Adverse events in nuclear medicine – cause for concern?

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Published online: 4 February 2012
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Introduction

In the public arena, nuclear medicine has struggled with the widely held perception of the risk associated with radiation exposure from the administration of radionuclides for diagnostic imaging. In the media and in public debate, and even among medical professionals, this risk has been highly exaggerated compared to the risks associated with other diagnostic and therapeutic interventions, obviously due to confusion with the risks associated with nuclear power plants and nuclear weapons. On the contrary, nuclear medicine has been characterized by the rare occurrence of acute and chronic adverse events. In the period 1980–2000 fewer than 50 reports were registered annually in Europe [1]. Hessewood, in a survey of adverse reactions to radiopharmaceuticals in Europe, found a frequency of 11 events per 10^5 administrations with no serious, life-threatening events [2]. Data from the US [3] and more recently from Japan [4] show even lower figures: 2.3 and 1.3 per 10^5 administrations, respectively. These figures, including all adverse events and no single serious adverse event in the data associated with radiopharmaceutical drugs, should be compared with the

overall incidence of serious adverse drug reactions of 6.7% and fatal adverse drug reactions of 0.32% in hospitalized patients, reported found a meta-analysis in 1998 [5]. It should be borne in mind, however, that under-reporting of adverse reactions is a significant problem [6], in part due to the mild and transient nature of most reactions. There are other confounding factors for collection of proper statistical data including confusion in terminology. The comprehensive WHO definitions include several different terms including adverse/side reactions/effects/events/experiences, as shown in Table 1.

Guidelines for the general treatment of adverse events in nuclear medicine do not exist. The treatment is supposed to follow general recommendations for treatment of adverse events, such as, for example, administration of a corticosteroid and an antihistamine in cases of supposed allergy [8]. However, the specific cause of an adverse event is not always obvious.

With important recent developments in nuclear medicine including hybrid imaging modalities and several new drugs for radionuclide therapy, different adverse events are being encountered. A dramatic increase in the use of PET/CT has occurred, frequently involving administration of intravenous or oral contrast media. The availability of PET/MRI is still limited, but growing, and this modality is associated with the use of other contrast agents. Expansion in the use of therapeutic radiopharmaceuticals has been modest, but is definitely on its way, and will be accompanied by the occurrence of other, completely different adverse events. The many new PET ligands have not been reported to cause a significant number of adverse events. Thus in 81,801 patients receiving a PET radiopharmaceutical no patient was reported to have developed an adverse reaction [9]. Moreover, the Summary of Product Characteristics for several brands of ^{18}F -FDG registered with the Danish Medicines Agency contains the statement: “No undesirable effects have been observed to date”.

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Table 1 WHO definitions [7]

Term	WHO definition
Adverse drug reaction	A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man. In this description it is of importance that it concerns the response of a patient, so that individual factors may play an important role.
Unexpected adverse reaction	An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug.
Side effect	Any unintended effect of a pharmaceutical product occurring at doses normally used by a patient, which is related to the pharmacological properties of the drug.
Adverse event or experience	Any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment. The basic point here is the coincidence in time without any suspicion of a causal relationship.
Serious adverse event	Any event that is fatal, life-threatening, permanently/significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly, requires intervention to prevent permanent impairment or damage.

New challenges in nuclear medicine

CT and MRI contrast agents

The ACR Manual on Contrast Media [10] is widely accepted by radiologists as a guide to enhance the safety and efficacy of the use of contrast media. This manual presents the scientific evidence and clinical experience concerning the use of both CT and MRI contrast media. High- and low-osmolality iodinated agents are used for CT, while gadolinium chelates are used for MRI.

CT Adverse reactions to iodinated contrast media are divided into (a) non-renal, allergic reactions and (b) renal reactions, so-called contrast nephrotoxicity. Allergic reactions occur in 1–3% of patients, usually during the first 20 min after administration of the contrast agent. Adverse reactions occur in 5–12% for high-osmolar agents and in 1–3% for low-osmolar agents. The latter are therefore now preferred and widely replacing the high-osmolar agents [11].

The risk of a non-renal adverse drug reaction is increased in patients with previous reactions to iodinated contrast media and in patients with known allergy or asthma. If a contrast agent must be used in a patient considered to have an increased risk of an allergic reaction, or if an allergic

reaction has occurred, interventions should follow general and local guidelines.

The risk of nephrotoxicity, defined as a sudden deterioration in renal function after administration of a contrast medium, is high in those with pre-existing acute or chronic renal disease. Poor hydration is also a significant contributing factor. Patients receiving iodinated contrast media with normal plasma creatinine can go through the examination without further evaluation of renal function. Patients with “moderately” elevated plasma creatinine should be further evaluated, e.g. with some form of GFR measurement if the examination is considered important and no alternative method can be offered. In patients with manifest renal insufficiency, the use of contrast agents is absolutely contraindicated.

MRI The frequency of acute adverse events after administration of gadolinium chelates is low, with all adverse reactions after administration of 0.1 or 0.2 mmol/kg of a gadolinium chelate reported to be in the range 0.07–2.4%. The vast majority of adverse events are mild. Adverse events resembling an acute “allergic” response are very unusual (0.004–0.7%) [12]. Contrast agents for MRI are thus well tolerated by the majority of patients.

However, administration of an MRI contrast agent in patients with acute or severe chronic renal failure may cause irreversible deterioration of the renal function, a syndrome called nephrogenic systemic fibrosis (NSF). Based upon current knowledge it is estimated that patients with severe chronic kidney disease have a 1–7% risk of developing NSF after exposure to a gadolinium-based contrast medium. In some series including selected subgroups of patients, the reported incidence has been as high as 18% [12]. It is therefore crucial to avoid the use of MRI contrast media in this group of patients.

Therapeutic radiopharmaceuticals

Adverse events related to the most important therapeutic radiopharmaceuticals are briefly discussed. Adverse events after ^{131}I -iodide therapy for benign and malignant *thyroid diseases* are well known and have been carefully reported and analysed in a number of series over several decades and are not further discussed here.

Radionuclide therapy of *prostate cancer* in patients with hormone-resistant bone metastases using various radiopharmaceuticals, including ^{89}Sr -chloride (Metastron), ^{153}Sm -lexidronam (Quadramet) and ^{186}Re -HEDP, has been quite successful. Acute adverse events associated with the treatment are modest, most often limited to transient worsening of pain in some patients. Serious adverse events, in particular bone marrow suppression similar to that seen with other kinds of cytotoxic therapy, are extremely rare [13–15].

Radiosynovectomy in arthritis and synovitis with ^{90}Y -citrate, ^{186}Re -sulphide and ^{169}Er -citrate is associated with very moderate adverse effects, limited to transient aggravation of pain in a few patients and, very rarely, radionecrosis [16].

Treatment of *neuroendocrine tumours* by somatostatin receptor analogues is growing. ^{131}I -MIBG has been used for many years, but has now largely been replaced by peptide analogues such as ^{111}In -DTPA-octreotide and more recently by ^{177}Lu - or ^{90}Y -DOTATATE. Adverse events are not uncommon: Bone marrow suppression is seen in about 20% of patients [17], and renal toxicity is a frequent and dose-limiting problem [18] that is caused by reabsorption and retention of radiolabelled peptides in the proximal tubular cells. Amino acid infusion and plasma volume expansion are quite effective for renoprotection and are now part of the standard treatment with these drugs [19].

Radioimmunotherapy of *lymphoma* with ^{90}Y -ibritumomab (Zevalin) or ^{131}I -tositumomab (Bexxar) is efficient and relatively safe compared with other therapeutic options, and hence the treatment is increasingly used, but adverse events are quite common [20], mostly due to bone marrow suppression. Fortunately serious adverse events such as myelodysplastic syndrome occur in only about 1% of patients.

Reporting of adverse events for radiopharmaceuticals

There is no single system for reporting of adverse events associated with radiopharmaceuticals. Different countries have different systems. In Europe, adverse events can be reported to national health authorities, to the manufacturer/importer or to the European Medicines Agency (EMA) for drugs with pan-European approval, or via any combination of these reporting routes. In addition, adverse events may be mentioned in scientific papers with or without the reporting described above. The Radiopharmacy Committee of the European Association of Nuclear Medicine maintains an adverse reaction and defective product database hosted by the British Nuclear Medicine Society.

Manufacturers with a marketing authorization for a radiopharmaceutical are obliged to conduct pharmacovigilance. This requires the manufacturer to register all adverse events and decide what action should be taken if unforeseen events occur. Such actions can take the form of a Rapid Alert, where relevant information about a radiopharmaceutical is distributed quickly (within a few days) to all European users, usually via the manufacturer/importer. Reported adverse events very seldom lead to Rapid Alerts. An example of a Rapid Alert relating to potential adverse events occurred in the mid-1990s, where the use of a macroaggregated albumin kit was halted because the albumin used in the formulation was suspected to contain pathogens.

Pharmacovigilance also requires the manufacturer to compile PSURs (Periodic Safety Update Reports) for each marketed radiopharmaceutical. The PSUR is a collection of all reported adverse events worldwide for a given period of time – usually 5-year periods – tabulated according to the type of adverse event. The PSUR must contain a critical summary and conclusion. PSURs are sent to the issuer of the marketing authorizations, typically national health authorities or EMA, for their information. PSURs offer a good way of relating the frequency of reported adverse events to the product information leaflet and as background data for updating this information.

The rules governing the licensing of use of non-marketed radiopharmaceuticals vary among European countries. Reporting of adverse events most often goes to the national health authorities and/or to the manufacturer. In some countries it is mandatory that a report (with analysis) of all observed adverse events accompany the submission of a license renewal.

Conclusions and clinical implications for the nuclear medicine community

Adverse events have been rare in nuclear medicine, but in the future they will be seen more frequently in our departments both because of administration of contrast agents in hybrid imaging and because of increasing use of therapeutic radionuclides with significant risks of causing subacute and chronic toxic effects. The potential exists for unexpected adverse events following the administration of new and future PET tracers, many of them likely to be noncommercial compounds that are produced locally. The new combined PET/CT, SPECT/CT and PET/MRI scanners require that nuclear physicians are familiar with the indications for the use of intravenous contrast media. The staff must be able to manage acute adverse events that may vary from minor to serious allergic reactions. It is therefore mandatory that protocols for the use of intravenous contrast media are available in departments, created in collaboration with departments of radiology.

All of this will lead to new demands on our departments. The clinical staff – physicians, technologists and nurses – must be educated to be aware of the risks of new kinds of adverse events and they must be increasingly alert in their daily work. Diligence in reporting events is more important than ever. The reporting systems should be easily accessible, as electronic national systems feeding into similar international systems. Although European systems are available, under-reporting is a recognized problem. Moreover, the annual reports from the EANM database, which have not been published in recent years, should be reinstated.

The handling of adverse events must follow up-to-date local instructions for the treatment of allergic, cytotoxic and

other kinds of adverse events in accordance with national and international guidelines. Regarding the responsibility for less acute adverse events in relation to radionuclide therapy, instructions about minimization of toxic effects to the kidneys and bone marrow etc. must follow the international recommendations, and clear agreements between the clinical and nuclear medicine departments must be in place, including careful communication about such adverse events between the departments.

The unique growth and expansion of our speciality will also undoubtedly lead to an increase in the frequency of adverse events, for which we must be well prepared.

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