Dosimetry, biodistribution, and safety of flurpiridaz F 18 in healthy subjects undergoing rest and exercise or pharmacological stress PET myocardial perfusion imaging

Jamshid Maddahi, MD, FACC, FASNC,[a,b] Frank Bengel, MD,[c,f] Johannes Czernin, MD,[a] Paul Crane, PhD,[d] Magnus Dahlbom, PhD,[a] Heinrich Schelbert, MD, PhD,[a] Richard Sparks, PhD,[e] Michael Phelps, PhD,[a] and Joel Lazewatsky, PhD[d]

[a] Department of Molecular and Medical Pharmacology (Nuclear Medicine), David Geffen School of Medicine at University of California, Los Angeles (UCLA), Los Angeles, CA
[b] Department of Medicine (Cardiology), David Geffen School of Medicine at University of California, Los Angeles (UCLA), Los Angeles, CA
[c] The Johns Hopkins Medical Institutions, Baltimore, Maryland
[d] Lantheus Medical Imaging, Billerica, MA
[e] CDE Dosimetry Services, Knoxville, TN
[f] Present address: Medizinische Hochschule Hannover, Hannover, Germany

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Abstract. **The objectives of this study were to evaluate radiation dosimetry, biodistribution, human safety, and tolerability of ^{18}F-labeled flurpiridaz (Flurpiridaz) in normal subjects undergoing rest and separate-day exercise or adenosine pharmacological stress PET imaging.**

Methods. **12 normal subjects were injected with 58.5 to 121 MBq (1.58 to 3.27 mCi) of Flurpiridaz intravenously at rest on Day 1 and 57 to 171 MBq (1.54 to 4.61 mCi) during stress on Day 2. Sequential whole-body imaging was performed for 5 hours. Blood samples were collected for up to 8 hours.**

Results. **The heart wall received the largest mean absorbed dose with both exercise and adenosine stresses. The mean effective dose was 0.054 rem/mCi (0.015 mSv/MBq) with exercise and 0.069 rem/mCi (0.019 mSv/MBq) with adenosine pharmacological stress. The maximum dose that may be administered without exceeding 1 rem (10 mSv) effective dose was 19 mCi (685 MBq) for exercise and 15 mCi (539 MBq) for adenosine pharmacological stress. There were no drug-related adverse events, and the tracer was well tolerated in all subjects.**

Conclusion. **Based on radiation dosimetry, biodistribution, and safety observations, ^{18}F-labeled flurpiridaz is found suitable for clinical PET myocardial perfusion imaging in conjunction with either exercise or pharmacological stress testing. (J Nucl Cardiol 2019;26:2018–30.)**

Key Words: Flurpiridaz • dosimetry and biodistribution • myocardial perfusion PET imaging • exercise cardiac PET imaging • safety

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Reprint requests: Jamshid Maddahi, MD, FACC, FASNC, Department of Molecular and Medical Pharmacology (Nuclear Medicine), David Geffen School of Medicine at University of California, Los Angeles (UCLA), 100 UCLA Medical Plaza Suite 410, Los Angeles, CA 90095-7064; *jmaddahi@gmail.com*

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Abbreviations	
Flurpiridaz	F-18-labeled flurpiridaz (flurpiridaz F 18)
PET	Positron emission tomography
MBq	Megabecquerel
mCi	Millicurie
rem	Roentgen equivalent man
mSv	Millisievert
MPI	Myocardial perfusion imaging
ECG	Electrocardiogram
EEG	Electroencephalogram
BMI	Body mass index
DE	Dosimetry estimate
ED	Effective dose
%ID	Percent injected dose
ROI	Region of interest
AE	Adverse event
SD	Standard deviation

See related editorial, pp. 2031–2033

INTRODUCTION

Flurpiridaz F 18 (Flurpiridaz), formerly BMS747158, is a novel ^{18}F-labeled PET myocardial perfusion imaging (MPI) tracer that is a structural analog of pyridaben and binds to mitochondrial complex 1 (MC-1) with high affinity[1] (Figure 1). As mitochondria constitute from 20% to 30% of the myocardial intracellular volume, molecules that target mitochondrial proteins are selectively retained in the myocardium with a high density.[2] Preclinical studies showed superior myocardial extraction and prolonged retention of Flurpiridaz compared with SPECT MPI tracers.[1,3–5] Thus, Flurpiridaz has the potential to yield steady-state myocardial imaging with the improved resolution and quantitation afforded by PET. Flurpiridaz also could provide improved clinical utility and ease of use because of the longer half-life of ^{18} F (110 minutes) that makes delivery of unit doses from regional PET pharmacies feasible.

In the first-in-human study of Flurpiridaz, dosimetry, biodistribution, and safety of this tracer were evaluated after a single-dose injection at rest.[6] The organ receiving the largest mean absorbed dose was the kidneys followed by the heart wall. Furthermore, after resting injection of Flurpiridaz, it was found that the heart exhibited high and sustained retention of radioactivity from the earliest images through approximately 5 hours after injection. There were no drug-related adverse events, and the tracer was well tolerated in all subjects.

The objectives of this study were to estimate the radiation dosimetry, biodistribution, safety, and tolerability of Flurpiridaz in healthy subjects undergoing either treadmill exercise or adenosine pharmacological stress in conjunction with 2-day rest/stress PET MPI.

METHODS

Study Population

This study was approved by the institutional review boards at both centers (David Geffen School of Medicine at the University of California, Los Angeles; and The Johns Hopkins Medical Institutions, Baltimore, Maryland) ,and all patients signed informed consent before any procedures. Twelve healthy adults (as determined by medical history, physical examination, vital signs, ECG, EEG, neurological examination, and clinical laboratory testing), ages from 22 to 37 years, participated in the study. Subjects had to meet all protocol-specified inclusion criteria and none of the exclusion criteria. Ten subjects were male and two were female, with no clinically significant deviation from normal ranges in physical examination, electrocardiogram (ECG), electroencephalogram (EEG), and clinical laboratory parameters. The two subjects who were women of child-bearing potential were nonpregnant

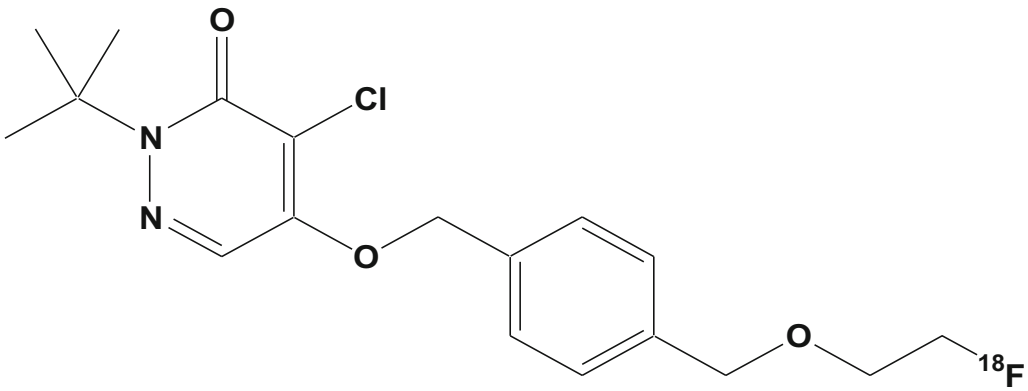

Figure 1. Structure of flurpiridaz F 18.

and were using an adequate and medically approved nonhormone-based method of contraception to avoid pregnancy from at least one month prior to study enrollment through one month following dosing, and had a negative serum pregnancy test within 24 hours prior to dose administration.

Subjects were excluded if they had any significant active or chronic medical illness or recent significant trauma or any condition that may have disrupted and/or increased permeability of the blood-brain barrier; any major surgery within 4 weeks prior to enrollment or planned within 2 weeks after completion of the study; a donation of blood or plasma to a blood bank or for a clinical study within 4 weeks prior to enrollment; a blood transfusion within 4 weeks of enrollment; any oral, transdermal, implanted, or injectable contraceptive hormones or hormone replacement therapy within 3 months; and any radiopharmaceutical within a period equal to 10 half-lives of the isotope. Subjects were excluded if they either had a positive urine screen for drugs of abuse at screening or before dosing, or if they had used any prescription drugs within 4 weeks prior to dosing or any other drugs including over-the-counter medications or herbal preparations within 1 week prior to dosing. Subjects were also excluded for any for other sound medical, psychiatric, or social reason as determined by the Principal Investigator (PI). All twelve subjects received Flurpiridaz on both Study Days 1 and 2 and completed all safety assessments. Only 10 of 12 subjects were considered evaluable for dosimetry measurements. Nine were males and one was a female, with mean ± SD age of 27.4 ± 5.0 (range 22 to 36) and mean ± SD BMI of 24.4 ± 2.9 (range 21 to 29).

Study Design

This study was conducted over a 4-month period. The major study events are displayed in Figure 2.

Flurpiridaz Dose and Method of Administration

The two doses of Flurpiridaz were calculated to deliver a total of approximately 8 mCi, but no more than 11 mCi. Each subject received from 1 to 3 mL IV bolus injection targeted to deliver approximately 3 mCi but no more than 4.5 mCi of Flurpiridaz at rest on Study Day 1, and approximately 5 mCi but no more than 6.5 mCi of Flurpiridaz during stress on Study Day 2. The Study Day 1 dose contained 0.09 to 0.37 μg of Flurpiridaz, while the Study Day 2 dose contained 0.15 to 0.63 μg of Flurpiridaz. The doses were administered in less than 10 seconds, followed immediately by a 3 to 5 mL saline flush. On both Study Day 1 (rest) and Study Day 2 (stress), the syringe was assayed for ^{18}F activity before and after study drug administration. The study drug catheter was also assayed for ^{18}F activity after study drug administration.

Exercise Testing

On Study Day 2, the six subjects in Cohort 1 underwent treadmill exercise stress using the Bruce protocol. Flurpiridaz was administered at peak exercise, and exercise continued for 1.5 to 2 minutes following injection. Following termination of exercise, subjects were transferred as quickly as possible to the scanner to commence PET imaging. The average time interval between Flurpiridaz stress injection and beginning of imaging was 2.5 minutes.

Pharmacological Stress Testing

On Study Day 2, the six subjects in Cohort 2, fasted for at least 3 hours before adenosine administration. They did not consume caffeine-containing beverages, food, or any caffeine-containing medications for at least 24 hours before adenosine administration. Adenosine was infused at a rate of 140 μg/kg body weight per minute (min) for 6 minutes using an infusion pump. An IV bolus of Flurpiridaz was injected 3 minutes after the start of the adenosine infusion through an IV line with a dual-port Y. Per standard practice, 12-lead ECG, HR, and blood pressure (BP) were recorded every minute during the infusion and for 5 minutes during the recovery.

PET Imaging Protocol

Whole-body PET imaging was performed in 2D format at protocol-specified time-windows using either a Siemens ECAT HR+ system (in 8 subjects) or a General Electric Discovery Rx PET-CT system (in 4 subjects). Corrections for attenuation, randoms, and scatter were applied. In all subjects, an emission study was obtained over the heart followed by six emission studies covering the length of the body from the head (included) to the mid-thigh and one acquisition from mid-thigh to the feet (included). For each imaging session, scan details were recorded, including time of injection, acquisition start time, etc. A low-to-moderate-resolution spiral computed tomography (CT) scan, including field of view (FOV) from upper chest to lower abdomen, was obtained before or after the PET imaging session to aid in organ volume assessment. The CT scan was performed in the event of difficulty assigning one or more concentrations of radioactivity to a known organ or anatomic structure using the PET scan alone.

Dosimetry and Biodistribution Analyses

Radiation dosimetry analysis was conducted by the core laboratory, CDE Dosimetry Services Inc, using image data only from Study Day 2. The primary dosimetry endpoints were the dosimetry estimates (DEs) for the total body and other standard organs of the MIRD schema, with the addition of the salivary glands, as well as the effective dose (ED).[7] Image analysis was performed according to the previously described method for Flurpiridaz injection at rest.[6] Entire dosimetry was determined by the medical internal radiation dose (MIRD) methodology using OLINDA/EXM software[8] with data derived from imaging studies, using methods consistent with MIRD Pamphlet no. 16.[9] The effective dose (ED) was determined using the methodology as described in International Commission of Radiological Protection (ICRP) Publication 60.[7] The absorbed doses were reported in both rem/mCi and mSv/MBq units for each organ. Calculation of

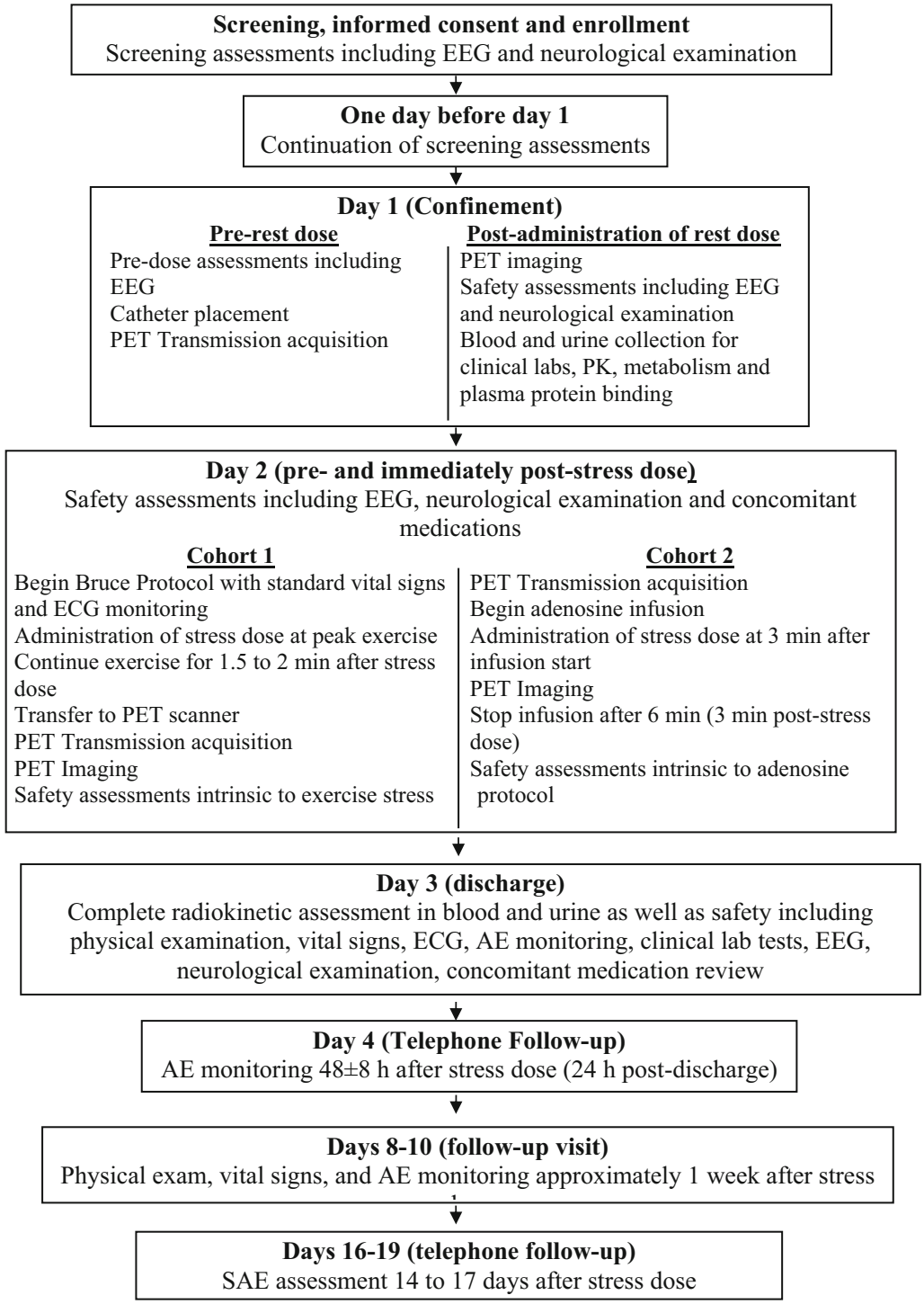

Figure 2. Study events overview.

ED involved multiplying organ doses by risk-relative weighting factors, and summing the result, yielding a single-dose estimate that was equivalent in risk to a uniform whole-body exposure of the ED level. These data were summarized for each organ and for the whole body for all subjects.

Percent injected dose (%ID), where 'dose' refers to radioactivity, was determined from whole-body images taken at protocol-specified time points. For each subject, the initial radiopharmaceutical %ID and its subsequent translocation as a function of time were determined for every organ or tissue that

showed significant specific uptake above the general body background. Time-dependent integrated image density for each organ was derived based on an ROI analysis of sums of planes of the imaging data encompassing that organ. Corrections were applied for attenuation and scatter (during image reconstruction), for overlapping organs, and for nontarget (i.e., background) radioactivity. Data were converted to %ID at each time point for each source organ. Descriptive statistics were calculated for each organ by time point. The result of this calculation, following correction for radioactive decay to the time of administration, constituted the biodistribution endpoint.

Residence times were determined by integration of empirically determined functions (sums of exponentials) from time equal zero to infinity, taking into account physical decay. Remainder of body residence times were determined by subtraction of appropriate organ residence times from whole-body residence times. Urinary bladder residence times were determined using the parameters determined by fitting the whole-body activity data with a urinary bladder model as implemented in the OLINDA/EXM software with 3.5-hour bladder voiding interval. Red marrow residence time was determined based on a region of interest drawn on a portion of the lumbar spine. The lumbar spine was assumed to contain 16.1%[10] of the total red marrow.

Safety and Tolerability Evaluation

Safety was assessed by monitoring AEs, vital signs, physical and neurological examinations, clinical laboratory tests (including Troponin T), ECGs, and EEGs. Spontaneous AE monitoring was initiated on Study Day 1 at the time of Flurpiridaz rest dose administration and continued until Study Day 3 discharge. All subjects were contacted by phone on Study Day 4 (48 ± 8 hours post-Study Day 2 dose administration) for AE monitoring. All subjects returned for a follow-up visit between Study Days 8 to 10 (approximately 1-week post-Study Day 2) for physical examination, vital signs, and AE monitoring. Clinically significant changes from baseline observed at the follow-up visit on Study Days 8 to 10 (approximately 1-week post-Study Day 2) were reported as AEs. All subjects were contacted by telephone between Study Days 16 to 19 (approximately 14 to 17 days post-Study Day 2 dose administration) for SAE monitoring, regardless of whether or not they returned during the Days 8 to 10 for the 1-week follow-up visit and post-Study Day 2 dose administration assessment. The safety and tolerability endpoints were number and percentage of AEs; change from baseline in vital signs, laboratory values, ECG, EEG, neurological examination, and physical examination that were of clinical significance as reported by the PI.

Statistical Analyses

All statistical analyses and all summary tables and listings were prepared using SAS® release 9.1.3 (SAS Institute, Inc., Cary, NC). Standard descriptive summaries included the N, mean, median, standard deviation (SD) and/or coefficient of variation (%CV), minimum and maximum for continuous variables, and the number and percent for categorical variables.

RESULTS

Radiation Dosimetry

The critical organ for Flurpiridaz when administered during exercise stress was the heart wall with a mean estimated dose of 0.15 rem/mCi (0.039 mSv/MBq) (Table 1). The critical organ for Flurpiridaz when administered during adenosine stress was also the heart wall with a mean estimated dose of 0.33 rem/mCi (0.090 mSv/MBq) (Table 2). The mean ED for Flurpiridaz was 0.054 rem/mCi (0.015 mSv/MBq) for exercise stress (Table 3) and was 0.069 rem/mCi (0.019 mSv/MBq) for adenosine stress (Table 4). Consequently, the maximum injected dose that may be administered without exceeding 1 rem ED was 19 mCi (685 MBq) for exercise stress and was 15 mCi (539 MBq) for adenosine stress. Furthermore, the maximum injected dose of the compound that may be administered without exceeding 5 rem to the critical organ was 34 mCi (1276 MBq) for exercise stress and was 15 mCi (554 MBq) for adenosine stress.

Radiation Dosimetry Comparison to Other Radiopharmaceuticals

The data acquired in this study can be used to compare the fraction of the injected dose retained by the myocardium for Flurpiridaz to that of other PET radiopharmaceuticals used in myocardial imaging (Table 5).[11–18] From the dosimetry analysis, it can be observed that approximately 17 minutes following injection, the mean %ID retained by the heart were 2.4% for exercise stress and 7.1 for adenosine stress. Our previously published data[6] showed that the mean %ID retained by the heart was 3.1 at 10.2 minutes following injection at rest. For comparison, F-18 FDG (Fluorodeoxyglucose), is reported to exhibit a mean percent injected radioactivity in the heart of 3.5%.[11] The percent of the injected dose in the myocardium for ^{82}Rb may be calculated by dividing the reported residence time of ^{82}Rb in the myocardium of 7.94×10^{-4} hours[14] by the theoretical maximum residence time of ^{82}Rb (3.0×10^{-2} hours) yielding a value of 2.6%. Since ^{82}Rb decays physically much more rapidly than it clears biologically, this may be taken as the fraction of the dose in the heart during imaging. Thus, it may be concluded that the fraction of injected dose of Flurpiridaz in the myocardium and that of both ^{18}F FDG and ^{82}Rb are comparable.

Table 1. Absorbed dose estimates (mSv/MBq) in exercise stress subjects, N = 5

Organ	Mean (SD)	%CV	Min	Max
Adrenals	0.014 (0.000)	0.95	0.014	0.014
Brain	0.011 (0.002)	15	0.0090	0.013
Breasts	0.010 (0.000)	0.93	0.010	0.010
Gallbladder wall	0.015 (0.000)	2.3	0.014	0.015
LLI wall	0.014 (0.000)	0.48	0.014	0.014
Small intestine	0.014 (0.000)	0.52	0.014	0.014
Stomach wall	0.024 (0.001)	6.2	0.022	0.025
ULI wall	0.014 (0.000)	0.44	0.014	0.014
Heart wall	0.039 (0.005)	13	0.035	0.048
Kidneys	0.027 (0.003)	12	0.023	0.029
Liver	0.015 (0.003)	17	0.013	0.019
Lungs	0.012 (0.000)	0.86	0.012	0.012
Muscle	0.012 (0.000)	0.48	0.012	0.012
Ovaries	0.014 (0.000)	0.39	0.014	0.014
Pancreas	0.015 (0.000)	0.83	0.015	0.015
Red marrow	0.015 (0.001)	7.9	0.013	0.016
Osteogenic cells	0.020 (0.001)	3.3	0.019	0.021
Salivary glands	0.0070 (0.002)	33	0.004	0.010
Skin	0.0090 (0.000)	0.49	0.0090	0.0090
Spleen	0.013 (0.000)	1.0	0.013	0.013
Testes	0.011 (0.000)	0.57	0.011	0.011
Thymus	0.013 (0.000)	1.6	0.013	0.013
Thyroid	0.014 (0.001)	6.4	0.013	0.015
Urinary bladder wall	0.016 (0.002)	12	0.014	0.019
Uterus	0.014 (0.000)	0.54	0.014	0.014
Total body	0.012 (0.000)	0.42	0.012	0.012
Effective dose equivalent	0.016 (0.000)	2.5	0.016	0.017
Effective dose	0.015 (0.000)	1.1	0.014	0.015

Whole-Organ Biodistribution

The biodistribution of Flurpiridaz, calculated as the percent of injected radioactivity as a function of time, was determined for brain, heart wall, kidneys, liver, lungs, red marrow (lumbar region), salivary glands, stomach wall, thyroid, and urinary bladder. The percent injected activity (%ID) summary statistics for subjects undergoing exercise stress and those undergoing adenosine stress are presented in Tables 3 and 4, respectively. In these tables, some of the organ measurements at different time intervals were based on less than 10 subjects due to anecdotal nonevaluable data. Figure 3 depicts coronal slices from whole-body images of a normal subject obtained at approximately 12 to 290 minutes after injection of Flurpiridaz at peak treadmill exercise. A high ratio of myocardial uptake to myocardial-to-background for an extended period of time is noted. Figure 4 depicts coronal slices from whole-body images of a normal subject obtained at approximately 12 to 295 minutes after injection of Flurpiridaz during adenosine infusion. Although visible radioactivity is present in the liver, the myocardial-to-liver ratio is well above 1 even early in the study.

For exercise stress subjects, the organ that showed the largest mean peak uptake following Flurpiridaz dose administration during stress was the liver with approximately 3.7% of the injected activity. The next largest mean peak uptake occurred in the brain with 2.9% of the injected activity, followed by the heart wall with 2.7% of the injected activity. For adenosine stress subjects, the organ that showed the largest mean peak uptake following Flurpiridaz dose administration during stress was the liver with approximately 21.4% of the injected activity. The next largest mean peak uptake occurred in

Table 2. Absorbed dose estimates (mSv/MBq) in adenosine stress subjects, N = 5

Organ	Mean (SD)	%CV	Min	Max
Adrenals	0.016 (0.001)	4.6	0.015	0.017
Brain	0.022 (0.004)	17	0.016	0.026
Breasts	0.0090 (0.000)	3.4	0.0090	0.0090
Gallbladder wall	0.018 (0.002)	8.9	0.015	0.019
LLI wall	0.011 (0.001)	8.2	0.010	0.013
Small intestine	0.012 (0.001)	5.1	0.012	0.013
Stomach wall	0.033 (0.014)	41	0.020	0.048
ULI wall	0.012 (0.000)	3.5	0.012	0.013
Heart wall	0.090 (0.024)	26	0.063	0.115
Kidneys	0.057 (0.013)	24	0.035	0.068
Liver	0.044 (0.012)	28	0.024	0.054
Lungs	0.012 (0.000)	1.4	0.012	0.012
Muscle	0.010 (0.000)	4.9	0.010	0.011
Ovaries	0.012 (0.001)	7.6	0.011	0.013
Pancreas	0.016 (0.001)	4.7	0.015	0.017
Red marrow	0.018 (0.002)	13	0.015	0.021
Osteogenic cells	0.019 (0.002)	9.9	0.017	0.022
Salivary glands	0.076 (0.033)	43	0.044	0.130
Skin	0.0080 (0.000)	6.2	0.0070	0.0080
Spleen	0.012 (0.000)	3.1	0.012	0.013
Testes	0.0090 (0.001)	9.0	0.0080	0.010
Thymus	0.012 (0.000)	3.9	0.011	0.012
Thyroid	0.036 (0.010)	28	0.023	0.050
Urinary bladder wall	0.021 (0.005)	23	0.016	0.026
Uterus	0.012 (0.001)	6.8	0.011	0.013
Total body	0.012 (0.000)	0.86	0.012	0.012
Effective dose equivalent	0.024 (0.002)	10	0.020	0.025
Effective dose	0.019 (0.002)	8.1	0.017	0.020

Table 3. Mean (SD) percent injected dose (%ID) vs. time (minutes post-dose) in exercise stress subjects (N = 5)

	17[a]	30	122	203	238
Brain	2.9 (0.47)	2.7 (0.47)	1.8 (0.37)	1.4 (0.43)	1.3 (0.45)
GI, stomach wall	0.30 (0.091)	0.28 (0.030)	0.29 (0.089)	0.27 (0.072)	0.27 (0.075)
Heart wall	2.7 (0.39)	2.8 (0.52)	2.4 (0.31)	2.0 (0.55)	1.7 (0.51)
Kidneys	2.0 (0.31)	1.7 (0.20)	1.1 (0.28)	1.0 (0.22)	0.94 (0.21)
Liver	3.7 (1.2)	3.7 (1.1)	3.1 (0.88)	2.7 (0.60)	2.6 (0.47)
Marrow (lumbar)	0.16 (0.043)	0.16 (0.048)	0.17 (0.053)	0.16 (0.055)	0.15 (0.049)
Salivary	0.08 (0.036)	0.10 (0.039)	0.13 (0.044)	0.14 (0.045)	0.13 (0.045)
Thyroid	0.026 (0.010)	0.027 (0.011)	0.042 (0.0060)	0.039 (0.0060)	0.039 (0.0080)
Urinary bladder	0.11 (0.031)	0.14 (0.097)	0.41 (0.391)	0.21 (0.077)	0.31 (0.095)

[a]Nominal times in hours post-dose (beginning of time window)

Table 4. Mean (SD) percent injected dose (%ID) vs time (minutes post-dose) in subjects injected during adenosine stress (N = 5)

	17[a]	30	122	203	238
Brain	6.0 (1.1)	6.0 (1.2)	4.8 (0.95)	3.8 (0.77)	3.5 (0.79)
GI, stomach wall	2.5 (1.5)	2.9 (1.6)	0.86 (0.19)	0.47 (0.14)	0.44 (0.12)
Heart wall	7.1 (2.0)	7.1 (2.0)	5.9 (1.5)	5.0 (1.4)	4.5 (1.2)
Kidneys	6.4 (2.1)	5.1 (1.6)	2.3 (0.46)	1.8 (0.28)	1.7 (0.32)
Liver	21 (6.6)	20 (6.5)	10 (3.6)	7.2 (2.0)	6.7 (2.1)
Marrow (lumbar)	0.38 (0.12)	0.38 (0.10)	0.30 (0.09)	0.32 (0.12)	0.30 (0.11)
Salivary	1.4 (0.59)	1.4 (0.60)	1.2 (0.50)	1.2 (0.55)	1.1 (0.54)
Thyroid	0.16 (0.068)	0.16 (0.068)	0.17 (0.068)	0.14 (0.037)	0.14 (0.036)
Urinary bladder[b]		0.29	0.71 (0.29)	1.2 (0.78)	1.8 (0.99)

[a]Nominal times in hours post-dose (beginning of time window)
[b]Urinary bladder %ID was not measured in any of the subjects at 17 minutes post injection and 8 of 10 subjects at 30 minutes post injection due to interfering radioactivity from urine. For this reason, SD is not reported for the two measurements at 30 minutes post injection

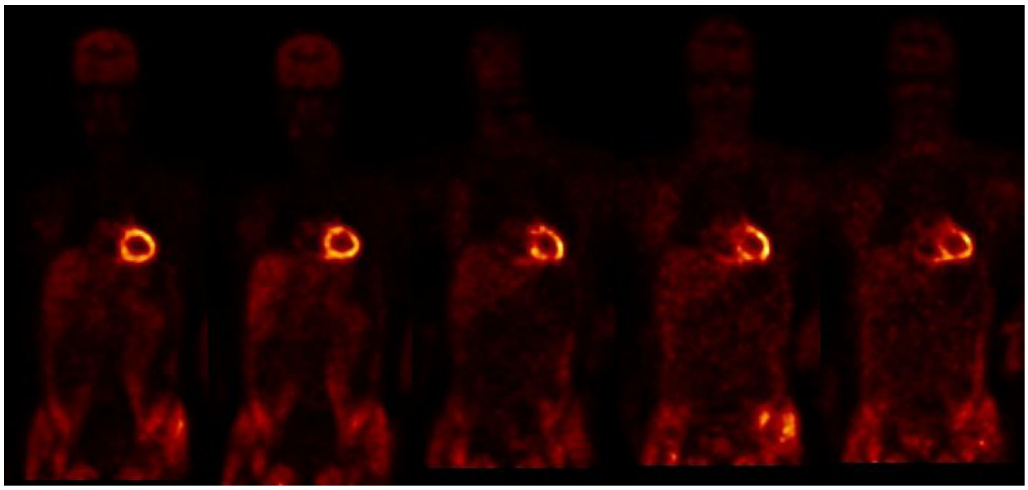

Image start times:

12-26 min 26-40 min 40-47 min 220-225 min 269-290 min

Figure 3. A sequence of coronal slices from whole-body images obtained following injection of F-18-labeled flurpiridaz at peak treadmill exercise.

the heart wall with 7.1% of the injected activity, followed by the kidneys with 6.4% of the injected activity.

Safety and Tolerability

No deaths or serious adverse events (SAEs) were reported in this study. All AEs (detailed in Table 6) were mild and were judged by the Investigators as unrelated to study drug, which were reviewed and confirmed by an independent data safety review board. Most AEs were considered to be possibly related to the known side effects of adenosine infusion and unlikely to be related to Flurpiridaz. Physical and neurological examinations (including EEGs) had normal findings in all subjects. None of the abnormal clinical laboratory

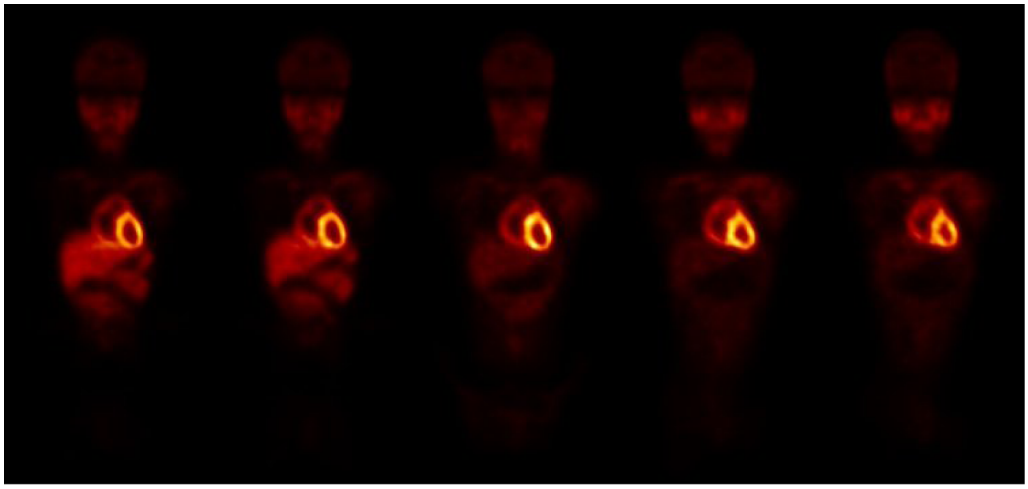

Figure 4. A sequence of coronal slices from whole-body images obtained following injection of F-18-labeled flurpiridaz during adenosine stress.

results were considered by the Investigators to be clinically significant or were reported as treatment-related AEs. None of the ECG abnormalities post-dose on either Study Day 1 or Study Day 2 were reported as AEs related to tracer administration. A few isolated QTc increases were observed on Study Day 2. All mean QT/QTc changes were within normal ranges following dose administration. The independent Data Monitoring Committee did not raise any safety concerns following periodic reviews of the safety data.

DISCUSSION

In this study, we evaluated dosimetry, biodistribution, pharmacokinetics, safety and tolerability of two doses of Flurpiridaz in normal subjects undergoing either exercise or adenosine pharmacological stress in conjunction with 2-day rest-stress PET myocardial perfusion imaging.

For dosimetry assessments, accuracy of radioisotope measurement is a paramount concern. As such, we used 2D acquisition mode at both sites for the dosimetry imaging since there were suggestions in the literature that 2D mode offered more accurate tissue count measurement than 3D mode, because scatter is more efficiently rejected in 2D acquisition mode.[19]

The results of dosimetry indicate that the critical organ is the heart wall with both exercise and adenosine stresses; a desirable feature for a myocardial perfusion imaging tracer. Interestingly, we observed that the mean % injected dose retained by the heart muscle at 17 minutes was 2.7 for exercise stress which was lower than that noted for adenosine stress (7.1) and was similar to our previously published value for 10 minutes after injection at rest (3.1). These observations may be explained by differences between exercise and adenosine pharmacological stresses in the partitioning of the injected Flurpiridaz dose in different states. With adenosine pharmacological stress, coronary flow increases without a significant increase in cardiac output, resulting in a relatively larger fraction of the injected tracer partitioned to the coronary flow and thus a higher myocardial %ID value. With exercise stress, both the coronary flow and the cardiac output increase by roughly the same amount above the resting state. Therefore, the fraction of the injected Flurpiridaz reaching the coronary circulation in the first pass is similar to that at rest resulting in similar %ID retained by the myocardium. For second and later passes of the tracer, it would also be expected that uptake of flurpiridaz F18 by skeletal muscle during exercise stress would further reduce the availability of the tracer to the coronary circulation, further enhancing the myocardial uptake difference between the two stress modalities.[20,21] This phenomenon would be expected to happen with all cardiac radiotracers, but the increased linearity of Flurpiridaz tissue uptake with perfusion, compared to that of Rb-82 and Tc-99m-based agents, makes the difference in tissue uptake and retention large enough to be readily apparent.

Table 5. Radiation dose due to rest-stress myocardial imaging protocols, comparing Flurpiridaz with other clinically used radiopharmaceuticals

	Tl-201	Tc99m-Sestamibi	Rb-82 (2D BGO/3D BGO/3D LSO)	Flurpiridaz F 18 exercise	Flurpiridaz F 18 pharmacologic	N-13 ammonia[d]
Rest Dose (MBq)	130[a]	296[a]	1850/1295/555[a]	102	102	555
Stress Dose (MBq)	N/A	888[a]	1850/1295/555[a]	342	231	555
Critical Organ, rest	Ovaries[b]	Gall Bladder Wall[b]	Kidneys[c]	Kidneys	Kidneys	Urinary Bladder Wall
Critical Organ,stress	N/A	Gall Bladder Wall[b]	Kidneys[c]	Heart	Heart	Urinary Bladder Wall
Critical organ, combined	Ovaries	Gall Bladder Wall	Kidneys[c]	Heart	Heart	Urinary Bladder Wall
Critical organ dose, combined (mSv)	95[b]	51[b]	40/28/12[c]	18	26	9
Effective Dose combined (mSv)	28[b]	12[b]	8.3/5.8/2.5[c]	7.0	6.3	3

[a]Midpoint of ASNC guideline range used for rest and stress doses. Administered dose ranges for Tl-201 and Tc-99m Sestamibi from[12] Administered dose ranges for Rb-82 from[13]
[b]Radiation doses for Tl-201[16] and Tc-99m Sestamibi[17] from ICRP 80
[c]Radiation dose for Rb-82 from Senthamizhchelvan, et al.[14] and Senthamizhchelvan, et al.[15]
[d]Radiation dose for N-13 ammonia from ICRP53[18]

Following adenosine stress, the mean %ID at 17 minutes post injection was 7.1 for the heart and 21 for the liver. The higher liver value relative to the heart is due to the higher mass of the liver tissue receiving a higher % of the injected dose compared with the myocardium. On actual flurpiridaz images, the liver count density at a similar time interval after injection is lower than the heart, as shown in Figure 4.

The maximum injected dose calculations for Flurpiridaz were based on <1 rem ED or < 5 rem to the critical organ. 1 rem is currently considered a typical radiation dose limit for myocardial perfusion studies using Tc-99m agents. 5 rem is the maximum allowed dose to radiation workers and to subjects receiving radiation exposure due to scientific studies providing no medical benefit under US Federal Regulations 21 CFR 361.1. We observed that the maximum injected Flurpiridaz dose that may be administered without exceeding 1 rem ED was 19 mCi (685 MBq) for exercise stress and was 15 mCi (539 MBq) for adenosine stress. Furthermore, the maximum injected dose of Flurpiridaz that may be administered without exceeding 5 rem to the critical organ was 34 mCi (1276 MBq) for exercise stress and was 15 mCi (554 MBq) for adenosine stress. These values are similar to the range of administered doses commonly used for radiopharmaceuticals incorporating ^{18}F such as ^{18}F FDG.[11] It is of note that stress Flurpiridaz doses that are used in clinical trials are 9.24 mCi (342 MBq) for exercise stress and 6.24 mCi (6.24 MBq) for pharmacological stress testing, which are well below the stated maximum limits.

Table 5 compares the radiation dose from an anticipated rest and stress dose of Flurpiridaz with the mid-points of the range of recommended rest-stress doses for other radiopharmaceuticals used for myocardial perfusion studies.[6,12–14] The radiation dose expected from a rest-stress Flurpiridaz study is less than that of the others (except for ^{82}Rb used with a 3D PET scanner) in terms of both critical organ and effective dose. Radiation dose to patients may be further reduced by 3D PET/CT image acquisition combined with optimized imaging protocol. Such approach has the potential of reducing Rb-82's effective dose to 0.6 mSv per scan.[22] Similarly, we observed that Flurpiridaz injected dose may be reduced to 1.71 mCi (63.27 MBq) per scan with an effective dose of 1.2 mSv.[23]

The topic of radiation exposure from Flurpiridaz to laboratory personnel is outside the scope of this manuscript and requires a separate investigation. We anticipate that the exposure to personnel from flurpiridaz is unlikely to be significantly different than it is from FDG. In later studies, total doses of F-18, including both rest and stress, were no more than approximately 12 mCi for exercise stress and approximately 10 mCi for pharmacological stress. This compares well with the recommended dose of FDG for most studies of 15 mCi.

Table 6. Details of adverse events

Subject ID	Type of stress	Symptoms	Timing after start of stress	Flurpiridaz already injected?
001-007	Adenosine	Throat pressure	1 minutes	No
		Chest flushing	1 minutes	No
		Mild headache	7 hours	Yes
001-011	Adenosine	Ear pressure	2 minutes	No
		Throat pressure	2 minutes	No
001-014	Adenosine	Chest pressure	2 minutes	No
001-015	Adenosine	Throat pressure	2 minutes	No
		Mild headache	3 minutes	Yes
		Flushing	1 minutes	No
001-018	Adeno	Flushing	2 minutes	No
002-003	Adenosine	Nausea	2 days 6 hours	Yes
		Leg muscle spasm	14 hours	Yes
		Headache	9 hours	Yes
		Headache	2 days	Yes
		Arm numbness	14.98 hours	Yes
002-004	Exercise	Nausea	2.75 hours before	No
		Vomiting	3.87 hours before	No
		Headache	3.87 hours before	No

Min, minute; *Hr*, hour; *Start of stress*; start of adenosine infusion or exercise treadmill

While it is true that personnel will have more exposure to radiation due to greater proximity to the patient during exercise procedures, this is compensated for by the lower injected dose of approximately 9 mCi for the exercise portion of the study.

No deaths or SAEs were reported in this study. All AEs were mild, and most were considered to be possibly related to the known side effects of adenosine infusion and unlikely to be related to Flurpiridaz. There were no significant changes in vital signs, laboratory values, ECG tracings, or neurological function related to Flurpiridaz. These observations are further confirmed in Phase 2 and Phase 3 clinical trials.[24,25]

STUDY LIMITATIONS

Although the study population was typical for a Phase 1 study, its characteristics were different from the population of patients referred for clinically indicated PET MPI; they were mostly men, were healthy, had low BMI and took no medications. It is expected that young and healthy subjects have higher organ blood flow and mitochondrial density, yielding a higher organ uptake of Flurpiridaz than older and diseased patients. Therefore, our biodistribution measurements represent ''the worst-case scenario''. Although BMI was relatively low in our study population, we anticipate that Flurpiridaz dose does not need to be weight adjusted based on current image quality and count statistics as well as clinical experience in phase 2 and Phase 3 studies[24,25] in which acceptable images were obtained in patients with a wide range of BMI's up to 72 injected with the same dose of Flurpiridaz. The reported safety and tolerability of Flurpiridaz in 12 healthy subjects in this study is not considered conclusive. These preliminary observations, however, have been subsequently confirmed in 143 patients in Phase 2[24] and 755 patients in Phase 3[25] clinical trials.

Pharmacological stress in this study was limited to adenosine infusion. Therefore, radiation dosimetry results cannot be directly extrapolated to dipyridamole stress, regadenoson stress, dobutamine stress, or any of the vasodilator stress agents combined with low-level treadmill exercise.

CONCLUSION

Stress PET myocardial perfusion imaging is feasible with ^{18}F-labeled flurpiridaz injected in conjunction with either treadmill exercise or pharmacological stress testing. Dosimetry of this tracer is within the clinically acceptable range. ^{18}F-labeled flurpiridaz was found to be safe and well tolerated.

NEW KNOWLEDGE GAINED

^{18}F-labeled flurpiridaz can be conveniently used for PET myocardial perfusion imaging in conjunction with either pharmacological stress or treadmill exercise. This radiotracer has a favorable dosimetry, consistent with current clinical radionuclide imaging guidelines. ^{18}F-labeled flurpiridaz, injected during stress, was found to be safe and well tolerated in this small population of normal subjects.

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