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Guidance for nuclear medicine staff on radiopharmaceuticals drug interaction

Ralph Santos-Oliveira*

Division of Radiopharmacy, Nuclear Engineering Institute, Brazil.

Numerous drug interactions related to radiopharmaceuticals take place every day in hospitals many of which are not reported or detected. Information concerning this kind of reaction is not abundant, and nuclear medicine staff are usually overwhelmed by this information. To better understand this type of reaction, and to help nuclear medicine staff deal with it, a review of the literature was conducted. The results show that almost all of radiopharmaceuticals marketed around the world present drug interactions with a large variety of compounds. This suggests that a logical framework to make decisions based on reviews incorporating adverse reactions must be created. The review also showed that researchers undertaking a review of literature, or even a systematic review that incorporates drug interactions, must understand the rationale for the suggested methods and be able to implement them in their review. Additionally, a global effort should be made to report as many cases of drug interaction with radiopharmaceuticals as possible. With this, a complete picture of drug interactions with radiopharmaceuticals can be drawn.

Uniterms: Nuclear medicine. Radiology. Radiopharmaceuticals/drug interaction. Molecular imaging.

Diversos casos de interações medicamentosas com radiofármacos ocorrem diariamente na rotina hospitalar, contudo muitos deles não são notificados ou mesmo percebidos. Informações a respeito desse tipo de reação não é abundante e os profissionais da medicina nuclear muitas vezes estão assoberbados por essas informações. De modo a entender esse tipo de reação e auxiliar a medicina nuclear a lidar com essa situação uma revisão da literatura foi realizada. Os resultados mostraram que a totalidade dos radiofármacos comercializados no mundo apresentam interação medicamentosa com uma enorme variedade de outros medicamentos. Dessa forma sugere-se que revisões sobre radiofármacos inclua um capítulo sobre efeitos adversos. Além disso, um esforço mundial para notificar efeitos adversos deve ser realizado, pois somente dessa forma se terá um quadro real da situação referente interações medicamentosas com radiofármacos.

Unitermos: Medicina nuclear. Radiologia. Radiofármacos/interações medicamentosas. Imagem molecular.

INTRODUCTION

According to Mather (2001), radiopharmacy is scientifically recognized as an essential sub-specialty of nuclear medicine. Radiopharmaceuticals are used for two purposes; most importantly, is their use as diagnostic tools in clinical medicine. Radiopharmaceuticals also serve a purpose in research, both clinical and nonclinical, where they are used as tracers to observe or quantify biochemical or physiological processes (Tewson and Krohn 1998, Santos-Oliveira et al 2008).

Radiopharmaceuticals have been in use for many years for diagnosis and therapy of a wide variety of diseases (Sampson, 2003). In the early days of radiopharmacy, radiopharmaceuticals were generally prepared "in-house," and were not regarded as true medicines. In fact, they were, more often than not, prepared on the open bench where proper quality testing was not officially recognized.

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,

***Correspondence:** R. Santos-Oliveira. Instituto de Engenharia Nuclear, Divisão de Radiofarmácia, Rua Hélio de Almeida 75, Ilha do Fundão, 21941-906 - Rio de Janeiro - RJ, Brasil. Email: roliveira@ien.gov.br

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.

Adverse drug reactions are a major cause of morbidity and mortality. In the United States, an estimated 701,547 people are seen every year at emergency departments due to adverse drug effects (Budnitz *et al.* 2006). Adverse event reporting databases provide no valuable information on incidence, as some events may not be recognized, and in many countries reporting is not mandatory. Therefore, the total incidence of drug-radiopharmaceutical interactions is unknown (Santos-Oliveira et al, 2008; Baranowska-Kortlylewicz, 2007).

It is important to clarify the difference between drug interaction and adverse reaction. Ryan *et al.* (1996) defined adverse reaction to radiopharmaceuticals as any response to a drug which is noxious and unintended, occurring at doses used in man for prophylaxis, diagnosis, therapy of disease, or for modification of physiological function.

Drug interaction is defined by the Food and Drug Administration (FDA, 2009) as drug-drug interactions that can lead to changed systemic exposure, resulting in variations in drug response of the co-administered drugs. Therefore, it is important to evaluate potential drug interactions prior to market approval as well as during the postmarketing period, especially with regard to radiopharmaceuticals.

MATERIAL AND METHODS

The location and the selection of studies is one of the most important steps in a review of literature, and it is necessary to develop a literature search strategy based on key elements. The review question determines the nature of the search strategy. In this case our question was simple:

"Do radiopharmaceuticals present drug interactions?"

To address this question a review of the literature was conducted for drug interactions with radiopharmaceuticals. We searched computerized databases on radiopharmaceuticals including MEDLINE, EMBASE, the International Pharmaceutical Abstracts and Science Citation Index (published from 1920 to April 2007) using "*radiopharmaceuticals / drug interactions,*" "*radiopharmaceuticals / interactions,*" and several other search terms. This was supplemented with manual searches of major radiopharmacy textbooks. This review of the literature uses a selection of the material collected, and includes controlled trials, cohort studies, case-control studies and case series, in English, French, Deutsch and Portuguese languages. The difficulties in finding studies related to radiopharmaceutical drug interactions forced the acceptance of studies of lower quality. Each of the papers were retrieved and reviewed.

RESULTS AND DISCUSSION

The search strategy identified forty potentially relevant papers. Two reviews described more than ten related cases. Other authors published aspects of a single study in a number of related papers. Each of the publications included in this study was located through our search, and all met the inclusion criteria.

The results are shown in Table I, which summarizes all of the principal studies related to radiopharmaceuticals and adverse reaction. In addition, this table can be used as a guide for all nuclear medicine staff as it is portable and easy to follow.

TABLE I – Summary of the compounds that might interfere with radiopharmaceuticals

Reference	Compound	Radiopharmaceuticals	Conclusion
Fisher *et al.*(1977)	Iodine-based Antiseptics	Technetium-99	Positive: reduce the uptake
Sampson & Hesselwood (1989)	Chlorhexidine gluconate	Technetium-99	Positive: reduce the uptake
Slater *et al.* (1983)	Syringe and catheter components	All radiopharmaceuticals	Positive: reduce the radiopharmaceuticals concentration in the sample
Millar *et al.* (1983)	Syringe and catheter components	All radiopharmaceuticals	Positive: reduce the radiopharmaceutical concentration in the sample
Hladik *et al.* (1987)	Spironolactone	Iodomethylnorcholesterol-131	Positive: increase the uptake
Fischer *et al.* (1982)	Spironolactone	Iodomethylnorcholesterol-131	Positive: increase the uptake
Khafagi *et al.* (1991)	Spironolactone	Iodomethylnorcholesterol-131	Positive: increase the uptake
Gross, *et al.* (1981)	Spironolactone	Iodomethylnorcholesterol-131	Positive: decrease the uptake

TABLE I – Summary of the compounds that might interfere with radiopharmaceuticals (continuation)

Reference	Compound	Radiopharmaceuticals	Conclusion
Gross *et al.* (1981)	Contraceptive	Iodomethylnorcholesterol-131	Positive: increase the uptake
Sampson (1993)	Cortisone	Gallium-citrate-67	Positive: suppression of the uptake
Waxman *et al.* (1977)	Cortisone	Gallium-citrate-67	Positive: suppression of the uptake
Sandler *et al.* (1991)	Etidronate or pamidronate	Technetium-99-labelled-phosphate	Positive: reduce the increase
Hommeyer *et al.* (1992)	Etidronate or pamidronate	Technetium-99-labelled-phosphate	Positive: reduce the uptake
Hesslewood and Leung (1994)	β-blockers	Thallous-201	Positive: reduce the uptake
Narahara *et al.* (1989)	β-blockers	Thallous-201	Positive: reduce the uptake
Sampson (1990)	Heparinised catheter	Technetium-pyrophosphate-99m	Positive: reduce the uptake
Lentle and Scott (1979)	Heparinised catheter	Technetium-pyrophosphate-99m	Positive: reduce the uptake
Chacko *et al.* (1977)	Heparinised catheter	Technetium-pyrophosphate-99m	Positive: reduce the uptake
Hegge *et al.* (1978)	Heparinised catheter	Technetium-pyrophosphate-99m	Positive: reduce the uptake
Estorch *et al.* (1990)	Doxorubicin	Antimyosin-indium-111	Positive: reduce the uptake
Reuland *et al.* (1992)	Doxorubicin	Antimyosin-indium-111	Positive: reduce the uptake
Pope and Bratke (1981)	Opioid analgesics	Technetium-iminodiacetic-99m	Positive: reduce the uptake
Feezer (1982)	Phenobarbital and Bethanecol	Technetium-iminodiacetic-99m	Positive: increase the excretion
Hladik *et al.* (1987)	Antibiotics and corticosteroids	Labelled-leukocytes	Positive: false-negative results
Chung *et al.* (1991)	Antibiotics and corticosteroids	Labelled-leukocytes	Negative: no interference
Datz and Thorne (1986)	Antibiotics and corticosteroids	Labelled-leukocytes	Negative: no interference
Latham *et al.* (1992)	Dipyridamole	Technetium-diethylenetriamine-pentact-acid-99m	Positive: affect the kidney handling.
Bobbinet *et al.* (1974)	Aluminium (antacids)	All radiopharmaceuticals	Positive: reduce the uptake.
Hesslewood and Leung (1994)	Iodide pharmaceuticals	Iodide-131 and Iodide-123	Positive: reduce the uptake
Sternthal *et al.* (1980)	Perchlorate and pertechnetate ions	Iodide-sodium-131	Positive: reduce the uptake
Dorr *et al.*(1993)	Octreotide	Indium-pentetreotide-111	Positive: reduce the uptake
Sampson (1993)	Cyclosphosphamide; vincristine and cisplatin	Gallium-67	Positive: alters the pharmacokinetics
Khafagi *et al.*(1989)	Labetalol	I-MIBG-131	Reduce uptake
Gomes *et al.* (2001)	Mitomycin C	99m Tc radiopharmaceuticals, 99m Tc-diethylene-triaminepentaacetic acid (99mTc-DTPA), 99mTc-dimercaptosuccinic acid (99mTc-DMSA), 99mTc-glucioheptonic acid (99mTc-GHA)	99mTc-DTPA: Increased the uptake in pancreas, ovary, uterus, stomach, kidney, spleen, thymus, heart, lung, liver, thyroid and bone. 99mTc-DMSA: Decreased the uptake in all organs except brain 99mTc-GHA Increased the uptake in liver and decreased in stomach, thymus, heart and thyroid.
Moreno et.al. (2007)	Extract of *Uncaria tomentosa*	Radiobiocomplex sodium pertechnetate	Increased uptake in pancreas and muscle Decreased the uptake in heart.
Moreno *et al.* (2007)	Extract of *Ginko biloba*	Sodium pertechnetate	Decreased the uptake in duodenum
Schroeder *et al.* (2007)	Cigarette smoke	FDG-18	Increased the uptake in lungs.

CONCLUSION

The results showed that numerous drugs may interfere with radiopharmaceutical metabolism or biodistribution, and consequently, efforts must be made to minimize this type of event.

Our findings (Table I) can be particularly useful for the daily routine of nuclear medicine staff in hospitals where quick guides are always welcome.

In light of our results, drug interactions with radiopharmaceuticals should be better documented and reported. Efforts to increase adverse event reporting, and ideally consolidate reports worldwide, can provide a critically needed resource for prevention of drug-radiopharmaceuticals interactions.

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