Utility of Late N-Isopropyl-p-(Iodine-123)-Iodoamphetamine Brain Distribution in Predicting Outcome Following Cerebral Infarction

S. Gupta, MD; D.L. Bushnell, MD; A. Mlcoch, PhD; G. Eastman, BS; W.E. Barnes, PhD; and S.G. Fisher, MS

Background and Purpose: The purpose of this study was to determine utility of late N-isopropyl-p-(iodine-123)-iodoamphetamine distribution in predicting neurological and language outcome.

Methods: We prospectively studied 29 patients with unilateral hemispheric ischemic cerebral infarction using the neuroimaging method of single-photon emission computed tomography and the above tracer. Four different imaging measures reflecting late tracer distribution or redistribution and three measures indicative of the patients' overall neurological or language outcome at 3 months were used in the data analysis. All patients had neuroimaging within 30 days of infarction, and 14 patients were imaged within 10 days of infarction. Data analysis was performed for all patients combined and then separately on the groups imaged within 10 days of and more than 10 days after infarction.

Results: The volume of the late image defect significantly correlated with one measure of neurological outcome in the whole group and in those imaged more than 10 days after cerebral infarction. However, these results are difficult to explain based on the present understanding of the physiology of late N-isopropyl-p-(iodine-123)-iodoamphetamine distribution.

Conclusions: We feel that the pattern of late N-isopropyl-p-(iodine-123)-iodoamphetamine distribution is probably not useful as an independent predictor of neurological and language outcome.

(Stroke 1991;22:1512-1518)

Single-photon emission computed tomography (SPECT) with N-isopropyl-p-(iodine-123)-iodoamphetamine (IMP) has been used to obtain physiological brain images in patients with cerebrovascular disease. After cerebral infarction, the early IMP images (up to 1 hour after the injection of IMP) show reduced tracer activity in the area of infarction. If imaging is repeated after 4 hours (late scan), an increase in tracer activity is often seen in the area that originally had shown reduced activity on the early images. However, the exact physiological and clinical relevance of this redistribution phenomenon has yet to be determined. It has been speculated that IMP redistribution indicates the presence of ischemic yet viable tissue at the periphery of the infarction. Based on this assumption, some investigators have used IMP redistribution in an attempt to predict recovery after cerebral infarction, with variable results.

This study was designed to assess the utility of late IMP distribution and redistribution in prediction of neurological and language outcome after cerebral infarction. It has been suggested that changes in the blood–brain barrier (BBB) after infarction may alter the physiological significance of the IMP pattern on late images. Consequently, we have also elected to study the effect of the time interval after infarction on the ability of late images to predict outcome.

Subjects and Methods

Twenty-nine patients with unilateral hemispheric ischemic cerebral infarction were studied within 1
month of infarction. The following criteria were included for entry into this study: 1) age <75 years; 2) no clinical or cranial computed tomography evidence of previous cerebral infarction or other pathological condition; 3) a speech reception threshold of ≤40-dB hearing threshold level unaided in the better ear; 4) at minimum, an eighth-grade level of education, with the ability to read and write English; and 5) written informed consent.

Neuroimaging studies were performed on all patients within 1 month of infarction. Initial neurological and language assessments were made within 24 hours of the initial SPECT/IMP study and again at 3 months after the onset of cerebral infarction. All clinical testing was done without the examiner's knowledge of the imaging results, and imaging analysis was performed without the imager's knowledge of recovery status.

The neurological examination consisted of assessments of motor and sensory systems, coordination, and gait. Each area was rated on a 4-point scale, with 1 indicating severe impairment and 4 indicating no impairment. Composite scores were then calculated; these ranged from 3 to 12 points each for the motor and sensory systems, 2–8 for coordination, and 1–4 total points for gait. These scores were then added to derive an overall neurological score (maximum score=36). The language battery consisted of the Porch Index of Communicative Ability, the Boston Naming Test, and the Raven Coloured Progressive Matrices. For the purposes of this study, only the overall severity scores obtained from Porch Index of Communicative Ability were used. This test was chosen since it has been shown to be a highly reliable test of aphasia and one that has been frequently used to measure recovery. An overall severity score is calculated by taking the average rating from 180 responses. A percentile is then given by using tables provided by Porch.

Three different measures of outcome were determined for both language and neurological function. An overall percentage recovery score was determined by calculating the percentage improvement in the clinical deficit from the initial language or neurological scores to the corresponding 3-month measures. In addition, the absolute difference between the initial and final clinical status (neurological and language) and the final 3-month neurological or language status was also used in the analysis of outcome.

Neuroimaging with SPECT/IMP was performed using a rotating truncated head gamma camera system with a medium energy collimator. Imaging was performed initially 15 minutes (early) and again 4 hours (late) after intravenous injection of 3–5 mCi IMP. The first 18 patients were studied using IMP produced by the (P,2N) reaction, and the remaining subjects were studied using (P,5N). Intravenous administration of this agent was performed in a quiet room with low-level ambient lighting to minimize the effects of sensory stimulation on cerebral blood flow. Images were reconstructed in the transaxial plane using a Wiener filter and reoriented approximately parallel to the canthomeatal line, with additional slices generated in the coronal planes as needed.

The following four parameters were obtained from the SPECT data:

1) VL: Measure of the defect volume as seen on the late images expressed as a percent of the hemisphere volume:

\[ VL = \frac{\text{Number of voxels within defect}}{\text{Number of voxels within hemisphere}} \]

2) AL: Measure of the relative (side-to-side) asymmetry in activity within defect on late images:

\[ AL = \frac{\text{Counts in defect} - \text{counts in contralateral normal region}}{\text{Counts in contralateral normal region}} \]

3) VR: Measure of the change in volume of the defect between the early and late defect, expressed as a percent of the volume of hemisphere:

\[ VR = \frac{\text{Defect volume early images} - \text{defect volume late images}}{\text{Volume of hemisphere}} \]

4) RI: Measure of the relative change or redistribution (between early and late images) in IMP activity occurring within the confines of IMP defect (as seen and outlined on the early images):

\[ RI = \frac{\text{Early image (side-to-side) activity asymmetry - late defect asymmetry}}{\text{Early defect asymmetry}} \]

In cases where VL was 0 (no defect seen on late images), AL was assigned a value of 0. Volume results were obtained by voxel summing from appropriate regions of interest corresponding to the measurement of interest. The region-of-interest placement was performed by a single observer for all patients. Images were displayed on a 24-grade color scale with constant thresholding for each subject for purposes of defining defect boarders. All volume measurements were determined by a single operator and obtained twice for each image set, with the average of the two values reported.

Associations between each imaging parameter and each parameter of neurological and language outcome were measured by correlational analysis for all patients combined and separately on the groups imaged within 10 days and after 10 days of cerebral infarction. For samples >10, the Pearson correlation coefficient was calculated. If <10 subjects were in a group, the Spearman method was used. Multiple regression techniques were used to examine the association between the neurological or language outcomes and each imaging parameter for all significant results from correlation analysis. Because the
<table>
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<th>Patient</th>
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<th>Clinical presentation</th>
<th>Time of initial imaging after infarction (days)</th>
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<tr>
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RHP, right hemiparesis; LHP, left hemiparesis.

time interval between SPECT and infarction influences late IMP distribution and initial neurological status influences outcome, adjustments for these variables were made in the regression models. A two-sided probability value of 0.05 was considered statistically significant. No adjustments for multiple comparisons were made.

**Results**

Table 1 summarizes the age, clinical presentation, and time between onset of infarction and the initial SPECT/IMP study for all 29 patients. All patients were men of average age 63.66 (mean±SD 6.24) years. Of the 29 patients, 17 demonstrated right hemiparesis and 11 demonstrated left hemiparesis. Eighteen subjects had clinically demonstrable aphasia.

Initial neurological and language measures were obtained from 26 and 18 patients, respectively. However, some patients were lost to follow-up, and, consequently, 3-month neurological and language measures were obtained in only 23 and 15 patients, respectively. The initial neurological scores ranged from 10 to 34 (maximum score=36), with a mean of 24. The initial language scores ranged from 20% to 94% (maximum=100%), with a mean of 56%. The final neurological status ranged from 14 to 36, with a mean of 29; the final 3-month language scores ranged from 32% to 99%, with a mean of 72%.

Table 2 summarizes the results of neuroimaging, neurological, and language measurements used in the data analysis. Twenty-five of the 29 SPECT/IMP studies showed significant focal decrease of IMP by visual assessment in one of the cerebral hemispheres on the early images. Two patients demonstrated "luxury perfusion," as indicated by an increase in IMP at the infarct site on early images, and two patients were felt to have normal early IMP images. VR and RI were not calculated for these four patients. Twenty-one of the late IMP studies showed focal decreases of IMP activity. Two patients with no defect on the late images also had no defect seen on the early images whereas five patients with a defect on the early images had no defect on the late images.
In one case, a floppy magnetic disc was damaged and quantitative analysis of late images was not possible. Interestingly, the two patients with luxury perfusion at the infarct site on the early images had substantial defects depicted on the late images. The ranges and mean values for the four image parameters are as follows: AL (0 to -46%, mean -13%); VL (0 to 30%, mean 9%); RI (-62 to 180%, mean 59%); and VR (0 to 40%, mean 9%). Figure 1 shows both an early and a late IMP study from patient 1 showing a substantial amount of IMP redistribution in the region of infarction (RI = 87%) in the left hemisphere.

The mean RI for the patients imaged <10 days after onset was 22%. This value is significantly less than the mean RI (93%) for patients imaged 10–30 days after onset (p < 0.01), which indicates much greater IMP redistribution in the latter group. Similarly, statistically significant differences were seen in the mean values for VR and VL between patients imaged <10 days and those imaged ≥10 days after infarction (p < 0.05). VR was greater and VL was smaller in patients imaged ≥10 days after infarction.

The correlation analysis revealed several significant relationships between the imaging parameters and the measures of outcome for the group as a whole. We found VR to be significantly related to the patient’s final neurological status (r = -0.60, p < 0.01), suggesting that as VR diminishes, the patient’s neurological outcome improves. In addition, VL was found to be related to absolute difference in neurological scores (r = -0.46, p < 0.05), suggesting that, as the volume of the late IMP defect decreases, the patient’s neurological recovery improves. However, when a multiple regression analysis was performed using the time at which the SPECT images were obtained after infarction (SPECTIME) and initial neurological severity as independent variables, the only imaging parameter that remained as a significant independent predictor of neurological recovery was VL (p < 0.01). The combination of VL, SPECTIME,
and initial neurological severity explained 67% of the total variance associated with the prediction of the absolute difference in neurological scores, with VL alone accounting for 21% of the variance in differences.

When correlation analysis was performed separately in the <10 days group and 10–30-day group, several significant correlations were obtained. In the <10 days group, AL correlated with final neurological status and absolute difference between initial and final neurological status ($r=0.66$, $p<0.05$ and $r=-0.62$, $p<0.05$, respectively). In the ≥10 days group, AL and VL both correlated with absolute differences between initial and final neurological status ($r=0.72$, $p<0.05$ and $r=-0.72$, $p<0.05$, respectively). However, when a multivariate regression analysis was performed using initial neurological severity as an independent variable, only VL remained a significant predictor of neurological recovery measured as the absolute difference between initial and final neurological status ($p<0.01$).

Discussion

It is well established that the early distribution of IMP in the brain is determined primarily by rCBF. However, several hours after injection, the IMP distribution is no longer dependent on rCBF but rather is determined by the regional concentration of various amine neurotransmitter receptors in the intact nerve synaptosomes. It has been speculated that brain regions that show decreased IMP on early images but normal activity on late images could represent, in part, ischemic but viable neurotissue. Based on this, it is reasonable to postulate a potential relationship between two of our imaging parameters (VR, RI) and clinical status or recovery because they measure the IMP redistribution phenomenon (VR is an index measure of the volume of redistributed neurotissue and RI is an indicator of the degree of redistribution that has been used in other published studies). We also used imaging parameters that reflect the IMP distribution at the time of delayed imaging only (VL, AL). We felt that if, in fact, such images reflected tissue viability, an association of those parameters with recovery and, particularly, final outcome or clinical function would be reasonable to postulate.

Defer et al. studied 24 patients using early and delayed SPECT/IMP imaging and correlated the results with the clinical recovery at 3 months. Redistribution amplitude (same as redistribution index in our study) significantly correlated with the clinical outcome after stroke. The higher the amplitude of redistribution, the better the clinical outcome in their study. We previously conducted a prospective study with SPECT imaging in unilateral cortical infarction in 14 patients to determine potential utility of SPECT imaging in prediction of language and neurological recovery after cerebral infarction. Although smaller volume early IMP defects correlated significantly with better language and neurological recovery, a limited analysis of IMP redistribution failed to demonstrate any definite relationship with the clinical outcome.

There are two basic differences between our studies and the study of Defer et al. The latter study included patients with reversible ischemic deficits and transient ischemic attacks whereas we studied patients only with infarctions. In addition, the mean
time between infarction and IMP imaging was 31 days in their study, 19 days in our original work, and 12 days in our current study. The timing of IMP imaging after stroke may be important since the findings from our study demonstrate that the degree of IMP redistribution is dependent on time after onset of infarction. Mean values for VR, RI, and VL differ significantly in the <10 and 10-30 day groups. Values for VR and RI were larger in those cases imaged after 10 days whereas VL values are larger in cases imaged within 10 days of cerebral infarction. The reason for these differences may be explained by temporal changes in the integrity of the BBB. The late IMP distribution is considered to be dependent on density of the different types of intact amine receptors and assumes the presence of an intact BBB. It is well known that approximately 10 days after infarction, the BBB becomes ineffective at excluding molecular entry into the central nervous system. Consequently, areas of the infarction would show “filling in” on the late image of the early IMP defect. This would readily explain why patients in our study imaged between 10 and 30 days after onset showed such high IMP redistribution. Similar results were found by Raynaud et al., who also suggested that such findings could be secondary to BBB disruption with accumulation of polar IMP metabolites in the zone of infarction. Consequently, temporal changes in IMP kinetics should be considered before drawing any conclusions from IMP results among patients in a study or between different studies.

Results from our multiple regression analysis identified VL as the only independent image predictor of neurological recovery. Measures of IMP redistribution (RI and VR) are considered to represent, in part, ischemic but viable tissue. Measures of late IMP distribution (AL, VL) may reflect binding to active amine receptor sites if imaging is done before disruption of BBB after cerebral infarction. Consequently, a large VL indicates a larger area of nonfunctional amine receptors, therefore a large area of injury, and thus poor recovery. However, considering the important effect of SPECTIME on the physiologic significance of VL, we find it puzzling that controlling for SPECTIME had only a minimal effect on the prediction of neurorecovery by VL in the group as a whole. Moreover, when VL was studied in subgroups of patients, it was found to be a significant predictor of neurological recovery only in those patients imaged 10 days after infarction. Again, if late IMP distribution simply reflects BBB disruption after 10 days postinfarction, it is difficult to explain why VL should correlate with outcome during this period. We therefore are hesitant to accept this finding as clinically relevant.

There is no generally agreed upon way to measure neurological or language recovery from stroke. The patient’s final neurological and language status, absolute difference between final and initial status, or percentage improvement of the initial deficit will all vary depending on the severity of initial deficit. In addition, each will react differentially to the inherent problem of the ceiling effect. We therefore decided to use each of these three measures of outcome in our analysis.

Our findings do not necessarily negate the premise that IMP redistribution (particularly within 10 days of infarction) reflects to a large extent ischemic but still viable neurotissue. Rather, the lack of independent association between measures of IMP redistribution and outcome may be related primarily to the variable natural outcome of ischemic tissue surrounding the infarction. There are probably many factors, presently unknown, that are involved in determining whether such tissue would result in infarction or would eventually recover function. Consequently, measurement of the volume or extent of this tissue at risk is not at this time a reliable predictor of the outcome of such tissue for a given patient.

Acknowledgment

We gratefully acknowledge the dedicated assistance of Miss Betty Michels in preparing this manuscript.

References


KEY WORDS • cerebral infarction • tomography, emission computed
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doi: 10.1161/01.STR.22.12.1512

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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