NORMAL OR ABNORMAL? EVENTS INVOLVING 99m-TECHNETIUM

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ABSTRACT

The aim of this study was to evaluate, by way of a systematic review, the adverse effects associated with Technetium-99m radiopharmaceuticals as reported in published articles. The radiopharmaceuticals have an innate toxicity due to the radioisotope, requiring close monitoring for their safe use. Most radiopharmaceutical users are elderly patients and people with undermining conditions who are more susceptible to adverse effects. On occasion, the co-prescription of interacting drugs has triggered synergic reactions. The search in databases for this systematic review found just a few studies that do not represent the reality and the routine of the Nuclear Medicine services. However, it may be relevant to clinical decision-making, to avoid repeating what is already known.

Keywords: Evidence-based medicine, systematic review, radiopharmaceuticals, drug interaction, adverse effects, ^{99m}Technetium.

INTRODUCTION

Technetium-99m is the most important radioisotope used in nuclear medicine. Its routine application is ensured by the introduction of 99Mo/99mTc generators[1]. The 99mTc radiopharmaceuticals play an important role in widespread applications of nuclear medicine. When 99mTc radiopharmaceuticals first came into use, major efforts were directed toward the development of 99mTc radiopharmaceuticals for bone imaging and for the excretory functions of the liver and kidneys. In the past 20 years, a significant advance has been made in technetium chemistry, which provided 99mTc radiopharmaceuticals for assessment of regional cerebral and myocardial blood flow. Recent efforts have been directed toward the design of 99mTc-labeled compounds for estimating receptor or transporter functions. A number of bifunctional chelating agents that provide 99mTc labelled proteins and peptides of high in vivo stability with high radiochemical yields have also been developed. More recently, organometallic technetium and rhenium compounds have been introduced as another type of 99mTc radiopharmaceutical design[2].

The progress in diagnostic nuclear medicine over the years since the discovery of 99mTc is indeed phenomenal. Over 80% of the radiopharmaceuticals currently being used make use of this short-lived, metastable radionuclide, which has reigned as the workhorse of diagnostic nuclear medicine. The pre-eminence of 99mTc is attributable to its optimal nuclear properties of a short half-life and a gamma photon emission of 140 keV, which is suitable for high-efficiency detection and which results in low radiation exposure to the patient. 99mTcO4-, which is readily available as a column eluate from a 99Mo/99mTc generator, is reduced in the presence of chelating agents. The versatile chemistry of technetium emerging from the 8 possible oxidation states, along with a proper understanding of the structure-biologic activity relationship, has been exploited to yield a plethora of products meant for morphologic and functional imaging of different organs. Newer methods of labeling involving bifunctional chelating agents (which encompass the "3 + 1" ligand system, Tc(CO)3(+1)-containing chelates, hydrazinonicotinamide, water-soluble phosphines, and other Tc-carrying moieties) have added a new dimension to the preparation of novel technetium compounds. These developments in technetium chemistry have opened new avenues in the field of diagnostic imaging. These include fundamental aspects in the design and development of target-specific agents, including antibodies, peptides, steroids, and other small molecules that have specific receptor affinity[3].

The last few decades have seen an immense growth in availability and consumption of medicines. Whilst most consumers derive far more benefit than harm, a proportion of patients experience undesirable effects (adverse effects) from the use of medicines at recommended doses and frequencies[4]. Jones[5] had already alerted to the fact that although ADRs (adverse reactions) can appear as isolated, specific clinical events that may be related to a number of factors in the patient's background and environment. In many situations it may not appear early as a detectable clinical event, but is instead clinically silent. With radiopharmaceuticals things are not different, since they are also drugs. The incidence of rarer effects is known for just a few drugs, as only recently have epidemiological methods and studies been directed to this area and the possibility of adverse reaction to an administered radiopharmaceutical does exist[6].

METHODOLOGY

A systematic review of the literature on adverse reaction with technetium was carried out, using an adaptation of the methodology described by Loke, et al, Papanikolaou, et al, Derry, et al, Golder, et al, McIntosh, et al and Santos-Oliveira, as described below[7-12].

Usually, when the focus of the research question is purely on safety and or tolerability, the effectiveness of the treatment is already known. However, in some instances reviewers intend to evaluate adverse effects as part of a combined review that also covers beneficial outcomes. Reviews that aim to evaluate benefit and harm together will usually require a more complex design that can efficiently handle different sets of studies for various outcomes. Selection of adverse outcomes for the review can be difficult and in fact, it is. Unlike reviews of effectiveness, where all beneficial outcomes are likely to be well recognized beforehand, specific adverse effects associated with a therapeutic intervention may be known in advance of the review, while others will not.

The research question about safety and tolerability in a review may be broad or narrow in scope. It will depend on the size of your sample. In many cases when the drug is well known the size is usually considerable and a meta-analysis can also be done. However, in dealing with radiopharmaceuticals, the difficulties to find studies are substantial. This lack of information causes delays in the research. In general, reviewers who have already identified important safety concerns should carry out a narrow-focused evaluation covering particular aspects of the relevant adverse effects. In relation to the types of studies, no single recommendation is possible here and any decisions have to be made case by case. The decision on what types of studies to include will depend primarily on the main focus of the research question, balancing the elements of type of adverse effects(s) of interest, rigor in searching, and time and resources available. The systematic evaluation of new or rare adverse effects may require the inclusion of other study designs: cohort, case-control, cross-sectional, and even case series[13]. An important recommendation specific to adverse reactions would be: authors planning to use such additional data sources should realize that estimates of the frequencies of adverse effects from published case reports and spontaneous reporting may differ greatly from the results obtained from a meta-analysis of double-blind, randomized controlled trials[14,8]. Regarding the radiopharmaceuticals case study, an algorithm described by was used[15].

The location and the selection of studies is one of the most important steps in a systematic review. In this case a literature search strategy was developed based on key words. The review question

Is the 99m Technetium safe? And,

Does it have adverse reactions?

Determining the nature of the search strategy

They strategy used to minimize the possible limitations was the agreement to maximize sensitivity. Most of the review was conducted by computer databases available at many sites like MEDLINE. The quality of the results lies on the quality of the material found and size of the sample. Using electronic data bases, searching for the limitations by key words we found the great variety of combinations to be enormous. So, it is advisable to make a list with as many key words as possible and all the terms should be researched. In this case, using the strategy proposed by Loke, et al, two main approaches were used. Each one had its own limitations[7].

Electronic databases using index terms:

a) Index terms such as MeSH (Medical Subject Headings) in MEDLINE and EMTREE in EMBASE were assigned to records in electronic databases to describe the studies. Subheadings were also added to index terms to describe specific aspects – for example, side effects of drugs, or complications from surgery. In this study the indexing terms used were: *adverse reactions*; *contraindications*, *complications*, *misdiagnosis*, *false negative*; and *toxicity,* among others.

b) Indexing terms in MEDLINE and EMBASE: Within a database, studies may be indexed in three different ways: (i) under the name of the intervention together with a subheading to denote that adverse effects and false positive reactions occurred, for example, *technetium/adverse effects*, *radiopharmaceuticals/ complications*; (ii) under the adverse event itself, together with the nature of the intervention, for example, *Misdiagnosis/and Technetium; Cancer/and Surgery/*; or (iii) occasionally only under the adverse event, for example, *adverse reaction/chemically-induced*.

Thus, no single index or subheading search term can be relied on to identify all data on adverse effects, but a combination of index terms and subheadings were used to detect reports of major adverse effects which the indexers considered significant[9,10].

Electronic databases using free-text terms ('text words'): Terms used by authors in the title and abstract of their studies were searched on databases of electronic records using free-text terms.

A sensitive free-text search should incorporate this potentially wide variety of synonymous terms used to denote data on adverse effects in studies, while also taking into account different conventions in spelling and variations in the endings of terms. So, it is necessary to include singular and plural terms. These terms used to describe adverse effects were then combined with the free-text terms used to describe the intervention of interest. Keep in mind that a systematic review, principally related to adverse effects, is always difficult to carry out for normal drugs, in the case of radiopharmaceuticals, this difficulty is greater.

The searches were supplemented with manual searches of the bibliographies of published articles in major radiopharmacy textbooks, and in the Cochrane Database of Systematic Review. The present review of the literature uses a selection of the collected material. Controlled trials, cohort studies, case-control studies and case series in English, French, German and Portuguese were considered. All the papers were retrieved and reviewed.

RESULTS

After the striking article by Hladik, et al, a paper by Spicer, et al, published in the Journal of Nuclear Medicine, described a true adverse allergic reaction to technetium-99m[16,17]. According to the authors, a 60-year-old white female had a comedo-type ductal 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 MDP (methylene diphosphonate associated to Tc-99m) 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 which persisted for 3-4 days. On February 16, 1984 a new MDP bone scan was performed showing new metastatic lesions in the bone. Forty-eight hours later she developed a sore throat and a generalized maculo-papular rash which was pruritic and erythematous. She was found to have conjunctivitis and a hyperemic ulcerated pharynx consistent with the diagnosis of erythema multiforme. It was also noted that the patient had been on several chemotherapy drugs and had whole brain irradiation without any report of adverse reaction.

The observed time delay (48 hr post-injection) is consistent with the report of Cordova, et al, Sampson, Silberstein, et al, Hesselwood, et al[6] and Silberstein, et al. indicating a 4-24 hr and sometimes longer time lag before the development of rash[18-20]. The rash development for MDP was also the most common allergic reaction reported for MDP. It can be corroborated by Sampson[19] when he states that the most commonly used diphosphonate, MDP, accounts for the most adverse reaction to radiopharmaceuticals, but this may be due to the fact that bone scanning is the single most common nuclear medicine procedure. Among the symptoms of the use of MDP are dermographism, nausea, malaise, vertigo and pruritus.

A severe systemic reaction to MDP was described by Balan, et al[21]. According to the authors a 42-year-old woman with a history of recurrent breast cancer was injected with 555MBq (15mCi) of MDP. Twenty-four hours later the patient felt ill. A puffiness developed around the eyes, together with an erythematous skin rash on the torso 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 alterations to either organ. The patient responded to a combination 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 were resolved within 1 week. This case confirmed the other one described above and showed that adverse reactions related to radiopharmaceuticals do occur and can be very severe.

A case of isosulphan blue associated with technetium-99m sulphur colloid was described by Steffanuto, et al[22]. According to the authors a 50-yr-old female with breast cancer was scheduled for left lumpectomy and left axillary SLNB with localization using isosulphan blue dye and technetium-99 sulphur colloid, in an outpatient setting. After radio colloid injection and lymphoscintography, she was transferred to the operating room facility and anaesthesia was administered using fentanyl 150 mg, propofol 120 mg and rocuronium 40 mg. Uneventful anaesthesia continued for 50 minutes during the initial stages of the operation. After 50 minutes, the surgeon injected isosulphan blue 3 ml subcutaneously around the tumour. Approximately 30 minutes after this injection, the patient's systolic arterial pressure fell abruptly from 104 to 70 mm Hg. Over the following few minutes, repeated ephedrine 10 mg and phenylephrine 200 mg boluses were administered intravenously. Her systolic arterial pressure further decreased to 64 mm Hg, and then to 52 mm Hg. SpO2 declined marginally from 99–100% to 95–96%, as is expected with isosulphan blue. Anaesthesia was reduced to the minimum necessary; i.v. epinephrine 100 μg was given and the patient's arterial pressure increased transiently. Resuscitation continued with i.v. fluids and epinephrine in repeated 100–300 μg i.v. boluses. During the next 30 minutes, 5 to 6 litres of i.v. fluid and epinephrine 2 mg were given. A right radial artery cannula was placed for continuous monitoring of arterial pressure. After 30 minutes, frequent repeated epinephrine boluses were still required to maintain cardiovascular stability. The patient's right internal jugular vein was cannulated, hydrocortisone 100 mg and diphenhydramine 50 mg were administered, and a continuous infusion of epinephrine 400 μg^{-1} h^{-1} was established. Her systolic arterial pressure stabilized at 100–110 mm Hg. Blood was obtained for measurement of serum mast cell tryptase concentration, routine blood tests, clotting and arterial blood gases. The decision was taken to continue with the lumpectomy to remove excess isosulphan blue and minimize the possibility of a biphasic anaphylactic reaction. The results led to the cancellation of the gynaecological surgery.

Regarding the case described above, Burton; Cashman[23] added further information, describing a case of 31-yr-old male weighing 75 kg that was admitted to hospital after previous removal of a malignant melanoma (Breslow thickness 1 mm) from over his left scapula, with a further wide local excision, lymphoscintigraphy, and sentinel node biopsy. He was taking no medication, and did not

have any significant medical history. There was no past history of asthma or any atopic episodes. On the day before surgery, he underwent an intradermal injection of technetium-99m nanocolloid albumen. Within 10 minutes of the injection of the colloid, the patient developed a widespread, non-itchy urticarial skin reaction. There was no associated wheeze, difficult breathing, or cardiovascular symptoms. Immediately, he was given chlorpheniramine 10 mg i.v., and the rash diminished without further consequence over the next hour.

The subsequent general anaesthetic was carried out uneventfully. The administering of the anaesthesia was facilitated with fentanyl 0.5 mg kg^{-1} and propofol 2.5 mg kg^{-1}. Anaesthesia was maintained using isoflurane in oxygen and nitrous oxide with the patient breathing spontaneously. Chlorpheniramine 10 mg and hydrocortisone 100 mg were given intravenously at induction. During surgery, patent V blue dye 0.5 ml was injected intradermally without incident. Another general anaesthetic 5 weeks later for block dissection of axillary nodes was equally uneventful.

The findings by the authors Stefanutto, et al[22] and Burton; Cashman[23] suggest that it is possible that there may be some synergic reaction between blue dye and the technetium-99m nanocolloid albumen and not by isolated isosulphan blue. Although the results of the study of Burton;Cashman[23] suggest that only technetium-99m nanocolloid albumen is solely responsible for the allergic reaction there are no solid results, until now, that justify this theory. So, in these specific cases patients who have urticarial reactions after lymphoscintigraphy using technetium-99m nanocolloid albumen and blue dye may have an increased risk of anaphylaxis intraoperatively, which anaesthetists must be aware of and give prophylactic treatment.

One case recently reported by Chicken, et al. [24] involved an 80-year-old woman with a 4-month history of a left breast lump. Past medical history included an untreated allergic rhinitis. She reported allergy to penicillin but not to other drugs or plasters. She was administered nanocolloidal albumin (re-constituted under sterile conditions in the hospital's radiopharmaceutical laboratory according to the manufacturer's instructions and labeled with 14.4 MBq of technetium-99m). A volume of 0.2 ml of the radiocolloid was intradermally injected over the tumor. One hour after the injection, the patient reported itching of the breast and axilla. On examination, a raised urticarial rash was noted on the upper half of the breast extending from the injection site to the axilla. No drop in blood pressure or oxygen saturation was clinically found. A topical steroid cream was applied with rapid resolution of both itching and rash within 30 minutes. A history of hypersensitivity to human albumin products is a contra-indication to the injection of nanocolloidal albumin, and this important clinical information is easily overlooked.

An anaphylactic reaction to Tc-99m sestamibi was described by Mujtaba, et al[25]. According to the authors, a 63-year-old white woman was injected with ten millicuries (370 MBq) of Tc-99m sestamibi. Immediately after the application, acute shortness of breath and generalized itching developed. Examination revealed tachypnæa, painless macroglossia, wheezing in bilateral lung fields and a nonblanching pruritic maculopapular rash. All these symptoms were presumptive of anaphylactic reaction and intravenous epinephrine and diphenhydramine were administered, with immediate results. This is the second case (the first was described by Thomson; Allman[26] and related a erythema multiforme as adverse reaction to Tc-99m sestamibi) described in the literature of anaphylactic reaction to Tc-99m sestamibi. Table 1 summarizes these data.

Table 1: Adverse reactions to ^{99m}Tc radiopharmaceuticals (1983 – 2007)

Radiopharmaceutical	Gender	Age	Time delay post-injection	Adverse reactions
^{99m}Tc – MDP	F	60	48 h	Sore throat and a generalized maculo-papular, pruritic and erythematous rash
^{99m}Tc – MDP	F	42	24 h	Puffiness around the eyes, with an erythematous skin rash on the trunk and around the eyes
^{99m}Tc – sulphur colloid associated with isosulphan blue	F	50	30 min	Systolic arterial pressure fall.
^{99m}Tc – nanocolloid albumen	M	31	10 min	Non-itchy urticarial widespread skin reaction
^{99m}Tc – nanocolloid albumen	F	80	60 min	Itching urticarial rash on the breast and axilla
^{99m}Tc – sestamibi	F	63	immediately	Acute shortness of breath and generalized itching (anaphylactic reaction)

DISCUSSION

The radiopharmaceuticals groups have an innate toxicity due to the radioisotope, requiring close monitoring for their safe use. In addition, radiopharmaceuticals are often used on elderly patients and people with undermining condition who are more susceptible to adverse effects. Close monitoring of patients taking radiopharmaceuticals especially technetium, could reduce the number of patients admitted with adverse reactions. Ensuring adequate monitoring of patients and avoiding co-prescription of drugs (i.e. isosulphan blue associated with technetium-99m sulphur colloid) during the diagnostic procedure could reduce the number of patients admitted due adverse effects. More effective computer warnings may help to avoid the co-prescription of interacting drugs and point out the need for increased monitoring.

Regarding the methodology, a focused review question is standard practice for assessing beneficial outcomes in systematic reviews and should also be when reviewing harmful results. Researchers conducting reviews need to make sure that they address a well-formulated question about harmful effects that are likely to impact clinical decisions. Focusing a review question about harmful effects will not necessarily mean restricting it to specific adverse events but may mean, for example, addressing a particular issue such as long-term effects, drug interactions, or the incidence of mild effects of importance to patients. If the aim of the research is to look for previously unrecognized harmful effects, analysis of primary surveillance data may be more appropriate than a systematic review. Researchers also need to be aware that scopes set by external commissioning bodies, despite having consulted with national professional and patient organizations, may not be a suitable question to address in a systematic review. The wisdom of broad and non-specific questions about harmful effects should be questioned because the resources, especially time, needed to do this comprehensively are usually insufficient[11].

The advantages of this study over earlier work include the prospective nature and the type, which allowed a more accurate recording of adverse effects. However, as with any other study of this nature, there is a potential weakness in that assignment of an admission as being related to an ADR is subject to clinical judgment, which may vary among individuals. To try to overcome this, comprehensive research in published work was done using as many “key words” as possible that could help in the investigation. Nevertheless, it is impossible to be absolutely certain of a causal link between a drug and an adverse reaction. However, it is important to remember that such figures are derived from case report based studies that yields more apt results and excludes subjective analysis.

It is important to realize that an unquestioning belief that observational studies are the best source of harmful effects data simply because they are not RCTs (randomized controlled trials) can be a pitfall. It is essential to think carefully about the review question before widening the inclusion criteria to include non-randomized study designs. Some harmful effects, such as very rare events or those emerging in the long-term are unlikely to be addressed adequately in RCTs. But even if observational studies are appropriate to the review question, researchers should be prepared for the difficulty of interpreting observational study data outweighing the anticipated benefits.

The importance of quality assessment of RCTs in systematic reviews of effectiveness is well established[27], but debate continues over the usefulness of checklists and scales. Quality assessment of other study designs in systematic reviews is far less well developed[28]. Although the feasibility of creating one quality checklist to apply to various study designs has been explored[29], and research has gone into developing an instrument to measure the methodological quality of observational studies[30], and a scale to assess the quality of observational studies in meta-analyses[31] there is as yet no consensus on how to summarize information about quality from a range of study designs within a systematic review. Furthermore, this review has shown that these difficulties are compounded when reviewing data on harmful effects.

It is essential that quality assessment is able to discriminate between poor and better quality studies of harmful effects. Levels of evidence hierarchies have several shortcomings. The hierarchy of evidence is not always the same for all harmful or beneficial outcomes. Another problem with ranking evidence in a hierarchy is that different dimensions of quality get condensed into a single grade, resulting in a loss of information[32] (Glasziou, et al 2004). Researchers need to clarify *a priori* what exactly they need to glean from their quality assessment of the primary studies in their own review of harmful effects and it may be necessary to differentiate clearly between internal and external validity.

We agree with the suggestion that further research is needed to collate, assimilate and build on the existing information relevant to systematically reviewing primary studies for harmful effects of health care interventions.

CONCLUSION

As stated by McIntosh, et al[11], we agree that appraisal of our recent experience highlighted some of the problems inherent in conducting systematic reviews of harmful effects of health care interventions, principally those related to radiopharmaceuticals. Such reviews need to address a well-formulated question to facilitate clear decisions about the type of research to include and how best to summarize it, and to avoid repeating what is already known. The review question about harmful effects needs to be relevant to clinical decision-making. A systematic review of the methodology pertinent to systematic reviews of harmful effects is warranted.

The literature on this topic shows that just a few studies

were done with this approach and the amount of radiopharmaceuticals in use nowadays is so great that it seems impossible that the few reported cases were all that have really happened. So, clearly, a great effort should be made to describe as many cases of adverse reactions as possible.

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