RADIATION DOSIMETRY IN INFECTION SCINTIGRAPHIC IMAGING

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ABSTRACT

The localization and delineation of sites of focal inflammation are crucial in the management of patients with infectious processes.
Nuclear medicine has multiple roles to play in the assessment of infection and several radiopharmaceuticals are currently employed for the scintigraphic imaging of infection and inflammation and especially the investigation of bone and joint infection can be aided by a number of available radiopharmaceuticals
In this study five radiopharmaceuticals are compared regarding their ability to localize and project an infectious lesion in combination with their dosimetric characteristics. The radiopharmaceuticals under consideration are Ga-67 citrate, Tc99m MDP, Tc99m HIG, Tc99m HMPAO and Tc-99m Anti-Granulocyte Fab' (Sulesomab). All five can be used for the detection of suspected infectious lesions in the lower extremities. The present study tried to deal with the issue from a dosimetric point of view getting the most diagnostic imaging and the least absorbed dose levels. The dosimetric results demonstrate a clear advantage of Tc-99m MDP and Anti-Granulocyte Fab' over the other three radiopharmaceuticals for the image diagnostic quality and the radiation burden to the patient aspects.

We used scintigraphic images data to calculate indices, Infection Projection Ratio (IPR) and we contributed to the conclusion that Tc-99m Anti -Granulocyte Fab' is characterized by high projection ratios and in certain cases it demonstrates the full extent of a lesion clearer than the other scintigraphic agents

INTRODUCTION

Early identification and localization of infectious and inflammatory process are of critical importance in the treatment of patients presenting with suspicion of infection and inflammation. Whilst other radiological techniques are used for the localization of infectious foci, they merely rely on anatomical changes. Therefore, they cannot discriminate active infectious processes from anatomical changes due to cureness or surgery. Additionally, there has to be a reasonable elapse of time before the infection is diagnosed. In contrast, scintigraphic detection of infection and inflammation is a non-invasive method of whole-body scanning based on functional tissue changes.

The scintigraphic detection of infection and inflammation is currently covered by a wide variety of conventional (Ga67, Tc99m MDP or Tc99m-nanocolloid) as well as some more specific (TC99m Human Polyclonal Immunoglobulin, Tc99m (In111-) WBC, Tc99m (In111-) Granulocytes or last years' infection seeking agent, Tc99m -antigranulocyte Fab' fragment. Especially in the case of bone and joint infection, there is a possibility of selection among most of the above referred radiopharmaceuticals for early detection and localization by scintigraphic imaging (1, 2).

In this study we are concerned with five alternative solutions Ga-67 citrate, Tc99m MDP, Tc99m HIG, Tc99m HMPAO and Tc-99m Anti-Granulocyte Fab' (Sulesomab) to present and compare absorbed doses in critical organs and the effective dose equivalent of the total body for each of them as a weight factor to the diagnostic quality of their scintigraphic imaging.

Tc-99m MDP is the commonest radiopharmaceutical used for the detection of bone disease. Phosphate analogues which can be labelled with 99m-Tc are widely used for bone imaging, as they have good localization in bone and rapid blood clearance from the soft tissues.
The radiopharmaceutical used in the bone scans studied in terms of this report, is 99m-Tc-MDP, methylene diphosphonate. When injected intravenously, it flows into plasma, equilibrates with extracellular interstitial fluids and then extracted by the bone mineral matrix, by heterotopic calcification (through adsorption) and by the kidneys (glomerular filtration). The rate of uptake by bone is related to the blood supply, the rate of bone turnover, the quantity of mineralized bone, capillary permeability, local acid-bone balance, the fluid pressure within the bone, vitamins and hormones.Bone scan changes occur whenever there is an increase in blood flow to a lesion or there is increased osteoblastic activity. Unfortunately, it is a non-specific investigation, any lesion in bone, such as fracture, infection, tumour or healing bone, appears as an area of increased activity and in cases of inflammation it may not always show the full extent of the lesion, depending on its causality (3).

Ga-67 citrate is bound to plasma transferrin and it localizes not only in inflammatory processes but also in malignant lesions, therefore being also not specific for diagnosis of infection. Skeletal uptake of Ga-67 citrate is related to both reticuloendothelial activity and bone turnover (4,5,6). Gallium-67-citrate is one of the most useful radiopharmaceuticals to detect tumors, stage extent of the disease, monitor response to treatment and distinguish recurrent disease from post-treatment changes. Gallium-67 is likewise very sensitive to detect and locate infections and inflammatory foci. The Ga-67 transferrin complex is more stable than Ga-67 citrate, and regardless of the citrate concentration, it is transported in vivo to many tissues as Gallium transferrin complex and in tissues where the pH is relatively acidic, gallium dissociation from transferrin increases. The plasma clearance of Ga-67 is slow and biexponential with a half life ($T_{1/2}$)=3 hours. In normal physiology Ga-67 is taken by the liver (5%), spleen (1%), kidneys (2%), bone marrow (5%) and skeleton (13%). It is excreted to the bowel (9%) during the first 24 hours and to the urine (26%) during the first 4 to 6 hours.
Images acquired at 4-6 h are useful to detect gastrointestinal infections, whereas 24 h imaging is used to evaluate chest infections and 24h to 72h certify bone and joint infection sites. SPECT imaging has been proven very helpful in the most accurate localization of abnormal uptake, with the radioactivity required being in the order of 10 mCi.

Radiolabelled human polyclonal IgG accumulates at inflammatory sites by a mechanism probably involving vascular leakage of immunoglobulins into an inflamed area and/or binding to Fc-receptors.
Tc-99m HIG has been found to accumulate in inflammatory lesions to such an extent that a target to background ratio develops, which permits scintigraphic detection of an inflammatory process. However the mechanism underlying this accumulation has not yet been clarified. Possible explanations involve specific binding of human immunoglobulin to Fc receptors on leukocytes and/or to bacteria (7,8).
Dynamic acquisition can be performed immediately after injection to provide information about perfusion in suspected areas. The liver shows a slightly higher uptake of radioactivity than would be expected from the presence in blood only. This uptake does not increase with time and there is no

excretion in the gallbladder. The kidneys and bladder become clearly visible, starting shortly after administration. Approximately 50% of the administered radioactivity is eliminated via the kidneys in the first 24 hours following administration. The spleen can be seen but shows considerably less radioactivity accumulation than liver or kidneys Diagnostic static images are usually obtained after 4-6 hours post injection. Additional 24 hours images can be made, if necessary, in those cases where large vascular structures obscure the inflamed area in the early images, or the outcome of the early scan is inconclusive. Clinical data indicate that Tc99m HIG is sensitive to detect and delineate inflammatory sites in the musculoskeletal system and to predict relapse or resolution of inflammatory processes after antibiotic therapy. Physiological uptakes of the tracer in liver, kidneys and to a smaller extend in spleen and the upper large intestine makes these organs less suitable for imaging with Tc99m- HIG.

A Tc99m-HMPAO (hexamethyl-propylene-amine-oxime) leukocyte is a lipophilic, low-molecular-weight, neutral complex of Tc99m that is passively taken by leukocytes.
Tc99m-HMPAO is labeled in-vitro by Tc99m leucocytes and re-injected for scintigraphy to be carried out to image the sites of localization. It may be used in the detection of sites of focal infection, in the investigation of known origin and the evaluation of inflammatory conditions not associated with infection such as inflammatory bowel disease.
Technetium-99m-labeled leucocytes distribute between the pools of the liver (within 5 minutes) and spleen (within about 40 minutes), and the circulating pool, (the latter represents approximately 50% of the leukocyte pool). Approximately 37% of the cell-associated technetium-99m is recoverable from the circulating pool 40 minutes after injection. Tc99m activity is slowly eluted from the cells and is excreted partly by the kidneys and partly via the liver to the gallbladder. This results in increasing amounts of activity being seen in the intestines.
Dynamic imaging may be performed for the first 60 minutes after injection to assess lung clearance and to visualize immediate cell migration. Static imaging at 0.5 - 1.5 hours, 2 - 4 hour, and if necessary, at 18 – 24 hours post injection, should be performed to detect focal accumulation of activity. Care should be taken to distinguish between leucocytes localization and normal biodistribution. During the first hour following injection of Tc99m labelled leucocytes, activity is seen in the lungs, liver, spleen, blood pool and bone marrow as well as in the bladder. The kidneys (parenchyma and/or renal pelvis) and gallbladder may also be visualized. This pattern of activity continues to be seen at 4 hours post-injection except that lung activity is greatly reduced and faint bowel activity may be visible. At 24 hours post-injection some colonic activity may be seen, in addition to the normal areas visualized in earlier scans.
The recommended radiation activity is 200MBq (5mCi) as Tc-99m labeled leucocytes by intravenous injection.

Monoclonal Antibody Preparation and Labeling

Tc99m-Sulesomab, that is, Tc99m-labeled Fab' fragment of IMMU-MN3, is an immunoglobulin GI murine monoclonal antibody produced from a hybridoma developed by fusion of murine myeloma cells with spleen lymphocytes obtained from a mouse immunized with carcinoembryonic antigen. The antibody reacts strongly with nonspecific cross-reacting antigen present on human granulocytes.
The Fab' fragment is provided in a ready to label lyophilized kit from Immunomedics, (Leukoscan). Labeling was accomplished by adding approximately 1000 to 1500 MBq of Tc99m-pertechnetate in saline directly into the vial containing 1.25 mg of the monoclonal antibody Fab' fragment.
The injected material contains 0.25 mg protein labeled with 555-925 MBq (15 to 25 mci) of Tc99m. It is prepared using a 5minute, 1 step procedure with a labeling efficiency greater than 99%. Tc99m LeukoScan has a biologic half-life of 10.5 hours. The kidneys are the primary target organs. LeukoScan does not significantly change granulocyte blood concentration in vivo, nor does it cause in vitro activation of granulocytes or inhibit their physiologic functions. The labeled antibody is injected intravenously over 30 seconds.

DOSIMETRIC ASPECTS

Basic schema for internal dosimetry calculations

Internal absorbed dose estimates are essential for the implementation of ALARA principle in routine clinical practice and for the evaluation of radiation burden or risk associated with radionuclide administration.

The MIRD schema, proposed by the Medical Internal Radiation Dose (MIRD) Committee, is a widely accepted complete system of absorbed dose calculations in the scale of human organs (i.e. greater than a centimeter). The MIRD schema attempts to calculate the mean absorbed dose, assuming an average tissue deposition of energy and a uniform distribution of the radiopharmaceutical.
The dose is calculated for the target region (T), by summing up the contribution of each source region (S) to the target and the contribution of the target region itself. A source region is any region containing activity greater than the average concentration of activity in the total body. It is assumed that non - penetrating radiation (beta particles, Auger electrons, internal conversion electrons and photons below 13 keV) is absorbed only if it is emitted within the target region.
On the other hand, penetrating radiation emitted by all source regions, including radiation emitted by the target region itself, contributes to the absorbed dose to the target region. The mean absorbed dose can be roughly estimated due to major limitations in absorbed dose calculations, resulting from the inherent difficulty in measuring radioactivity inside the body, as well as from the use of standard generalized biokinetic models which vary considerably in each patient.
In order to calculate the absorbed dose to the target organ, it is necessary to calculate the cumulative source activity A_s in the source organ, which is the sum of the all the radioactive decays over the time interval of interest, using the following equation:

$$A_s = A_0 \times \tau \qquad (1)$$

where
A_0: administered activity
τ: residence time

Residence time is the effective time that the administered radioactivity "remains" to the source organ and is calculated from the equation
where

$$\tau = \frac{1}{\ln 2} \times T_{eff} = 1{,}443 \times T_{eff} \qquad (2)$$

T_{eff}: radiopharmaceutical effective half – life in the source organ.

According to MIRD schema, the mean absorbed dose to a target organ from the source organ is calculated using the following equation:

$$D_{target} = A_s \times S_{(target \leftarrow source)} \qquad (3)$$

where $S_{(target \leftarrow source)}$: is a factor which takes into account all the time –independent parameters and is designated as the mean dose per unit of cumulative activity. S –factors have been calculated for a variety of sources and target distributions in several anthropomorphic geometrical phantoms. S –factors are tabulated for most of the nuclides used for medical purposes. Their values depend on the nuclide in use, the shape and size of the source and target organs, the distance between them, as well as on the mass of the source organ.

Patient specific individualized dosimetric data

The need for precise radiation dosimetry is critical when we are dealing with patients, who are referred for infection scanning. The theoretical formalism, with the accepted assumptions, leads in a certain amount of unaccuracy, which is in general considered acceptable. However, as theoretical calculations do not usually account for pathologic concentration, the need for greater accuracy in dose estimates emerges.
Using the standard MIRD formalism for macroscopic dosimetry the marked non-uniform distribution of radionuclide in both inflammation site and normal tissue has resulted in limited correlation between computed absorbed dose and biological response in clinical trials. Several efforts are underway aimed at improving this dose-response correlation which include individualized patient specific dosimetry and selected biological parameters
Single photon emission tomography (SPECT) provides an extra tool for quantitative evaluation of organ uptake and therefore for more accurate dosimetric calculations. The principal advantage of the quantitative imaging using SPECT is the elimination of superimposing structures that characterizes planar imaging. The problems involved in a quantitative approach have to do with scattering, attenuation and the noise in the reconstructed image.

MATERIALS - METHOD

All five of the above mentioned radiopharmaceuticals are recommended for the detection of infection of the musculoskeletal system. All of them have the renal system as their main excretion way, while Ga-67 citrate and Tc99m WBC are also excreted by the hepatobiliary system. Ga-67 citrate concentrates physiologically in the liver; less in the spleen and in skeleton parts and owing to its excretion characteristics it exhibits a high activity uptake in the G.I. tract. Tc-99m HIG is characterized by normal uptake in the liver, kidneys, spleen and the upper large intestine. Tc-99m MDP concentrates in the skeleton and in the kidneys. Tc-99m Anti-Granulocyte Fab' normally concentrates to the liver, spleen, kidneys, and bladder.
Ten-minute planar (and occasionally single photon emission tomography) scintiphotos were taken at 3 hours, 6 to 8 hours and 24 hours post injection, using standard nuclear medicine imaging procedures, for the radiopharmaceuticals: Tc99m MDP, Tc99m HIG and Tc99m Sulesomab. The scans were obtained on an El Scint SPX SPECT gamma camera system; planar views of the region of interest were obtained and the suspected focus is defined.
Single photon emission tomography images of the suspected for inflammation focus area were performed 3 to 4 hours after injection. Single photon emission tomographic imaging was performed using a 128 x 128 matrix with 32 projections acquiring approximately 200,000 counts per projection.
Ga67-citrate planar images were recorded on an average of 8, 24, 48 and 72 hrs post injection. SPECT Ga67- citrate imaging of the infection focus was completed at 48h scanning time.

The distribution and dosimetry is evaluated using the information from simultaneous anterior and posterior whole body scintigrams, as well as from tomographic views, recorded. The geometric means of conjugate views and region-of-interest analysis are used to determine target organ and pathologic area uptakes, mean residence times and absorbed radiation dose estimates induced by the tracer.
For all radiopharmaceutical used, the effective half-life of the radiopharmaceutical, both to inflammated focus and critical organs, was calculated from the corresponding acquired attenuation curves that where produced by using data of the whole series of planar views. Based on MIRD schema, the residence time of the radiopharmaceutical to the source organ (equation 1), as well as its cumulative activity (equations 2) were calculated for each administration of the corresponding cases. Finally, using equation 3, the absorbed dose to the inflammation site and most critical organs were calculated for each case.

Based on the above, the organs of interest from a dosimetric point of view are the liver, spleen, kidneys, intestine and bone. From a physical point of view Ga-67 citrate presents the disadvantage of a longer

half-life, therefore a higher radiation burden. We calculated dosimetric data on Ga-67 citrate, Tc-99m HIG, Tc-99m MDP and Tc99m Sulesomab by MIRD values and MIRDOSE3 program, compared them with the published literature. Tc99m HMPAO leucocytes radiation absorbed doses were calculated only theoretically by MIRD standard man data because of enough scintigraphic data lack. (10).

The practical dosimetric and diagnostic comparison was based on six patients that were referred for a radionuclide scan on the suspicion of an infectious lesion in the extremities. The patients were scanned with a combination of the above radiopharmaceuticals**.** Table I includes data on the exact infection site, the radiopharmaceuticals used, the injected dose and the post injection time intervals for the acquisition of the images. When two or more radiopharmaceuticals were used for the same case there was one week period left between two successive scans and Ga-67 citrate was the last scan to be performed.

TABLE A
Clinical and diagnostic scintigraphic imaging data

SUBJECTS	Suspected Infection site	Ga-67 citrate	Tc99m-HIG	Tc99m-MDP	Tc99m Sulesomab
• 1	Right thigh	5 mCi	20 mCi	25 mCi	2O mCi
		24-48-72 hrs p.i	6-24 hrs p.i.	3-24 hrs p.i.	3-24 hrs p.i.
• 2	Right hip	4 mCi		26 mCi	19mCi
		24-48-72 hrs p.i		3-24 hrs p.i	3-24 hrs p.i.
• 3	Left knee		18 mCi	27 mCi	19 mCi
			6-24 hrs p.i.	3-24 hrs p.i.	4-18 hrs p.i.
• 4	Left tibia			25 mCi	15 mCi
				3-24 hrs p.i.	3-24 hrs p.i
• 5	Right thigh	4 mCi	20 mCi		15 mCi
		24-48-72 hrs p.i	6-24 hrs p.i.		3-6-24 hrs p.i
• 6	Left knee			24 mCi	16 mCi
				3-24 hrs p.i.	3-6-24 hrs p.i

Three regions of interest (ROI) were drawn on each one of the images of the pathologic area. One that encompassed the whole pathologic area, a ROI on a soft tissue area to obtain the background counts as well as a ROI on a neighboring to the lesion area that presented a normal uptake for the evaluation of the projection of the infectious area. From the measured counts an index representing the projection of the lesion for each radiopharmaceutical was calculated. The mean projection ratio for each radiopharmaceutical is presented in Table V

Theoretical dosimetric data concerning the organs that exhibit a normal uptake of the radiopharmaceuticals have been presented in the following tables I, II, III. Estimated absorbed doses, calculated according to MIRD method for the mean amount of radioactivity injected per radiopharmaceutical assumes a bladder voiding at 2 hours intervals, post injection

From radiation protection point of view (to minimize the radiation dose to the bladder) as well as for dosimetric calculations most accuracy, patients should be encouraged to drink liberally after the examination and void as often as possible during the first 24 hours after examination, no means which of the radiopharmaceuticals was administered.

TABLE I

Tc99m Human Immuno Globulin (HIG)	
Absorbed Dose	*mGy/740 MBq*
Organs	
Bladder wall	5.18
Lung	2.96
Kidneys	39.22
Ovaries	17.02
Upper large intestine	8.14
Lower large intestine	32.56
Red bone marrow 5.92	
Testes	10.36
Small intestine	7.40
Spleen	5.92
Liver	7.40
Total body remainder	2.96
***Effective dose equivalent**	**3.11 mSv/ 740MBq**

TABLE II

Tc99m HMPAO leucocytes *Absorbed Dose in mGy/200MBq*	
Bladder wall	0.52
Heart	1.80
Stomach wall	1.6
Small intestine	0.98
ULI wall	0.98
LLI wall	0.78
Kidneys	1.98
Liver	4.0
Ovaries	0.84
Uterus	0.76
Pancreas	2.8
Red bone marrow	4.4
Bone surfaces	2.6
Breast	0.62
Testes	0.34
Spleen	30.00
Thyroid	0.48
Adrenals	1.78
Total body remainder	0.68
***Effective Dose Equivalent**	**2.2mSv/200MBq**

TABLE III

Tc99m anti-granulozyte Fab' (Leukoscan)	
Mean Absorbed Dose	mGy/740MBq
Organs	
Bladder wall	15.91
Kidneys	33.23
Spleen	11.62
Myocardium surface	8.73
Lungs	7.40
Liver	6.66
Bone surface	5.92
Adrenals	5.33
Red marrow	5.25
Pancreas	5.03
Thyroid gland	4.96
Gallbladder wall	4.59
Uterus	4.37
Ovaries	3.63
Small Intestine	3.55
Stomach	3.55
Upper large intestine wall	3.48
Lower large intestine wall	3.48
Thymus	3.33
Muscle	2.59
Testes	2.22
Breast	2.07
Brain	1.78
Skin	1.55
Total Body	2.90
*** mSv/740 MBq**	
EDE (Effective Dose Equivalent)	**6.2**
ED (Effective Dose)	**4.9**

TABLE IV
Absorbed dose data calculated by scintigraphic data

	Absorbed dose mGy/5mCi	*Absorbed dose mGy/20mCi*	*Absorbed dose mGy/25mCi*	*Absorbed dose* mGy/20mCi
Radiopharmaceutical	Ga-67 citrate	Tc99m-HIG	Tc99m-MDP	Tc99m- Sulesomab
Target organs				
Liver	17,8	7,0	1,5	6,8
Spleen	20,7	5,6	1,6	16,0
Kidneys	16,3	37,3	8,4	30,1
Intestine	18,1	45,7	9,1	3,2
Skeleton	17,8	5,6	72,6	5.5

RESULTS

The results exhibit a difference in absorbed dose and mean residence time in normal and pathologic subjects, as well as differences corresponding to the individual body geometry.

The calculated indices, according to the radiopharmaceutical used are presented in Table V. The indices represent the ratio of the counts in the pathologic area to the counts of a normal area adjacent to the infected tissue. Both numbers have subtracted the background counts, obtained from a normal soft tissue area.

TABLE V

Mean Scintigraphic projection ratios of Infection focus

Radiopharmaceutical	Ga 67 Citrate	Tc99mHIG	Tc99mMDP	Tc99m Sulesomab
I P R *[**I**nfection **P**rojection **R**atio]*	**1.38**	**1.4**	**4.7**	**4.9**

DISCUSSION

Theoretical dosimetric data provided by the use of internal dosimetry models are in general a good approximation of the actual figures. However, absorption and retention of a radiopharmaceutical depend highly on the presence of areas of pathologic uptake . The application of practical dosimetric approaches centered to the individual patient can lead to useful conclusions concerning dose modifications, optimal post injection time for image acquisition as well as comparative effectiveness of different radionuclide agents that present similar diagnostic applications.
The results presented above indicate a difference from the theoretical approach in pathologic cases. SPECT data have a slight difference from the planar data calculated. It is believed that the quantitative analysis of SPECT images do provide more precise results. As SPECT is a more accurate technique for the localization of pathologic uptake, it could at the same time be used for quantitative analysis not only for dosimetric needs but also for the differentation of healthy and infectional tissue or for the extraction of various functional parameters.

Dosimetric calculations based on the individual patient's diagnostic images can provide us with more reliable data that account for the pathology of the particular patient and the body characteristics.

From a dosimetric point of view, radiopharmaceuticals labeled with Tc-99m have a clear advantage over the Ga-67-citrate. Tc99m is characterized by a shorter physical half-life than Ga-67 and by dosimetrically better energy characteristics. The theoretical data on absorbed dose by selected target organs manifest the fact mentioned above. It is clear from Table IV that both Tc99m Leukoscan and Tc99m MDP are the radiopharmaceuticals which lead to the less absorbed dose.

As far as the projection of the infectious lesion is concerned Tc-99m MDP and Tc99m Leukoscan present high lesion to normal area ratio. In three cases Tc-99m MDP was characterized by a slightly higher ratio and this fact is expected as the patients included in the study suffered from infections in the musculoskeletal system. But Tc-99m Anti-Granulocyte Fab' (Leukoscan) revealed that the infectious lesion had a greater extent than MDP showed. Ga-67 citrate and Tc-99mm HIG demonstrate a relatively low pathologic to normal area ratio as well as higher background counts, an expected fact owing to their uptake mechanism and for Tc-99m HIG to its prolonged presence in the blood pool. Another disadvantage of Ga-67 is the long time post injection required for the acquisition of the images.

Anti-granulocyte Fab' antibodies are being evaluated regarding their ability to localize and rate the full extent of infections and inflammations (11, 12). The present tried to deal with the issue from a dosimetric as well as a diagnostic point of view on lesions concerning the lower extremities. The dosimetric results demonstrate a clear advantage of Tc-99m MDP and Anti-Granulocyte Fab' over the other two radiopharmaceuticals. The calculated indices IPR in combination with the acquired contribute to the conclusion that Tc-99m Sulesomab might not be characterized by higher projection ratios than MDP but it demonstrates the full extent of a lesion clearer than MDP.

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