Synthesis and Kinetics of [^{18}F]4′-Fluoroantipyrine in Normal Mice

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Antipyrine labeled with radioiodine has proven useful for studying the symmetry of human brain perfusion by gamma-camera techniques. The feasibility of preparing F-18-labeled antipyrine for eventual use with a positron camera was investigated. The preparation of [^{18}F] 4′-fluoroantipyrine and its distribution in normal mice were used to evaluate this potential. 4′-Fluoroantipyrine was prepared in 7–20% chemical yield by the pyrolysis of the 4′-diazonium fluoroborate salt of antipyrine. This Schiemann salt was prepared by a five-step synthesis from 1-(4′-nitrophenyl)-3-methyl-5-chloropyrazole. Fluorine-18 labeling of the diazonium fluoroborate salt by exchange with aqueous F-18 and pyrolysis of the dried labeled salt produced [^{18}F] 4′-fluoroantipyrine with specific activities of 0.83–2.7 μCi/mg. The incorporated F-18 activity ranged from 0.53 to 1.9%. The labeling procedure took about 3 hr.

The labeled antipyrine was administered by tail vein to fasting female Swiss-Cox mice. Distribution of F-18 at 12, 30, 60, and 120 sec, and 10 min, after injection showed that radioactivity persisted in the brain up to 120 sec at a level greater than that of the skin and the bone. (Skin and bone samples were chosen as representative of activities in the scalp and skull surrounding the brain.) Thus, perfusion imaging of the CNS should be possible when greater quantities of high-specific-activity F-18-labeled antipyrine become available.

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There has been considerable interest in the development of F-18-labeled radiopharmaceuticals because of the short physical half-life of F-18 (109.8 min) and its ability to be imaged with positron-imaging equipment. Fluorine-18, the only radioisotope of fluorine with a useful half-life, is a positron emitter and the resulting annihilation photons (0.51 MeV) are easily detected with positron-imaging equipment. The perfusion imaging of the brain requires lipophilic compounds that rapidly penetrate the blood-brain barrier. Reduction of the patient's absorbed radiation dose dictates that these compounds be labeled with radionuclides of short half-life. Antipyrine is a lipophilic compound that has been labeled with the radioiodines [I-123 (*1*) and I-131 (*2*)] and used to study the symmetry of human brain perfusion by external scanning with gamma-camera techniques. Antipyrine (*3*), as well as its radioiodinated analog, 4-iodoantipyrine (*2*),

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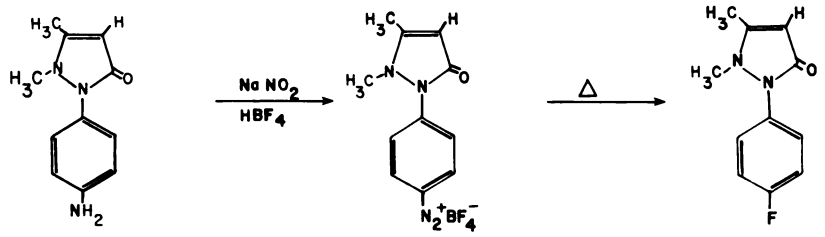

FIG. 1. Scheme for preparation of 4′-fluoroantipyrine.

(V) (VI) (VII)

has been shown to have rapid uptake by the brain. Fluorine-for-hydrogen substitution in molecules often results in compounds that have nearly unchanged biologic behavior (*4*). Also, the large-scale production and nationwide commercial distribution of F-18 has been admirably demonstrated. Thus, a F-18-labeled analog of antipyrine is potentially a suitable brain-imaging agent. Preparation of medically useful quantities of F-18-labeled compounds will provide radiopharmaceuticals for facilities with positron cameras.

This paper describes the synthesis of [^{18}F] 4′-fluoroantipyrine, with distribution studies in mice to evaluate it for use as an imaging agent in human brain perfusion. We originally planned to prepare [^{18}F] 4-fluoroantipyrine by the Schiemann reaction starting with commercially available 4-aminoantipyrine (1-phenyl-2,3-dimethyl-4-amino-5-pyrazolone). This proved to be impossible, as a pyrazopyrazolone was the only product isolated from the pyrolysis of antipyrine 4-diazonium fluoroborate (*5*). The alternative was to prepare 4′-aminoantipyrine [1-(4′-aminophenyl)-2,3-dimethyl-5-pyrazolone] and use it in the Schiemann-type reaction according to the following approach: 4′-aminoantipyrine is converted to antipyrine 4′-diazonium fluoroborate. Fluorine-18 is exchanged with this diazonium salt. The F-18-labeled fluoroborate (Schiemann salt) is then pyrolyzed to [^{18}F]4′-fluoroantipyrine. The preparation of 4′-fluoroantipyrine by the methylation of 1-(4′-fluorophenyl)-3-methyl-5-pyrazolone was reported by Danek and Nouzova (*6*), but its preparation by the Schiemann route has not been reported in the literature. Consequently the method of preparation of the Schiemann salt and pyrolysis to 4′-fluoroantipyrine had to be developed and F-18 labeling applied to this preparation scheme.

Syntheses. 4′-Aminoantipyrine (V) was prepared by a four-step synthesis starting with 1-(4′-nitrophenyl)-3-methyl-5-pyrazolone (I)*. The preparation of 4′-aminoantipyrine and its precursors was confirmed by melting-point determination (uncorrected) and comparison with the literature values. 1-(4′-nitrophenyl)-3-methyl-5-chloropyrazole (II) was prepared according to Michaelis (*7*), in 43% yield, m.p. 98–101° [lit. 101.5–102° (*8*)]. The iodomethylate of 1-(4′-nitrophenyl)-3-methyl-5-chloropyrazole (III) was prepared from II (*7*), in 90% yield, m.p. 190–192° (lit. 196°). 1-(4′-nitrophenyl)-2,3-dimethyl-5-pyrazolone (IV) was prepared from III (*7*), in 45% yield, m.p. 130–132° (lit. 132°). 4′-Aminoantipyrine (1-[4′-aminophenyl]-2,3-dimethyl-5-pyrazolone) (V) was prepared from IV (*7*), in 70% yield, m.p. 210–212° (lit. 210°).

Analysis: Calculated for $C_{11}H_{13}N_3O$:
C, 65.04; H, 6.40; N, 20.68; O, 7.88.
Found: C, 64.87; H, 6.50; N, 20.52; O, 8.02.

4′-Fluoroantipyrine was prepared from 4′-aminoantipyrine according to the scheme in Fig. 1. Figure 2 shows the exchange of F-18 with the Schiemann salt and its pyrolysis to [^{18}F] 4′-fluoroantipyrine.

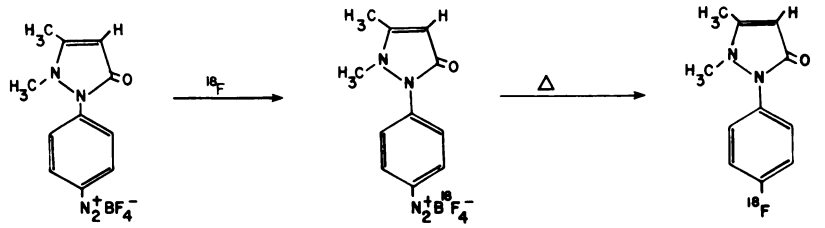

FIG. 2. Scheme for preparation of [^{18}F] 4′-fluoroantipyrine.

(VI) (VIa) (VIIa)

Antipyrine 4'-diazonium fluoroborate (1-phenyl-2,3-dimethyl-5-pyrazolone 4'-diazonium fluoroborate) (VI). A mixture of 2.0 g (9.8 millimol) 4'-aminoantipyrine (V), 4.50 ml 50% fluoroboric acid (33.3 millimol), and 20 ml of absolute ethanol was stirred in a 150-ml beaker until solution occurred. After cooling to 0°C, 0.7 g $NaNO_2$ (10.1 millimol) in 2 ml water was added dropwise over 10 min. To the resultant yellow slurry 50 ml of 50:50 ethanol:ether solution was added to ensure precipitation of all the diazonium fluoroborate. The resulting diazonium fluoroborate (VI) was collected in a fine-porosity sintered glass funnel, and washed three times with ice-cold ether (10–15 ml). This yellow powder was dissolved in approximately 50 ml of acetonitrile and reprecipitated by adding 100 ml of ice-cold ether with stirring. This precipitate (2.82 g, 95%) was collected in a fine-porosity sintered glass funnel and air-dried overnight. The yellow crystals decomposed at 165° and gave a positive spot test for fluorine. Infrared analysis showed absence of the NH_2 doublet [ν max (KBr disc) 3200 cm^{-1} and 3350 cm^{-1}] of the 4'-aminoantipyrine and the presence of the diazo peak [ν max (KBr disc) 2280 cm^{-1}] of the diazonium salt. Gas chromatography and mass spectrometry of VI were performed by dissolving a portion of the compound in acetone and injecting into the SE-30 GC column at 180°C. A small peak that appeared in the GC trace had a mass spectrum identical to that recorded for 4'-fluoroantipyrine. Mass spectrometry of the acetone solution of compound VI was done by direct introduction into the ion source of the mass spectrometer by the direct probe inlet; it gave a mass spectrum identical to that recorded for 4'-fluoroantipyrine.

Analysis: Calculated for $C_{11}H_{11}BF_4N_4O$:
C, 43.74; H, 3.67; N, 18.55.
Found: C, 43.59; H, 3.65; N, 18.36.

4'-Fluorantipyrine (1-[4'-fluorophenyl]-2,3-dimethyl-5-pyrazolone) (VII). Antipyrine 4'-diazonium fluoroborate (0.176 g, 0.582 millimol) (VI) was dried in a 105° oven in a 15-ml round-bottom flask. The flask was transferred to an oil bath held at 130° and its contents decomposed under water-aspirator vacuum. The brown residue was mixed with approximately 20 ml hot ethanol and made basic with 6 *N* NaOH (three drops). A pinch of activated charcoal was added and the mixture filtered through a fine-porosity sintered glass funnel. After washing of the funnel with hot ethanol, the filtrate was evaporated to dryness on a low hot plate using a stream of air. The orange solid was extracted with hot toluene (~50 ml) and the toluene phase was filtered through anhydrous sodium sulfate. The toluene was evaporated to 10 ml and a yellow precipitate (22.7 mg, m.p. 113–115°C) was produced by addition of 10 ml of low-boiling petroleum ether during cooling on a block of dry ice. The precipitate was collected by filtration and recrystallized twice from benzene-ligroin to yield 20.1 mg (16.7%) VII, m.p. 126–127°, [lit. 131° (*6*)], beige crystals, giving a positive spot test for fluorine. Infrared analysis showed absence of the diazo peak [ν max (KBr disc) 2280 cm^{-1}] of its progenitor. The C-13 NMR spectrum showed sharp singlets at δ 27.92 ($\overset{*}{C}H_3$—C=C), 49.19 ($\overset{*}{C}H_3$—N), and 108.58 (=$\overset{*}{C}$—H), in addition to multiplets at 132.61–133.78 (N—$\overset{*}{C}_6H_4$—, and F—$\overset{*}{C}_6H_4$—) and 146.67–147.08 (aromatics). Gas chromatography and mass spectrometry of the product gave one GC peak, and the mass spectrum of that peak gave the molecular ion at m/e 206. Other fragments expected for VII were also identified.

Analysis: Calculated for $C_{11}H_{11}FN_2O$:
C, 64.07; H, 5.38; N, 13.58; F, 9.21.
Found: C, 64.30; H, 5.51; N, 13.56; F, 9.00.

The picric acid complex derivative if VII was also prepared, m.p. 151–152°.

Analysis: Calculated for $C_{17}H_{14}FN_5O_8$:
C, 46.90; H, 3.24; N, 16.09; F, 4.36.
Found: C, 47.13; H, 3.34; N, 16.05; F, 4.12.

Preparation of [^{18}F] 4'-fluoroantipyrine (VIIa). Fluorine-18 was produced by a 3-hr irradiation of four quartz tubes containing 750 mg Li_2CO_3 (3 g total), enriched in Li-6 (95%), in a thermal-neutron flux of 2×10^{13} n cm^{-2} sec^{-1}†. The tubes containing the irradiated Li_2CO_3 were sealed in a tygon tube and crushed with a heavy object (*9*). The powder and quartz were transferred to a disposable beaker and the Li_2CO_3 was dissolved in 15 ml of 7.2 *M* H_2SO_4. The solution was decanted to a small distillation apparatus, rinsing the quartz residue with 5 ml water. Aqueous F-18 (14 ml) was distilled from this solution with a small stream of air bubbling through the solution to speed up the distillation. The acidity of the distillate was slowly adjusted from pH 2 to the pH 5–6 range with an OH^- form anion resin‡. After the resin was filtered from the solution in a fine-porosity sintered glass funnel, the activity was measured in a dose calibrator. The aqueous solution of F-18 was added to a (4-ml) acetonitrile solution of 100 mg (3.3 millimol) of antipyrine 4'-diazonium fluoroborate, and allowed to stand for 15–30 min. After rotary evaporation of the acetonitrile and water from the solution at 55–60°C, the

residue was dried over P_2O_5 under vacuum for 15 min. Water-aspirator vacuum was applied to the flask, and the dried salt was pyrolyzed in a 165°C oil bath. The brown residue was extracted with ethanol and toluene as described in the preparation of unlabeled 4′-fluoroantipyrine. After evaporation to about 3 ml, the toluene solution was chromatographed on 10 g of chromatographic grade alumina (80–200 mesh)|| in a 15-mm-diameter column. The product was eluted from the column with 50 ml toluene, then 150 ml of toluene:chloroform (1:1) at ambient pressure and a flow rate of 50 ml/min. Only the final 80 ml of toluene:chloroform were collected, and it was evaporated to dryness. After solution of the product in 2 ml water, the activity was measured in a dose calibrator. The solid obtained by evaporation of an aliquot (0.2 ml) to dryness was weighed and the specific activity calculated.

On one run, measurement of the activity and absorbance of 10-ml fractions eluted from the column was done to determine radiochemical purity of the product. Its identity and purity were confirmed by melting point, IR, GC, mass-spectrometry, and elemental analyses of an aliquot from one batch prepared for mouse studies.

Mouse studies. *Method.* Swiss-Cox female mice weighing 25–34 g were fasted for 8 hr and given i.v. injections of [^{18}F] 4′-fluoroantipyrine by tail vein. The mice received 0.10–0.15 ml of the radiotracer, whose specific activity was 0.83–2.70 μCi/mg. This is equivalent to 0.33–1.59 μCi of F-18. The mice were killed by decapitation at 12, 30, 60, and 120 sec, and 10 min, after injection. Samples of blood were taken immediately in heparinized syringes. Urine samples were collected when available. The blood and urine were weighed and then diluted to 2 ml in counting tubes. Samples of the various organs were obtained, weighed, and counted in an automatic gamma counter after addition of water to same level as the standards. Standards were prepared by the appropriate dilution of a 0.10- or 0.15-ml aliquot of the radiopharmaceutical and were counted along with the samples. The concentration of F-18 was computed and expressed as the percentage of kilogram dose per gram sample (*10*).

RESULTS AND DISCUSSION

The synthesis of 4′-aminoantipyrine (V) from a commercially available compound, 1-(4′-nitrophenyl)-3-methyl-5-pyrazolone (I), was accomplished by methods given in the literature (*7*). The chemical yields and melting points for Compounds II–V are given in the Syntheses section. Elemental analysis of V was added to confirm its structure.

According to our literature search, antipyrine 4′-diazonium fluoroborate had not been prepared. The method described here is the best of several attempts to prepare this compound. The mass spectra for this sample were identical to that recorded later for 4′-fluoroantipyrine. This indicates that the diazonium fluoroborate is thermally degrading to the 4′-fluoroantipyrine in both the GC column and the ion source of the mass spectrometer. The elemental and IR analyses also confirmed preparation of the diazonium fluoroborate.

Unlabeled 4′-fluoroantipyrine (VII) was prepared by the pyrolysis of the diazonium salt. The chemical yield ranged from 7 to 20%. The melting point was somewhat lower than that found in the literature (*6*). The GC and mass-spectral data for VII and elemental analyses of the compound and of its picrate derivative provide additional proof of the structure of the compound.

The reactions producing the fluorine-18 are:

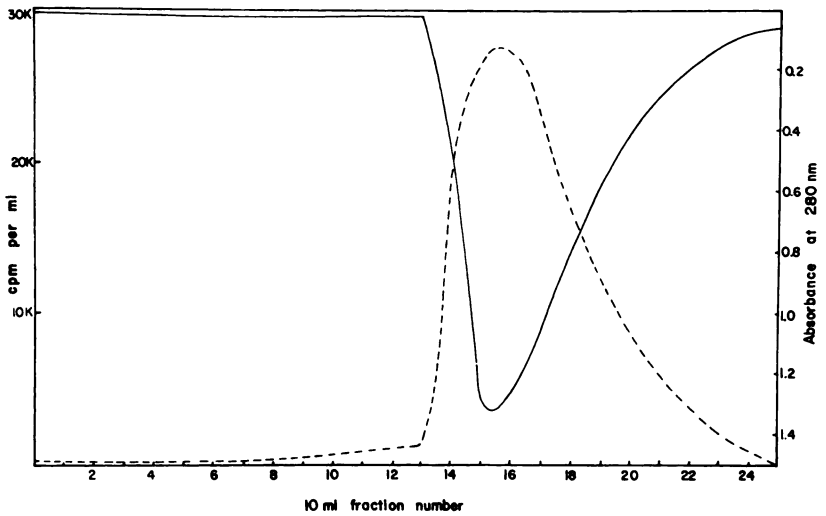

FIG. 3. Elution pattern for [^{18}F] 4′-fluoroantipyrine, chromatographed on an alumina column (- - - - F-18 activity; —— absorbance at 280 nm).

$^{6}Li(n,^{4}He)^{3}H$; $^{16}O(^{3}H,n)^{18}F$. A run yielded 20–50 mCi carrier-free F-18 e.o.b. at the Ann Arbor reactor. After a 5.5-hr drive and 1 hr for distillation and titration with the anion-exchange resin, a pH 5–6 aqueous solution containing 2–5 mCi F-18 was obtained. The titration with the OH^- form anion resin was included to remove SO_4^{-2} ions from the distillate, since they interfered with the pyrolysis in one of the trial runs. A chromatography column was used in the preparation of VIIa to remove the oily by-products of the pyrolysis of VIa. Measurement of the activity and absorbance of the 10-ml fractions eluted from the chromatography column (Fig. 3) shows that all the activity was associated with the 4′-fluoroantipyrine.

The procedure for preparation and isolation of [^{18}F] 4′-fluoroantipyrine, free of solvents and oily by-products of the pyrolysis, took about 3 hr (1.6 half-lives) from the addition of aqueous F-18 to the end of the run. Table 1 gives the results for various runs. The product contained 6–14 μCi F-18 associated with 5–8 mg of 4′-fluoroantipyrine. The specific activity of these preparations ranged from 0.83 to 2.70 μCi/mg. The chemical yields (7.3–12%) limited the activity incorporated into the product. Moreover, if a true exchange of F-18 for the F of the diazonium fluoroborate salt occurred, only one of every four F-18 atoms would be available for labeling to antipyrine; thus, 25% labeling is the theoretical maximum. The activity incorporated, corrected to beginning of the exchange, ranged from 0.53 to 1.90%. This is reasonable in the light of the above considerations (*11*). Improvement of the preparation and isolation steps of the procedure would improve the yield somewhat, but a different approach to the synthesis—possibly the use of crown ether induced nucleophilic exchange of F-18 in the KF form for bromine of a substituted bromoantipyrine (*12*)—would probably improve the yield to a greater extent. Use of a larger quantity of F-18 in the exchange procedure would also increase the specific activity. In our case, reduction of the delivery time (5.5 hr) from the reactor would increase the quantity of F-18 available.

The results of the distribution of [^{18}F] 4′-fluoroantipyrine in selected organs of Swiss-Cox mice are shown in Table 2. To assist in the extrapolation of tissue distribution data between species, kilogram dose percentage per gram was chosen as the unit to express this distribution. Any value greater than 0.1% kg dose/g (10 in the table) reflects a tissue concentration of the radiopharmaceutical greater than that evident if it were homogeneously distributed throughout the test animal. This unit is computed by multiplying the percentage of dose per gram of organ by the weight of the animal in kilograms.

The radioactivity persisted in the brain for up to 120 sec at a level that is relatively constant throughout the course of the study. At 10 min, however, the brain level is seen to approach that of the bone and to fall below that of the skin. The radioactivity ratios of brain to bone and brain to skin, calculated for 12–120 sec (3.9:1 to 1.9:1), agree with the ratios of brain to scalp and skull levels of I-131 radioactivity determined after the i.v. administration of [^{131}I] iodoantipyrine reported by Uszler et al. (*1*). Bone and skin samples from the mice were chosen to represent the activity in skull and scalp, respectively, because these organs were easily obtained at necropsy. Studies in larger animals should also include samples at times between 120 sec and 10 min. At each sampling time, the level of activity in the blood was greater than that of the brain, indicating a significant amount of recirculation of 4′-fluoroantipyrine (*3*). The decrease in blood level between 2 and 10 min can be compared to the precipitous drop in blood radioactivity during the first 5 min described by Gabrieli et al. (*13*) for I-131 antipyrine given to patients in their clinical study. Levels of F-18 in the liver increased rapidly up to 120 sec, indicating that the metabolism of 4′-fluoroantipyrine is by the liver microsomal enzymes and similar to the metabolism of antipyrine (*14*). Levels of F-18 in the urine from 12 to 120 sec are very low or equal to background, indicating that the [^{18}F] 4′-fluoroantipyrine or any of its F-18-labeled metabolites are excreted only to a small extent during the first 2 min after injection. Samples of urine could not be obtained at the 10-min sampling time. If [^{18}F] 4′-fluoroantipyrine is metabolized similarly to antipyrine and/or [^{131}I] 4-iodoantipyrine, one would expect to see only a small amount of a F-18-labeled glucuronide of 4-hydroxy-4′-fluoroantipyrine, or of unaltered [^{18}F] 4′-fluoroantipyrine, in

TABLE 1. SUMMARY OF YIELDS FOR PREPARATION* OF VIIa

Run No.	Chemical yield of VIIa mg (%)	Specific activity μCi/mg	F-18 incorporated, corrected to t_0‡ %
1	7.5 (11)	1.29	1.49
2	†	0.85†	1.90
3	8.0 (12)	0.83	0.53
4	5.2 (7.3)	2.70	0.92

* 100 mg is weight of VI to which F-18 was added.
† Not weighed; specific activity was based on the chemical yield (10%) from a nonradioactive run.
‡ t_0 is the time at which F-18 was added to the Schiemann salt.

TABLE 2. DISTRIBUTION OF [^{18}F] 4′-FLUOROANTIPYRINE IN NORMAL MICE* (% KG DOSE/G) × 100†

	12 sec	30 sec	60 sec	120 sec	10 min
Blood	14.0 (13.0 –14.8)	15.5 (11.1 –21.4)	15.3 (13.9 –16.3)	14.3 (12.8 –15.9)	9.29 (9.05– 9.53)
Brain	10.3 (7.4 –12.0)	11.9 (10.7 –12.9)	12.3 (10.3 –13.7)	11.0 (10.1 –12.5)	4.40 (4.01– 4.84)
Liver	9.67 (4.7 –12.3)	14.8 (13.5 –16.6)	21.8 (20.3 –23.4)	24.1 (23.1 –25.1)	11.7 (11.4 –12.2)
Bone	3.47 (0 – 5.04)	3.12 (2.32– 3.53)	3.16 (2.96– 3.19)	3.00 (2.13– 4.39)	3.55 (3.38– 3.81)
Skin	3.43 (2.51– 4.09)	5.32 (4.66– 6.36)	4.91 (4.39– 5.31)	5.92 (4.83– 7.99)	5.79 (5.43– 6.27)
Urine	2.29 (0 – 4.26)	0.60 (0.05– 1.60)	0.00	0.00	—

* 0.10 or 0.15 ml administered by tail vein to female Swiss-Cox mice; equivalent to 0.33 to 1.59 μCi of F-18.
† Mean value for three mice, range in parentheses.

the urine during the first 10 min (*13*). Our data confirm this route of metabolism and elimination. The metabolism of antipyrine was noted to be slow by Brodie and Axelrod (*15*) and by Vesell et al. (*16*). Thus the appearance in the urine of the conjugate, the glucuronide of 4-hydroxy-4′-fluoroantipyrine, will be slow. In this study, samples of urine were not examined to determine the state of F-18. As with I-123-labeled antipyrine, the mouse data for [^{18}F] 4′-fluoroantipyrine suggest that the F-18 activity remains in the brain for at least 2 min at levels greater than those of the scalp and skull surrounding the brain. This would permit perfusion imaging when sufficient quantities of high-specific-activity [^{18}F] 4′-fluoroantipyrine are available. While the specific activities of [^{18}F] 4′-fluoroantipyrine obtained in the study are not high enough to predict the immediate use of [^{18}F] 4′-fluoroantipyrine for perfusion imaging of the CNS with the positron camera, the distribution of this labeled compound does appear to follow that of antipyrine. To overcome the probable toxic effects of 4′-fluoroantipyrine [LD_{50} of oral antipyrine = 1.8 mg/kg in rats (*17*)], the specific activity of the [^{18}F] 4′-fluoroantipyrine would have to be increased for consideration for human studies.

We have shown that it is possible to prepare and isolate small quantities of [^{18}F] 4′-fluoroantipyrine in less than two half-lives at a laboratory distant from a reactor site. It is possible to prepare F-18-labeled radiopharmaceuticals in useful quantities at many locations around the U.S. because of the proximity of many laboratories to nuclear reactors (*9*) and cyclotrons, and of the widespread availability of F-18 in aqueous solution due to the distribution system developed for F-18 when it was used as a bone-imaging agent. The distribution studies in normal mice have demonstrated that this radiopharmaceutical has potential for use in perfusion imaging of CNS with a positron camera, when larger quantities of F-18 are labeled to the compound.

FOOTNOTES

* Pfalz and Bauer, Stamford, CT.
† The irradiations were done at the Phoenix Memorial Laboratory Reactor, University of Michigan, Ann Arbor, MI. The shielded tubes were transported by car to the Nuclear Medicine Laboratory for separation of F-18 and the chemistry.
‡ Dowex 1 × 8, 100–200 mesh.
|| Matheson, Coleman and Bell Co., Norwood, OH.

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