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A COMPARISON OF SEVERAL POTENTIAL MYOCARDIAL IMAGING AGENTS

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ABSTRACT

Although myocardial imaging is currently dominated by Tl-201, several alternative agents with improved physiologic or radionuclidic properties have been proposed. Based on human and animal studies in the literature, the metabolism of several of these compounds was studied for the purpose of generating radiation dose estimates. Dose estimates are listed for several I-123 labeled free fatty acids, an I-123 labeled phosphonium compound, Rb-82, Cu-64, F-18 FDG (all compounds which are taken up by the normal myocardium), and for Tc-99m pyrophosphate (PYP) (which localizes in myocardial infarcts). Dose estimates could not be generated for C-11 palmitate, but this compound was included in a comparison of myocardial retention times. For the I-123 labeled compounds, I-124 was included as a contaminant in generating the dose estimates. Radiation doses were lowest for Rb-82 (gonads 0.3-0.5 μGy/MBq, heart wall 15 μGy/MBq). Doses for the I-123 labeled fatty acids were similar to one another, with IPPA being the lowest (gonads 20 μGy/MBq, heart wall 15 μGy/MBq). Doses for Tc-99m PYP were also low (gonads 4-7 μGy/MBq, heart wall 4 μGy/MBq, skeleton 15 μGy/MBq). The desirability of these compounds is discussed briefly, considering half life, imaging mode and energy, and dosimetry, including a comparison of the effective whole body dose equivalents.

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INTRODUCTION

The study of myocardial perfusion is currently dominated by Tl-201. It is used to produce both planar and tomographic reconstructions of images of the myocardium. Its emission energies are not ideal (low abundance 137 and 165 gammas and 70-80 keV X-rays from Hg-201), but its biological properties (3-4% uptake in the myocardium with an initial 4.4 hour biological half time (1,2)) make it a very useful agent. Thallium may be extracted by the myocardium by activation of the sodium potassium ATPase system (3). Several other radioactive agents have been developed for myocardial imaging, but have not been as useful, for one reason or another. K-43 is rapidly cleared by the blood and efficiently extracted by the myocardium, however, it is rapidly cleared from the myocardium, precluding imaging more than one hour post injection. Cs-129 is another potassium analog which has a slightly longer radioactive half life, but it is not efficiently extracted by the myocardium. N-13 ammonia ($^{13}NH_3$) has a very short radioactive half life, and has a complex metabolic behavior which makes it difficult to use for quantitative studies.

In the past few years, a variety of myocardial imaging agents have emerged which employ radioisotopes with more favorable imaging characteristics attached to radiopharmaceuticals which take advantage of other cellular uptake mechanisms. Several of these utilize some of the cell energy cycles to enter the myocardial cells. For example, F-18 fluorodeoxyglucose is a glucose analog which enters the cell's normal glucose cycle, but does not complete the glycolytic pathway. Other radionuclides (mostly I-123) have been attached to modified fatty acids, which are taken up by the cells through their fatty acid metabolic pathways and retained. Some, being monovalent cations, are believed to employ some of the same metabolic pathways as thallium. Still other unique radiopharmaceuticals have been observed to be taken up in the normal or infarcted myocardium. Most of these new products employ a radionuclide which has more favorable imaging characteristics than Tl-201. If they are to find widespread application, they must as well be easy to obtain and store, and must show at least similar, or more desirable, imaging and radiation dose characteristics. In this paper, the radiation doses received by patients from these compounds will be discussed and compared. Some discussion will also be developed which compares the availability and expected biological properties with those of Tl-201.

Agents Which Localize in the Healthy Myocardium

1) F-18 Fluorodeoxyglucose (FDG)

Radiation dose estimates for ^{18}FDG may be calculated using a combination of the dog data of Gallagher et al. (4) and the human data of Jones et al. (5). Jones et al. provided data for uptake and retention of ^{18}FDG in the urinary bladder, brain, and remander of the body while Gallagher et al. provided uptake values for lungs, heart, brain, ovaries, spleen, liver, pancreas, and kidneys, and collected urine samples at 60 and 135 minutes. Jones et al. monitored the activity in the urinary bladder with a collimated probe over the first 120 minutes

post injection and estimated cumulated activity by integrating under these curves. These values, however, will only be applicable for the experimental schema used by the investigators (which involved voiding of the bladder and drinking two glasses of water before injection, no voiding for two hours, and voiding at the end of two hours), therefore the biological half time for elimination through the urine (from the data of Gallagher et al.) was used to estimate bladder dose in the two general cases of regular 2.0 hour and 4.8 hour voiding after injection. The standard MIRD formulas were used, applying the remainder of the body correction proposed by Cloutier et al. (6).
The dose estimates in Table 1 use the values for brain uptake from the data of Jones et al. and the uptake values for the other organs and the remainder of the body using the data of Gallagher et al., assuming that the effective half time in all of these organs is equal to the physical half time of ^{18}F. Myocardial uptake predicted by the data of Gallagher et al. is 3.5%, and the effective half time would be 1.8 hours.

2) Radiolabeled Free Fatty Acids

A. I-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP)

A radiolabeled fatty acid will be very useful as a myocardial imaging agent, provided that the compound is rapidly extracted by the myocardium and retained for a significant period of time, i.e. at least long enough so that the compound is removed from the blood enough that interference from activity in the heart chambers is minimized. The fatty acid molecule is degraded in the mitochondria of the cells by progressive release of 2-carbon segments in the form of acetyl coenzyme A (acetyl Co-A); this process is referred to as β-oxidation. The acetyl Co-A molecules are ultimately broken down in the citric acid cycle into carbon dioxide and hydrogen atoms (7), which will not be selectively retained by the myocardial cells. Researchers at Oak Ridge National Laboratory (ORNL) have developed fatty acid molecules which are modified enough that they do not participate in the fatty acid metabolism, but not so drastically that the myocardial cells will not extract them efficiently. Early efforts involved tellurium-123, which had an attractive gamma energy for imaging, but had a long physical half life, a high production cost, and a low specific activity (8). Attention was then given to the preparation of iodine-123 labeled fatty acids which had been modified with nonradioactive tellurium. The difficulty of the preparation of these compounds then led to the investigation of the use of radioiodinated iodophenyl- and iodovinyl-substituted fatty acids which employed methyl-branching as the structural abnormality which would inhibit β-oxidation, and thus "trap" the fatty acid molecule in the myocardium.

Detailed distribution studies were performed at ORNL in female Fisher rats for one such compound, I-123 labeled BMIPP. The I-125 labeled compound was administered to the rats, which were sacrificed at various time intervals, for times up to 3 days. Excretion data were also obtained over this time period. Organ retention data were extrapolated from % kg injected activity per gram in the rat to % injected activity per organ in the human, and least squares fit to one or two compartment uptake and elimination models. Whole body retention, from the % of

injected activity in the excreta, was extrapolated directly to humans from the animal values. Radiation dose estimates were calculated based on the residence times for I-123 using the standard MIRD technique and the remainder of the body correction. For this compound, and all of the I-123 labeled compounds, a contaminant level of 5% I-124 was assumed so that the dose estimates would be more representative of what would be expected in practice. The I-124 contribution to the total dose to any organ for these compounds is typically half or more. Dose estimates are listed in Table 2. Myocardial uptake was 2.9%; elimination was biphasic, with 86% having an effective half time of 2.8 hours, and 14% having an effective half time of 8.0 hours.

B. I-123 15-(p-iodophenyl)-3,3-dimethylpentadecanoic acid (DMIPP)

This agent, prepared similarly to BMIPP, was also studied by ORNL researchers in female Fisher rats. The study techniques and data reduction techniques were identical to those for BMIPP, desribed above. Radiation dose estimates are listed in Table 3. Myocardial uptake was 2.5% and retention was biphasic again, with 91.6% having an effective half time of 3.0 hours and 8.4% having an effective half time of 9.8 hours.

C. I-123 Phenylpentadecanoic Acid

I-123 Phenylpentadecanoic acid (IPPA) is another fatty acid which has been investigated as a myocardial imaging agent. Kulkarni et al. (9) published detailed distribution studies performed in Sprague-Dawley rats. Their values of % injected activity per gram of tissue were converted to % kg injected activity per gram, using an average body weight of 0.19 kg. These results were then analyzed using the same methods as for BMIPP and DMIPP. Radiation dose estimates based on these assumptions are listed in Table 4. Predicted myocardial uptake was 3.0%, with 89% having an effective half time of 0.79 hours and the remaining 11% having an effective half time of 9.2 hours. Studies done in human subjects (10-12) also showed a biexponential clearance of this compound from normally perfused myocardium. Although the myocardial uptake was not quantitated, the half lives were given, without the associated fractions associated with each half life. The values were between 10 and 15 minutes (0.17-0.25 hours) for the short lived fraction, and around 80 minutes (1.3 hours) for the long lived fraction.

D. C-11 Palmitate

Carbon-11 labeled palmitic acid is another free fatty acid which has been studied in humans and animals as a potential myocardial imaging agent. It is a short lived (20.4 min) positron emitter. Although many papers discussed the metabolism of this agent in the myocardium, no detailed distribution studies were found which could be used to generate a comprehensive set of radiation dose estimates. Reske et al. (13) found that the biological behavior of C-11 palmitate was similar to that of I-123 IPPA, but that levels in tissues were generally lower, with the exception of the liver. Most researchers (14-18) found a biexponential elimination curve for the myocardium. For the studies carried out in dogs, the short half time was between 3 and 5 minutes, and the long half

time was between 150 and 360 minutes. In the human studies, the short half time was between 6 and 14 minutes, and the long half time was 157 minutes (only reported for one study (14)).

3) I-123 (E-1-Iodo-1-Penten-5-yl) Triphenylphosphonium Iodide

Phosphonium cations labeled with I-123 have been suggested as myocardial perfusion agents, as these cations penetrate the hydrophobic core of the myocardial cell membrane. Detailed distribution studies were performed in female Fischer rats at ORNL, where the compound was developed. Animals were sacrificed at various times up to three days, and urine and feces samples were collected each day. Data reduction techniques were identical to those used for I-123 BMIPP and DMIPP. Radiation dose estimates are listed in Table 5. The resulting curve for the heart predicted a myocardial uptake of 4.5% of the injected activity, with an effective half time of 10.5 hours.

4) Rubidium-82

Rubidium-82 is thought to be a potassium analog. This radionuclide is a short lived (76 seconds) positron emitter which can be obtained from a Sr-82/Rb-82 generator system (parent half life 25.6 days). The Rb-82 is rapidly extracted by the myocardium; the short half life permits closely spaced repeat studies. Kearfott (19) published detailed distribution studies for Rb-86 in Sprague-Dawley rats. Ryan et al. (20) collected distribution data in two adult men for Rb-82. Radiation dose estimates in Table 6 use the data of Ryan et al. where possible and fill in the other organ radiation doses from the data of Kearfott. The dose estimates based on extrapolation of the rat data to Rb-82 in humans agreed fairly well with those based on the human data. Data obtained from one generator system suggested contamination levels of 2×10^{-5} and 2×10^{-4} for Sr-82 and Sr-85, resepectively. The dose estimates in Table 6 include radiation doses from these contaminants, with the following assumptions:

1) 50% of the strontium is taken up by bone and retained with an infinite biological half time; the activity is assumed to be uniformly distributed throughout the bone volume (21).
2) 0.5% of the strontium is taken up in the testes and retained with a 1.5 day biological half time.
3) The remaining 49.5% is uniformly distributed in the remainder of the body and retained with a biological half time of 1.5 days.

Rb-82 produced in the bone by decay of Sr-82 is assumed to stay in the bone, while Rb-82 produced in the remainder of the body is considered free, and treated like the injected Rb-82. Neither Kearfott nor Ryan et al. gave the uptake fractions and effective half times for Rb-82 in the myocardium; they only listed the cumulated activities. The uptake fraction may be inferred from the cumulated activity values because the effective half time is probably equal to the physical half life. Kearfott's value (rats) for the heart wall was 1.4 μCi-hr/mCi, while that of Ryan et al. (humans) was 4.4 μCi-hr/mCi. From this, the uptake

fraction is either 4.6% or 14.4%, respectively. While the former value is closer to those of the other heart agents studied, the latter value is probably to be preferred, because it came from human subjects. The effective half time would then be 1.27 minutes, or 0.0212 hours.

5) Copper-64

Copper-64 is a relatively long-lived (12.7 hours) positron emitter. Similarities between the effects produced in animal tissues due to copper deficiencies and those in humans due to heart disease have caused some to speculate that copper metabolism is important in the formation of ischemic heart disease (22-26). Distribution studies were performed in rats at the Medical and Health Sciences Division (MHSD) of Oak Ridge Associated Universities (ORAU). Cu-64 levels in the liver, spleen, kidneys, lungs, muscle, bone, and marrow were determined at 0.5, 1, 2, 4, 6, 12, 24, and 26 hours post injection. Residence times were determined by least squares fitting of the % injected activity per organ values at these times (extrapolated from the % kg injected activity per gram in the rat) to one compartment exponential elimination curves. Radiation dose estimates were calculated as in the above cases. The estimates are listed in Table 7. Activity in the heart was estimated for only two time points in these distribution studies; the maximum uptake fraction, occurring at 26 hours, was 0.43%. The effective half times in all of the other organs were very long (8.7-12.7 hours), possibly indicating that myocardial retention would also be long.

6) Tc-99m Labeled Cations

Because many compounds accumulate in the myocardium which are not clearly potassium analogs, but simply are monovalent compounds at physiological pH, several researchers have concentrated on the development of monovalent cations labeled with Tc-99m (27). The availability and excellent imaging characteristics of this radioisotope make it attractive for any nuclear medicine procedure, and many procedures are currently done with Tc-99m labeled compounds.

Early efforts to produce Tc-99m labeled cations resulted in the development of two technetium (III) complexes, tr-[Tc-99m(DIARS)$_2$X$_2$], (where DIARS represents the o-phenylene-bis(dimethylarsine) lignad and X is a chloride or bromide) and tr-[Tc-99m(DMPE)$_2$Cl$_2$] (where DMPE represents the 1,2-bis(dimethylphosphino)ethane ligand). Although these agents showed promising distributions in dogs and rats, in humans the hepatic uptake was very high, and interfered with the myocardial images. Work with technetium (I) complexes resulted in the development of [Tc-99m(DMPE)$_3$], [Tc-99m(TMP)$_6$] (where TMP represents trimethylphosphite), and [Tc-99m(POM-POM)$_3$] (where POM-POM represents 1,2-bis(dimethoxyphosphino)ethane), which again showed promising results in several animal species, but which cleared very slowly from the human bloodstream. Another such compound, [Tc-99m(TBIN)$_6$] (where TBIN represents t-butylisonitrile), exhibited early lung uptake, with late (approximately one hour p.i.) clearance to the liver and myocardium, providing the best, although still difficult to interpret, myocardial images from the Tc-99m cationic species. The hypothesis that

the Tc-99m labeled species are being reduced in vivo to a neutral technetium (II) species which may precipitate in colloidal form, thus explaining the liver uptake, have led some to develop technetium (III) complexes with redox potentials which will inhibit in vivo reduction. Results of these efforts are still forthcoming.

In summary, although much work has been done, no agent has been produced which can be used to routinely image the myocardium. Distribution data are not available for any of these experimental agents which would allow calculation of even preliminary dose estimates, so these agents can not be considered in the comparison developed in this paper.

Agents Which Localize in the Infarcted Myocardium

1) Tc-99m Pyrophosphate

Although principally used as a bone imaging agent, Tc-99m pyrophosphate is taken up in the infarcted myocardium (28, e.g.). Radiation dose estimates for Tc-99m pyrophosphate in Table 8 are based on the distribution and retention data of Subramanian et al. (29) and on the data of Bonte et al. (28) for the dog myocardium. For the myocardium, an uptake fraction of 1.27×10^{-3} and an effective half time of 6.02 hours were assumed.

2) Other compounds

Evidence exists (30,31) that enhaced F-18 FDG uptake may occur in areas of ischemic but viable myocadium. Radiation dose estimates for F-18 FDG are listed in Table 1. There has also been limited evidence (32) that In-111 and Tc-99m labeled antimyosin (Fab fragments of antibodies directed against human cardiac myosin) will also selectively locate in infarcted myocardial tissue. This raises the possibility of using labeled antibodies for myocardial infarct imaging, although it is too early for enough data to be available to calculate the radiation dose estimates.

TABLE 1

RADIATION DOSE ESTIMATES FOR F-18 FDG

Organ	Estimated Radiation Dose 2.0 hour** rad/mCi	2.0 hour** mGy/MBq	4.8 hour** rad/mCi	4.8 hour** mGy/MBq
Bladder	0.86	0.23	1.7	0.46
Brain	0.064	0.017	0.064	0.017
Heart Wall	0.23	0.061	0.23	0.061
Kidneys	0.076	0.020	0.077	0.021
Liver	0.062	0.017	0.064	0.017
Lungs	0.067	0.018	0.068	0.018
Ovaries	0.062	0.017	0.082	0.022
Pancreas	0.094	0.025	0.095	0.026
Red Marrow	0.054	0.014	0.058	0.016
Spleen	0.14	0.039	0.14	0.039
Testes	0.068	0.018	0.084	0.023
Total Body	0.054	0.015	0.060	0.016

** Bladder voiding interval

TABLE 2

RADIATION DOSE ESTIMATES* FOR I-123 BMIPP

Organ	Estimated Radiation Dose 2.0 hour** rad/mCi	mGy/MBq	4.8 hour** rad/mCi	mGy/MBq
Bladder	0.19	0.050	0.38	0.10
Stomach	0.050	0.014	0.050	0.014
Small Intestine	0.19	0.052	0.19	0.052
Upper Large Intestine	0.42	0.11	0.42	0.11
Lower Large Intestine	0.61	0.16	0.61	0.16
Heart Wall	0.094	0.025	0.094	0.025
Kidneys	0.069	0.019	0.069	0.019
Liver	0.076	0.021	0.076	0.021
Lungs	0.058	0.016	0.058	0.016
Ovaries	0.12	0.033	0.13	0.035
Red Marrow	0.068	0.018	0.069	0.019
Testes	0.045	0.012	0.049	0.013
Thyroid	0.28	0.075	0.28	0.075
Total Body	0.053	0.014	0.055	0.015

* 5% I-124 assumed. 0.48% free iodide assumed; treated as in MIRD Dose Estimate Report No. 5 (25% uptake).

** Bladder voiding interval.

TABLE 3

RADIATION DOSE ESTIMATES* FOR I-123 DMIPP

Organ	Estimated Radiation Dose 2.0 hour** rad / mCi	mGy / MBq	4.8 hour** rad / mCi	mGy / MBq
Bladder	0.13	0.035	0.16	0.043
Stomach	0.10	0.027	0.10	0.027
Small Intestine	0.72	0.19	0.72	0.19
Upper Large Intestine	1.7	0.46	1.7	0.46
Lower Large Intestines	2.6	0.70	2.6	0.70
Heart Wall	0.083	0.022	0.083	0.022
Kidneys	0.11	0.029	0.11	0.029
Liver	0.19	0.051	0.19	0.051
Lungs	0.056	0.015	0.056	0.015
Ovaries	0.44	0.12	0.44	0.12
Red Marrow	0.11	0.031	0.11	0.031
Spleen	0.068	0.018	0.068	0.018
Testes	0.040	0.011	0.041	0.011
Thyroid	3.4	0.91	3.4	0.91
Total Body	0.085	0.023	0.086	0.023

* 5% I-124 assumed. 6.4% free iodide assumed; treated as in MIRD Dose Estimate Report No. 5 (25% uptake).

** Bladder voiding interval.

TABLE 4

RADIATION DOSE ESTIMATES* FOR I-123 IPPA

Organ	Estimated Radiation Dose 2.0 hour** rad/mCi	mGy/MBq	4.8 hour** rad/mCi	mGy/MBq
Bladder	0.25	0.067	0.57	0.15
Heart Wall	0.067	0.018	0.067	0.018
Kidneys	0.12	0.033	0.12	0.033
Liver	0.12	0.032	0.12	0.032
Lungs	0.11	0.029	0.11	0.029
Ovaries	0.048	0.013	0.054	0.015
Red Marrow	0.048	0.013	0.048	0.013
Spleen	0.060	0.016	0.061	0.016
Testes	0.034	0.0094	0.042	0.011
Total Body	0.040	0.011	0.044	0.012

* 5% I-124 assumed. No free iodide considered.

** Bladder voiding interval.

TABLE 5

RADIATION DOSE ESTIMATES* FOR I-123 (E-1-IODO-1-PENTEN-5-YL) TRIPHENYLPHOSPHONIUM IODIDE

	Estimated Radiation Dose			
	2.0 hour**		4.8 hour**	
	rad	mGy	rad	mGy
Organ	mCi	MBq	mCi	MBq
Bladder	0.15	0.042	0.21	0.057
Stomach	0.13	0.034	0.13	0.034
Small Intestine	0.39	0.10	0.39	0.10
Upper Large Intestine	0.79	0.21	0.79	0.21
Lower Large intestine	1.2	0.32	1.2	0.32
Heart Wall	0.46	0.12	0.46	0.12
Kidneys	0.19	0.051	0.19	0.051
Liver	0.071	0.019	0.071	0.019
Lungs	0.087	0.023	0.087	0.023
Ovaries	0.23	0.061	0.23	0.061
Red Marrow	0.15	0.040	0.15	0.040
Spleen	0.088	0.024	0.088	0.024
Testes	0.10	0.027	0.10	0.027
Thyroid	4.0	1.1	4.0	1.1
Total Body	0.12	0.031	0.12	0.032

* 5% I-124 assumed. 7.1% free iodide assumed; treated as in MIRD Dose Estimate Report No. 5.

** Bladder voiding interval.

TABLE 6

RADIATION DOSE ESTIMATES FOR RB-82

Organ	Estimated Radiation Dose mrad/mCi	μGy/MBq
Adrenals	4.8	1.3
Stomach	3.6	0.97
Small Intestine	5.9	1.6
Upper Large Intestine	3.7	1.0
Lower Large Intestine	3.9	1.1
Heart Wall	57	15
Kidneys	33	8.8
Liver	3.8	1.0
Lungs	7.3	2.0
Ovaries	0.98	0.27
Pancreas	2.9	0.78
Trabecular Bone	5.9	1.6
Cortical Bone	7.0	1.9
Red Marrow	7.2	1.9
Testes	1.9	0.52
Total Body	3.0	0.81

TABLE 7

RADIATION DOSE ESTIMATES FOR CU-64

Organ	Estimated Radiation Dose rad / mCi	mGy / MBq
Heart Wall	0.10	0.028
Kidneys	1.4	0.39
Liver	0.44	0.12
Lungs	0.12	0.033
Muscle	0.047	0.013
Ovaries	0.11	0.030
Skeleton	0.084	0.023
Red Marrow	0.18	0.048
Spleen	0.14	0.037
Testes	0.12	0.032
Total Body	0.098	0.026

TABLE 8

RADIATION DOSE ESTIMATES FOR TC-99M PYROPHOSPHATE

Organ	Estimated Radiation Dose 2.0 hour** rad / mCi	mGy / MBq	4.8 hour** rad / mCi	mGy / MBq
Bladder	0.098	0.026	0.23	0.061
Heart Wall	0.015	0.0041	0.015	0.0041
Kidneys	0.047	0.013	0.047	0.013
Ovaries	0.019	0.0051	0.025	0.0068
Skeleton	0.055	0.015	0.056	0.015
Red Marrow	0.042	0.011	^.044	0.012
Testes	0.013	0.0036	0.017	0.0047
Total Body	0.019	0.0051	0.021	0.0056

** Bladder voiding interval.

DISCUSSION

Three basic parameters may be compared to estimate the desirability of these agents: (1) the availability of the radionuclide, (2) the image quality obtainable with the radiopharmaceutical, and (3) the radiation dose received by the patient from a typical procedure. The first parameter includes the cost and ease of procurement as well as the physical half life. The second parameter considers the photon energy, the effective half life of the radiopharmaceutical at the imaging site, and the type of detector which may be used for imaging.

(1) Availability

In general, a generator based radionuclide will be less expensive and will present fewer logistic problems than either an accelerator produced or reactor produced radionuclide. A product utilizing Tc-99m would probably be the most attractive, due to its low expense, widespread availability, and good imaging energy. To this point, no such product has been demonstrated, although at least two groups (see reference 27) are working on this approach. Infarct imaging with Tc-99m PYP will probably continue, but cannot answer all of the questions involved with evaluation of myocardial perfusion. The Sr-82/Rb-82 generator would make the ultrashort lived Rb-82 widely available in a generator with a long shelf life. The extremely long shelf life of this generator would, however, bring up questions of long term product sterility.

The half lives of the accelerator and reactor produced radionuclides, F-18, I-123, and C-11 are 1.8 hours, 13.2 hours, and 0.34 hours, respectively. Besides the expense, the additional problems associated with the production and transport of these isotopes increases with decreasing radionuclide half life and increasing distance of the nuclear medicine facility from the production facility. This would make I-123 the most attractive isotope for institutions which do not have an in house production facility.

(2) Image Quality

The principle photon energies for Rb-82, Cu-64, F-18 and C-11 are the 0.511 MeV photons, the annihilation radiation from the positron emissions. These radionuclides could be used in PET studies, which can provide excellent anatomical detail. The principle photon energy of I-123 (159 keV) within the optimum range of nuclear medicine cameras, allowing I-123 labeled compounds to be used for planar or tomographic imaging with SPECT. I-123 has two problems associated with its use, both of which are managable. First, free iodine will concentrate in the thyroid, causing unnecessary radiation dose to the patient and possible interferences on images. Secondly, accelerator-produced I-123 usually contains significant levels of I-124 (and possibly other contaminants), which also produce unwanted radiation doses and can cause image degradation. The use of a thyroid blocking agent will reduce the thyroid dose from free iodide, and the choice of a radiopharmaceutical which has been produced with good quality control can minimize the

amount of free iodide and contaminants. Some control of the latter problem can be exerted on site, as Palmer and Rao (33) have shown that a simple laboratory method can be used to quantitate the I-124 level in I-123 samples.

Increasing the fraction of administered activity taken up in the myocardium would offer significant advantages over the relatively low 3-4% value for Tl-201. The effective half time for myocardial retention is also important, because performance of stress/redistribution studies depends on having a significant amount of activity in the myocardium 2-4 hours post injection. Table 9 lists the uptake fractions and effective half lives in the myocardium for the compounds studied. BMIPP and DMIPP have very similar values for these parameters, as would be expected. Each show about 2.5-3.0% uptake, with the majority of the activity having a short (2-3 hour) half time, and the remainder (about 10%) having a longer (8-10 hour) half time. I-123 IPPA had an uptake fraction of about 3%; most of the activity had a relatively short effective half time (0.79 hours), while the remainder (about 12%) had a long effective half time (9.2 hours). F-18 FDG had a slightly higher uptake fraction, but a much shorter effective half time. I-123 triphenylphosphonium iodide had an uptake fraction of 4.5% and an effective half time of over 10 hours. If the data of Ryan et al. are correct, and they showed good agreement between the two subjects, Rb-82 had the highest uptake fraction (14%). The short effective half time allows for the possibility of doing repeat studies over short time periods without interference from earlier studies, or continuous infusion studies, but precludes quantitation of myocardial washout.

(3) Radiation Dose

To properly compare the expected radiation doses from use of these radiopharmaceuticals, some estimate must be made of the amount of activity expected to be used per study. Table 10 shows the radiation dose to the critical organ and the gonads based on an assumed amount of activity per study for each of the compounds studied in this paper for which radiation dose estimates could be obtained. The assumed values for activity per study were taken from various sources, including estimations from researchers who developed some of the compounds and quoted values in journal articles and abstracts. In addition, the committed effective whole body dose equivalent, as defined in ICRP 26 (34), was calculated for each compound, and is also displayed in Table 10. This parameter provides an at-a-glance estimate of the radiation dose from a compound, taking into account the relative risk of irradiation of specific tissues. It is stated in ICRP 26 that "it is not appropriate to apply the quantitative values of the Commission's recommended dose-equivalent limits to medical exposures." This statement does not imply that the use of the effective whole body dose equivalent concept is inappropriate for medical situations, only that the suggested limitations on dose equivalents received by workers should not be imposed on patients, who receive directly the benefit as well as the risk of the procedures.

The highest critical organ doses were seen for I-123 triphenylphosphonium iodide and for I-123 DMIPP, for which thyroid doses were

150-200 mGy per study. This number will be highly dependent on the amount of free iodide and I-124 contaminant in the product. Because these parameters are controllable to some degree, the actual doses seen in practice will probably not be this high. Radiation dose to the LLI and bladder were relatively high for I-123 DMIPP, I-123 triphenylphosphonium iodide, and F-18 FDG.

The results in Table 10 show that the gonadal dose (in this table, the average of testicular and ovarian dose) is lowest for Rb-82 (0.12 mGy). I-123 IPPA is the next highest, with 0.92 mGy. F-18 FDG, I-123 BMIPP, I-123 DMIPP, I-123 triphenylphosphonium iodide, Cu-64, and Tc-99m PYP had similar gonadal estimates, near 5-10 mGy per study. The I-123 DMIPP gonadal dose was about a factor of three higher than BMIPP. This is because ovarian dose is primarily determined by activity in the GI tract for these compounds; excretion data on the two compounds suggested that about 16% of the activity was excreted through the feces for BMIPP, while 74% was excreted through the feces for DMIPP.

The effective whole body dose equivalents were lowest for I-123 IPPA and Rb-82, both under 1 mSv. F-18 FDG, I-123 BMIPP, and Tc-99m PYP all had values between 1 and 10 mSv, with Tl-201 having a value near 10 mSv. I-123 triphenylphosphonium iodide and I-123 DMIPP had the highest effective whole body dose equivalent, at 18 and 24 mSv, respectively.

CONCLUSIONS

Table 11 summarizes the comparisons made above. The compounds were given a rather arbitrary ranking of low to high availability, based on the expense and difficulty anticipated with acquisition of the radionuclide. The biological distribution parameters of uptake fraction and effective half time, as well as the effective whole body dose equivalent, were compared to Tl-201.

F-18 FDG is expected to be difficult to obtain, unless an accelerator is very near to the location where the studies will be performed. The distribution and radiation dose characteristics were either about equal or inferior to those of Tl-201. The free fatty acids labeled with I-123 were all assigned a 'medium' availability. BMIPP and DMIPP had somewhat lower uptake fractions than Tl-201 and similar effective half times in the myocardium for the majority of the activity taken up by the myocardium. In both cases, about 10% of the initial activity in the myocardium had a long (8-10 hours) effective half time. The radiation dose for DMIPP, based on the preliminary animal studies, was higher than that for Tl-201, and that for BMIPP was about the same as for Tl-201. I-123 IPPA has a lower radiation dose than Tl-201, however, the effective half time for the majority of the activity is short. All of the I-123 triphenylphosphonium iodide taken up by the myocardium had a long effective half time; its radiation dose is predicted to be higher than most of the other agents and Tl-201, but follow-up human studies should be performed to see whether or not this result predicted from animal models is valid. Rb-82 is not a candidate for stress/redistribution studies because of its short half life, but based on the other categories, it would appear to be useful for producing resting images. Tc-99m PYP gives different information than

Tl-201, and seems well suited to perform the studies it is designed for. There are not enough data to evaluate C-11 palmitate or Cu-64 against the other agents.

TABLE 9

UPTAKE FRACTIONS AND EFFECTIVE HALF LIVES IN THE MYOCARDIUM OF THE COMPOUNDS STUDIED IN THIS PAPER

COMPOUND	UPTAKE FRACTION	EFFECTIVE HALF TIME
F-18 FDG	0.035	1.8 hours
I-123 BMIPP	0.029	86% 2.8 hours 14% 8.0 hours
I-123 DMIPP	0.025	91.6% 3.0 hours 8.4% 9.8 hours
I-123 IPPA	0.030	89% 0.84 hours 11% 9.2 hours
C-11 Palmitate	No data	0.05-0.08 hour 2.5-6.0 hours
I-123 Triphenyl-phosphonium Iodide	0.045	10.5 hours
Rb-82	0.14*	0.021 hours
Cu-64	0.0043	No data
Tc-99m PYP	0.0013	6.01 hours

* Inferred from cumulated activity results in human subjects (16). Result from animal studies (15) would be 0.046.

TABLE 10

SOME RADIATION DOSE CHARACTERISTICS OF THE COMPOUNDS STUDIED IN THIS PAPER

COMPOUND	ASSUMED AVERAGE ACTIVITY/STUDY (MBq)	ESTIMATED RADIATION DOSE (mGy) CRITICAL ORGAN	GONADS	COMMITTED EFFECTIVE WB DOSE EQUIVALENT (mSv)
^{18}FDG	180	Bladder 83	4.0	8.3
^{123}I BMIPP	180	LLI 29	4.3	7.1
^{123}I DMIPP	180	LLI 130 Thyroid 160	12	24
^{123}IPPA	40	Bladder 4.8	0.82	0.92
^{123}I Triphenyl-phosphonium Iodide	180	LLI 58 Thyroid 200	7.9	18
^{82}Rb	300	Heart Wall 4.5	0.12	0.69
^{64}Cu	260	Kidneys 100	8.1	14
^{99m}Tc PYP	550	Bladder 34 Skeleton 8.2 Red Marrow 6.6	3.2	4.7
^{201}Tl	100	Kidneys 32	14	8.3

TABLE 11

COMPARISON OF THE COMPOUNDS STUDIED IN THIS PAPER
BASED ON AVAILABILITY, DISTRIBUTION, AND RADIATION DOSE

COMPOUND	AVAILABILITY	DISTRIBUTION PARAMETERS RELATIVE TO Tl-201	RADIATION DOSE RELATIVE TO Tl-201
^{18}FDG	Low	~same uptake shorter T_{eff}	~same
^{123}I BMIPP	Medium	lower uptake ~same T_{eff}	~same
^{123}I DMIPP	Medium	lower uptake ~same T_{eff}	higher
^{123}IPPA	Medium	~same uptake shorter T_{eff}	lower
^{11}C Palmitate	Low	uncertain	uncertain
^{123}I Triphenyl-phosphonium Iodide	Medium	~same uptake longer T_{eff}	higher
^{82}Rb	High	higher uptake shorter T_{eff} (T_{eff} too short for washout study)	lower
^{64}Cu	Medium	lower uptake (uptake, T_{eff} uncertain)	higher
^{99m}Tc PYP	High	lower uptake longer T_{eff} (restricted information)	lower

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