Exploring drug safety of radiopharmaceuticals

N. Schreuder, PharmD, PhD
October 15, 2021
University of Groningen

Promotors:
Prof. E.P. van Puijenbroek, MD, PhD
Prof. J.G.W. Kosterink, PharmD, PhD

Co-promotor:
P.L. Jager, MD, PhD

Nuclear medicine provides essential information for diagnosis and treatment of patients. The field relies on radiopharmaceuticals. During the past decades, radiopharmaceuticals have proven to be very safe. Undoubtedly, the reason for this is that radiopharmaceuticals generally do not have a pharmacologic effect due to use in very low quantities—in the range of micrograms. Despite the fact that radiopharmaceuticals have an excellent safety profile, relatively little is known about adverse events, interactions and use in some specific patient groups. Research on these aspects of drug safety in radiopharmaceuticals can help to gain more knowledge and improve the drug safety of radiopharmaceuticals. For this reason, we studied drug safety issues of radiopharmaceuticals, with the main topics being adverse reactions, interactions with drugs, and considerations in specific patient populations.

Adverse reactions

The first drug safety topic we cover concerns adverse reactions with the use of radiopharmaceuticals. In a systematic review we found a very low median frequency for adverse events in diagnostic radiopharmaceuticals reported in literature of 0.0016%. Most reported adverse events are skin disorders (such as rash and itching) and general disorders (such as fever). Interestingly, very little attention has been paid to the patient's experience with adverse events from radiopharmaceuticals.
In order to study adverse events of radiopharmaceuticals from a patient perspective, we developed a validated questionnaire with input from patients undergoing a nuclear medicine examination. Subsequently, we used the developed questionnaire in a larger study of 1,002 patients in a regional hospital in the Netherlands (Isala Hospital in Zwolle). In this study we aimed to determine the characteristics and frequency of patient-reported adverse events of radiopharmaceuticals and to assess the outcome of these adverse events from the patient's perspective. Using the questionnaire, we collected patient-reported information on adverse events that patients attributed to the radiopharmaceutical; we included events that occurred immediately after administration of the radiopharmaceutical as well as those that occurred later. Two independent researchers analysed, coded, and assessed the adverse events for causality. Most patient-reported adverse events of radiopharmaceuticals were a hot feeling, a sense of oppressed breathing, chest discomfort, headache, and fatigue. Of the patient-reported adverse events, 43.0% were possibly or probably causally related to radiopharmaceuticals. The other adverse events were not or were unlikely to be causally related to radiopharmaceuticals. We found the frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals to be 2.8%. This is higher than the frequency of 0.0016% as we found in the literature. No important medical events were related to the administration of diagnostical radiopharmaceuticals. Most adverse events (80%) occurred shortly after administration of the radiopharmaceutical and resolved within a few hours. Some events (20%) emerged after patients had left the nuclear medicine department, took longer to resolve, and sometimes (27.5%) prompted the patient to consult a healthcare professional.
Our study findings imply that adverse events of diagnostic radiopharmaceuticals, as experienced by patients, are more common than previously assumed. Our study shows that patients can provide useful information about radiopharmaceuticals adverse events, complementing the information available in the literature.

Interactions

The second drug safety topic we cover concerns interactions with other drugs. One well-known interaction is the high uptake of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) in the colon seen on PET scans in patients using the oral antidiabetic drug metformin. Although healthcare professionals do not generally use [^{18}F]FDG PET to study primary colorectal cancer, the increased uptake of [^{18}F]FDG in the colon could still obscure

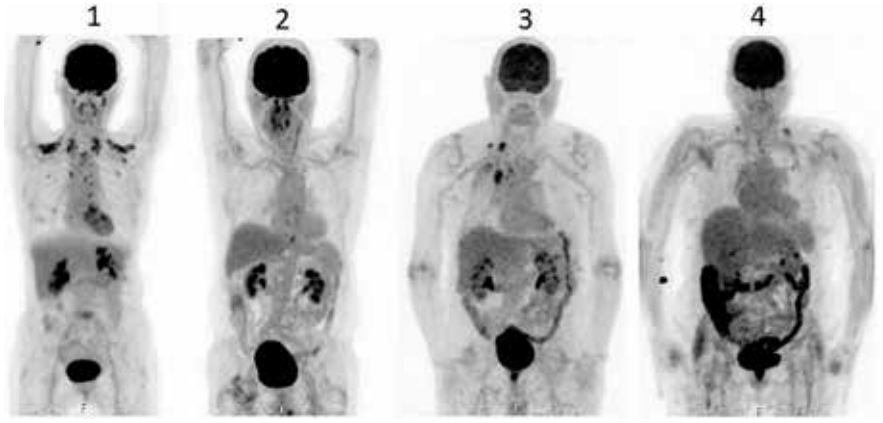

Figure 1. [^{18}F]FDG PET/CT images of four patients from our study with different grades of [^{18}F]FDG uptake in the colon, from left to right, corresponding to the four-point scale method of Gontier et al. [1]

lesions and cause findings to be missed. While several studies recommended that metformin should be discontinued before the [^{18}F]FDG PET scan, there is no consensus on the optimal discontinuation period. We therefore examined whether discontinuing metformin for at least 48 hours prevents metformin-induced [^{18}F]FDG uptake in all segments of the colon. For this, we included patients with type 2 diabetes who were using metformin before undergoing an [^{18}F]FDG PET/CT scan and created two groups: patients who discontinued metformin for less than 48 hours and patients who discontinued metformin for between 48 and 72 hours. We included a control group comprised of non-diabetic patients who were not using metformin before undergoing an [^{18}F]FDG PET/CT. We visually scored the uptake of [^{18}F]FDG in four segments of the colon (figure 1). We found that discontinuing metformin for 48 hours before undergoing an [^{18}F]FDG PET/CT still gives a high uptake in the distal parts of the colon when compared with non-diabetic patients who are not using metformin. This raises the question of whether patients should discontinue metformin even longer than 48 hours. However, longer discontinuation periods may not be feasible for patients and could influence their diabetic control and health. Discontinuing metformin for 48 hours did normalise colonic uptake in the more proximal segments of the colon and thus 48 hours seems to be useful.

Specific patient populations

A third and final drug safety topic we cover is the safe use of radiopharmaceuticals in specific patient populations. For patients with renal insufficiency or patients carrying the acute porphyria gene, clear recommendations are not yet available. For this reason, we have further investigated the use of radiopharmaceuticals in these two specific patient populations.
The acute porphyrias are a group of rare metabolic disorders of the haem biosynthetic pathway. Carriers of the acute porphyria gene are prone to acute attacks, which can be precipitated by drug exposure. The symptoms of an attack of acute porphyria may include severe abdominal pain, constipation, nausea, confusion, and seizures. These attacks can be life-threatening. Hence, knowing whether a drug is safe for carriers of acute porphyria genes is important. We assessed radiopharmaceuticals on their porphyrogenicity, i.e., the potential of a drug to induce an attack. For this assessment, we used an algorithm for predicting the risk that a certain drug may activate the disease in a gene carrier of acute porphyria. We based our assessment on information about metabolism, (particle) size, and plasma concentration of the drug. Of the 41 radiopharmaceuticals assessed, most radiopharmaceuticals are probably safe to use. We classified five radiopharmaceuticals ([^{131}I]Iodomethyl norcholesterol, [^{99m}Tc]Tc-mebrofenin, [^{99m}Tc]Tc-phytate, [^{99m}Tc]Tc-sestamibi and [^{201}Tl]Tl-chloride) as possible porphyrogenic and concluded they should not be prescribed for patients suffering from acute porphyria unless an urgent indication is present and no safer alternative is available. In such cases, potential users should seek advice from a porphyria expert; preventive measures may be required.
Another specific group of patients where extra precautions may be needed are those suffering from renal insufficiency. As renal insufficiency will reduce excretion and elevate plasma concentrations of some pharmaceuticals and their metabolites, dose adjustment of the radiopharmaceutical may be necessary, especially when cleared by the kidney. However, standards for dosing of radiopharmaceuticals in renal insufficient patients are still lacking. We performed a systematic review aiming to provide dose recommendations of radiopharmaceuticals in renal insufficient patients. Surprisingly, we could find no consistent recommendations about radiopharmaceutical dosing in patients with renal insufficiency. Although some studies mention difficulties with dosing in patients with insufficiency in renal function, information about only a few radiopharmaceuticals is available and recommendations are often contradictory.

nanno.schreuder@ge.com ♦

Reference

- Gontier E, Fourme E, Wartski M, et al. High and typical 18F-FDG bowel uptake in patients treated with metformin. Eur J Nucl Med Mol Imaging 2008;35:95-9