PRELIMINARY NOTE

A New Brain Perfusion Imaging Agent: [I-123]HIPDM:N,N,N′-Trimethyl-N′-[2-Hydroxy-3-Methyl-5-Iodobenzyl]-1,3-Propanediamine

Hank F. Kung, Kenneth M. Tramposch, and Monte Blau

State University of New York at Buffalo, and Veterans Administration Medical Center, Buffalo, New York

Based on the pH-shift mechanism, a new brain imaging agent I-123 HIPDM (N,N,N′-trimethyl-N′-[2-hydroxy-3-methyl-5-[^{123}I]iodobenzyl]-1,3-propanediamine) has been developed. This agent can be prepared by a simple exchange reaction suitable for routine clinical use. The physicochemical parameters, partition coefficient vs. pH profile, and protein binding, as well as biodistribution in rats, were very similar to those of I-123 IMP (N-isopropyl-p-iodoamphetamine). High brain uptake was found in animals after i.v. injection. The brain radioactivity persists for at least 1 hr in rats and monkeys. Regional distribution in sections of rat brain appeared to reflect regional perfusion. In conjunction with single-photon emission tomography (SPECT), this agent may provide useful information on local cerebral perfusion in humans.

J Nucl Med 24: 66–72, 1983

Recent interest in the external measurement of regional cerebral perfusion with single-photon emission computed tomography (SPECT) devices has created substantial interest in new brain seeking radiopharmaceuticals (*1–3*). Several CNS-active iodinated monoamines showed high brain localization. An iodinated catecholamine analog, 4-[^{131}I]iodo-2,5-dimethoxyphenylisopropylamine, exhibited high brain uptake (2% of dose in dog) and was proposed as a potential brain-imaging agent (*4*). Another monoamine, N-isopropyl-p-[^{123}I]iodoamphetamine (IMP), also displayed high brain uptake in animals (*5,6*), and several recent reports have validated qualitatively and quantitatively the clinical usefulness of this monoamine as a local cerebral blood-flow indicator (*7–9*). It was suggested that the mechanism of brain concentration of IMP depends on lipid solubility and affinity of this molecule to "non-specific high-capacity" binding sites in brain cells (*6,8*).

Based on a totally different mechanism, "pH shift," we have developed a new class of gamma-emitting diamines for brain perfusion imaging (*10*). These diamines can take advantage of the pH gradient that exists between blood (pH ≈7.4) and brain (intracellular pH ≈7.0). At high pH these compounds are neutral and lipid soluble and can diffuse freely into cells, but at the lower interval pH they become charged and can no longer diffuse out. A series of Se-75-labeled pH-shift agents was prepared. These Se-75 diamines displayed high brain uptake and retention after intravenous injection in animals and in humans (*10–12*). However, the usefulness of Se-75-labeled imaging agents is limited by two factors: (a) some of the gamma photons of Se-75 (260–410 kev) are too energetic for effective gamma-camera imaging, and (b) the long physical half-life (120 days) limits the clinical dose to about 1 mCi. A more useful agent might be realized by substituting I-123 ($T_{1/2}$ = 13.2 hr, 159 keV) for the Se-75.

We have previously reported (*11–14*) several aromatic iodinated diamines with high brain uptake. When the iodine is on a benzene ring, the diamines are relatively resistant to in vivo deiodination. However, the labeling of this type of molecule by exchange is difficult because it requires extensive heating and purification. Therefore,

Received June 3, 1982; revision accepted Sept. 21, 1982.

For reprints contact: Hank F. Kung, Nuclear Medicine, Bldg 5, VA Medical Center, 3495 Bailey Ave., Buffalo, NY 14215.

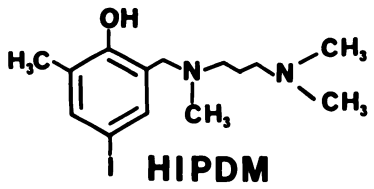

FIG. 1. Chemical structure of HIPDM.

the labeling procedure for these compounds cannot be adapted to kit form for routine clinical use with I-123. In order to facilitate the exchange reaction, a phenol instead of a benzene ring was used as the iodine carrier. The exchange reaction for iodophenolic diamines is faster and more efficient (*14*). Despite the structural modification, these iodophenolic diamines exhibited high brain localization in animals. This report describes the best compound in this group: N,N,N′-trimethyl-N′-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3-propanediamine (HIPDM, Fig. 1) and presents some data comparing it with IMP.

MATERIALS AND METHODS

Radiolabeling. The synthesis of HIPDM and related compounds was accomplished by a procedure to be reported elsewhere (*14*). The final product purity (>97%) was determined by TLC, ir and NMR spectroscopy, and elemental analysis. The radiolabeling of HIPDM was achieved by a simple exchange reaction. A solution of HIPDM (1 mg in 1 ml of 0.07 *N* HCl) and ~100 μl of 0.1 *N* sodium hydroxide solution containing 0.8–1 mCi of $Na^{125}I$* (17 Ci/mg), or 2–8 mCi of $Na^{123}I$† (no carrier added), in a sealed 10-ml serum vial was heated in a boiling-water bath for 30 min. The reaction mixture was analyzed by TLC in two systems: (a) silica gel 60-F‡ with $CHCl_3/EtOH/NH_4OH$ (8:1.5:0.5), R_f = 0.6–0.8 for labeled HIPDM and 0.0 for free iodide; and (b) ITLC, $EtOH/NH_4OH$ (9.5:0.5), R_f = 0.5–0.8 for labeled HIPDM and 1.0 for free iodide. In all cases the radiochemical incorporation was greater than 95%. The mixture was diluted with 1 ml of 0.9% saline and sterilized by passage through a 0.22-micron filter. There was no change in radiochemical purity after the filtration. Iodine-125-labeled IMP was prepared by the reported method (*8*) and was >95% pure.

Partition coefficients. These were measured by mixing I-125-tagged HIPDM or IMP (1–5 mCi/mg) with three grams each of 1-octanol and buffer (0.1 *M* phosphate) in a test tube. This tube was vortexed (3 × 1 min) at room temperature and then centrifuged for 5 min. Two weighed samples (0.5 g each) from the 1-octanol and buffer layers were counted in a well counter. The partition coefficient was determined by calculating the ratio of cpm/g of octanol to that of buffer. Samples from the octanol layer were repartitioned until consistent values of partition coefficient were obtained. Usually the measurement was repeated three times.

Protein binding. The binding of I-125 HIPDM or IMP to human serum proteins was determined by equilibrium dialysis. Human serum (0.4 ml, pooled) and 0.4 ml of phosphate buffer (0.15 *M*, pH 7.4) containing the test compound (~0.025 μCi) were separated by a dialysis membrane§. The dialysis cells were rotated in a water bath at 37°C for 18 hr. At the end of the incubation, aliquots from both sides were weighed and counted. The %free of protein binding was determined by calculating the radioactivity concentration ratio of buffer to serum multiplied by 100 (*15*). To determine possible membrane binding, the membrane was counted at the end of the experiment. Usually less than 5% of the original activity was found on the membrane.

Animal distribution. *Rats.* Sprague-Dawley male rats (220–300 g) under light ether anesthesia were injected intravenously with 0.2 ml of a saline solution containing both I-123 HIPDM (~7 μCi, 12.5 μg) and I-125 IMP (~5 μCi, 12.5 μg). At various times after injection, the animals were put under ether anesthesia and killed by cardiectomy. The organs of interest were excised, weighed, and counted with a two-channel gamma counter. The % dose/organ was determined by comparison of tissue radioactivity with suitably diluted aliquots of the injected dose. Spillover counts into each window were corrected by a computer program. The effect of specific activity on biodistribution was studied in a similar experiment in which carrier HIPDM was added to the injected solution.

The approximate % dose/g of wet tissue or organ can be calculated by dividing the % dose/organ by the mean organ weight (mean weights: heart 0.85 g, brain 1.65 g, blood 18 g, liver 9 g, kidneys 1.9 g, lungs 1.6 g).

Monkeys. Monkeys were sedated with ketamine (10 mg) and then anesthesized with nembutal. For the imaging studies, a dose of 3–5 mCi of I-123 HIPDM (specific activity ~5 mCi/mg) was injected intravenously. Immediately after the injection, images (1 min per frame) were collected and stored in a MDS computer. The brain area was flagged and the total net counts in this area were plotted against time. Static imaging was obtained by adding the frames from 1 min to 30 min.

For dissection experiments, monkey #1 (female, weight 2.8 Kg) was injected intravenously with a dose of I-131 HIPDM (~100 μCi, specific activity ~0.36 mCi/mg). One hour later the monkey was killed by an overdose of nembutal. Organs of interest were excised, weighed, and counted. Percent dose per organ was obtained as in the rat distribution study. Based on body weight, several organ weights were estimated: blood = 7%, muscle = 40%, fat = 27.5%, skin = 15%, thyroid = 0.029%, bone = 10%. To block thyroid uptake, monkey #2 (female, weight 2.4 Kg) was given 1 l of grape-flavored sucrose solution (Kool-aid) containing 400 mg of sodium iodide 24 hr before the injection. A dose of I-123

HIPDM (~100 μCi, specific activity 1 mCi/mg) was injected intravenously and the animal was killed and necropsied as described above.

Autoradiography. Male Sprague-Dawley rats (200-300 g) were injected intravenously under light ether anesthesia with 0.2 ml of a solution containing ~100 μCi of I-125 HIPDM (specific activity ~1-10 mCi/mg). At 2 min or 1 hr after injection, the rats were killed under ether anesthesia. The brain was removed and the radioactivity measured. After freezing at −25°C in embedding medium Tissue-Tek II¶, 20-micron sections were cut with a cryostat microtome maintained at −15°C to −20°C. Each section was mounted on a glass slide and air-dried. Autoradiograms were made with Ultrafilm ^{3}H**. The exposure time depended on the amount of activity in each section (10 days for a section giving ~7000 cpm). The exposed films were developed with Kodak D-19 developer (1 to 10 dilution, 5 min) and fixed.

RESULTS AND DISCUSSION

Exchange reaction. As expected, the exchange reaction in an aqueous solution between the iodophenolic compound, HIPDM, and I-123 or I-125 as iodide went easily at 100°C (yield >95%). There was a small percentage (usually below 2%) of noniodide radiochemical impurity (R_f = 0.9-1.0, using TLC system A). This impurity probably leaked from the walls and stoppers of the container, since it increased dramatically when autoclaved water or serum vials were used. In a parallel experiment, using the same autoclaved water or vials but in the absence of HIPDM, the same contaminant was detected (usually >10%). This finding strongly suggests that this phenomenon may occur in some other iodine-exchange reactions when autoclaved water or vials are used.

Biodistribution of HIPDM in monkeys. In the monkey studied by external imaging, immediately after the intravenous injection, activity in brain increased sharply to ~75% of that at the end of 30 min (Fig. 2). The continued gradual increase in brain uptake probably reflects the redistribution of HIPDM from other high-uptake organs, especially the lung. The static image of this

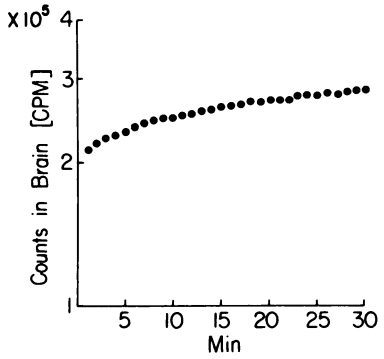

FIG. 2. Kinetics of brain uptake in a monkey after i.v. injection of I-123 HIPDM (~3.5 mCi).

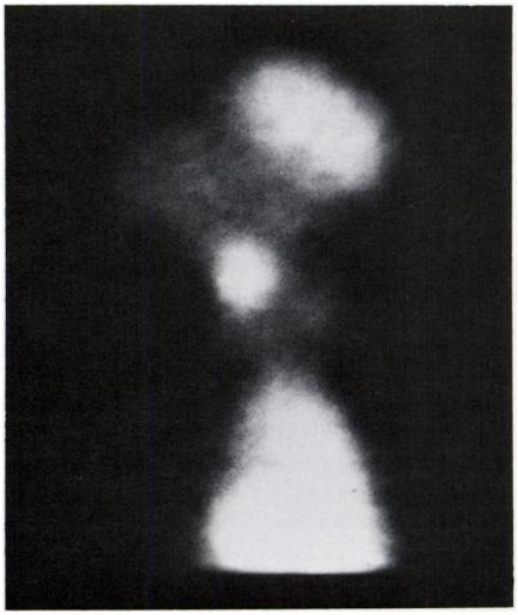

FIG. 3. Lateral scintigram of monkey. Counts were accumulated from 1 min to 30 min after i.v. injection of I-123 HIPDM.

TABLE 1. BIODISTRIBUTION OF HIPDM IN MONKEYS 1 HR AFTER I.V. INJECTION

Organ	Monkey 1*		Monkey 2†	
	%Dose/organ	%Dose/g	%Dose/organ	%Dose/g
Brain	5.19	0.0787	3.68	0.0643
Blood	1.47	0.00743	1.24	0.00716
Muscle	10.0	0.00882	9.42	0.00952
Heart	1.65	0.173	1.28	0.163
Lungs (2)	13.8	0.948	14.6	0.891
Spleen	2.30	0.517	4.95‡	0.329
Kidneys (2)	4.49	0.300	4.74	0.390
Liver	6.78	0.122	3.77	0.0723
Fat	16.07	0.021	26.95	0.0396
Skin	—	—	4.36	0.0118
Ovaries (2)	0.068	0.121	—	—
Uterus	0.388	0.050	—	—
Thyroid	0.0805	0.0980	0.0286	0.0398
Salivary gland	1.27§	0.180	0.167	0.0886
Inj. site	0.282	—	0.249	—
Bone	3.75	0.0132	3.59	0.0145

* Monkey #1 (weight 2.8 Kg) received ~100 μCi of I-131 HIPDM (specific activity 0.36 mCi/mg).

† Monkey #2 (weight 2.4 Kg) received ~100 μCi of I-123 HIPDM (specific activity 1 mCi/mg). A liter of grape-flavored sucrose solution (Kool-aid) containing 400 mg of sodium iodide was given 24 hr before the experiment.

‡ Monkey had an enlarged spleen (weight 15.05 g).

§ Monkey had an enlarged salivary gland (weight 7.04 g).

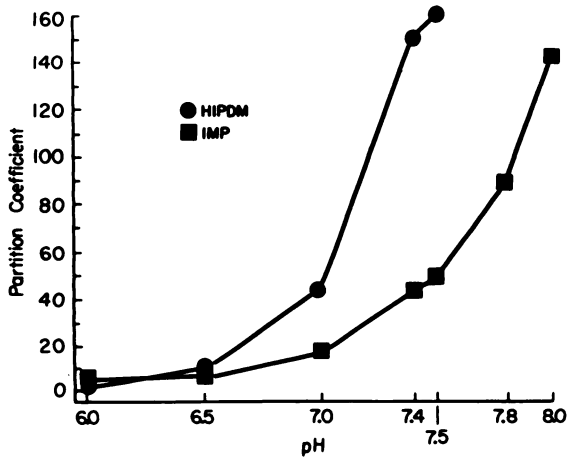

FIG. 4. Partition coefficient vs. pH profiles for HIPDM and IMP.

monkey clearly showed the activity concentrated in brain, chest (lungs), and thyroid (Fig. 3).

Quantitative distribution was also determined in two monkeys (Table 1), one with unblocked thyroid (monkey #1) and one with it blocked (monkey #2). High brain uptake was confirmed. At one hour after i.v. injection, total brain uptakes were 5.2% and 3.7% for #1 and #2, respectively. At the time of injection the monkey was sedated with ketamine and under light nembutal anaesthesia. The effect of these drugs on cerebral blood flow, and therefore net brain uptake, is currently under investigation. Our preliminary results in rats indicate that nembutal and ketamine cause a decrease in brain uptake of HIPDM relative to the untreated animal. Halothane and ether, on the other hand, cause an increased uptake in brain.

High uptakes in lungs, liver, and kidneys were also observed. This distribution pattern is very similar to that in rats. Thyroid and salivary-gland uptake in the unblocked monkey was higher than in the monkey pretreated with iodide.

Comparison of HIPDM and IMP. *Partition coefficients.* The uptake of "pH shift" agents is closely related to the shapes of the curves for partition coefficient vs. pH (*10*). Partition-coefficient profiles of HIPDM and IMP are presented in Fig. 4. The profiles are similar, with slopes of 3.5 and 2.8 (between pH 7.0 and 7.4) for HIPDM and IMP, respectively. The lipid-solubility of these two compounds is high (P.C. >2 at all of the pHs measured). Affinity of these two compounds to human serum protein is also similar; IMP is slightly less protein bound (43% free) than HIPDM (34% free). It is apparent that the two compounds displayed similar physical properties despite differences in chemical structure.

Biodistribution in rats. In order to compare directly the biodistribution of HIPDM and IMP, a dual-radiotracer experiment was performed in rats. Each received a solution containing both I-125 IMP and I-123 HIPDM. Biodistribution (Table 2) was very similar for

TABLE 2. BIODISTRIBUTION OF HIPDM AND IMP IN RATS %DOSE/ORGAN; AVG. OF 3 RATS (RANGE)

	I-123 HIPDM				
Organ	2 min	15 min	30 min	1 hr	2 hr
Brain	2.74	2.89	2.39	2.50	2.53
	(2.58–2.99)	(2.71–3.14)	(2.21–2.66)	(2.37–2.72)	(2.24–2.98)
Blood	2.02	1.06	1.09	0.849	0.736
	(1.68–2.21)	(0.97–1.10)	(1.06–1.13)	(0.77–0.93)	(0.56–0.86)
Muscle	5.66	11.7	13.3	12.8	11.4
	(5.05–6.46)	(9.51–15.5)	(10.4–16.8)	(9.24–17.5)	(9.89–13.8)
Heart	2.71	0.827	0.399	0.288	0.218
	(2.51–3.08)	(0.72–0.94)	(0.34–0.47)	(0.21–0.34)	(0.19–0.26)
Lungs (2)	36.5	22.7	23.7	18.3	18.5
	(33.3–40.5)	(20.1–24.1)	(20.8–25.5)	(13.0–28.4)	(14.0–22.3)
Spleen	0.721	0.975	0.968	1.58	1.55
	(0.61–0.88)	(0.82–1.21)	(0.82–1.05)	(1.13–1.81)	(1.17–1.80)
Kidneys (2)	8.06	6.51	5.76	2.87	2.34
	(6.73–9.74)	(5.77–6.90)	(3.82–9.03)	(2.18–3.67)	(2.18–2.65)
Stomach	0.797	1.36	1.38	0.928	0.849
	(0.65–0.88)	(0.93–1.81)	(1.14–1.81)	(0.74–1.12)	(0.67–0.97)
Liver	5.52	7.84	6.16	4.68	5.03
	(3.01–7.82)	(6.33–9.72)	(5.64–7.03)	(4.07–5.35)	(4.58–5.29)
Skin	6.73	7.36	8.89	9.21	8.77
	(4.52–8.00)	(6.27–8.23)	(7.55–9.69)	(8.16–11.07)	(7.95–9.68)
Thyroid	0.183	0.168	0.130	0.056	0.043
	(0.17–0.20)	(0.16–0.18)	(0.12–0.15)	(0.051–0.064)	(0.030–0.052)

continued

TABLE 2. *(continued)*

Organ	I-125 IMP				
	2 min	15 min	30 min	1 hr	2 hr
Brain	2.64	2.84	2.44	2.34	2.20
	(2.49–2.92)	(2.65–3.09)	(2.25–2.75)	(2.18–2.55)	(1.97–2.43)
Blood	4.75	2.79	2.62	2.94	3.05
	(4.04–5.12)	(2.61–2.89)	(2.55–2.70)	(2.36–3.38)	(2.37–3.41)
Muscle	7.07	16.0	19.1	19.0	19.8
	(6.25–8.50)	(14.7–18.4)	(16.7–21.6)	(15.6–25.4)	(17.3–23.5)
Heart	2.19	0.596	0.451	0.393	0.348
	(1.95–2.66)	(0.56–0.64)	(0.41–0.49)	(0.35–0.42)	(0.32–0.35)
Lungs (2)	30.0	12.5	14.4	11.4	13.4
	(27.8–33.9)	(10.5–14.0)	(12.2–16.7)	(7.96–16.9)	(10.4–16.3)
Spleen	0.683	0.984	0.964	1.05	0.905
	(0.58–0.82)	(0.85–1.15)	(0.91–1.05)	(0.98–1.16)	(0.71–1.01)
Kidneys (2)	7.31	3.77	2.86	2.51	2.38
	(6.31–8.75)	(3.67–3.93)	(2.64–3.04)	(2.41–2.70)	(2.25–2.49)
Stomach	1.01	2.45	3.48	3.24	3.32
	(0.85–1.10)	(1.86–3.18)	(2.80–4.39)	(2.42–3.65)	(2.06–4.27)
Liver	5.89	13.3	9.39	8.19	8.29
	(3.44–8.07)	(11.0–15.6)	(8.46–10.3)	(7.26–9.52)	(8.15–8.50)
Skin	8.10	9.75	10.7	12.2	11.3
	(6.12–9.20)	(8.95–10.5)	(10.2–11.1)	(8.71–16.4)	(10.7–12.6)
Thyroid	0.177	0.162	0.179	0.093	0.062
	(0.15–0.21)	(0.14–0.19)	(0.17–0.19)	(0.031–0.13)	(0.024–0.12)

these two compounds, with high brain uptake at 2 min persisting through the 2-hr course of the study. High uptakes in lungs, liver, and kidneys were observed with both compounds. Thyroid uptake appeared to be low for both compounds, indicating slow in vivo deiodination in rats.

Effects of carrier. In order to determine the possible influence of specific transport or binding sites on the biodistribution of HIPDM, the effect of added carrier on biodistribution was studied. The results are given in Table 3. From 12.4 μg/dose up to 3.6 mg/dose there was no significant effect on brain uptake, indicating no saturable binding sites through this wide dose range. There was, however, a shift from lung to liver uptake as the carrier level was increased. Similar results have been observed for IMP (private communications, T. H. Lin and J. L. Wu, Medi-Physics).

Autoradiography. For regional cerebral perfusion studies, it is important to have a fixed regional cerebral distribution pattern that correlates with the blood flow. Using autoradiographic technique, brain sections of rats at 2 min and 1 hr after an i.v. injection of I-125 HIPDM were obtained (Fig. 5). The initial regional distribution in brain (2 min) reflected cerebral perfusion, with high activity in gray matter and low activity in white matter. The same pattern was found at 1 hr, which suggests no significant shifting of radioactivity during this 1-hr period.

Mechanism of localization. In addition to the data reported here, we have investigated a large series of diamine pH-shift agents labeled with Se-75 and I-125 (11–14). By and large, the brain uptake of these compounds can be explained in terms of their lipid solubility. Compounds with high lipid solubility penetrate the blood-brain barrier easily in both directions. However, if there is a sharp decrease in lipid solubility at the lower intracellular brain pH, then exit from brain is inhibited,

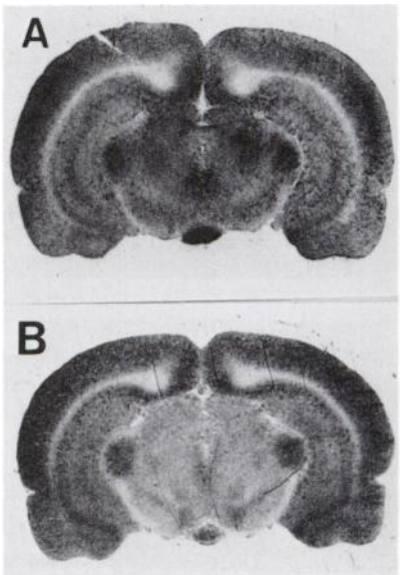

FIG. 5. Autoradiograms of rat brain sections at 2 min (A) and 1 hr (B) after i.v. injection of I-125 HIPDM.

TABLE 3. EFFECT OF SPECIFIC ACTIVITY ON BIODISTRIBUTION OF HIPDM IN RATS AT ONE HOUR AFTER INJECTION

	%Dose/organ, avg. of three rats (range)			
Carrier dose	3.6 mg	0.72 mg	0.072 mg	0.0125 mg
Brain	2.52 (2.49–2.55)	2.79 (2.51–3.08)	2.51 (2.46–2.59)	2.50 (2.37–2.72)
Blood	1.53 (1.52–1.54)	1.46 (1.43–1.49)	1.38 (1.21–1.50)	0.849 (0.77–0.93)
Muscle	17.1 (16.8–17.4)	16.5 (16.1–17.0)	12.3 (11.4–13.6)	12.8 (9.24–17.5)
Heart	0.367 (0.352–0.381)	0.379 (0.346–0.398)	0.349 (0.311–0.416)	0.288 (0.21–0.34)
Lungs (2)	5.78 (5.02–6.86)	8.47 (7.79–9.12)	15.4 (12.9–19.1)	18.3 (13.0–28.3)
Spleen	1.38 (1.35–1.42)	1.41 (1.20–1.67)	1.12 (0.902–1.40)	1.58 (1.13–1.81)
Kidneys (2)	3.28 (3.11–3.43)	3.57 (3.20–4.04)	3.40 (2.80–4.01)	2.87 (2.18–3.67)
Stomach	2.60 (1.96–3.27)	2.84 (1.57–4.82)	1.94 (1.72–2.08)	0.928 (0.74–1.12)
Liver	18.0 (17.3–19.5)	12.3 (11.4–13.1)	9.02 (8.04–9.79)	4.66 (4.07–5.35)
Skin	11.6 (10.3–13.0)	9.73 (8.84–10.5)	10.5 (10.3–10.8)	9.21 (8.16–11.1)
Thyroid	0.171 (0.145–0.194)	0.181 (0.160–0.200)	0.186 (0.162–0.213)	0.056 (0.051–0.06)

establishing a brain to blood concentration gradient. This gradient can be calculated from the dissociation constants (*16*) and should be a factor of about 5 or 6 for the pH shift of 0.4 units between blood and brain. The observed ratios (37 at 2 hr) are significantly higher, however. The cause of this is not well understood at present. It may be due to rapid metabolism of the diamine (possibly demethylation by N-methyltransferase and oxidation by monoamine and diamine oxidase) or to uptake in acid structures (e.g., lysosomes) within the cell. In view of the extremely wide variation in compound structure and the total inability to change brain uptake by adding carrier (Table 3), it is extremely unlikely that binding to specific receptors in brain cells can account for the high brain-to-blood ratios.

In view of the very similar physical, chemical, and biological behavior of IMP, it is tempting to explain the brain concentration of this compound by pH shift rather than its uptake on CNS receptor sites.

In summary, a new brain-perfusion imaging agent, HIPDM, is reported. The agent can be labeled with I-123 by a simple exchange reaction. In conjunction with single-photon emission tomography (SPECT), I-123 HIPDM may provide useful information on brain perfusion.

FOOTNOTES

* New England Nuclear.

† Crocker Nuclear Laboratory.

‡ Merck.

§ Fisher Scientific Company.

¶ Lab Tek Products.

** LKB Company.

ACKNOWLEDGMENTS

The authors would like to thank Elongia Farrell, Jeffery Billings, and Xue-Bin Wang for their technical assistance.

Unlabeled IMP was kindly provided by Medi-Physics, Inc.

REFERENCES

1. HILL TC: Single-photon emission computed tomography to study cerebral function in man. *J Nucl Med* 21:1197–1199, 1980
2. OLDENDORF WH: Nuclear medicine in clinical neurology: An update. *Ann Neurol* 10:207–213, 1981
3. BUDINGER TF: Revival of clinical Nuclear Medicine brain imaging. *J Nucl Med* 22:1094–1097, 1981
4. SARGENT T, BUDINGER TF, BRAUN G, et al: An iodinated catecholamine congener for brain imaging and metabolic studies. *J Nucl Med* 19:71–76, 1978
5. WINCHELL HS, BALDWIN RM, LIN TH: Development of I-123 labeled amines for brain studies: Localization of I-123 iodophenylalkylamines in rat brain. *J Nucl Med* 21:940–946, 1980
6. WINCHELL HS, HORST WD, BRAUN L, et al: N-isopropyl [^{123}I]-p-iodoamphetamine: Single-pass brain uptake and washout; binding to brain synaptosomes; and localization in dog and monkey brain. *J Nucl Med* 21:947–952, 1980

7. LAFRANCE ND, WAGNER HN, WHITEHOUSE P, et al: Decreased accumulation of isopropyl-iodoamphetamine (I-123) in brain tumors. *J Nucl Med* 22:1081-1083, 1981
8. KUHL DE, BARRIO JR, HUANG S-C, et al: Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I]-iodoamphetamine (IMP) tomography. *J Nucl Med* 23:196-203, 1982
9. HILL TC, HOLMAN L, LOVETT R, et al: Initial experience with SPECT (single-photon computerized tomography) of the brain using N-isopropyl-I-123-p-iodoamphetamine: Concise communication. *J Nucl Med* 23:191-195, 1982
10. KUNG HF, BLAU M: Regional intracellular pH shift: a proposed new mechanism for radiopharmaceutical uptake in brain and other tissues. *J Nucl Med* 21:147-152, 1980
11. KUNG H, BLAU M: Synthesis of selenium—75 labeled tertiary diamines: New brain imaging agents. *J Med Chem* 23:1127-1130, 1980
12. WICKS R, KUNG H, ACKERHALT R, et al: Radiation dose to humans from Se-75 MOSE pH shift brain imaging agent. In *Third Radiopharmaceutical Dosimetry Symposium* (1980) Watson EE, Schlafke-Stelson AT, Coffey JL, et al., Eds. FDA 81-8166
13. TRAMPOSCH KM, KUNG HF, BLAU M: Synthesis and tissue distribution study of iodine labeled benzyl and xylyl amines. *J Med Chem* 25:870-873, 1982
14. TRAMPOSCH KM, KUNG HF, BLAU M: Radioiodine labeled N,N-dimethyl-N'-(2-hydroxyl-3-alkyl-5 - iodobenzyl) - 1,3-propanediamines for brain perfusion imaging. *J Med Chem* (Feb, 1983)
15. VALLNER JJ: Binding of drugs by albumin and plasma protein. *J Pharm Sci* 66:447-465, 1977
16. LOBERG MD: Radiotracers for cerebral functional imaging-A new class. *J Nucl Med* 21:183-185, 1980