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Overview on radiochemical purity control for ^{99m}Tc radiopharmaceuticals commonly used in nuclear medicine.

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ABSTRACT

Most radiopharmaceuticals are used for the purpose of medical diagnosis. These radiopharmaceuticals contain small amount of the active substances with a radionuclide attached to them to allow scintigraphic imaging or measurement of biodistribution. Radiation is a general property of all radiopharmaceuticals, which when administered give the patient an imminent radiation dose. Quality control (QC) tests are mandatory for radioactive drugs which are intended for human administration [1]. The safety and efficacy of radiopharmaceuticals are important factor of the quality assurance protocol. QA in radiopharmacy is critical for practice. A poor-quality diagnostic radiopharmaceutical, while not in itself unsafe, it could give incorrect information about the patient's condition leading to an inappropriate choice of therapy [2]
In this study a considerable number of DMSA, PYP, MAG-3, DTPA and HMPAO radiopharmaceuticals samples are analyzed for their radiochemical purity using radiochemical purity standard procedure. These products used in nuclear medicine Department of University Hospital Centre "Mother Theresa" and some private clinics in Albania are collected and tested for 5 years period. The aim of the work is to present the results for their radiochemical purity and to emphasize the need for the radiopharmaceutical quality control. The mean radiochemical purity was 96.94% (standard deviation 7.82%) and 4.52% of all tested preparations failed to meet radiochemical preparation limits.

INTRODUCTION

Most radiopharmaceutical kits are prepared using Tc-99m. The Tc-99m attached to a substrate molecule in the kit, called a ligand, designed to localize in a specific organ system. Most of the Tc-99m should tag to the ligand for the radiopharmaceutical to be efficient. Very little free Tc-99m should be present to the final product. Hydrolyzed reduced Tc-99m, another byproduct of the tagging process, should also be present in low levels. Both free and hydrolyzed Tc-99m can give artifacts on scans, which may mislead diagnosis or make assessing scans difficult. While are setting minimum tagging efficiency standards for most radiopharmaceuticals, each radiopharmaceutical compounded must be tested for radiochemical purity before use in patients. Unless the radiopharmaceutical is efficiently tagged, the accuracy of the patient diagnosis may be compromised.
The radiochemical purity is defined as the proportion of the total radioactivity of the nuclide concerned present in the stated chemical form. For many radiopharmaceuticals the radiochemical purity will be expected to be greater than 95%, but this is not universally so. Low radiochemical purity may lead to confusion in the diagnosis for the diagnostic agent. For radiopharmaceuticals purchased, manufactured will normally declare the radiochemical purity and the nuclear medicine department may not need to perform any further determinations. But it is strongly recommended that the radiochemical purity determinations are useful to establish the suitability of the final product.

A range of techniques is available for such determinations, but the techniques must be reliable and simple and preferably rapid to perform such that in an ideal situation, the radiochemical purity of materials containing short lived radionuclides can be established prior to their administration.

Radiochemical purity is assessed by a variety of analytical techniques such as liquid chromatography, paper chromatography, thin layer chromatography and electrophoresis. After or during separation, the distribution of radioactivity on the chromatogram is determined. Different measuring techniques are used depending on the natyre of the radiation and the chromatographic technique. The quantity of substance applied to the chromatographic support (paper, plate or column) is often extremely small (because of the high sensitivity of detection of the radioactivity) and particular care has to be taken in interpretation with regard to the formation of the artifacts.

MATERIALS & METHODS

The radiochemical purity of DMSA (99mTc-Dimercaptosuccinic acid), PYP (99mTc-Pyrophosphate), MAG-3 (99mTc-Mercaptoacetyltriglycine), DTPA (99mTc-Diethyltriamine-pentaacetic acid) and HMPAO (99mTc-Exametazime) radiopharmaceuticals samples was tested using standard techniques presented in Table 1.

Table 1

Standard methods for the determination of the radiochemical purity of ^{99m}Tc radiopharmaceuticals and quality limits

Radio-Pharmaceuticals	Method	Reagents	Limits
DMSA	TLC	MEK(2-butanone)/ITLC-SG	95
PYP	TLC	Saline/ITLC-SG	95
MAG-3	1. TLC	A) MEK(2-butanone)/ITLC-SG B) 50%acetonitrile/ITLC-SG	96
	2. Mini column	C18 Seppak, 0.001N HCl, 50% ethanol	96
DTPA	TLC	A) MEK(2-butanone)/ITLC-SG B) Saline /ITLC-SG	95
HMPAO	TLC	A) MEK(2-butanone)/ITLC-SG B) Saline/ITLC-SG	80

In total 98 samples from different lots and different radiopharmaceuticals are tested for their radiochemical purity.
A drop (1-10 µl) of the radiopharmaceutical is spotted on a miniaturized paper or instant thin layer chromatography (ITLC) strip and developed in a solvent by ascending method under atmospheric conditions. Generally, the solvents are selected in such a way that the radiopharmaceutical and impurity will be widely separated. The developed strips are dried and cut into two segments, referred to as origin and the solvent front. Each segment is assayed separately in a dose calibrator. Background radioactivity is subtracted, and percentages are calculated.

The radiochemical impurity present at the origin or at the solvent front depends upon the solvent system and the type of radiopharmaceutical.
For 99mTc-radiopharmaceuticals, in most cases, two solvent systems are used: organic and aqueous solvents. The organic solvent is used to separate the 99mTc-labelled radiopharmaceutical (at the origin) from 99mTcO-4 (at the solvent front), while aqueous solvent (saline) is used to separate it (at the solvent front) from reduced hydrolyzed 99mTcO2 (at origin). The radiochemical purity of the 99mTc-labeled radiopharmaceutical (percentage labeling efficiency) is then determined.

RESULTS & DISCUSSIONS

The results for the radiochemical purity control of DMSA, PYP, MAG-3, DTPA and HMPAO radiopharmaceuticals samples are summarized in Table 2.

Table 2

Results for Radiochemical Purity determination

Radio-Pharmaceuticals	No. of tested	Range (%)	Mean percent ±s	No. of failures
DMSA	28	94.8-99.8	99.12 ± 0.43	1
PYP	25	94.1-99.8	99.23 ± 0.51	2
MAG-3	10	93.9-99.7	99.42 ± 0.63	4
DTPA	20	98.9-99.8	99.32 ± 0.40	0
HMPAO	15	68.9-96.8	89.52 ± 0.43	5

The results taken from all procedures for determination of the radiochemical purity for 5 types of the 99mTc-radiopharmaceuticals shows clearly that 12 did not meet the required quality criteria, which is equivalent to 12.2% of all preparations tested. The reasons for poor radiochemical purity were in most cases not related to poor quality kits or generators, but to laboratory specific conditions and the fact that the chemical reactions behind simple kit procedures are complex, involving stoichiometry, side reactions and possible impurities. In 3 of 12 cases the low radiochemical purity was related to the generator eluate. The others because of the other reasons.

CONCLUSIONS

- Our results show that although 99m-Tc radiopharmaceuticals can generally be regarded as safe, impurities can occur, normally because of laboratory specific circumstances.
- The need for radiopharmaceutical quality control as stressed by other authors is emphasized.
- This issue will be important for some time because most problems occurred in 99m-Tc radiopharmaceuticals mainly due to their low stannous content.
- The all steps of the procedure must be performed correctly.