Potential Agents for Regional Cerebral Blood Flow Measurement Using PET

TO THE EDITOR: In a recent article Kizuka, Elmaleh, Boudreaux et al. (*1*) reported the synthesis and biodistribution of N-[^{11}C-methyl]chlorphentermine and N,N-[^{11}C-dimethyl] chlorphentermine as potential agents for regional cerebral blood flow measurements (rCBF) using positron emission tomography (PET). These agents were proposed as positron-emitting equivalents of the radioiodine-labeled amines (IMP, HIPDM) which are under evaluation as agents for rCBF measurement by single photon emission computed tomography (SPECT). As reasoning for their work, these authors state, "Several positron-labeled radiopharmaceuticals have been suggested for the measurement of rCBF; to date, however, no completely satisfactory technique has been developed." As support for this view, the authors cite work by one of us (*2*). We feel this statement is totally irrelevant to the present-day state of affairs in rCBF measurement by PET.

With the arrival of the new generation of fast PET imaging devices, by far the most heavily used radiopharmaceutical is $H_2{}^{15}O$, whose characteristics have been thoroughly studied (*3, 4*). More than 2,000 studies of blood flow with $H_2{}^{15}O$ have been performed at Washington University alone. The flow limitations of water have been duly noted, and in some instances use is made of carbon-11 (^{11}C) butanol, a freely diffusible tracer with no flow limitations (*5*). In fact, the uses of such radiopharmaceuticals were discussed in the aforementioned article by Welch and Tewson (*2*). But these are not the only methods for rCBF measurement by PET; there are reported applications of [^{18}F]fluoroantipyrine (*6*), [^{18}F]fluoromethane (*7*), and the equilibrium inhalation of $CO^{15}O$; the latter has been thoroughly studied by the Hammersmith group and others (*8*).

The rationale of the synthesis of the ^{11}C-labeled amines as new "brain blood-flow" agents thus seems unclear. The mechanism of uptake and retention of iodinated amines such as IMP or HIPDM is complex and not well defined (*9*) so to develop ^{11}C-labeled analogs for use in PET, when well validated techniques are available, has little justification.

References

1. Kizuka H, Elmaleh DR, Boudreaux GJ, et al. N-[^{11}C-Methyl]chlorphentermine and N,N-[^{11}C-dimethyl]chlorphentermine as brain blood-flow agents for positron emission tomography. *J Nucl Med* 1986; 27:532–537.
2. Welch MJ, Tewson TJ. Radiopharmaceuticals for neurological studies. In: Radiopharmaceuticals II. New York, The Society of Nuclear Medicine, 1979:201–217.
3. Herscovitch P, Markham J, Raichle ME. Brain blood flow measurement with intravenous $H_2{}^{15}O$. I. Theory and error analysis. *J Nucl Med* 1983; 24:782–789.
4. Raichle ME, Martin WRW, Herscovitch P, et al. Brain blood flow measurement with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 1983; 24:790–798.
5. Herscovitch P, Raichle ME, Kilbourn MR, et al. Use of O-15 water and C-11 butanol to measure cerebral blood flow (CBF) and water permeability with positron emission tomography (PET) [Abstract]. *J Nucl Med* 1985; 26:P6.
6. Sako K, Diksic M, Kato A, et al. Evaluation of [^{18}F]-4-fluoroantipyrine as a new blood flow tracer for multiradionuclide autoradiography. *J Cereb Blood Flow Metab* 1984; 4:259–263.
7. Holden JE, Gatley SJ, Hichwa RD, et al. Cerebral blood flow using PET measurements of fluoromethane kinetics. *J Nucl Med* 1981; 22:1084–1088.
8. Subramanyam R, Alpert NM, Hoop B Lr, et al. A model for regional cerebral oxygen distribution during continuous inhalation of $^{15}O_2$, $C^{15}O$, and $C^{15}O_2$. *J Nucl Med* 1978; 19:48–53.
9. Lucignani G, Nehlig A, Blasberg R, et al. Metabolic and kinetic considerations in the use of [^{125}I]HIPDM for quantitative measurement of regional cerebral blood flow. *J Cereb Blood Flow Metab* 1985; 5:86–96.

Michael R. Kilbourn
Michael J. Welch
Mallinckrodt Institute of Radiology
Washington University Medical Center
St. Louis, Missouri

REPLY: Drs. Welch and Kilbourn's indicated in their letter that the 1979 review (*1*) is outdated. In many respects it is; however, the quote included in our article is valid and very relevant to the present state-of-the-art in rCBF measurement by PET. Their conclusion concerning the potential utility of carbon-11 (^{11}C) phentermine or its analogs as a blood flow indicator, is a result of their preference for techniques based on the use of tracer freely diffusible into and out of the brain.

The use of positron-emitting tracers such as $H_2{}^{15}O$, [^{11}C] butanol, $CH_3{}^{18}F$, ^{11}C- or [^{18}F]antipyrine to measure rCBF are based on the classic approach using inert gases that diffuse freely into and out of tissue in accordance with blood flow. They have proven to be useful measurements in clinical situations. However, the washin/washout techniques suffer from problems associated with fast sampling and data handling. The equilibrium inhalation of ^{15}O-CO_2 suffers from disadvantages associated with measurements of high and low flows, blood level corrections and other statistical errors. The limitations of the different techniques for the use of ^{15}O-labeled water, such as their dependence on flow and various errors due to parameter estimation, data sampling, and compartmental modeling and methods for dealing with these are discussed in some of the recent papers and references therein (*2, 3*). The permeability measurement of a freely diffusible tracer such as [^{11}C]butanol for positron emission tomography (PET) has its drawbacks, specifically, the permeability of [^{11}C] butanol or other alcohols could be overestimated if the image sampling time exceeds the mean transit time through a region. The problem becomes more acute when a high resolution image that gets closer to the limits of the PET instrumentation is required. Furthermore, a recent study using ^{11}C-butanol suggests that there is a diffusion restriction of butanol clearance in some regions but not in others (*4*); a careful regional analysis of blood brain barrier permeability is recommended when using this agent.

The recent use of $CH_3{}^{18}F$ without arterial sampling is an improvement (noninvasive blood sampling) however this technique also suffers from the need for venous sampling, parameter estimation in a multicompartmental system, and the need for 25 min of measurement time. These sources of error are especially acute in patients with respiratory problems. The usefulness of [^{11}C] or [^{18}F]antipyrine in man has not as