A Reawakening of Interest in Radionuclide Brain Imaging

Institutions performing positron emission tomography (PET) imaging of the brain emphasize the value of the procedure as an investigative tool in studying complex clinical and cognitive conditions (*1–3*). Not as well appreciated is the impetus provided by PET on catalyzing the discovery of more practical gamma-emitting radiopharmaceuticals that, unlike their predecessors, technetium-99m (^{99m}Tc) pertechnetate and ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (DTPA) and glucoheptonate, efficiently cross the intact blood-brain barrier (BBB) and localize in brain tissue. Several neutrally charged lipophilic radiolabeled compounds have been developed with this capacity and, based on pharmacokinetic studies, they can be divided into two reasonably distinct groups: (a) those with which brain distribution is proportional to *blood flow*, and (b) those with which the pattern of localization is related to *receptor-binding* (Table 1). Nearly all of the cerebral blood flow (CBF) agents are presently undergoing clinical evaluation, with a significant number of patient studies using iodoamphetamine (IMP) and its analog HIPDM already completed, and a new drug application (NDA) for IMP has been filed with the Food and Drug Administration. Of the receptor-binding agents, only the acetylcholine receptor radiopharmaceutical (4-[^{123}I]-QNB) is radiolabeled with a gamma-emitting radionuclide and can be imaged by single-photon emission computed tomography (SPECT), while dopamine and opiate receptor radiotracers are radiolabeled with positron emitters and require PET for imaging.

TABLE 1
New Brain Radiopharmaceuticals

Cerebral blood flow
- Iodoamphetamines
  - (a) N-isopropyl-p-[I-123]-iodoamphetamine (IMP)* (*1*)
  - (b) N,N,N′-trimethyl-N-[2-hydroxy-3-methyl-5-[I-123]-iodobenzyl]-1,3-propane diamine (HIPDM)* (*2*)
  - (c) [^{201}Tl]-Diethydithiocarbamate (DDC) (*3*)
- Cyclic amines
  - (a) [^{99m}Tc]Propyleneamine oxime (PnAO) (*4*)
  - (b) [^{99m}Tc]Hexamethyl-propyleneamine oxime (Hm-PAO)* (*5*)
- Cyclic diaminodithiol
  - (a) [^{99m}Tc]Bis-aminoethanethiol (BATS) (*6*)
  - (b) [^{99m}Tc]-N-piperidinylethyl-diaminedithiol (DADT)* (*7*)

Receptor binding
- Muscarinic acetylcholine receptor (mAChR)
  - (a) 3-quinuclidinyl 4-[I-123]-iodobenzilate (4-IQNB)* (*8*)
- Dopamine receptors
  - (a) (3-N-[^{11}C]-methyl) spiperone* (*9*)
  - (b) [^{18}F]spiroperidol (*10*)
  - (c) [^{18}F]haloperidol (*11*)
- Opiate receptors
  - (a) [^{11}C]carfentanil* (*12*)

* Under FDA approved IND's for clinical trials

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In this issue of the Journal, several articles appear that address important physical and pharmacokinetic characteristics of three of the newer brain imaging radiopharmaceuticals. The results reported may greatly influence the clinical use of these agents. Bice et al. (*4*) from the Johns Hopkins Neuro-PET facility describe a new method for measuring in vivo neuro receptor cerebral binding using a nonimaging dual detector system equipped with coincidence circuitry for external counting of the brain. They report that this device is practical and technically accurate for quantitating brain uptake of carbon-11 (^{11}C) carfentanil—a high affinity synthetic opiate. Serial measurements in patients differentiated specific opiate receptor-binding from nonspecific binding using naloxone, a competitive opiate antagonist, administered both before and after the [^{11}C]carfentanil. The authors suggest that their counting system, euphemistically called HEADS, is an economic alternative to PET imaging in receptor-binding studies of the brain. Because of its high sensitivity, a dose of several hundred microcuries of the radionuclide is adequate for a study, rather than the millicurie amounts needed for the PET imaging studies. Although the authors convincingly demonstrate the feasibility of such a counting device, the necessity to produce positron emitting radiopharmaceuticals on-site means that studies using this device will have to remain exclusively within PET imaging facilities.

Clinical studies of stroke, epilepsy, and dementias that have been reported using the iodine-123- (^{123}I) labeled iodoamphetamines (*5–7*), have suggested that iodoamphetamine uptake from sites such as the lung may recirculate and redistribute in the brain. No previous mention has been made, however, of the fact that this alters the image resolution or lesion detection accuracy. In an article by Creutzig et al. in this issue (*8*) the phenomenon of [^{123}I]IMP "redistribution" was studied in 113 patients (23 with no neurologic disease, 47 with primary brain tumors, and 43 with an occlusion of one middle cerebral artery, under consideration for bypass surgery). Serial SPECT images performed in normal patients at 15–45 min, 1.0–1.5 hr, and 3.5–4.0 hr post-base, demonstrated an absolute decrease in cortical and cerebellar activity with time, but no change in basal ganglia activity was observed over this same time period. Nearly two-thirds of the patients audiovisually stimulated demonstrated increased activity in the stimulated regions of the brain on the early images, but only a quarter of these remained evident on the late images. As expected, areas of stroke showed diminished activity on the early and late images, but nearly a quarter of them showed an increase or "hyperperfusion" on the late images and a loss of the cerebellar diaschisis that occurs with supratentorial vascular lesions (*9*). These temporal variations in the cortical distribution of the [^{123}I]IMP places in question some earlier reports that did not adhere to a strictly timed imaging protocol, particularly when prolonged imaging was done using a rotating head SPECT camera. If, as it appears, the conversion from early diminished activity to late hyperactivity in stroke patients can predict better results following bypass surgery, then serial SPECT imaging of the brain for redistribution should become a routine procedure. More rapid imaging devices are a paramount need for SPECT brain imaging in the future, if this is going to be practical. Two novel instruments, one in clinical trial (the Technicare "TRIAD"), and the other under construction, (the Missouri University Multiplane Imager = "MUMPI"), may provide such imaging devices.

The third article by Sharp et al. (*10*) discusses the pharmacokinetics of two stereoisomers of Technetium-99m- (^{99m}Tc) hexamethyl-propyleneamine oxime (HM-PAO), a derivative of [^{99m}Tc)PnAO under development by Amersham International. The meso form showed no specific cerebral uptake and although adequate cortical extraction was observed with the mixture of meso and d,l forms, the pure d,l form showed optimum brain uptake, prolonged cortical retention, and excellent gray and white matter differentiation. Unlike the radioiodinated amphetamines, [^{99m}Tc]HM-PAO can be prepared by the user from a radiopharmaceutical kit, and can be injected into the patient within 30 min of preparation. Once injected, the radiopharmaceutical shows excellent in vivo stability, as brain lesions demonstrable on the early images are also well seen several hours later. Autoradiographic studies presently ongoing in our laboratory at the University of Missouri, correlating HM-PAO distribution with radiolabeled microspheres indicate that the cortical distribution of HM-PAO is blood-flow related, and early clinical data emanating from Europe and our laboratory suggests it may be the optimum SPECT brain imaging agent for routine use.

Thus, the array of topics addressed in these three reports give some indication of the renewed interest in radionuclide studies of brain function and metabolism not only in academic centers, but by commercial suppliers as well. With such cooperation between research institutions, industry, and government, we and our patients should all benefit from this renaissance in neuro-nuclear medicine.

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