Pitfalls With Radiopharmaceuticals

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Abstract: *Introduction:* There is a considerable body of evidence describing that the pharmacokinetics and pharmacodynamics of radiopharmaceuticals may be changed by a variety of drugs, disease states and in some cases, surgical procedures. *Objective:* To systematically search the medical literature and review the published evidence on adverse reactions to radiopharmaceuticals. *Method:* MEDLINE, EMBASE, International Pharmaceutical Abstracts and Science Citation Index were searched for studies reporting adverse reactions to radiopharmaceuticals. Controlled trials, cohort studies, case-control studies and case series published in major Western languages were considered for the review. Each study included in the present review was described in a narrative way, and major components of each study were reported (ie, research design, patient characteristics, types of drugs and radiopharmaceuticals, dosing information and adverse reactions). *Results:* The majority of adverse reactions to radiopharmaceuticals described in the literature required little or no treatment, and their negative effects were generally mild and self-limited. Large longitudinal greater than 5-year studies reported prevalence rates of adverse reactions due to radiopharmaceuticals ranging from 0 to 25 cases per 100,000 administrations. Case studies on the use of technetium reported mild adverse reactions; however, some led to potentially harmful complications. Similarly, studies involving fluorodeoxyglucose reported more severe adverse reactions. *Conclusion:* The literature on radiopharmaceuticals adverse effects is scarce, and just a few studies were conducted to investigate the association between radiopharmaceuticals and adverse reactions. Despite relatively mild and self-limited symptoms, the current widespread use of radiopharmaceuticals requires constant monitoring for adverse reactions.

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There is a considerable body of evidence describing that the pharmacokinetics and pharmacodynamics of radiopharmaceuticals may be changed by a variety of drugs, disease states and in some cases, surgical procedures.[1] Sampson and Hesselewood[2] stated that the interactions of radiopharmaceuticals with other compounds are sometimes unknown and unrecognized, which can lead to a state of nondesirable effects. Adverse drug reactions (ADRs) are major causes of morbidity and mortality. In the United States, an estimated 701,547 people are seen (on a yearly basis) at emergency departments because of ADRs.[3] Adverse event-reporting databases cannot provide entirely reliable information on incidence, as events may not be correctly identified, and in many countries, reporting is simply voluntary. Thus, the incidence of drug-radiopharmaceutical interactions is unknown in many countries around the world.

Unlike drugs given for therapeutics purposes, radiopharmaceuticals rarely cause adverse reactions. A recent survey conducted in Japan reported an incidence rate of 1.3 events per 100,000 administrations.[4] A European study reported a greater incidence (11 events/100,000 administrations; 95% confidence limits: 3.3–19.2).[5] These different rates of adverse events may be explained by many aspects including the usually small amount of drug administered or ingested and the type of identification of ADRs in different studies.

Nevertheless, the possibility of adverse reaction to an administered radiopharmaceutical does exist.[1] Adverse reaction reports may be sent to manufacturers, regulatory authorities and/or described in the medical literature as case studies. Although there may be a small number of reported cases, studies have demonstrated that only 10% or less of possible adverse reactions are actually reported.[6,7] Also, if a reaction is not considered serious or life-threatening, reporting by the manufacturer to regulatory authorities may not be required.[7,8]

Among the various factors that can affect the biodistribution of radiopharmaceuticals, ingestion of drugs (eg, prescription medications) is the most commonly reported.[9] As much of the literature is based on case studies and nonclinical (laboratory) experiments, there is little hard clinical and epidemiological data to inform day-to-day decision making. When considering the potential for interaction in a clinical setting, Callahan and Rabito[10] suggested that special attention must be given to extrapolating observational data to the clinical situation, as the observed effects may depend on the amount of drug present, patient characteristics and the design of the study. Additionally, many suspected interactions may eventually be proven false due to chance or noncausal confounding associations.

Drug-radiopharmaceutical interactions may also arise as a result of the pharmacological mode of action of the drug, physiochemical interactions between drugs and radiotracers and competition for binding sites. Diseases induced by drugs, which may be aggravated by a radiopharmaceutical, could also be considered an adverse event.[1]

Although we focus on drug-radiopharmaceutical interactions in situ, it is also important to consider that handling and processing may also cause or increase the risk of adverse reactions. For example, contamination during dispensing or administration may alter the subsequent biodistribution of radiopharmaceuticals and subsequently change their pharmacological effect. The most well known of such interactions are those with the antiseptics povidone-iodine and chlorhexidine. Iodine-based antiseptics, in presence of labeled compounds such as Technetium-99-m (99-m-Tc), may cause the release of free pertechnetate.[11] Similarly, chlorhexidine gluconate can react to form a technetium-gluconate complex, which is accumulated in the kidney.[9] Although less commonly reported, radiopharmaceuticals may also interact with the syringe or catheter components.[12,13] Lifestyle factors, such as smoking, alcohol intake and dietary habits (eg, high-dose vitamins), also have the potential of interacting with radiopharmaceuticals.[14]

Therefore, the objective of the present research was to systematically search the medical literature and review the published evidence on adverse reactions to radiopharmaceuticals.

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METHODS

Computerized databases were searched for studies reporting radiopharmaceutical adverse reactions, such as MEDLINE, EMBASE, International Pharmaceutical Abstracts and Science Citation Index, published between 1956 and 2008, using the terms "radiopharmaceuticals/drug interactions," "radiopharmaceuticals/interactions," "fdg + safety," "technetium + adverse reaction" and many others as keywords. The searches were supplemented with manual searches of references from published articles on major radiopharmacy textbooks and in the Cochrane Database of Systematic Reviews.

The present review of the literature used an a priori selection criteria for the collected material. No restriction was placed on research designs. Thus, controlled trials, cohort studies, case-control studies and case series describing radiopharmaceutical adverse reactions and published in major Western languages such as English, French, German, Italian, Spanish and Portuguese were considered for the review. The difficulty in finding studies related to radiopharmaceutical-drug interaction and/or adverse reactions forced the acceptance of low-quality study designs (ie, case reports); however, such studies might provide additional information not found in other designs. Studies fulfilling our inclusion criteria but not describing relevant data or published as letters, commentaries or editorials were excluded from the review.

Each study included in the present review was described in a narrative way, and the major components of each study were reported (ie, research design, patient characteristics, types of drugs and radiopharmaceuticals, dosing information and adverse reactions).

REVIEW RESULTS

Adverse Reactions to Technetium

A case report by Spicer et al[11] described a true adverse allergic reaction to 99-m-Tc. According to the authors, a 60-year-old white female had a comedo-type duct carcinoma of the breast in 1980, which resulted in a left mastectomy. By April 1983, multiple lung metastases were apparent on a chest X-ray. On April 4, 1983, she underwent a bone scan with 99-m-Tc-methylene diphosphonate (MDP associated with 99-m-Tc), which revealed multiple metastases to thoracic and lumbar spine and right ischium. Forty-eight hours later, she had a scratchy sore throat and a pruritic, raised, erythematous rash that persisted for 3 to 4 days. On February 16, 1984, a new 99-m-Tc-MDP bone scan was performed showing new metastatic lesions in bone. Forty-eight hours later, she developed a sore throat and a generalized maculopapular rash, which was pruritic and erythematous. She was found to have conjunctivitis and a hyperemic ulcerated pharynx consistent with the diagnosis of erythema multiform. It was also noted that the patient had been on several chemotherapy drugs and had whole brain irradiation without any report of reaction.

The observed time delay (48 hours postinjection) is consistent with the report of Cordova et al,[12] Sampson,[8] Silberstein and Ryan[6] and Hesselewood and Keeling,[5] indicating a 4 to 24 hours and sometimes longer time lag before the development of rash. The rash development for 99-m-Tc-MDP was also the most common allergic reaction reported for 99-m-Tc-MDP. It was corroborated by Sampson,[8] who stated that the most commonly used diphosphonate 99-m-Tc-MDP accounts for most of the adverse reactions to radiopharmaceuticals, but this may be due to the fact that bone scanning is the commonest single nuclear medicine procedure. Among the symptoms of the use of 99-m-Tc-MDP are dermographism, nausea, malaise, vertigo and pruritus.

Balan et al[13] described a severe case of systemic reaction to 99-m-Tc-MDP. According to the authors, a 42-year-old woman with a history of recurrent breast cancer was injected with 555 MBq (15mCi) of 99-m-Tc-MDP. Twenty-four hours later, the patient felt unwell. Puffiness developed around the eyes, together with an erythematous skin rash on the trunk and around the eyes. Biochemical tests at that time, compared with those before the bone scan, suggested abnormal liver and kidney function; however, an ultrasound scan showed no, gross alterations in cited organ. The patient responded to a regime of intravenous fluids and corticosteroids, with a return to normal renal function 15 days after the bone scan and to normal liver function another 6 days later. The dermatological manifestations resolved within 1 week. This case confirmed the other case described earlier and showed that adverse reactions related to radiopharmaceuticals do occur and sometimes can be severe.

One case recently reported by Chicken et al[15] involved an 80-year-old woman with a 4-month history of a left breast lump. Medical history included untreated allergic rhinitis. She reported allergy to penicillin but not to other drugs or plasters. She was administered nanocolloidal albumin reconstituted under sterile conditions in the hospital's radiopharmaceutical laboratory according to the manufacturer's instructions and labeled with 14.4 MBq of 99-m-Tc. A volume of 0.2 mL of the radiocolloid was intradermally injected overlying the tumor. After 1 hour of the injection, the patient reported itching over the breast and axilla. On examination, a raised urticarial rash was noted over the upper half of the breast extending from the injection site to the axilla. No drop in blood pressure or oxygen saturation was found. A topical steroid cream was applied with resolution of both itching and rash within 30 minutes. A history of hypersensitivity to human albumin products is a contraindication to the injection of nanocolloidal albumin, and this important clinical information is easily overlooked.

Mujtaba et al[16] described an anaphylactic reaction to 99-m-Tc sestamibi. According to the authors, a 63-year-old white woman was intravenously injected at rest with 10 millicuries (370 MBq) of 99-m-Tc sestamibi. Immediately after the application, acute shortness of breath and generalized itching developed. Examination revealed tachypnea, painless macroglossia, wheezing in bilateral lung fields and a nonblanching pruritic maculopapular rash. All these symptoms were presumed to represent an anaphylactic reaction, and intravenous epinephrine and diphenhydramine were administered to control the anaphylactic symptoms, with immediate symptom reduction. This is the second case (the first was described by Thomson and Allman[17]) found in the literature of anaphylactic reaction to 99-m-Tc sestamibi.

Adverse Reactions to 18-Fluorodeoxyglucose

In recent years, positron emission tomography (PET) scans with 18-fluorodeoxyglucose (FDG) have been playing an increasingly important role in the evaluation of the response to induction chemotherapy and in the detection of primary tumor and metastatic lesions in several malignancies.[18–20] In 1 reported case, a 66-year-old man was referred to the hospital for investigation of an abnormal shadow measuring 5.2 cm in diameter in the left upper lung field on a chest X-ray. The patient was eventually diagnosed with lung cancer classified as clinical stage IIIA (T2N2M0) and underwent induction chemotherapy with paclitaxel.

All dissected lymph nodes showed sarcoid reactions, and no tumor cells were found to be pathological. The patient had