Cerebral Perfusion Imaging Tracers for SPECT: Which One to Choose?

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Radionuclide imaging and semiquantitation of cerebral perfusion by SPECT are important issues in patients with neurological and psychiatric diseases. The search for an ideal brain SPECT radiopharmaceutical is complicated and competes with other imaging modalities such as dynamic CT and MRI. Unfortunately, currently available radiopharmaceuticals are far from ideal.

The ideal agent should be commercially available, easy to label, possess in vivo and in vitro stability, have short arterial input to facilitate intervention (stimulation) studies and a high extraction fraction at the first pass. Such an agent should reach a steady state in the brain quickly and be able to penetrate intact blood-brain barriers regardless of the blood cell-plasma protein partition. They also must have high passive retention in the brain independent of a metabolic or enzymatic system or a specific binding site. An ideal agent would also reflect regional distribution, which is linear to the cerebral blood flow over a wide range and remain fixed in the brain with a constant pattern to permit SPECT imaging with minimal extra brain activity.

The ideal radiopharmaceutical should be neutral, lipophilic (log p octanol/water between 1.0–2.5) and of small size (under 500 dalton) (*1*). All of the technetium-amines and iodo-amines discussed in this editorial [hexemethylpropyleneamine oxime (HMPAO), bicisate (1,1-ECD) or isopropyl iodoamphatamine (IMP)] meet these criteria at different levels of lipophilicity, which determines biodistribution. At higher levels of lipophilicity, there is a trade-off between binding to the brain cells and plasma proteins in favor of the latter (*2*). A ^{99m}Tc-labeled compound that behaves like IMP would represent a major advance for routine brain perfusion imaging. However, a consensus has not yet been reached on the best agent.

A clear understanding of the absence of a true flow agent is crucial before comparing the available radiopharmaceuticals, since correlation found between PET or microspheres and SPECT blood flow agents has demonstrated that the relationship is curvilinear. Recently, several researchers suggested that the rising asymptotic plateau is caused by washout from high-flow regions (*3,4*). The uptake, extraction fraction and retention of the agents used vary among different regions of normal and abnormal brain (*1*) and the fixation can be altered by local or regional parameters. The kinetic behavior and trapping mechanism specific to each tracer must be well understood for the clinical application and interpretation of SPECT images. Technetium-99m-d,1 HMPAO (exametazime) and ^{99m}Tc-1,1 ECD (bicisate) are both available and easy to label, however, HMPAO has poor in vitro stability (RP = 85% after 30 min) (*5*) and susceptibility to radiolysis, whereas ECD is much more stable (RP = 96% at 6 hr) (*6*). These technetium-amines demonstrate in vivo instability following blood contact and have a short arterial input of the bioavailable compound (*7–9*). The moiety of compounds changes in circulating blood, which results in relatively poor extraction (E) by the brain (HMPAO 77%, ECD 60%) (Table 1). The retention in the brain parenchyma is linked to the enzymatic reactions with glutathione (GSH) for HMPAO (*10,11*) and with stereospecific deesterification to acid derivatives for ECD (*12–15*). These mechanisms have slow turnover and yield nondiffusible polar metabolites.

The first-pass extraction rate is flow-dependent for ECD, similar to HMPAO, and results in decreased uptake in the higher flow of a normal range (*16*). Conversely, extraction is higher when the flow is reduced. Due to a low backflux from brain (k2), the retention of ECD is higher than HMPAO (Table 1). Backdiffusion of HMPAO is more pronounced in high flow regions and a higher extraction in low flow regions results in poor contrast. Technetium-99m-ECD images hold a slightly better contrast between high and low flow regions. ECD has some washout from the brain and negligible redistribution (*17,18*). HMPAO has slow clearance and liver accumulation contrary to ECD, which has rapid blood clearance with renal excretion of acid metabolites (EC) yielding a better signal-to-noise ratio.

IMP, which is not readily available in every country and is cumbersome to label, was the first iodo-amine (*19*) used for brain imaging with a high brain extraction rate (96%)

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TABLE 1
Comparison of Brain SPECT Imaging Agents

Characteristic	IMP	HMPAO	ECD
Log P	1.40	1.90	1.64
Purity	96%	85%	96%
Stability	6 hr	30 min	6 hr
Head uptake (%ID)	6.0 ± 1	5.2 ± 1	6.3 ± 1.9
BUI	113	77	73
E%	90	77	60
k1	0.43	0.26*	0.29*
		0.27†	0.25†
k2	0.014	0.60*	0.22*
		0.59†	0.19†
$\lambda = k_1/k_2$	32.4	0.43*	1.31*
		0.46†	0.31†
k3	0.93	0.58*	0.57*
		0.57†	0.59†
α = k2/k3	70	0.97*	2.6†
		0.97*	3.1†
R%	98%	50%*	72%*
		49%†	75%†
Ē%	88	38.5*	43.2*
		37.7*	45†
Ki	0.42	0.13*	0.21*
		0.13†	0.19†
Redistribution	++	10	0
t (min)	20	10	10
Mean washout rate of steady state (hr)	1%	2%	10%
Heterogeneous washout	+	0	+

*See References 49, 50 and 51. See Reference 48 for IMP data.
†See References 16 and 51.
k1 = unidirectional influx constant corresponding to flow × extraction (first pass) (F × E) ml g^{-1} min^{-1}; k2 = back-flux in 1/ml, k1/k2 = partition coefficient in the cortex, k3 = transformation constant (1/min), α = k3/k2 = conversion rate, R = retention fraction = k3/k2 + k3, Ki = steady-state influx constant = $K_1 \cdot K_3/K_2 + K_3$/ E = extraction at first pass, Ē = E*R Extraction at steady state, BUI = brain uptake index, log P = decimal logarithm of the partition coefficient octanol on water, t = time to reach the steady state, W = washout rate after steady state (hr^{-1}) from brain.

(Table 1). Its uptake linearly follows a wide range of flow assessed by microspheres (*20*). The gradual increase in the brain uptake of IMP (50% at 5 min and 90% at 20 min) is linked to its clearance from the lung, which functions as a buffer releasing the tracer into the circulation (*21*). The stereoselective retention mechanism of IMP in brain tissue involves a possible conversion to hydrophilic metabolites (*22*), and an affinity to high capacity and relatively nonspecific binding sites. Intracellular pH can play a role in many instances: (1) rate of exchange through the BBB; (2) strength of binding to the nonspecific sites of the brain; and (3) metabolic conversion rate of amines through the enzymatic system linked with binding sites. When blood pH is decreased due to local lactate discharge, the uptake of IMP is notably decreased (*23*).

Brain retention of IMP reflects the balance of the washin and washout of the tracer in individual structures. Washout from brain is influenced by blood flow, retention mechanism and metabolism of the tracer. This washin/washout balance is clearly demonstrated in the study performed by Nishizawa et al. (*24*) who observed a temporal change of radioactivity among normal brain structures. Likewise, IMP uptake is different between white and gray matter and favors the latter. The first possible explanation for this is the first come, first served principle. Since the penetrating capillaries enter the gray matter, more tracer is available to be extracted by gray matter before reaching the white matter. The second explanation is the difference in the extraction coefficient of IMP between gray and white matter (*21*). Rapin et al. demonstrated by autoradiography that the activity in the brain redistributes with time in favor of the white matter possibly due to backflux from gray to white matter (*25*). For this reason, it is crucial to perform early imaging at 20 min. Afterwards, polar metabolites such as p-iodobenzoic acid (PIBA) will appear in the plasma in non-negligible amounts with time (*26*), diffusing passively through a damaged blood-brain barrier. Therefore the delayed images have to be acquired at 3 hr.

One of the most active and exciting fields of nuclear medicine has been evaluating cerebral perfusion in several pathologies. There are certain conditions where different lipophilic tracers give similar images such as drug addiction, dementia, interictal epilepsy, psychiatric disorders and head trauma. Ictal, postictal epilepsy, stimulations and stroke are not among these conditions.

ICTAL AND POSTICTAL EPILEPSY

Interictal perfusion SPECT was performed with iodoamines (*27*) and Tc-amines (*28*) yielding a sensitivity of 60% to 75% which correlates well with EEG stereolocalization. Fluctuations in perfusion and metabolism in the interictal period do not allow the detection of more than 75% epileptic hypoactive foci with perfusion SPECT or FDG-PET (*29*). During the ictal phase, higher metabolic activity coupled with high perfusion results in increased uptake in the epileptic foci. True ictal studies are difficult to perform in vitro with unstable HMPAO, rendering it impossible to store in the neurology department. In this case, compounds of higher stability such as IMP or ECD are more appropriate. In the early postictal phase, cerebral blood-flow remains elevated decoupling from the rapidly declining glucose metabolism (*30*). Blood flow remains elevated long enough to allow lipophilic tracers to detect the hyperactive foci. Since ECD has a shorter arterial input, it appears to be more appropriate than IMP. Sensitivity increases by 10% during the immediate postictal phase (*31*).

STIMULATION

In normal cerebral autoregulation, cerebral blood flow increases in response to neuronal metabolism; SPECT has demonstrated sufficient sensitivity to detect changes in activity related to stimulation of metabolic activity (*32*). These activation tasks must generate detectable and reproducible changes in cerebral blood flow which are sustained

during the period after injection, while the tracer reaches steady state. In the activation studies, the tracer distribution has to reflect high flow rates, like IMP, in order to quantify the stimulation accurately. The trapping process of the tracer should not be saturable in test/retest studies using split dose technique within a short interval. In the test/retest studies, assumption is that the original distribution pattern is still the same during the second SPECT image acquired after activation on the same day. Due to the heterogeneous washout pattern, a test/retest protocol would introduce significant errors, therefore a two day protocol is preferable (*33*).

As the radioactivity of d,1 HMPAO changes with time after preparation (in vitro and in vivo), even if equal doses of radioactivity are injected, one cannot be sure of the same bioavailability for brain. Using HMPAO in a test/retest activation study requires a long stimulation of the same intensity. ECD has the same uptake and retention characteristics of HMPAO, but it is more stable and more convenient to handle. Like HMPAO, however it underestimates high flow areas (*5*).

CEREBROVASCULAR DISEASE

Tomographic images of cerebral perfusion with lipophilic radiotracers are extremely useful in early detection of acute and chronic stroke. SPECT is superior to CT in detecting ischemia since it reflects alterations in perfusion before structural changes occur. This is an advantage for determining the appropriate therapy, which must be initiated as early as possible in acute stroke.

In stroke, two differentiated regions are observed in the brain: one the central infarct core known as the structural abnormality, which can be imaged by CT and two a peripheral area that reflects peri-infarct ischemia, known as the penumbral zone (*34*). SPECT perfusion imaging can demonstrate both of these regions depending on the tracer used. There is a correlation between the penumbral zone and the severity of the neurological deficit which may be related to outcome (*35*).

Because of the high extraction rate in low-flow regions and the high level of perfusion in ischemic regions due to vasodilation, HMPAO cannot be reliable to detect peri-infarct ischemia in the subacute phase (4–15 days). If images are acquired at 4 hr, clearance of the plasma activity and leakage of the tracer from the cells allows imaging of hypoactive peri-infarct ischemia (*36*). On the contrary, early IMP images demonstrate both structural abnormalities (40% decrease) and the penumbral zone (15% decrease). With time, even if the central area remains unchanged, redistribution occurs in the peripheral zone resulting in a partially filled delayed images. The degree of redistribution is correlated with the local cerebral blood flow and regional consumption of oxygen but not with the regional oxygen extraction fraction which reflects viability (*37*). IMP redistribution indicates a tissue with low CBF and a remaining metabolism (*38*). This implies that blood flow is inadequate relative to the energy/metabolic demand for oxygen and substrate (misery perfusion). In these instances, slower metabolism and washout of IMP would cause retention in the peri-infarct zone. The only definitive conclusions made on redistribution IMP SPECT images is whether non-necrotic cells are present or not. The redistribution of IMP was formerly related to a good clinical outcome (*39*).

With ECD in the acute phase of stroke, when the esterase enzyme system is still functioning, a higher extraction and retention of the tracer results in low blood flow areas (*40*). In the subacute phase, hypoxia may alter the function of esterase, resulting in minimal retention, even if the extraction is preserved. The hypoactive area will be larger and deeper on delayed images, demonstrating increased clearance from the ischemic areas (*41,42*). Diminished activity of ECD in subacute stroke may be due to the lack of oxygen and enzyme activity, which causes an accumulation of unmetabolized tracer candidate to leak out from the peripheral ischemic zone. By contrast, at low blood flow, since the GSH system is more resistant to hypoxia and continues to function, cells retain HMPAO in the ischemic area.

During the period of luxury perfusion after recanalization, there is transient decoupling of metabolic demand and cerebral blood flow in the subacute phase of ischemic regions. Increased glucose consumption is observed, indicating anaerobic glycolysis and production of lactate accompanied by local acidosis all of which decrease the uptake of IMP. In this condition, the behavior of the perfusion tracers is different. Most of the time HMPAO shows a focal area of hyperactivity, whereas IMP and ECD demonstrate hypoactive zones and IMP is related to low extraction in acidic pH and ECD caused by low retention, which is linked to altered esterase function in hypoxia (*43,44*).

In reversible ischemic stroke, structural imaging has little to offer and perfusion imaging has low sensitivity (60% within the first 24 hr (*45*), declining further with time). To increase sensitivity, it is necessary to assess vasodilatory reserve by an acetazolamide stimulation test as demonstrated by us with IMP (*46,47*). The weak contrast obtained with HMPAO and ECD in very mild ischemia is a drawback incorrectly delineating lesions. Because activity of these ^{99m}Tc-labeled amines is not linear at high flow rates, the response to acetazolamide is blunted as is lesion contrast.

CONCLUSION

Although IMP because of its linearity with flow and capacity to depict mild ischemic regions seems to remain the reference in assessing cerebrovascular diseases, ECD, due to its availability and improved stability, will likely become widely used even though it is far from being an ideal chemical microsphere agent. Technetium-99m-ECD is a powerful diagnostic tool to facilitate critical management decisions in neurologic and psychiatric diseases. It is

necessary to be cautious, however, in using this tracer in extreme conditions of low and high brain blood flow and in test/retest examinations. Iodine-123-IMP has not been replaced by Tc-labeled amines. The search continues for an optimal brain tracer of perfusion and viability as a reliable first step for functional and receptor imaging. Although the task to find the ideal agent is difficult, the challenge is worthwhile. With early diagnosis of cerebrovascular disease, there is an opportunity for improved outcome.

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development of ^{123}I-MIBG, ^{111}In-pentetreotide or other receptor-specific radiolabeled ligands. I did not tell them of the men and women who work in the middle of the night to produce and deliver those magic bullets, or of those who work day after day in hospitals and offices obtaining images and data. Nor did I describe the wonder of a gamma camera or my delight when watching three-dimensional image acquisition, volume reconstruction and fusion with MRI or CT images. There is never enough time to relate the fascination of watching the brain think, the heart pump, or the marvels of other organ function.

Nuclear medicine is more than a medical specialty. It is a wonder to behold.

Stanley J. Goldsmith, MD, Editor-in-Chief

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