Radiopharmaceuticals drug interactions: a critical review

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ABSTRACT

Radiopharmaceuticals play a critical role in modern medicine primarily for diagnostic purposes, but also for monitoring disease progression and response to treatment. As the use of image has been increased, so has the use of prescription medications. These trends increase the risk of interactions between medications and radiopharmaceuticals. These interactions which have an impact on image by competing with the radiopharmaceutical for binding sites for example can lead to false negative results. Drugs that accelerate the metabolism of the radiopharmaceutical can have a positive impact (i.e. speeding its clearance) or, if repeating image is needed, a negative impact. In some cases, for example in cardiac image among patients taking doxirubacin, these interactions may have a therapeutic benefit. The incidence of drug-radiopharmaceuticals adverse reactions is unknown, since they may not be reported or even recognized. Here, we compiled the medical literature, using the criteria of a systematic review established by the Cochrane Collaboration, on pharmaceutical-drug interactions to provide a summary of documented interactions by organ system and radiopharmaceuticals. The purpose is to provide a reference on drug interactions that could inform the nuclear medicine staff in their daily routine. Efforts to increase adverse event reporting, and ideally consolidate reports worldwide, can provide a critically needed resource for prevention of drug-radiopharmaceuticals interactions.

Key words: radiopharmaceuticals, radiopharmacy, drug interaction, systematic review.

INTRODUCTION

Radiopharmaceuticals are used for two purposes. The most important, and most common, is their use as diagnostic tools in clinical medicine. Radiopharmaceuticals, in the form of a traced compound, are administered to a patient in order to observe physiological alterations or abnormal distribution in the body. Radiopharmaceuticals serve a purpose in research, both clinical and nonclinical, where they are used as tracers to observe or quantitate biochemical or physiological processes (Tewson and Krohn 1998).

There is a considerable body of evidence that biodistribution and pharmacokinetics of radiopharmaceuticals may be altered by a variety of drugs, disease conditions, and in some cases, surgical procedures (Hesslewood and Leung 1994). Drs. Sampson and Hesslewood (1989), state that these unknown and unrecognized interactions of radiopharmaceuticals with other compounds can lead to a state of total disorder. For example, interactions that result in poor organ visualization may require repeating the procedure, thus resulting in a excess (unnecessary) irradiation of organs or if the interaction is unrecognized, it may result in misdiagnosis. Such misdiagnosis could delay appropriate treatment (e.g. a

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tumor is not visualized) or lead to unnecessary treatment (e.g. an interaction that creates spurious findings).

Adverse drug reactions are a major cause of morbidity and mortality. In the United States, an estimated number of 701,547 people are seen at emergency departments because of adverse drug effects (Budnitz et al. 2006). Adverse event reporting database provides no information on incidence, as events may not be recognized, and in many countries reporting is not mandatory. The incidence of drug-radiopharmaceutical interactions is unknown.

Unlike drugs given for therapeutic purposes, the literature suggests that radiopharmaceuticals rarely cause adverse reactions. A recently survey in Japan reported a rate of 1.3 events per 100,000 administrations (Kusabe et al. 2006). An European study, conducted approximately one decade earlier, reported a rate of 11 events per 100,000 administrations (95% confidence limits 3.3-19.2) (Hesslewood and Keeling 1997). These relatively low rates of adverse events may be explained, at least partially, by the usually small mass of drug injected or ingested. Additionally, radiopharmaceuticals are typically administered only once or at very limited number of times to any given patient (Silberstein and Ryan 1996) limiting the potential for allergic reactions and events which might be caused by cumulative exposures. Finally, patients are typically screened prior to imaging for known risk factors.

The possibility, however, of adverse reaction to a radiopharmaceutical does exist (Hesslewood and Keeling 1997, Cordova et al. 1982). Adverse reaction reports may be sent to manufacturers, regulatory authorities, and/or published in the professional literature. While there may be a small number of reported cases, studies have demonstrated that only 10% or less of possible adverse reactions are actually reported (Keeling 1994). Also, if a reaction is not serious or life-threatening, reporting by the manufacturer to regulatory authorities may not be required (Keeling 1994).

Just as the incidence of adverse events associated with radiopharmaceuticals is unknown, so is the incidence of interactions between radiopharmaceuticals and prescription drugs. Any drug or chemical agent which alters the chemical identity of the tracer or alters the physiological status of the organ of interest could be ex-

pected to alter the disposition of the radiopharmaceutical (Sampson 1993). Given the extent of prescription drug use, and particular trends toward polypharmacy, even if the individual risk of any interaction is low, the potential burden of drug-radiopharmaceutical interactions maybe substantial on a population basis. In this review, we summarize the available literature on drug-radiopharmaceutical interactions by organ class.

DRUG INTERACTIONS WITH RADIOPHARMACEUTICALS

Over 400 articles have been published on incompatibilities between drugs and radiopharmaceuticals. Amongst the various factors that can affect biodistribution of radiopharmaceuticals, ingestion of drugs (e.g. prescription medications) is the most commonly reported factor (Sampson 1990). As much of the literature is based on case studies and nonclinical (laboratory) experiments, there is little objective data to inform clinical decision-making (Kvasz et al. 2000, Lazarou et al. 1998). When considering the potential for interaction in a clinical setting, Callahan and Rabito (1990) suggest that special attention be given to extrapolating experimental data to the clinical situation, as the observed effects may depend on the amount of drug present.

Because much of the evidence is in the form of case studies (e.g. anecdotal) many suspected interactions may eventually be proven false; be they due to chance or noncausal associations (i.e. confounding). Here, we do not make causal assessments of individual case reports, but instead provide an overview of what has been reported in the medical literature.

Drug-radiopharmaceutical interactions may arise as a result of a variety of factors including the pharmacological action of the drug, physiochemical interactions between drugs and radiotracers, and competition for binding sites for example. Diseases induced by drugs, which may be potentiated by a radiopharmaceutical, would also be considered an adverse event (Hesslewood and Leung 1994).

While 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 the dispensing or administration may alter the sub-

sequent biodistribution o the radiopharmaceuticals. The most well known are interactions with the antiseptics povidone iodine and chlorhexidine. Iodine-based antisepsis, in presence of labeled compounds as ^{99}Tc, may release free pertechnetate (Fisher et al. 1977). Similarly, chlorhexidine gluconate can react to form technetium-gluconate complex, which is taken up by the kidney (Sampson and Hesslewood 1989). Although less commonly reported, radiopharmaceuticals may also interact with the syringe or catheter components (Slater et al. 1983, Millar et al. 1983).

Lifestyle factors, such as cigarette smoking, alcohol intake, and dietary habits (e.g. high dose of vitamins) also have the potential of interacting with radiopharmaceuticals.

A study carried out in Brazil showed that the concentration of ^{99m}Tc-RBC (Technetium-99-m labeling of erythrocytes) and ^{99m}Tc-PP (Technetium-99-m labeling of plasma protein) in blood can be decreased among cigarette smokers, even those whose habit is classified as light or moderate. The lack of a dose-response suggests that the effect may be ascribed to the generation of ROS (reactive oxygen species). Regardless of the mechanism, this can interfere with the performance of nuclear imaging procedures that use labeled Technetium (Vidal et al. 1998).

REVIEW

Radioisotopes are used in nuclear medicine for diagnostic and therapeutic purposes. Radiopharmaceuticals may be used in oncology for the initial staging, to assess response to treatment, residual disease, recurrent diagnosis and restaging, but specifically among the different types of tumor. Another field of study is that of large vessel vasculitis, granulomatous diseases and dementias (Ruiz-Laiglesia et al. 2008).

ORGANS-ADVERSE REACTION

ADR's (Adverse Drug Reactions) are typically thought of as serious, isolated clinical events that may be related to patient characteristics, environment, and the particular exposure. However, an ADR is not always a readily detectable clinical event, but instead can be clinically silent (Jones 1982). For example, subclinical elevations of hepatic transaminases and blood urea nitrogen, or de-

crease in sperm count may go unrecognized, or may be detected only by chance. The possibility of clinically silent adverse events with radiopharmaceuticals, and particularly radiopharmaceutical-drug interactions, should be considered. Here we review the literature on reports of both overt and clinically silent adverse events associated with radiopharmaceutical-drug interactions by organ system.

ADRENAL

Interactions with adrenal cortex and adrenal medulla agents have been reported. In view of the difference in physiology of the two regions of the gland, it is not surprising that these interactions occur with different groups of drugs (Solanki et al. 1992). Such interactions can have varying effects on the resulting image, depending on whether the drug increases or decreases the uptake of the radiopharmaceutical. In many cases the effect may be predicted based on the known pharmacological actions of the interacting drug (Hesslewood and Leung 1994).

Spironolactone affects the uptake of ^{131}Iodometil-nor-cholesterol by the adrenal cortex. It has been reported to both increase uptake (Hladik et al. 1987, Fischer et al. 1983, Khafagi et al. 1991) as well as decrease uptake (Hladik et al. 1987, Gross et al. 1981). An increase in ^{131}Iodomethyl-nor-cholesterol uptake by the adrenal gland is a result of the steroid synthesis from plasma. As such, it may result in false positive diagnosis of adrenocortical adenomas, adrenal incidentalomas and pheochromocytoma (Fischer et al. 1972, Hladik et al. 1987, Bardet et al. 1996, Mansmann et al. 2004). Spironolactone can also decrease aldosterone synthesis by decreasing the uptake of radiolabeled cholesterol by the adrenal cortex. This also has the potential to interfere in tumor diagnosis (Hesslewood and Leung 1994, Fischer et al. 1972).

Oral contraceptives have been found to increase the binding of adrenal cortex imaging agent ^{131}Iodomethyl-nor-cholesterol by increasing plasma renin activity. This results in adrenocortical stimulation; increased cortisol secretion and hyperplasia. They may cause false positives or just uninterpretable results complicating the interpretation of adrenal scintigrams (Gross et al. 1981, Swanson et al. 1990) potentially requiring retesting and exposing the patient to unnecessary radiation.

Yurekli et al. (2005) investigated the cytoprotective potential of amifostine against doxorubicin-induced cardiotoxicity. Using the radiopharmaceutical ^{99m}Tc-MIBI, they demonstrated that amifostine (amifostina – Ethyol$^®$) administration, 30 minutes before doxorubicin injection, resulted in a significant decrease in absorption of radioactivity by the adrenal, compared with doxorubicin alone. These results showed that amifostine may significantly attenuate doxorubicin-induced cardiotoxicity. They also show the potential for amifostine to impact radiopharmaceutical imaging of the adrenal gland.

GASTROINTESTINAL

The uptake and secretion of ^{99m}Tc-pertechnetate by the gastric mucosa may be affected by drugs, thereby interfering with the imaging of Meckel's diverticulum (Hesslewood and Leung 1994). Moreno et al. (2007b) showed that extracts of *Ginkgo biloba* decreased the uptake of ^{99m}-Tc-sodium-pertechnetate in the duodenum, kidney and liver. The alteration of uptake was significant in the duodenum. Radiobiocomplexes as sodium pertechnetate (Na^{99m}Tc0^4) are tracers widely utilized for scintigraphic studies mainly for thyroid, brain and stomach. Na^{99m}Tc0^4 has also been used to label blood constituents (Early and Sodee 1996). Therefore, alterations in the uptake by the duodenum may be crucial for the hepatobiliary scintigrahy in the diagnosis of duodenogastric reflux and dysfunction of the Oddi's sphincter in post-cholecystectomy syndrome for example (Pope and Bratke 1981).

BRAIN

The major risk of drug-radiopharmaceutical interactions occurs with pharmaceuticals that can alter the permeability of the blood-brain barrier. Verhoeff (1991) states that some pharmaceuticals may influence the receptor-bound neurotransmitters. This may cause false results and subsequently, misdiagnosis. Also, cytotoxic drugs such as cyclophosphamide, vincristine, bleomycin and cisplatin are reported to affect the pharmacokinetic response of radiopharmaceuticals, such as the tumor-seeking radiopharmaceutical ^{67}Ga-citrate. This radiopharmaceutical localizes in some neoplasms as well as other sites, including the liver and regions of infection or inflammation. That may result in a very high uptake of tracer in blood with little or no uptake by the tumor (Lentle and Scott 1979, Sampson 1993). Another study made by Van Leeuwen-Stok et al. (1998) demonstrated that ^{67}Gallium used with other cytostatic drugs except for methotrexate might be used together or sequentially in therapy because it potentiated the cytostatic effect.

One of the most well documented drug/radiopharmaceutical interactions is the suppression of ^{67}Ga-citrate uptake in cerebral tumors among patients taking cortisone preparations (Sampson 1993, Waxman et al. 1997). This is thought to result from a decrease in extracellular sodium and fluid volume. As the tracer is often associated with the oedematous fluid, it creates the appearance of a tumor decreased in size in the scintigraph. This effect may be so pronounced that it suppresses all uptake of tracer into the tumor, causing the tumor to be missed completely, possibly resulting in misdiagnosis. Similarly, among patients treated with deferoxamine, a chelating agent used to treat iron overload and aluminum toxicity, there was diffuse tracer activity and poor tissue localization with complete absence of normal uptake by ^{67}Ga-citrate. This occurs because deferoxamine forms a complex with ^{67}Ga that is stronger than that of ^{67}Ga with tranferrin, thus interfering with ^{67}Ga-transferin binding and subsequent cellular uptake. (Sampson 1993, Hesslewood and Leung 1994, Waxman et al. 1997).

BONE

The constant remodeling of bone guides the choice of tracers, to identify anomalies in the bone structure or pathologies related to the remodeling process. Therefore, pharmaceuticals that have an impact in any of these processes have the potential to interact with radioimaging of bone. Due to the complex process involving the uptake of phosphate by the bone, a number of pharmaceuticals may modify the biodistribution of the ^{99m}Tc-labeled-diphosphate. For example, etidronate and pamidronate, which are diphosphonates used in the treatment of Paget's disease, compete with MDP (^{99m}Tc-methylene-diphosphate) due to structural similarity (Sandler et al. 1991, Hommeyer et al. 1992). Such competition may result in false negative images (faulty diagnosis).

Also used in bone imaging, the biodistribution of ^{99m}Tc-PYP (sodium pyrophosphate / sodium trimeta-

phosphate-tin) may be altered by concomitant use of sodium diatrizoate. Use of diatrizoate with ^{99m}Tc-PYP has been shown to cause significant renal and liver uptake of the radiopharmaceutical, interfering with the performance of nuclear imaging procedures (Crawford and Gumeran 1978). In the worst case, this can result in a faulty diagnosis.

There have been numerous reports of interactions between the intramuscular iron dextran and ^{99m}Tc-MDP. Taken together, iron dextran modifies the biodistribution of ^{99m}Tc-MDP, such that the tracer concentrates at the site of injection, instead of diffusing throughout the skeleton (Forauer et al. 1994, Eisenberg et al. 1990). It is thought that localized complexing occurs between reduced technetium and ferric hydroxide, as the latter is released from the iron dextran complex. This may impact the skeletal scintigraphy of tumors (Mazzole et al. 1976, Sampson 1993), potentially preventing or delaying their diagnosis.

HEART

The most commonly used radiopharmaceutical for visualizing the heart is labeled thallous (^{201}Tl). The use of thallous with β-blockers can result in a temporary decrease in the severity of perfusion defects (Van Der Wall et al. 1983) Other studies (reports) have suggested that there is actually a net increase in the assessed severity among patients with minor coronary disease upon angiography (Hesslewood and Leung 1994). While β-blockers may interfere in the imaging results, suspending use prior to imaging is not recommended, as it may increase the risk of myocardial ischaemia (Bridges et al. 1992) Doxorubicin also has the potential to impact cardiac imaging. In an experimental study, ^{201}Tl uptake was significantly higher in the hearts of doxorubicin-treated rats compared to the control rats, indicating a slow wash-out of ^{201}Tl from the myocardium (Miyagawa et al. 1991, Yurekli et al. 2005).

According to Narahara et al. (1989), this apparent decrease in severity of perfusion defects upon radioimaging is dependent on the dose of the radiopharmaceutical (201-Tl) that goes to heart. When this occurs, the quality of the imaging is insufficient for accurate analysis and in consequence, is of limited value for diagnosis.

The radiopharmaceutical ^{99m}Tc-pyrophosphate is widely used to detect myocardial infarctions. Diminished cardiac activity and increased renal activity has been observed with the use of heparinised catheters for in vivo red cell labeling with ^{99m}Tc-pyrophosphate. This results in increased renal elimination of the radiopharmaceuticals, which can adversely effect visualization of the organ (Sampson 1990, Lentle and Scott 1979, Chacko et al. 1997, Hegge et al. 1978). Another labeled tracer, ^{99m}Tc-DTPA is also used in cardiac imaging. Mitomycin C has been shown to decrease the uptake of ^{99m}Tc-DTPA by cardiac muscle, potentially interfering in the performance of the diagnostic procedure (Gomes et al. 2001).

Antimyosin labeled with ^{111}Indium is specific for myocyte necrosis and is used in the detection of infarct, myocarditis and cardiac rejection. Chemotherapeutic drugs, notably doxorubicin, have been shown to cause increased myocardial uptake of the radiopharmaceutical (Estorch et al. 1990). Reuland et al. (1992) determined that doxorubicin decreased the uptake of ^{111}Indium antimyosin by the kidney. One randomized trial investigated the value of cardiac radioimmunoscintigraphy with ^{111}Indium antimyosin monoclonal antibodies in the early detection of cardiac damage. The results of these trials demonstrate that DEX (dexrazoxane) is able to ameliorate doxorubicin- and epirubicin-induced cardiotoxicity, even when high single drug doses are used (Lopez and Vici 1998). Radioimmunoscintigraphy was very sensitive in detecting anthracycline cardiac damage, but its specificity is low and it cannot be considered a primary test for guiding anthracycline treatment. This suggests that ^{111}Indium-antimyosin could potentially be used to monitor the degree of cardiotoxicity produced by doxorubicin (Carrio et al. 1993).

The extract of *Uncaria tomentosa* (cat's claw) is used as complementary treatment for AIDS and cancer (Sheng et al. 2000, Williams 2001). It can reduce the uptake of radiobiocomplex sodium pertechnetate in heart (Moreno et al. 2007a). Again, this may decrease the visualization of the organ, requiring a repeat procedure. There is also the potential for misdiagnosis.

Recent studies showed that cardiac ^{18}F-FDG uptake was significantly lower among diabetics and also among patients taking either bezafibrate or levothyroxine. Cardiac ^{18}F-FDG uptake was significantly higher in men,

patients less than 30 years old, patients with heart failure, and those receiving benzodiazepines. Potentially, pharmaceutical manipulation of ^{18}F-FDG may provide an opportunity to optimize PET/CT imaging (Israel et al. 2007).

HEPATOBILIARY

The radiopharmaceutical, ^{99m}Tc-iminodiacetic (^{99m}Tc-IDA) is used in the diagnosis of cholecystitis, focal nodular hyperplasia, degree of functional disorder in acute hepatic disease and to evaluate the severity of diffuse hepatic disease among others functions (Alobaidi et al. 2004, Broglia et al. 1998, Aburano et al. 1993). As an acid, the ^{99m}Tc-iminodiacetic acid is removed from blood by hepatocytes. Acids are subsequently transported to the gallbladder, where they are discharged through the cystic duct into the common bile duct and then into the intestines (Feezer 1982). A variety of drugs have been reported to interfere with hepatobiliary imaging by affecting the movement of the radiopharmaceuticals through the hepatobiliary system (Hesslewood and Leung 1994). These include isoniazid and pyrazinamide, which are anti tubercular drugs that have been shown to elevate liver enzymes and consequently hepatobiliary system is the most common system affected (Pv et al. 2008).

Technetium gluceptate is a radiopharmaceutical drug widely used to visualize renal structures, particularly kidney parenchyma. Concurrent administration with penicilamine, penicillin G potassium, penicillin V potassium, acetaminophen or trimetroprim-sulfamethoxazole, may substantially alter the biodistribution of ^{99m}Technetium gluceptate. If the impact is large enough, abnormal gallbladder images may result. Affected images can mimic abnormal kidney localization on posterior views (Hinkle et al. 1982), resulting in misdiagnosis.

KIDNEY

Appropriate imaging in uro-oncology is a crucial component at primary diagnosis, follow up and recurrence to achieve accurate assessment of the disease and determine the most effective treatment. The recent published literature on positron emission tomography and positron emission tomography/computerized tomography in uro-oncology has shown a great number of radiopharmaceuticals that may be used for urological malignancies

e.g. for prostate cancer ^{18}F-fluorodeoxyglucose, ^{11}C-choline, ^{18}F-fluorocholine, ^{11}C-acetate and ^{18}F-fluoride (Bouchelouche and Oehr 2008).

As most drugs are metabolized in the kidney, there is great potential for drug-radiopharmaceutical interactions. Many drugs alter kidney function in a dose-dependent manner. In patients with unilateral renal artery stenosis, angiotensin converting enzyme inhibitors (ACE-Inhibitors) decrease glomerular filtration in the affected kidney by the interruption of autoregulatory mechanism causing problems in the distribution of the radiopharmaceuticals (Hesslewood and Leung 1994). A case report showed that calcium antagonists can cause false-positive captopril renograms. These medications should be stopped before captopril renography, and physicians should be aware of this possible drug interaction if bilateral symmetrical renal function deterioration is seen in a patient's captopril renogram (Claveau-Tremblay et al. 1998).

The authors Latham et al. (1992), state that the use of drugs like dipyridamole increases or, depending on the concentration may decrease, the excretion of ^{99m}Tc DTPA (^{99m}Tc-diethylenetriamine penta-acetic acid) by the kidney. Diuretics as furosemide may improve renal function so that misleading good renograms and flow curves are obtained when using the renal imaging agent ^{9m}Tc DTPA (Sampson 1993).

INFECTION/INFLAMATION

Labeled leukocytes are used to the diagnosis of lung disease, rheumatoid arthritis, detection of inflammation and a variety of other diagnostic modalities (Van Hemert et al. 2007) A very common problem related to labeled leukocytes in infection and inflammation diagnosis are false-negative results. This drug-interaction has been attributed to the use of antibiotics and corticosteroids. This occurs because of the reduction in the chemoattractant stimuli for the labeled leukocytes (Hladik et al. 1987). However, Chung et al. (1991) and Datz and Thorne (1986), state that the use of antibiotics does not affect the results.

An important case of false-positive reaction is related to the hip arthroplasty. A retrospective and prospective study conducted by Zhuang et al. (2002) with 710 patients and 9 patients respectively, concluded that,

following hip arthroplasty, non-specifically increased FDG uptake around the head or neck of the prosthesis persists for many years, even in patients without any complications. Therefore, to minimize the number of false-positive results with PET studies, caution should be exercised when interpreting FDG uptake around the head or neck portion of prostheses.

LIVER/SPLEEN

The imaging agent ^{99m}Tc-hepato-iminidiacetic acid (^{99m}Tc-HIDA) used to pancreas scintigraphy. Drugs that alter the transport in the reticuloendothelial may decrease the uptake of radiopharmaceuticals, such as ^{99m}Tc-HIDA, in the liver and spleen (Hesslewood and Leung 1994). As such, they can lead to misdiagnosis. The impact can be quite large. A case report has been published on the complete absence of ^{99m}Tc-HIDA upon imaging, in a patient taking nicotinic acid (Sampson 1993).

Aluminum is present in a number of medications, most commonly in antacids. There is an increasing number of case reports of interactions between aluminum and radiopharmaceuticals. Aluminum-containing drugs can cause flocculation of colloidal particles of sulfur (used in liver scanning), such that the particles get trapped in the microvasculature of the lungs decreasing the uptake of the radiopharmaceutical (Bobinet et al. 1974). Labetalol, used for the treatment of pheocromacytoma, reduces the uptake of ^{131}Iodine- metaiodobenzylguanidine (^{131}Iodine- MIBG) in liver and spleen (Khafagi et al. 1989). Gomes et al. (2001) noted that mitomycin C increased the uptake of ^{99m}Tc-DTPA by the spleen and liver and also increased the uptake of ^{99m}Tc-GHA by the liver causing misdiagnosis and or a false positive result.

THYROID

The most commonly used thyroid imaging radiopharmaceuticals are ^{131}iodide and ^{123}iodide. Thus, drugs or pharmaceuticals with iodide in their formulation, may affect directly in the absorption of these radiopharmaceuticals through competition for receptor sites. Somatostatin also interferes with thyroid imaging through the same mechanism, absorption by receptor sites (Hesslewood and Leung 1994).

Competing anions, such as perchlorate and pertech-netate ions, act as competitive inhibitors of the iodine transport mechanism. This can lead to decreased uptake of ^{131}I sodium iodide. Inorganic iodine-containing medications such as Lugol's iodine as well as some vitamin/mineral supplements, are thought to release iodine thereby decreasing the specific activity of iodide in the body pool. This would also decrease uptake of radioiodine into the thyroid gland (Sternthal et al. 1980, Laurie et al. 1992). Similarly, use of mitomycin C decreased the uptake of ^{99m}Tc-GHA by the thyroid (Gomes et al. 2001).

Radioiodinated meta-iodobenzylguanidine (MIBG) plays a role in both the diagnosis and treatment of a wide range of tumors; phaeochromacytoma, neuroblastoma, carcinoid tumors and medullary carcinoma of the thyroid (Sisson et al. 1981, Horne et al. 1984, Fischer et al. 1983, Kimming et al. 1984, Bomanji et al. 1987, Sone et al. 1985). Over 20 medicines have the potential to interfere with the biodistribution of MIBG, sometimes many hours after they have been taken. Among those, the most commonly encountered interacting agents are chlorpromazine; clomipramine, diltiazem, dopamine, fluphenazine, labetalol, mazindol, nifedipine, promethazine and salbutamol. This interference is enough to impact the efficacy of MIBG as a diagnostic and therapeutic modality because of the extremely low quantities of radiolabeled MIBG that are present in the radiopharmaceutical. Therefore, it is recommended that treatment with any potentially interacting drug be stopped one week prior to imaging with MIBG (Solanki et al. 1992).

Thyrostatic drugs have modified the kinetics of radioiodine in the thyroid and through this mechanism may also have a radioprotective effect. Pre-treatment with thyrostatic medication lowers the effective half-life and uptake of radioiodine. However, this interaction also reduces the effective dose of the thyrostatic medication in the thyroid. Discontinuation of such medications shortly before radioiodine administration can increase the absorbed energy dose in the thyroid. These drug-radiopharmaceutical interactions may also have a clinical role in lowering the effective dose of radioiodine while achieving an equally effective target dose in the thyroid (Moka et al. 2002). While it does not impact imaging, administration of non-radioactive iodine within a few days after radioiodine administration

can increase the effective half-life of radioiodine in the thyroid. Therefore, its use should be suspended until few days after imaging with radioiodine, to facilitate clearance of the radioisotope.

NONSPECIFIC INTERACTIONS

There are a number of drugs which interact across a range of radiopharmaceuticals including those used for whole body (e.g. non-organ specific) imaging. Also, drug-induced disease states can alter the biodistribution of radiopharmaceuticals (Sampson 1990). For example, cytotoxic drugs such as cyclophosphamide, vincristine, and cisplatin are reported to affect the pharmacokinetic response of radiopharmaceuticals, particularly the tumor-seeking radiopharmaceutical ^{67}Ga.

Antimetabolites, such as cytarabine and methotrexate, have similar effects (Sampson 1993). Analogues of somatostatin (nonlabeled) are used therapeutically in the Carcinoid Syndrome. There have been reports of false-negative results when patients using somatostain were imaged with ^{111}In-pentetreotide due to a competition for the receptors sites (Dorr et al. 1993, Hesselwood and Leung 1994).

RESUMO

Os radiofármacos desempenham função crítica na medicina moderna, primariamente para fins diagnósticos, mas também no monitoramento da progressão de doenças assim como na avaliação de respostas ao tratamento. O uso da tecnologia por imagem tem crescido e conseqüentemente as prescrições de medicamentos (radiofármacos em especial) com esse propósito. Este fato, aumenta o risco de interações entre medicamentos e radiofármacos. Interações que podem ter um impacto na imagem, podem resultar em falso negativo e assim ter sérias conseqüências para o paciente. Já drogas que aceleram o metabolismo podem ter resultado positivo pois podem aumentar a taxa de eliminação do radiofármaco (clearance acelerado). Contudo, podem ainda ter resultados negativos, se a interação resultar em necessidade de repetição do exame. Em alguns casos, por exemplo em imagem cardíaca, entre pacientes sob o uso de doxarubicina, essas interações podem ter efeito terapêutico. A incidência de efeitos adversos envolvendo radiofármacos é desconhecida, além de não ser oficialmente reconhecida, nem notificada, principalmente no Brasil. Nesse estudo foram compilados da literatura médica, usando a metodologia da revisão sistemática, estabelecida pela Cochrane Collaboration, estudos e relatos de interações medicamentosas com radiofármacos. O objetivo é prover uma referência (sumário) de interações medicametosas com radiofármacos que possa auxiliar a medicina nuclear na sua rotina diária. Contudo, esforços devem ser feitos na tentativa de instituir a notificação de efeitos adversos com radiofármacos, e assim prevenir esse tipo de interação.

Palavras-chave: radiofármacos, radiofarmácia, interação medicamentosa, revisão sistemática.

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