EDITORIAL

Physiologic Modeling of PET Data: Quantitative Conflict and Challenge

The purpose of in vivo quantification of physiological, biochemical and/or pharmacological processes using PET or SPECT and tracer kinetic models is to extract unique information not only of significance to the understanding of normal and disease processes but also of clinical importance. Quantitative estimation of ultimate in vivo parameter(s) of interest, however, is a challenging process in many cases. This is particularly the case for the estimation of the parameter k_3 that reflects the L-DOPA decarboxylating enzyme (AADC) activity within the terminals of the presynaptic dopaminergic neuron using FDOPA and PET. The major factor complicating the parameter estimation procedure with FDOPA PET is related to the diffusible metabolites of FDOPA in both the blood and the brain, necessitating formulation of kinetic models that accurately represent this complex biological system. The complexity of such kinetic modeling is reflected in the large number of kinetic parameters included in the model. Given the limitations of the current PET methodology, including those imposed by instrumentation, the physical half-life of a tracer and the feasibility of human experimentation among others, there is, however, a limit to which the number of parameters can be adequately determined from tracer time-activity data. To reduce the number of parameters, therefore, certain constraints need to be imposed in the model by making fundamental or physiologically reasonable assumptions. This process is usually a challenge that requires scientific ingenuity. The elegant work on FDOPA PET data analysis to derive k_3 reported by several groups of investigators, including the Montreal and the Los Angeles groups (*1–5*), is a tremendous accomplishment. As suggested by Wahl et al., but the recently reported development of a new tracer fluoro-m-tyrosine (*6,7*) may be an alternative approach because this tracer is not subject to O-methylation. This would simplify the kinetic model, resolving some of the parameter estimation controversies in the present communications. An analogy may be made to the use of FDG rather than ^{11}C-glucose, where the kinetic modeling for ^{11}C-glucose is virtually impractical because it undergoes a substantial number of reaction steps in the glycolytic pathway.

For the particular parameter of interest in the model to be clinically useful, its diagnostic performance needs to be established. In addition, simplicity and practicality of imaging as well as image-data analysis procedures are important for widespread clinical use. For the latter reason, K_i^{FD} and SOR are an attractive alternative to k_3. An analogous situation may be found in imaging studies of dopamine receptors and transporters in which the tissue ratio of the striatum to the cerebellum or the frontal cortex at a fixed time has been commonly used as an index of receptor or transporter binding. As pointed out here by Cumming et al. (*8*), however, these parameters reflect a dynamic interplay of multiple factors including those not primarily related to the biochemical process of interest, such as blood flow, blood-brain permeability-surface area, peripheral metabolism and clearance. Therefore, efforts have been made, in the case of dopamine receptor or transporter imaging, to obtain parameters that are simple and practical yet independent of other complicating factors (*9,10*). Studies to address the feasibility of such measurements with FDOPA PET may be warranted, although the complexity of the FDOPA model may make this task difficult.

Given this limitation of K_i^{FD} and SOR, the potential clinical usefulness of these parameters as an index of the integrity of the presynaptic dopaminergic neuron and hence a diagnostic index of the disease such as Parkinson's disease must be rigorously evaluated. The problem is not simply the sensitivity of the test but the specificity of the test must be carefully determined. This would mean that studies must be designed to include not only normal control subjects and Parkinson's disease patients but also patients with a wide spectrum of central nervous system disorders including, for example, Alzheimer's disease and other neurodegenerative as well as vascular disorders. In particular, patients with coexisting small-vessel disorder may have an abnormal blood-brain permeability (*11*). Additionally, the diagnostic performance of these parameters should be compared with that of yet other kinds of objective indices that reflect the disease process. The function of presynaptic dopaminergic neurons can be also assessed by imaging of dopamine transporters. The New York group (*12*) recently reported such a comparative imaging investigation using FDOPA PET and ^{123}I-βCIT-FP SPECT and found that both methods discriminated Parkinson's disease patients from controls with comparable accuracy, although only SOR's were measured for both tracers and compared in their study.

Ideally, as argued by Cumming et al. (*8*), the purpose of parameter estimation using PET or SPECT is to measure a biological variable of interest to pathophysiology. Hence, the parameter of interest in the case of FDOPA studies is the AADC activity; for dopamine transporter imaging, it is the number of dopamine reuptake sites. Studies to measure these parameters are essential in furthering the understanding of the regulation of dopaminergic neurotransmission. In the face of decreasing presynaptic dopaminergic neurons, for example, the AADC activity may be up-regulated while the dopamine reuptake sites may be down-regulated (*13–15*). If the progression of Parkinson's disease, for example, were to be measured in terms of the degeneration of the nigrostriatal dopaminergic neurons, then the former might underestimate while the latter might overestimate the process. Another marker yet to be developed that accurately reflects the number of the presynaptic dopaminergic neurons might then be a more accurate diagnostic index of disease progression.

The controversies presented in the communications published in this issue (*8,16,17*) regarding the parameter estimation with FDOPA PET represent an important impetus and a challenge toward further advances and new developments in search of robust yet practical methodologies for parameter estimation in nuclear medicine.

Masanori Ichise
Mount Sinai Hospital
Toronto, Ontario, Canada

James R. Ballinger
Princess Margaret Hospital
Toronto, Ontario, Canada

Received Jan. 1, 1997; accepted Jan. 9, 1997.
For correspondence or reprints contact: Masanori Ichise, MD Rm. 635, Nuclear Medicine Department, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario, MG5 1X5 Canada.

REFERENCES

1. Reith J, Dyve S, Kuwabara H, Guttman M, Diksic M, Gjedde A. Blood-brain transfer and metabolism of 6-[^{18}F]fluoro-L-dopa in rat. *J Cereb Blood Flow Metab* 1990;10:707–719.
2. Gjedde A, Reith J, Dyve S, et al. Dopa decarboxylase activity of the living human brain. *Proc Natl Acad Sci USA* 1991;88:2721–2725.
3. Huang SC, Yu DC, Barrio JR, et al. Kinetics and modeling of L-6-[^{18}F]fluoro-dopa in human positron emission tomographic studies. *J Cereb Blood Flow Metab* 1991;11:898–913.
4. Kuwabara H, Cumming P, Reith J, et al. Human striatal L-dopa decarboxylase activity estimated in vivo using 6-[^{18}F]fluoro-dopa and positron emission tomography: error analysis and application to normal subjects. *J Cereb Blood Flow Metab* 1993;13:43–56.
5. Kuwabara H, Cumming P, Yasuhara Y, et al. Regional striatal DOPA transport and decarboxylase activity in Parkinson's disease. *J Nucl Med* 1995;36:1226–1231.
6. Nahmias C, Wahl L, Chirakal R, Firnau G, Garnett ES. A probe for intracerebral aromatic amino-acid decarboxylase activity: distribution and kinetics of [^{18}F]6-fluoro-L-m-tyrosine in the human brain. *Mov Disord* 1995;10:298–304.
7. Barrio JR, Huang SC, Yu DC, et al. Radiofluorinated L-m-tyrosines: new in-vivo probes for central dopamine biochemistry. *J Cereb Blood Flow Metab* 1996; 16:667–678.
8. Cumming P, Gjedde A, Reith J. Controversies arising from recent FDOPA articles [Letter]. *J Nucl Med* 1997;38:1267–1269.
9. Laruelle M, Wallace E, Seibyl JP, et al. Graphical, kinetic, and equilibrium analyses of in vivo [^{123}I]β-CIT binding to dopamine transporters in healthy human subjects. *J Cereb Blood Flow Metab* 1994;14: 982–994.
10. Ichise M, Ballinger JR, Golan H, et al. Noninvasive quantification of dopamine D2 receptors with iodine-123-IBF SPECT. *J Nucl Med* 1996;37:513–520.
11. Wallin A, Blennow K, Fredman P, Gottfries CG, Karlsson I, Svennerholm L. Blood brain barrier function in vascular dementia. *Acta Neurol Scand* 1990;81: 318–322.
12. Ishikawa T, Dhawan V, Kazumata K, et al. Comparative nigrostriatal dopaminergic imaging with iodine-123-β-CIT-FP/SPECT and fluorine-18-FDOPA/PET. *J Nucl Med* 1996;37:1760–1765.
13. Kish SJ, Zhong XH, Hornykiewicz O, Haycock JW. Striatal 3,4-dihydroxyphenylalanine decarboxylase in aging: disparity between postmortem and positron emission tomography studies? *Ann Neurol* 1995;38:260–264.
14. Reith J, Benkelfat C, Sherwin A, et al. Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc Natl Acad Sci USA* 1994;91:11651–11654.
15. Bannon MJ, Poosch MS, Xia Y, Goebel DJ, Cassin B, Kapatos G. Dopamine transporter mRNA content in human substantia nigra decreases precipitously with age. *Proc Natl Acad Sci USA* 1992;89:7095–7099.
16. Wahl L, Nahmias C. Controversies arising from recent FDOPA articles [Letter]. *J Nucl Med* 1997;38:1269–1270.
17. Dhawan V, Ishikawa T, Patlak C, Eidelberg D. Controversies arising from recent FDOPA papers [Letter]. *J Nucl Med* 1997;38:1270–1271.

EDITOR'S NOTE

A recent Letter to the Editor by Cumming P, Gjedde A and Reith J (*8*) and the replies by Wahl L and Nahmias C (*16*), and Dhawan V, Ishikawa T, Patlak C and Eidelberg D (*17*) raised issues which deserved further comment. This editorial was requested to provide an additional perspective on the issue of quantifying and modeling physiologic processes with PET.

Stanley J. Goldsmith, MD
Editor-in-Chief,
The Journal of Nuclear Medicine

Letters to the Editor

Controversies Arising from Recent FDOPA Articles

TO THE EDITOR: In three recent articles, Dhawan et al. (*1*), Ishikawa et al. (*2*) and Wahl and Nahmias (*3*) examined the use of the tracer FDOPA to quantify the decarboxylation of DOPA to dopamine in human brain. Although we commend the authors for their desire to evaluate the issues pertaining to interpretation of positron emission tomograms of FDOPA metabolism in human brain, their citations are selective and their arguments noticeably biased. In particular, we feel that the current debate about the utility and merits of the several approaches to the assay of FDOPA metabolism with PET would benefit from consideration of the following points:

1. The authors' conclusions that it may be unnecessary to assay a specific biological variable (as opposed to a less specific variable) to obtain clinically relevant information.
2. The authors' demands that an uncertain disease process be the criterion of model of quantitation of a biological variable, and that the estimates of model parameters be independently clinically (as opposed to biologically) validated.
3. The authors' selections of cited articles.

Choice of Assay

With present PET methods, Dhawan et al. (*1*) conclude that FDOPA yields clinically more relevant information with the simple multiple-time graphical analysis of Patlak (*4–6*) than with the computationally more demanding compartmental techniques of Gjedde et al. (*7*) and Kuwabara et al. (*8,9*). According to Dhawan et al. (*1*), the information obtained with the simpler approach is clinically relevant because it agrees with clinical information already in evidence. It matters little whether the simpler approach yields any information of biological interest.

Diagnosticians and neuroscientists of course may have divergent interests in the outcome of specific tests, but we believe it is wrong to suggest that the only criterion of interest of such a measurement is whether or not it clearly distinguishes between specific groups of preselected subjects. For example, the failure of a particular assay to establish a conclusive difference between the activities of an enzyme in patients and healthy control subjects does not mean that the measurement is of no value to the understanding of the disease; on the contrary, the observation may be the key to that understanding. We only emphasize this truism because Dhawan and Ishikawa et al. incorrectly claim that attempts to measure the activity of the enzyme DOPA decarboxylase (DDC) in Parkinson's disease are misguided because another less specific measurement of the net transfer of FDOPA across the blood-brain barrier in their hands discriminates more clearly between patients and healthy volunteers. Ishikawa et al. (*2*) give an unintended but excellent example of this dilemma: The authors conclude that "Estimates of striatal DDC activity cannot discriminate between normals and Parkinson's disease patients as accurately as K_i^{FD} (i.e., the slope of the Patlak plot, not a "unidirectional" transfer constant as claimed by the authors) or SOR (i.e., striatum-occiput ratio)." The authors base this conclusion on the F-statistics of the measures which in reality is a reference to the precision rather than the accuracy of the measures.

Accuracy is the more illuminating property, which in the case of FDOPA may not apply to measures such as the Patlak slope and the SO ratio if they have no specific biological meaning. The accuracy of the two measures is placed in further serious doubt by the lack of correlation between the values of the SOR and measures of the disease's severity (UPDRS), as revealed by the authors' own Figure 3 (*2*) and by the restrictive biological bounds on the Patlak slope dictated by blood flow and the blood-brain permeability-surface area (PS) product of FDOPA. It is entirely possible that both the Patlak slope and the SO ratio fail to reveal this variation for methodological reasons.

In many scientific studies, the purpose of the assay is not to distinguish between patient groups but to measure a biological variable of interest to pathophysiology. In this respect, lack of discrimination need not be less revealing than discrimination. Also, were the activity of the enzyme that synthesizes dopamine from