to detect hemodynamic compromise in occlusive cerebrovascular disease. *Stroke* 1992;23:1733–1742.
6. Layton WM Jr, Hallesy DW. Deformity of forelimb in rats: association with high doses of acetazolamide. *Science* 1965;149:306–308.
7. Karasawa J, Kikuchi H, Yamagata S, et al. Cerebral hemodynamics in moyamoya disease. Recovery of cerebral blood flow after hyperventilation. *Neurol Med Chir* 1988;28:327–332.
8. Shiv KS, Donald HW, Noor MG, et al. Epidural anesthesia for a patient with moyamoya disease presenting for cesarean section. *Anesth Analg* 1994;79:183–185.
9. Harald D, Siegfried E, Annemarie B, et al. Radiopharmacokinetics and radiation dose from ^{99m}Tc-HM-PAO (preliminary report). *Eur J Nucl Med* 1987;13:429–431.
10. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 1993 Report to the General Assembly with Scientific Annexes. New York: United Nations; 1993.
11. Conor M, Steven F, John EP, et al. Hepatic uptake of technetium-99m HM-PAO in a fetus. *J Nucl Med* 1990;31:237–239.

Technetium-99m-HMPAO, Technetium-99m-ECD and Iodine-123-IMP Cerebral Blood Flow Measurements with Pharmacological Interventions in Primates

Irene C. Dormehl, Douglas W. Oliver, Karl-Josef Langen, Niek Hugo and Sandra A. Croft
AEC Institute for Life Sciences, University of Pretoria, Pretoria, South Africa; Department of Pharmacology, Potchesfstroom University, Potchefstroom, South Africa; and Institute for Medicine, Research Centre, Jülich, Germany

Technetium-99m-bicisate ethyl cysteinate dimer (ECD) presents a different pattern from cerebral blood flow (CBF) in the subacute phase of cerebral infarction, as measured by PET, perhaps due to lack of oxygen and enzyme activity; this pattern is contrary to that of hexamethyl-propyleneamine oxime (HMPAO) but similar to that of N-isopropyl-[^{123}I]β-iodoamphetamine ([^{123}I]IMP). This study explores possible CBF differences among HMPAO, ECD and IMP, with various relevant drug interventions. **Methods:** Anesthetized adult baboons were used in these SPECT studies. Four studies (n = 6 baboons for each study), one control study and three intervention studies involving intravenous acetazolamide, nimodipine infusion and intramuscular sumatriptan, were followed with ^{99m}Tc-HMPAO, ^{99m}Tc-ECD and [^{123}I]IMP. The split-dose method was used as follows. For each tracer, intervention data from the second SPECT (SPECT-2) after the second tracer injection (444 MBq) reflected a change in CBF with respect to the baseline SPECT (SPECT-1) data from the initial injection (222 MBq). These changes as a ratio, R (R = SPECT-2/SPECT-1), for each study, and the R values for each tracer were compared to R values from the corresponding control studies, yielding a quantitative estimate of drug effects. **Results:** There were no significant differences ($p > 0.05$) between HMPAO and ECD for the control, acetazolamide and sumatriptan studies, but there was indeed a difference between the two for the nimodipine study, indicating a nimodipine-dependent underestimation of CBF with ECD (and also with IMP), with respect to HMPAO. A further significant difference was that larger CBF increases were observed with acetazolamide, as measured with [^{123}I]IMP. **Conclusion:** This is a crucial observation for the clinical interpretation of CBF SPECT data and should direct the choice of tracer for a specific examination.

Key Words: drug–tracer interaction; CBF SPECT; baboon model
J Nucl Med 1997; 38:1897–1901

There is considerable interest in the development of tracers to measure cerebral blood flow (CBF) with SPECT. Such tracers should be trapped in the brain long enough so that their distribution can be quantitated and should demonstrate good spatial resolution.

Among the tracers that have been found useful are the iodine-labeled amines, e.g., N-isopropyl-[^{123}I]β-iodoamphetamine ([^{123}I]IMP) (*1*). Its uptake linearly corresponds to a wide range of flow, as assessed by microspheres (*2*). The brain retention of IMP will be a balance of washin and washout, which in turn will be influenced by blood flow, a retention mechanism that is stereoselective, and by metabolism of the tracer (*3*). Despite its widespread use as a cerebral blood perfusion agent, IMP appears to redistribute in the brain with time (*4*). Of several ^{99m}Tc-labeled compounds synthesized as cerebral perfusion agents, ^{99m}Tc-hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO) has been used extensively, in spite of its unfavorable stability after preparation. Its retention in the brain is limited to the enzymatic reactions with glutathione, of which there is a high prevalence (*5,6*). The CBF agent N,N′−1,2-ethylene-di-yl-bis-L-cysteinate diethyl ester, labeled with ^{99m}Tc-bicisate ethyl cysteinate dimer (ECD), has a high initial brain extraction with a slow clearance (*7*). The retention in the brain is associated with stereospecific deesterfication to hydrophilic acid derivatives (*8,9*). As a CBF agent in healthy subjects, it corresponds well with ^{133}Xe (*10*), although ECD underestimates higher flow rates, as HMPAO is also known to do. However, in cases of subacute stroke, ECD failed to show reflow hyperemia in the infarct area, contrary to the action of HMPAO (*11,12*) but similar to the known action (albeit to a lesser extent) of [^{123}I]IMP (*13*).

It is important to know and understand quantitative and qualitative differences that are related to CBF, as measured by the various CBF agents. Such differences between the tracers may occur during various pathological conditions, as well as after relevant pharmacological interventions. Changes in the metabolic states of the brain appear to influence the kinetics and net accumulation of ^{99m}Tc-HMPAO at the cellular level by modifying the uptake, the backdiffusion or both (*14*). Studies comparing these tracers under pharmacological intervention conditions have not yet been reported, and these comparisons were the aim of this study.

The drugs used for this purpose were chosen from previous studies reported in the literature. Acetazolamide has been used frequently in neuro-SPECT studies to evaluate cerebrovascular reserve. The recently developed lipophilic dihydropyridine calcium channel blocker, nimodipine, demonstrates superiority in its influence on CBF compared to other calcium channel blockers and has been used for migraine and dementia (*15*). The recent introduction of the 5-HT_{1D}-agonist, sumatriptan, for the treatment of migraine has been a therapeutic breakthrough, with its undoubtable influence on abnormal CBF.

Drug intervention on CBF can ideally be investigated by the

Received Sep. 23, 1996; revision accepted Mar. 11, 1997.
For correspondence or reprints contact: Irene C. Dormehl, DSc, AEC Institute for Life Sciences, University of Pretoria, P.O. Box 2034, Pretoria 0001, South Africa.

split-dose technique, whereby two doses of the tracer are administered within a ~1-hr interval (*16,17*), with the scan after the first administration acting as a control for the scan after the second administration, which is made with the subject at the appropriate response time of the drug to be evaluated. The baboon model, together with the split-dose method used in this study, has repeatedly proven to be ideally suited to the investigation of pharmacological interventions (*18–21*).

This study reports the results of the above-mentioned pharmacological interventions on CBF as measured by the tracers ^{99m}Tc-HMPAO, ^{99m}Tc-ECD and [^{123}I]IMP, using the baboon model and split-dose SPECT.

MATERIALS AND METHODS

Adult male baboons (*Papio ursinus*; average weight, 27 kg) were used for this investigation. The studies performed were approved by the Ethics Committee of the University of Pretoria, according to the guidelines of the National Code for Animal Use in Research, Education and Testing of Drugs and Related Substances in South Africa.

Four different procedures, with six animals per procedure, were performed for each of the three CBF tracers, ^{99m}Tc-HMPAO, ^{99m}Tc-ECD and [^{123}I]IMP.

Procedure A was a control experiment with no pharmacological intervention, in which an intravenous injection of 222 MBq of ^{99m}Tc-HMPAO or, alternatively, ^{99m}Tc-ECD was administered at time zero into a baboon sedated with 10 mg/kg ketamine hydrochloride intramuscularly (Ketalar; Parke Davis, Cape Town, South Africa). This served as the induction of anesthesia and was followed immediately by a maintained controlled infusion of a 0.5% solution of thiopentone sodium [Intraval, Rhône-Poulenc, Rorer, South Africa (Pty) Ltd.] at 70 ml/hr using an administration (drip) set. Five minutes after the tracer injection, the first SPECT acquisition (SPECT-1) began. The Siemens Orbiter gamma camera performed 32 projections during a 360° rotation, at 20 sec per view. The baboons were viewed in the supine position with a special head rest to ensure reproducible repositioning for comparable tomographic slices. SPECT-1 was followed by a second intravenous administration of tracer ^{99m}Tc-HMPAO or ^{99m}Tc–ECD, at double the first dose (i.e., 444 MBq) and at a time 29 min after the first injection and 5 min before a second similar SPECT acquisition, SPECT-2: this procedure is known as the split-dose method (*16,17*). The data from SPECT-1 and SPECT-2 represent HMPAO or ECD distribution (uptake and retention) in the brain, resulting from CBF during ketamine hydrochloride and maintained (~29 min) thiopentone anesthesia, respectively. Procedure A, therefore, served as the procedure that represented the effects of anesthesia on CBF (*18*) and explained bioavailability changes of the tracer when comparisons were drawn between the interventional studies.

Procedure B was the same as Procedure A until the completion of SPECT-1, which was then succeeded by an intravenous injection of 500 mg of acetazolamide (Diamox; South Africa Cyanamid (Pty) Ltd.), at 24 min, i.e., 5 min before the second tracer administration. Thus, SPECT-2, which again followed 5 min after the second ^{99m}Tc-HMPAO/ECD injection, as in Procedure A, reflected the influence of acetazolamide (5-min response time) on CBF.

Procedure C had the same protocol as Procedure B, but the intervention was an infusion of nimodipine (Nimotop IV; Bayer (Pty) Ltd.), at 1 μg/kg/min, which started 10 min before the second tracer injection and continued as an infusion for a total of 15 min. SPECT-2 as before, began at this stage.

During Procedure D, the effect of sumatriptan (Imigran; Glaxo (Pty) Ltd.), was investigated. A response time of 23 min was chosen to permit (because of stability limitations) the use of the same vial of HMPAO for the second injection at 29 min. The intramuscular administration of sumatriptan, therefore, took place at 6 min, i.e., 1 min after SPECT-1 had commenced. SPECT-2 thus reflected the effect of sumatriptan at the 23-min response time, which is close to the time that leads to optimal effect.

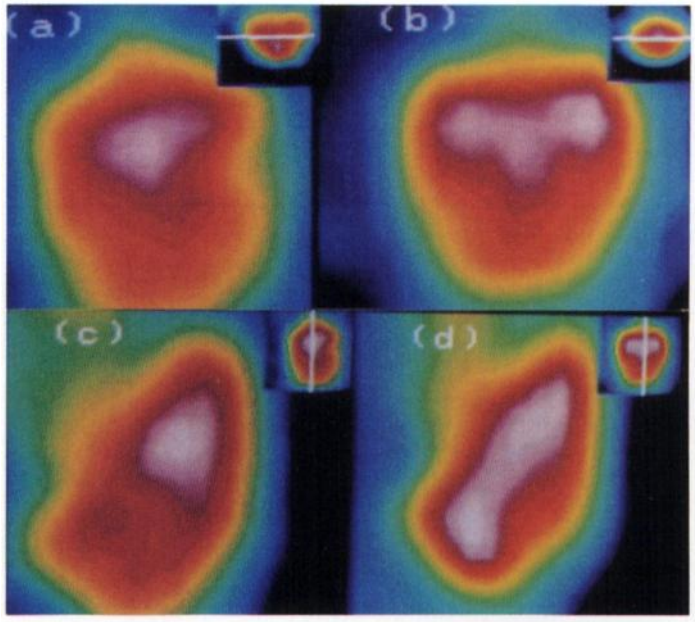

FIGURE 1. Typical coronal (a and b) and sagittal (c and d) views, representing, in each view, baseline and changed postnimodipine CBF patterns obtained with ^{99m}Tc-HMPAO.

After backprojection and reconstruction of SPECT-1 and SPECT-2 data, the brain images in all procedures consisted of transaxial, sagittal and coronal slices, representing CBF- and regional CBF-related information. Eight slices of one pixel thickness represented the brain in all three views [Fig. 1, coronal (a and b) and sagittal views (c and d)].

Regions of interest were placed on the total brain, as viewed in each slice, and counting rate data (counts/pixel) thus obtained were inserted into the following equation to obtain the ratio R:

$$R = \frac{(\text{SPECT-2}) - (\text{SPECT-1})^*}{\text{SPECT-1}},$$

where * refers to decay-corrected data from SPECT-1 that is present during SPECT-2 and has to be subtracted from the SPECT-2 data as a background correction. R is an indication of the level change of regional CBF during extended anesthesia or in addition, because of the drug interventions, as measured with ^{99m}Tc-HMPAO or ^{99m}Tc-ECD. A value of R = 2 indicates no change during the procedure. The arterial blood pressures (BPs) were recorded during all the procedures from a catheter in the femoral artery. Heart rates were also monitored, as were blood gases from an arterial line.

Procedures A–D were repeated using [^{123}I]IMP (National Accelerator Center, Faure, South Africa) as tracer for both injections (i.e., 148–296 MBq) in the protocols described above.

The R values for eight slices in transaxial, sagittal and coronal view could be compared between control and interventional studies for each tracer and also between tracers for similar procedures. A two-tailed Student's t-test for paired variables was used, with a 5% level of confidence.

RESULTS

The results are summarized as curves of mean (n = 6) R values versus slice number in the transaxial view for all procedures and tracers (Fig. 2). Values from the sagittal and

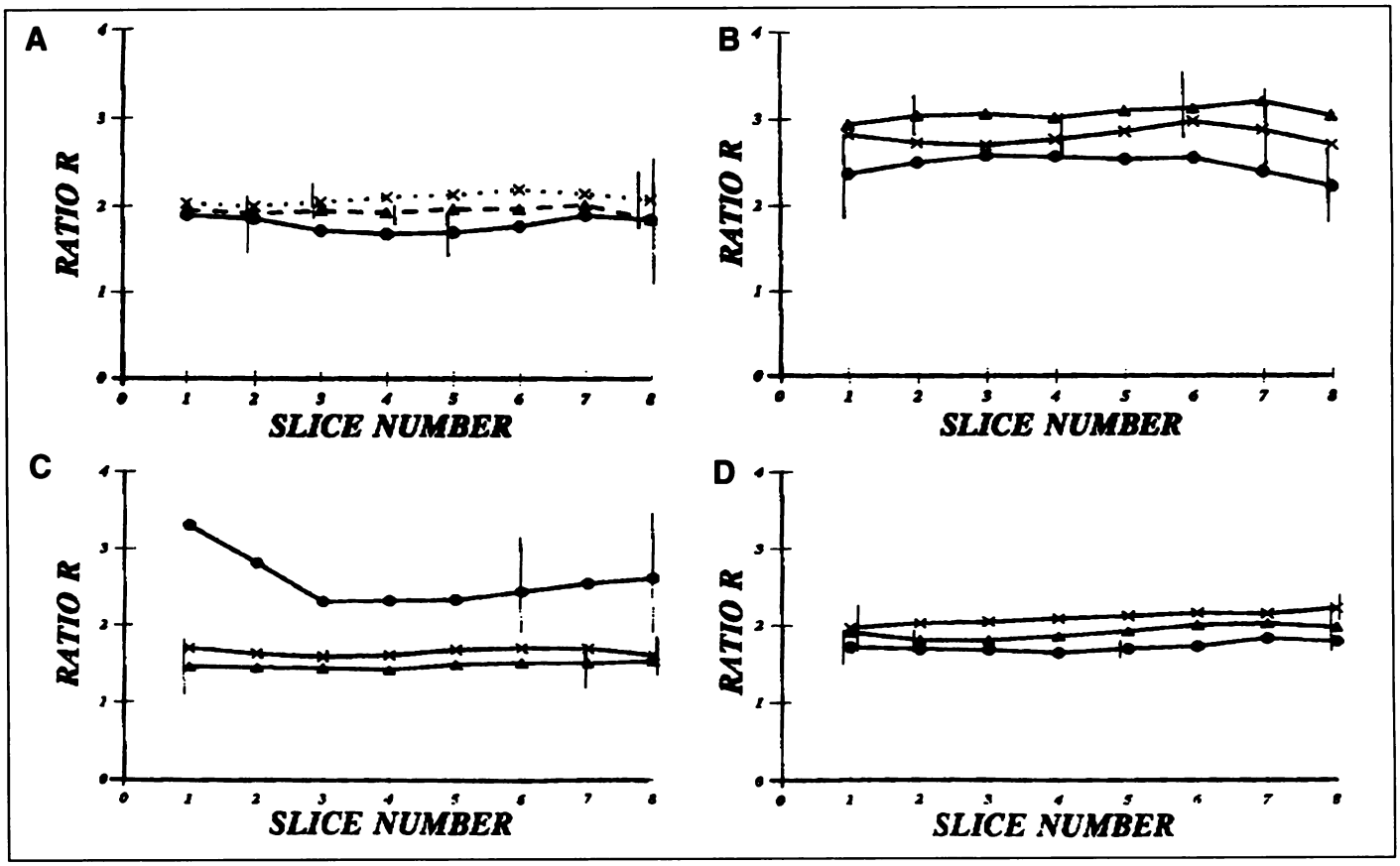

FIGURE 2. (A-D) Mean ratios R (n = 6) versus tomographic slice number in the transaxial views (occipital to frontal) comparing ^{99m}Tc-HMPAO (●), ^{99m}Tc-ECD (×) and [^{123}I]IMP (▲) for the control (A) and each intervention, acetazolamide (B), nimodipine (C) and sumatriptan (D).

coronal views in all cases confirm the measured drug effects, as represented by the transaxial view, and were, therefore, not included in the figure.

Regional effects are only crudely represented by the slice-related information of this method. No such regional effects could be established from any of the mean R versus slice number curves as being meaningful interslice differences, except for nimodipine-induced changes, as measured by ^{99m}Tc-HMPAO. In this case, the increased CBF was significantly more pronounced in the cerebellum [Fig. 1, sagittal view (c and d). Average R values were thus calculated using all slices to represent total brain R values and are presented in Table 1. Percentage differences based on these R values are presented for each procedure with respect to the control of that particular tracer (Table 1). For all three tracers, CBF increases were noted after acetazolamide intervention. Technetium-99m-HMPAO measured a CBF increase after nimodipine intervention, but ^{99m}Tc-ECD and [^{123}I]IMP measurements showed decreases in CBF under similar conditions. Changes in the physiological parameters due to the drug interventions are presented in Table 2. The only statistically significant changes ($p < 0.05$) were seen in pO_2 and Bp for acetazolamide (+20 and −8, respectively).

DISCUSSION

To date, various comparisons have been drawn between cerebral perfusion imaging agents for SPECT (*13,22–24*), but the general conclusion remains that all currently available radiopharmaceuticals, including ^{99m}Tc-HMPAO, ^{99m}Tc-ECD and [^{123}I]IMP, are far from ideal. Although all three of the above tracers are neutral and lipophilic, their kinetic behavior and trapping mechanisms differ. Consequently, there are certain conditions where they have been found to give different images; among these are cases of stroke and neurophysiological stimulations (*11,25*). From this study, it appears that interpretation of data from pharmacological interventions could also be a challenge and should be treated with caution.

R values, as defined in this study, should ideally reach the value of two (*18*), to confirm the second double dose of tracer if no change in CBF or influencing metabolism had occurred

TABLE 1
Mean Ratios from the Total Brain Region as Obtained from Various Interventions and Percentage Change from Each with Respect to Its Own Control

	Mean ratio (R) ± s.d. (n = 6)			% difference with respect to control		
Intervention	Technetium-99m-HMPAO	Technetium-99m-ECD	Iodine-123-IMP	Technetium-99m-HMPAO	Technetium-99m-ECD	Iodine-123-IMP
Control	1.79 ± 0.13	2.07 ± 0.24	1.95 ± 0.05			
Acetazolamide	2.53 ± 0.15	2.78 ± 0.13	3.02 ± 0.06	41.3%	34.3%	54.9%
Nimodipine	2.51 ± 0.14	1.67 ± 0.13	1.48 ± 0.34	40.2%	−19.3%	−24.1%
Sumatriptan	1.74 ± 0.10	2.09 ± 0.08	1.90 ± 0.06	−3%	1%	−2.5%

TABLE 2
Effects of Procedures B (Acetazolamide), C (Nimodipine) and D (Sumatriptan) on Heart Rate, Blood Pressure, pCO_2 and pO_2 in Arterial Blood in Baboons

Procedure	Heart rate	Blood pressure	pCO_2	pO_2
B_1	116.25 ± 12.74	118.00 ± 2.58	41.10 ± 2.37	56.35 ± 4.91
B_2	111.50 ± 16.84	110.25 ± 4.50*	40.08 ± 4.87	76.43 ± 7.47*
C_1	115.33 ± 22.38	132.50 ± 29.93	42.85 ± 7.55	61.12 ± 4.39
C_2	116.33 ± 24.58	112.89 ± 20.26	40.50 ± 1.27	68.50 ± 5.37
D_1	115.31 ± 11.05	119.20 ± 9.90	41.91 ± 7.60	59.17 ± 8.39
D_2	114.31 ± 14.13	112.13 ± 8.81	39.83 ± 5.33	66.55 ± 9.32

*$p < 0.05$, for postintervention compared to corresponding preintervention values.
Each value indicates the mean ± s.d. of six experiments. Subscript 1 and 2 refer to the measurements before the intervention and at the chosen response time, respectively.

before the second tracer injection. R values from the interventional procedures can be compared to their corresponding controls to establish the effect of each intervention, which will be CBF- and/or metabolism-related, while controlling for common anesthesia effects and tracer effects.

Of the mean control R values obtained in this study, those obtained by ^{99m}Tc-ECD and [^{123}I]IMP reach the value two more closely and are also not significantly statistically different ($p > 0.05$) from each other. Neither do they differ statistically significantly from the mean control R value obtained by the ^{99m}Tc-HMPAO studies ($p > 0.05$), although the last appears to be lower. By now, this low R value has been repeatedly reproduced with this experimental model and can be explained in terms of backdiffusion of the tracer (*26*) and the ketamine hydrochloride anesthesia, which leads to increased BP (+30) and heart rate (+15) during the first ^{99m}Tc-HMPAO administration and is not maintained during the second barbiturate phase of the study (*18*).

The lower ^{99m}Tc-ECD back-flux from the brain leads to a higher retention of ^{99m}Tc-ECD than ^{99m}Tc-HMPAO, which may contribute to the higher control R values obtained with ^{99m}Tc-ECD (2.07 ± 0.24 compared to 1.79 ± 0.13) (*26*). The time to reach the steady state is the same for these two tracers and will not contribute to the difference (*26*).

All three tracers measure the familiar increase of CBF by acetazolamide (*12,21,27,28*). In comparison the highest CBF increase (+54.9%) is measured by [^{123}I]IMP, which has previously been reported (*19*) and has been partly attributed to a pH effect. Alkaline urine, which results from a carbonic anhydrase inhibitor such as acetazolamide ($\Delta pCO_2 = 0$; $\Delta pO_2 = +20$; $\Delta BP = -8$) (*21*), leads to reabsorption and an increase of the serum levels of basic drugs, with subsequent higher concentrations in the central nervous system compartment (*29,30*). N-Isopropyl-β-iodoamphetamine as a basic compound is, therefore, more susceptible to possible drug interactions (in particular, those with marked influences on systemic and urine pH) than are ^{99m}Tc-HMPAO and ^{99m}Tc-ECD, explaining the significantly enhanced CBF effect with [^{123}I]IMP and acetazolamide. N-Isopropyl-[^{123}I]β-iodoamphetamine could, thus, be the more sensitive tracer to assess cerebrovascular reserve through acetazolamide intervention.

The underestimation of acetazolamide-induced CBF increases, which would normally have been expected with ^{99m}Tc-HMPAO due to high flow, was not obvious in this study (41% compared to 35%) (*26,31*) but was indicated with ^{99m}Tc-ECD (34.3%) (*32*). The first-pass extraction rate is flow-dependent for ^{99m}Tc-ECD and ^{99m}Tc-HMPAO, and back-flux affects ^{99m}Tc-HMPAO retention more than it does ^{99m}Tc-ECD retention. Therefore, the question arises of whether a certain degree of saturation of enzymatic reactions had occurred that might have accompanied the high rate of bioavailability of ^{99m}Tc-ECD, as follows with a high CBF from acetazolamide. Protein binding plays an important role in the distribution of drugs, and the difference in binding between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD could contribute to different concentrations of un-ionized hydrophobic metabolites so that a metabolic parameter, such as saturation, becomes a factor, particularly at higher flow rates. Saturation is not expected with ^{99m}Tc-HMPAO (*11*).

The Ca^{2+}-blocker nimodipine was shown to increase CBF by 40.2% for ^{99m}Tc-HMPAO and decrease it by 19.3% and 24.1% for ^{99m}Tc-ECD and [^{123}I]IMP, respectively; all changes were statistically significant ($p < 0.05$) (Fig. 2). The larger effect measured by [^{123}I]IMP as compared to that of ^{99m}Tc-ECD was not significantly different ($p > 0.05$). The difference in R values among the tracers after the nimodipine intervention, especially with ^{99m}Tc-HMPAO, immediately warns that a drug–tracer interaction must be considered and allowed for when measuring CBF with SPECT. The role of cofactors in metabolism, such as magnesium cations, is well-established, and drugs that influence such factors could indeed contribute to changed accumulation of compounds that are dependent on these factors for their metabolism. Nimodipine, as a calcium-channel blocker, may exert its effects through such a mechanism, resulting in unexpected blood flow patterns that manifest as being tracer-selective. It is unclear why nimodipine should influence the transport of ^{99m}Tc-HMPAO across the blood–brain barrier differently than it does the transport of ^{99m}Tc-ECD and [^{123}I]IMP.

It should, however, be noted that, for nimodipine, not only have CBF increases been measured (*33*) but also, at higher doses than those in the present experiment, CBF reductions have been accompanied by reduced BP (*34*), suggesting a loss of autoregulation at high doses. Studies indicate that even low doses of nimodipine can inhibit the autoregulatory adjustment to altered BP (*33,35*), depending on the size of the BP stimulus. The large s.d., which is more obvious for nimodipine, suggest a contribution in this study from biological variability of BP responses to the results.

The intervention with sumatriptan had no effect on normal CBF, as measured by all three tracers ($p > 0.05$).

CONCLUSION

The most obvious observations noted in the CBF values, as measured by [^{123}I]IMP, are the close approximation to $R = 2$ in the control study and the high R values with acetazolamide. Furthermore, [^{123}I]IMP measures, after nimodipine intervention, a reduction in CBF, as does ^{99m}Tc-ECD, contrary to ^{99m}Tc-HMPAO. It is known that [^{123}I]IMP follows a pattern of

linearity with flow over a wider flow range than do ^{99m}Tc-HMPAO and ^{99m}Tc-ECD, and it could, therefore, be regarded as the truer CBF agent. On the other hand, as a basic drug, amphetamine uptake is influenced by urinary and intracellular pH, as is seen when it is used with acetazolamide (increased uptake) and in subacute stroke (decreased uptake), respectively. Technetium-99m-ECD also demonstrates hypoactivity in subacute stroke, which is linked to altered esterase function in hypoxia, and its low CBF values, measured after the nimodipine intervention (which [^{123}I]IMP also measures), could, therefore, be seen as relating to a drug–tracer interaction, in which metabolic processes play a role. Technetium-99m-HMPAO shows a focal area of hyperactivity during subacute stroke. The inclination to caution due to drug–tracer interactions with CBF SPECT measurements is, therefore, not unfounded. The familiar differences of back-flux and, possibly, saturation between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD were also observed, which could influence the diagnostic sensitivity of the particular tracer.

It is, in addition, an interesting finding that sumatriptan does not appear to change normal CBF.

This study confirms that the interpretation of CBF SPECT data after pharmacological interventions could be a challenge and should be viewed with cognizance of tracer and drug characteristics.

ACKNOWLEDGMENTS

This study was financially supported in part by the Medical Research Council of South Africa. We would also like to thank the staff of the H.A. Grové Research Center for technical assistance.

REFERENCES

1. Winchell HS, Baldwin RM, Lin TH. Development of I-123-labeled amines for brain studies: localization of I-123 iodo-phenyalkyl amines in rat brain. *J Nucl Med* 1980;21:940–947.
2. Kuhl DE, Barrio JR, Huang SC, et al. Quantifying cerebral blood flow by N-isopropyl-p-^{123}I-iodoamphetamine (IMP) tomography. *J Nucl Med* 1982;23:196–203.
3. Nishizawa S, Tanada S, Yonekura Y, et al. Regional dynamics of N-isopropyl-(^{123}I)-iodo-amphetamine in human brain. *J Cereb Blood Metab* 1989;30:150–156.
4. Lassen NA, Henriksen L, Holm S, et al. Cerebral blood flow tomography: xenon-133 compared with isopropyl-amphetamine-iodine-123. *J Nucl Med* 1983;27:17–21.
5. Lassen NA, Anderson AR, Friberg L, Paulson OB. The retention of [^{99m}Tc]-d,l-HMPAO in the human brain after intracarotid bolus injection: a kinetic analysis. *J Cereb Blood Flow Metab* 1988;8(suppl):S13–S22.
6. Neirinckx RD, Burke JF, Harrison RC, Forster AM, Andersen AR, Lassen A. The retention mechanism of technetium-99m-HMPAO: intracellular reaction with glutathione. *J Cereb Blood Flow Metab* 1988;8(suppl):S4–S12.
7. Walovitch RC, Hill TC, Garrity ST, et al. Characterization of technetium-99m-L,L-ECD for brain perfusion imaging, part 1: pharmacology of technetium-99m ECD in non-human primates. *J Nucl Med* 1989;30:1892–1901.
8. Holman LB, Hellman RS, Goldsmith SJ, et al. Biodistribution, dosimetry and clinical evaluation of technetium-99m ethyl cysteinate dimer in normal subjects and in patients with chronic cerebral infarction. *J Nucl Med* 1989;30:1018–1024.
9. Vallabhajosula S, Zimmermann RE, Picard M, et al. Technetium-99m ECD: a new brain imaging agent. In vivo kinetics and biodistribution studies in normal human subjects. *J Nucl Med* 1989;30:599–604.
10. Huglo D, Rousseaux M, Leys D, Fialdes P, Steinling M. Regional cerebral blood flow imaging: a quantitative comparison of 99m-Tc-bicisate with 133-Xe using single photon emission computed tomography. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S76–S83.
11. Lassen NA, Sperling B. 99m-Tc-bicisate reliably images CBF in chronic brain diseases but fails to show reflow hyperemia in subacute stroke: report of a multicenter trial of 105 cases comparing 133-Xe and 99m-Tc-bicisate (ECD, Neurolite) measured by SPECT on the same day. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S44–S48.
12. Nakagawara J, Nakamura J, Takeda R, et al. Assessment of postischemic reperfusion and diamox activation test in stroke using ^{99m}Tc-ECD SPECT. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S49–S57.
13. Moretti J-L, Defer G, Tamgac F, Weinmann CB, Cesaro P. Comparison of brain SPECT using 99m-Tc-bicisate (L,L-ECD) and [^{123}I]IMP in cortical and subcortical strokes. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S84–S90.
14. Ahn CS, Tow DE, Yu CC, Greene RW. Effect of metabolic alterations on the accumulation of Tc-99m-labeled D,L- HMPAO in slices of rat cerebral cortex. *J Cereb Blood Flow Metab* 1994;14:324–331.
15. Höllerhage H-G, Gaab MR, Zumkeller M, Walter GF. Nimodipine treatment has been implicated in impaired CBF autoregulation. *J Neurosurg* 1988;69:919–922.
16. Holm S, Madsen PL, Sperling B, Lassen NA. Use of 99m-Tc-bicisate in activation studies by split-dose technique. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S115–S120.
17. Wyper DJ, Hunter R, Patterson J, Goodwin G, McCulloch J. A split-dose technique for measuring changes in cerebral blood flow patterns [Abstract]. *J Cereb Blood Flow Metab* 1991;11(suppl):S449.
18. Dormehl IC, Redelinghuys IF, Hugo N, Oliver D, Pilloy W. The baboon model under anaesthesia for in vivo cerebral blood flow studies using SPECT techniques. *J Med Prim* 1992;21:270–274.
19. Dormehl IC, Oliver DW, Hugo N. Dose response from pharmacological interventions for CBF changes in a baboon model using ^{99m}Tc-HMPAO and SPECT. *Nucl Med Commun* 1995;14:573–577.
20. Dormehl IC, Oliver DW, Hugo N, Rossouw D. A comparative cerebral blood flow study in a baboon model with acetazolamide provocation: ^{99m}Tc-HMPAO vs. ^{123}I(IMP). *Nucl Med Biol* 1995;22:373–378.
21. Oliver DW, Dormehl IC, Redelinghuys IF, Hugo N, Beverley G. Drug effects on cerebral blood flow in the baboon model: acetazolamide and nimodipine. *Nuklearmedizin* 1993;32:292–298.
22. Moretti JL, Caglar M, Weinmann P. Cerebral perfusion imaging tracers for SPECT: which one to choose? *J Nucl Med* 1995:36:359–363.
23. Suzuki S, Sakai F, Akutsu T, Tazaki Y. Tracer kinetics of ^{123}I-IMP, Tc-99m-HM-PAO and Tc-99m-ECD: measurements of temporal changes in arterial and jugular venous radioactivity [Abstract]. *J Cereb Blood Flow Metab* 1991;11(suppl 2):S774.
24. Yonekura Y, Tsuchida T, Sadato N, et al. Brain perfusion SPECT with ^{99m}Tc-bicisate: comparison with PET measurement and linearization based on permeability-surface area product model. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S58–S65.
25. Holm S, Madsen PL, Rubin P, Sperling B, Friberg L, Lassen N. Tc-99m HMPAO activation studies: validation of the split-dose, image subtraction approach [Abstract]. *J Cereb Blood Flow Metab* 1991;11(suppl):S766.
26. Murase K, Tanada S, Inoue T, et al. Kinetic behavior of Tc-99m ECD in the human brain using compartment analysis and dynamic SPECT: comparison with Tc-99m HMPAO. *J Nucl Med* 1992;33:135-143.
27. Bonte FJ, Devous MD, Reisch JS. The effect of acetazolamide on regional cerebral blood flow in normal human subjects as measured by single photon emission computed tomography. *Invest Radiol* 1988;23:564–568.
28. Nakagawara J, Takeda R, Tanaka Y, Nakamura J, Suematsu K. Assessment of hemodynamic reserve in candidates for carotid bypass surgery using SPECT and [^{123}I]-IMP activated with acetazolamide test. *Adv Funct Neuroimag* 1989;2:8–15.
29. Gerhardt RE, Knouss RF, Thyrium PT, Luchi RJ, Morris JJ. Quinidine excretion in aciduria and alkaluria [Abstract]. *Ann Intern Med* 1969;71:927.
30. Goodman LS, Gilman AG. In: Gillman AG, Rall TW, Nies AS, Taylor P, eds. *The pharmacological basis of therapeutics*, 8th Ed. New York: Pergamon Press; 1990: 716–717.
31. Vorstrup S. Tomographic cerebral blood flow measurements in patients with ischemic cerebrovascular disease and evaluation of the vasodilatory capacity by the acetazolamide test. *Acta Neurol Scand* 1988;77(suppl 144):1–48.
32. Friberg L, Andersen AR, Lassen NA, Holm S, Dam M. Retention of ^{99m}Tc-bicisate in the human brain after intracarotid injection. *J Cereb Blood Flow Metab* 1994; 14(suppl):S19-S27.
33. McGalden TA, Nath RG. Cerebrovascular autoregulation is resistant to calcium channel blockade with nimodipine. *Experientia* 1989;45:305–306.
34. Haws CW, Heistad DD. Effects of nimodipine on cerebral vasoconstrictor responses [Abstract]. *Am J Phys* 1984;247:H170.
35. Sahlin C, Brismar J, Delgado T, Owman C, Salford LG, Svengaard NA. Cerebrovascular and metabolic changes during the delayed vasospasm following experimental subarachnoid hemorrhage in baboons, and treatment with a calcium antagonist. *Brain Res* 1987:403–413.