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Revisión/Review

Radiopharmaceutical Drug Interactions

Interacciones Medicamentosas con Radiofarmacéuticos

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ABSTRACT

There has been considerable under-reporting of drug and radiopharmaceutical interactions, security and adverse reactions. The increasing use of radiopharmaceuticals has come to the attention of nuclear medicine staff and regulatory bodies. The aim is to provide reference for adverse reactions which could help all nuclear medicine staff in their daily routine. Reporting adverse events, including situations where an adverse event may have occurred but was actually avoided, is essential when assessing the magnitude of problems, alerting health professionals to these problems and ultimately for improving diagnostic accuracy.

Key Words: Review, systematic, drug safety, radiopharmaceuticals (*source: MeSH, NLM*).

RESUMEN

Se ha identificado que la información sobre la interacción entre medicamentos y radiofármacos es considerablemente insuficiente. El incremento en la utilización de radiofármacos ha llamado la atención de los grupos de medicina nuclear y los organismos reguladores. El objetivo es proporcionar información que podrían ayudar a los grupos de medicina nuclear en su rutina diaria, sobre las reacciones adversas. Presentación de informes de eventos adversos, incluidas las situaciones en que un acontecimiento adverso podría haber ocurrido, pero se evitó, es esencial para evaluar la magnitud de los problemas, alertar a los profesionales de la salud sobre estos problemas y, en definitiva, para mejorar la precisión diagnóstica.

Palabras Clave: Revisión, interacción, radiofármacos, (*fuente: DeCS, BIREME*).

Radiopharmaceuticals are used for two purposes. The first, and most important of them, is their use as a traced compound administered to a patient for observing physiological alterations or abnormal distribution throughout the body. The second is their use as a tracer for biochemical or physiological studies (1).

There is considerable evidence that radiopharmaceutical biodistribuion or pharmacokinetics may become altered by a variety of drugs, disease states and surgical procedures (2). Sampson (3) has stated that remaining ignorant of such factors (interactions-drug interactions) can lead to a state of total disorder. For example, interactions leading to poor organ visualisation may require a procedure to be repeated, thereby resulting in excess (unnecessary) irradiation of organs or even misdiagnosis.

METHODOLOGY

The literature was systematically reviewed for identifying the role, use/indications, effectiveness of interventions using radiopharmaceuticals and cost-effectiveness. Computerised databases were searched for articles concerning radiopharmaceuticals published between 1956 and 2007; the searches were supplemented by manual searches of published articles' bibliographies and information from a major radiopharmacy textbook.

The literature thus selected provided 34 articles which were representative examples of articles, priority being given to randomised controlled trials. All the selected articles were then reviewed, ensuring that they had sufficient detail to classify them as being useful.

The primary study formed the unit of analysis, being defined as an experiment having one treatment and one comparison group. However, several other conventions were used. The following inclusion criteria were applied to the collected studies; articles had to have investigated treatment indication and drug interaction using radiopharmaceuticals, have reported a comparison, have reported findings and results in a way which led to quantitative analysis and have reported cost-effectiveness studies.

RESULTS AND DISCUSSION

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 expected to alter radiopharmaceutical disposition (4).

Over 400 articles have been published relating the incompatibility between drugs and radiopharmaceuticals. Amongst the various factors that can affect the biodistribution of radiopharmaceuticals, the ingestion wth others drugs is the most common (5). Callahan (6) has suggested that special attention should

be paid when applying experimental data to the clinical situation, since the observed effects may depend on the amounts of drug present.

Many accounts of drugs interacting with radiopharmaceuticals are false or anecdotal and, in some instances, have not unequivocally established a direct cause-effect relationship. Special attention must thus be paid to the use of cytotoxics, often in combination with radiopharmaceuticals, thereby leading to problems in analysing drug/radiopharmaceutical interactions (2).

Drug interactions may arise from a variety of factors including a particular drug's pharmacological action, physicochemical interactions between drugs and radiotracers, age, stress, smoking and many other factors, even disease induced by drugs which would be considered an adverse event in some cases too (2).

Contamination when dispensing or administering drugs represents one of the reasons for alterations in radiopharmaceutical biodistribution. The most well-known ones arise from interactions with povidone, iodine and chlorhexidine (antiseptics). Fisher (7) has demonstrated that iodine-based antiseptics in the presence of labelled compounds, such as ^{99}Tc, may release free pertechnetate. When chlorhexidine gluconate is used it forms a technetium-gluconate complex which is taken up by the kidneys (5). Although being less common, radiopharmaceuticals may also interact with the syringe or catheter components (8,9).

A study carried out in Brazil revealed that Tc-99m RBC (technetium-99-m labelling of erythrocytes) and Tc-99m PP9 (technetium-99-m labelling plasma protein) concentration in blood can become reduced in the presence of normal and light cigarette smoking, suggesting that this effect may be ascribed to reactive oxygen species (ROS) being produced and may thus interfere with nuclear imaging performance, mainly when using technetium labelling (10).

Drug interactions with organs

Adrenal

Interactions with both adrenal cortex and adrenal medulla agents have been reported. In view of the difference in physiology of the gland's two regions, it is not surprising that interactions occur with different groups of drugs (11). This can affect the image in different ways, depending on whether the drug increases

or decreases radiopharmaceutical uptake. In many cases this can be predicted by the interacting drug's known pharmacological actions (2).

Spironolactone's effects on ^{131}iodomethylnorcholesterol uptake by the adrenal cortex have been reported in terms of both its increased (12-14) and decreased uptake (12,15). Increased ^{131}iodomethylnorcholesterol uptake by adrenal results from steroid synthesis from plasma thereby resulting in a false positive diagnosis of adrenocortical adenomas, adrenal incidentalomas and pheochromocytoma (12,16,17). Spironolactone can also decrease aldosterone synthesis which may result in decreased radio-labelled cholesterol uptake by the adrenal cortex, thereby also interfering with the diagnosis (2).

Oral contraceptives also increase ^{131}iodomethylnorcholesterol (i.e. the binding adrenal cortex imaging agent) by increasing plasma rennin activity. This results in adrenocortical stimulation, increased cortisol secretion and hyperplasia, leading to problems in interpreting adrenal scintigrams (15,4).

Gastrointestinal

Tc-99m pertechnetate uptake and secretion by the gastric mucosa may also be affected by drugs, thereby interfering with the imaging of Meckel's diverticulum (2).

Brain

The greatest incidence occurs with pharmaceuticals which alter blood-brain barrier penetration. Verhoeff (19) has stated that some pharmaceuticals may influence receptor-bound neurotransmitters and thus provide false results or incorrect diagnoses. Cytotoxic drugs, such as cyclophosphamide, vincristine, bleomycin and cisplastin, have been reported to affect radiopharmaceutical tumour-seeking radiopharmaceutical ^{67}Ga-citrate's pharmacokinetic response. This material localises in some neoplasms as well as other sites such as the liver and regions of infection or inflammation, thereby resulting in a very high uptake of tracer in blood and little or no uptake in tumours (20,4).

One of the most well-documented drug/radiopharmaceutical interactions concerns the suppression of ^{67}Ga-citrate uptake in cerebral tumours amongst patients taking cortisone preparations (4,21). It is thought that this occurs as a result of decreased extracellular sodium and water content, leading to a decrease in oedema. The tracer is often associated with the oedematous fluid so that an apparent decrease in tumour size is observed on the scintigram. The effect may be so pronounced as to completely suppress uptake within a tumour, possibly

leading to a complete misdiagnosis. There may have been reports of misdiagnosis because there was so little uptake that the tumour was missed – or the need to re-test may have arisen because of poor image quality due to such drug-radiopharmaceutical interaction. It has been observed that patients who are being treated with deferoxamine (a chelating agent used to treat iron overload and aluminium toxicity) have shown diffuse activity and poor tissue localisation, accompanied by the complete absence of normal uptake by ^{67}Ga-citrate. This occurs because deferoxamine forms a complex with ^{67}Ga stronger than that of ^{67}Ga-transferin, interfering with ^{67}Ga-transferin binding and subsequent cellular uptake, thereby altering normal ^{67}Ga distribution.

Bone

Due to the complex process involving phosphate uptake by bone, a variety of pharmaceuticals may interfere or modify ^{99}Tc-labelled-phosphate biodistribution. Recent studies, such as those by Sandler (22) and Hommeyer (23), have proved that administering etidronate or pamidronate (both being diphosphonates used in treating Paget's disease) compete with methylene diphosphate (MDP/technetium-99m MDP) due its structural similarity.

The use of sodium diatrisoate has been described as an alteration factor in Tc-99m PYP (sodium pyrophosphate/sodium trimetaphosphate-tin) biodistribution. A related case has shown that using diatrizoate with Tc-99m PYP can cause intense renal and liver radiopharmaceutical uptake thereby interfering with nuclear imaging performance and can induce a wrong diagnosis in the worst cases (24).

Many reports have been published regarding the effect of intramuscular iron dextran on Tc-99m MDP biodistribution. A diffuse concentration of activity is usually observed at the site of injection instead of being localised throughout the skeleton. It is thought that local complexing occurs between reduced technetium and ferric hydroxide as the latter is released from the iron dextran complex which interferes with skeletal scintigraphy of tumours (25,4).

Heart

Thallous has been the most used radiopharmaceutical for the heart (^{201}Tl). Many studies have suggested that using thallous and â-blockers causes a decrease in the severity of perfusion defects, whereas others have suggested that there is a net increase in severity in patients suffering from minor angiographic coronary disease (2). It has been reported that ^{201}Tl uptake was significantly higher in the hearts of doxorubicin-treated rats compared to control rats, indicating a slow

wash-out of ^{201}Tl from the myocardium (26,27). According to Narahara (28), decreased severity of perfusion directly affects the amount of radiopharmaceutical (20-Tl) going to the heart and imaging quality is thus not sufficiently good for providing an accurate analysis and diagnosis. Studies such as that by Bridges (29) have suggested that even â-blocker use may interfere in imaging results; it is not recommended that they be stopped because suppressing them may lead to the risk of myocardial ischemic complications.

^{99m}Tc-pyrophosphate use in detecting heart-attacks is widely known. When heparinised catheter has been used *in vivo* red cell labelling with ^{99m}Tc-pyrophosphate it has been observed to diminish cardiac activity and increase renal activity. This leads to increasing renal elimination of a radiopharmaceutical but does not allow proper visualisation of the organ during the exam (5; 20; 30; 31). Mitomycin C decreases 99mTc-DTPA uptake by the heart which interferes with diagnostic performance (32).

Indium-111-labelled antimyosin is specific for myocyte necrosis and has been used in detecting heart attack, myocarditis and cardiac rejection. Chemotherapeutic drugs (notably doxorubicin) have been shown to cause increased myocardial radiopharmaceutical uptake (33). Reuland (34) has stated that doxorubicin and indium-111-labelled antimyosin use decreases uptake by the kidneys. This suggests that indium-111-labelled antimyosin could be used for monitoring the degree of cardiotoxicity produced by doxorubicin (35).

Uncaria tomentosa extract (cat's claw), used as complementary treatment for AIDS and cancer (36,37), has reduced radiobiocomplex sodium pertechnetate uptake in the heart (28).

Hepatobiliary

^{99m}Tc-iminodiacetic acids are removed from blood by hepatocytes and transported to the gallbladder where they are subsequently discharged through the cystic duct into the common bile duct and into the intestines. A variety of drugs has been reported as interfering with hapatobiliary imaging by affecting radiopharmaceutical movement through the hepatobiliary system (2).

Opioid analgesics (such as methadone and morphine) may cause biliary tract spasm due to contraction of the sphincter of Oddi (38). Enzyme inducers such as phenobarbital may enhance biliary excretion of similar imaging agents and cholinergic drugs, such as bethanecol, may also induce gallbladder emptying (39).

Technetium gluceptate is a widely used radiopharmaceutical for visualising renal structures, particularly kidney parenchyma. When it is concurrently administered with penicilamine, penicillin G potassium, penicillin V potassium, acetaminophen and trimetroprim-sulfamethoxazole it may cause substantial alteration of technetium-99m gluceptate biodistribution. This leads to abnormal gallbladder images which could mimic abnormal kidney localisation on posterior views (40).

Kidney
The amount of drug administered may alter the kidneys' function. Angiotensin-converting enzyme inhibitors decrease glomerular filtration in the affected kidney of patients suffering unilateral renal artery stenosis by interrupting the auto-regulatory mechanism (2).

Infection/inflammation
False-negative results with labelled leukocytes have been attributed to the use of antibiotics and corticosteroids. This occurs because of reduced the chemoattractant stimuli for the labelled leukocytes (12). However, Chung (41) and Datz (42) have stated that using antibiotics does not affect the results.

Latham (43) has stated that using drugs like dipyridamole has been shown to affect kidney handling of Tc-99m DTPA (Tc-99m diethylenetriamine penta-acet acid). Diuretics such as furosemide may improve renal function so that misleadingly good renograms and flow curves are obtained when using the Tc-99m DTPA renal imaging agent (4)

Liver/spleen
Drugs used in liver and spleen studies which alter transport in the reticuloendothelial interfere negatively in radiopharmaceutical uptake (2). A case report has been published concerning the complete absence of the Tc-99m hepato-iminidiacetic acid (HIDA) imaging agent in a patient receiving nicotinic acid (4).

Aluminium is increasingly being reported as interacting with radiopharmaceuticals. Aluminium in aluminium-containing drugs such as antacids could cause flocculation of colloidal sulphur particles (liver scanning) so that the particles become trapped in pulmonary microvasculature (44). Using labetalol for treating pheocromacytoma reduces Iodine-131 metaiodobenzylguanidine (Iodine-131 MIBG) uptake in the liver and spleen (14). Gomes (32) has stated

that using mitomycin C increases Tc-99m DTPA uptake by the spleen and liver and Tc-99m GHA uptake by the liver.

Thyroid

The most commonly used radiopharmaceuticals for thyroid imaging are 131-iodide and 123-iodide. Drugs or pharmaceuticals having iodide in their formulation may thus directly affect these radiopharmaceuticals' absorption. This interaction's mechanism is the same as that for somatostatin (competition for receptors sites) (2).

Decreased 131-sodium iodide uptake results from competing anions (such as perchlorate and pertechnetate ions) acting as competitive iodine transport mechanism inhibitors. Inorganic iodine-containing medications (such as Lugol's iodine and vitamin and mineral supplements) are thought to release iodine, thereby decreasing iodide's specific activity in the body pool, resulting in decreased radioiodine uptake into the thyroid gland (45). Using mitomycin C decreases Tc-99m GHA uptake by the thyroid (32).

Radioiodinated meta-iodobenzylguanidine (MIBG) has been used in diagnosing and treating phaeochromacytoma, neuroblastoma, carcinoid tumours and medullar carcinoma of the thyroid (46; 47;48; 49; 50; 51). Over 20 medicines may potentially interfere with MIBG biodistribution, sometimes many hours after they have been taken. The most commonly encountered interacting agents amongst them would be chlorpromazine, clomipramine, diltiazem, dopamine, fluphenazine, labetalol, mazindol, nifedipine, promethazine and salbutamol which may affect MIBG's diagnostic and therapeutic efficacy. It is recommended that treatment with the potentially interacting drug be stopped one week prior to imaging with MIBG to prevent even small amounts challenging the extremely low quantities of radio-labelled MIBG present in the radiopharmaceutical (11).

Drug interactions with no organs

Somatostatin

Somatostatin analogues (such as unlabeled octreotide which is therapeutically used in the Carcinoid Syndrome) may give false-negative results when used together with ^{111}In-pentetreotide due to competition for receptors sites (52; 2).

Tumour/abscess

Both drug-induced disease states and drugs have been reported to alter ^{67}Ga biodistribution (18). Cytotoxic drugs such as cyclophosphamide, vincristine,

and cisplatin have been reported to affect radiopharmaceuticals' pharmcokinetic response, particularly the ^{67}Ga tumour-seeking radiopharmaceutical. Similar effects, although less frequent, also occur with antimetabolites such as cytarabine and methotrexate (4) [2%] ♣

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