalence of adverse reactions in Nuclear Medicine. *J Nucl Med* 1996;37:185–192.