Ictal SPECT Using Technetium-99m-HMPAO: Methods for Rapid Preparation and Optimal Deployment of Tracer During Spontaneous Seizures

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Ictal SPECT provides unique information for the clinician treating patients with refractory epilepsy and reveals insights into the pathophysiology of seizures. We describe our methods for the routine attainment of ictal images using ^{99m}Tc-HMPAO. We have devised and implemented techniques for rapid reconstitution of ^{99m}Tc-HMPAO adjacent to the video-EEG monitoring suite such that the tracer can be rapidly injected into patients when spontaneous seizures occur. Our quality assurance data show that this can be done safely outside a nuclear medicine department. The clinical results in patients with temporal lobe epilepsy show that ictal injections (97% correct lateralization of focus, 0% incorrect) are more sensitive and accurate compared to interictal studies (48% correct, 10% incorrect), demonstrating that the implementation of these techniques is worthwhile.

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Single-photon emission computed tomography (SPECT) brain perfusion agents have been increasingly used in the localization of epileptic foci (*1–9*). SPECT studies of seizures show transient marked changes in regional cerebral perfusion that are of far greater diagnostic value than interictal studies (*1–3,6,8*). Initial experience was restricted to cyclotron-generated iodonated ligands (*1,2*), but the development of the ^{99m}Tc binding agent hexamethylpropylene amine oxime (HMPAO, exametazime, Ceretec Amersham, UK (*10*)) promised a more widely applicable SPECT ligand.

The unpredictable and spontaneous nature of seizures and the limited expiration time of reconstituted ^{99m}Tc-HMPAO demand that the ligand be reconstituted near the monitoring suite. This provides a number of technical requirements including a ready supply of freshly eluted sodium pertechnetate, dosage calculation, storage and radiation safety, a method of rapid reconstitution and quality control.

We previously showed that SPECT following injection of ^{99m}Tc-HMPAO minutes after seizure termination (postictal injection) revealed characteristic and reliably localizing features in 70% of patients with unilateral temporal lobe foci (*5,8,9*). Injections *during* seizures, however, were difficult to achieve. In 1990, Devous et al. (*11*) wrote, "true ictal studies with HMPAO are nearly impossible to obtain. This compound is unstable in the vial and cannot be prepared until seizure activity is observed. This typically leads to delays between onset of activation and HMPAO injection of 5 to 20 min."

Our previous methods (*5,8,9*) have been improved and streamlined to make this ligand ready for injection within 30 sec. Here we describe the methods of rapid ^{99m}Tc-HMPAO preparation and deployment as well as the details of data acquisition and image creation that have allowed us to obtain routine ictal and immediate postictal injections. These are the principal developments that have enabled exploitation of the great clinical and scientific potential of ictal SPECT with ^{99m}Tc-HMPAO in the functional imaging of epileptic seizures.

METHODS

Context of Use of HMPAO-SPECT in the Epilepsy Program

Since 1987, all patients undergoing intensive investigation of refractory partial seizures in the Austin Hospital's comprehensive epilepsy program have undergone SPECT study using ^{99m}Tc-HMPAO. SPECT data complements the diagnostic information provided by detailed clinical appraisal, video-EEG review of seizures, MRI and neuropsychological testing. The development of the SPECT arm of the epilepsy program has been

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facilitated by dedicated research fellows working closely within both neurology and nuclear medicine disciplines.

The methods of ligand preparation have been progressively revised during this period to allow injection of ^{99m}Tc-HMPAO either during (ictal) or immediately after (postictal) seizures. All injections are performed during long-term video-EEG recording in a monitoring suite situated in the neurology ward. Video-EEG recording permits precise classification of the seizure and documents the exact timing of the injection relative to seizure onset, clinical characteristics and seizure termination.

Preparation and Injection of ^{99m}Tc-HMPAO

Technetium-99m Preparation. Standard elution techniques and quality control procedures are performed on each eluate from a technetium generator. Because the epilepsy program requires technetium eluate over a 12 hr period, it was decided to extend the life of eluates for the reconstitution of HMPAO. In quality control studies, we found that eluates could be used for 6 hr before a fresh eluate is required. Eluates are only used from generators which have been eluted in the previous 24 hr. The activity of required eluate is diluted to 5 ml with normal saline and drawn up ready for use in a luer-lock 5 ml disposable syringe.

Dosage Calculation. The activity provided for each 6 hr period is standardized to approximately 1500 MBq/5 ml. A printed calibrated dose slip, generated by the Capintec radioisotope calibrator (Model ARC-30 Ramsey, NJ), is provided for each preloaded syringe dispensed. This indicates the corresponding volumes for the standard administered dose (700 MBq) at set time intervals.

Storage and Radiation Safety. The 5 ml luer-lock syringe, preloaded with sodium pertechnetate, is covered with a syringe shield and placed in a stainless steel lead-lined syringe carrier. The carrier also contains the HMPAO vial ready for reconstitution in a lead pot. This kit is prepared twice a day and stored in a cupboard adjacent to the monitoring suite in the neurology ward. Here, a stainless steel tray lined with plastic-backed absorbent sheets provides the work area for reconstitution of the HMPAO.

An emergency plan involving nuclear medicine and the medical radiation safety officer was drawn up in case of spillage. These guidelines were posted next to the ligand storage area at the monitoring suite. All medical and nursing staff involved in the patient monitoring were well-briefed in safety precautions. Physicians performing the reconstitution procedure were initially trained with nonradioactive practice runs prior to performing actual studies.

Seizure Alert and HMPAO Reconstitution. Patients, their attending family members or nursing staff alert the duty medical staff of a seizure by pressing a buzzer. When medical staff are not on the ward, one of the authors (MRN) is summoned to the monitoring suite by means of a dedicated emergency paging system by the ward staff.

The entire contents of the preloaded sodium pertechnetate syringe are injected into the HMPAO vial and the vial is mixed for 10 sec. The appropriate volume for the dose (read from the accompanying calibrated slip) is then removed. Thus the needle of the syringe is only inserted and removed once during the whole procedure.

This method of preparation takes approximately 30 sec. The ligand is then injected through an in situ venous cannula and flushed with normal saline from a preloaded syringe that is stored next to the HMPAO kit. The standard dose for adults being injected in the monitoring suite is 700 MBq. This provides adequate counts for good image production up to 2 hr post-injection. Such delays may occur while the gamma camera is otherwise used.

Quality Assurance. Following the injection of ^{99m}Tc-HMPAO, the reconstitution and injection times are recorded and the nuclear medicine department immediately notified. The unused ^{99m}Tc-HMPAO is transferred to the nuclear medicine department for determination of dosage and radiochemical purity. The dose administered is calculated back to time of injection and the radiochemical purity is tested by thin layer chromatography. Three chromatographic systems are used to detect secondary ^{99m}Tc-HMPAO complex, free pertechnetate and reduced-hydrolyzed ^{99m}Tc using solvents and stationary phases as recommended by Amersham (*12*).

SPECT Imaging

Patient Preparation and Positioning. Immediately prior to scanning, the patient is given a small intravenous dose of a benzodiazepine (1 mg clonazepam) to prevent seizures during acquisition. Consistent and accurate head positioning is essential for the comparison of the datasets derived from interictal, ictal and postictal studies. This is achieved by using a hairline projector, a protractor for correctly angling the head and simple strap restraints.

The scanning table (with head holder attachment), camera and a positioning projector are initialized to a center location and the diameter of rotation is set. The patient lies supine and his/her head is positioned with the orbito-meatal line at an angle of 65° to the horizontal line using a protractor. With the projected "cross hair" lines on the patient's face, the head is adjusted so that the horizontal line connects the outer canthi and the vertical line bisects the face. The head is firmly secured with two velcro straps over the forehead and one around the chin. Two ear plugs, fitted with ^{57}Co markers (used in the reconstruction process), are placed in the external auditory meati and a third ^{57}Co marker is taped to patient's forehead at the glabella (midway between the apices of the eyebrows).

Acquistion Parameters. The tomographic planar data is collected on large field-of-view gamma camera (Starcam 400AC, General Electric Medical Systems, Milwaukee, WI) equipped with a low-energy, high-resolution parallel-hole collimator. An elliptical orbit is employed to acquire 64 planar images for 360° at 30 sec per frame, resulting in a total acquisition time of approximately 40 min. The image matrix is 128 × 128 word dataset. A dual-energy dataset is required for the scatter correction.

Image Reconstruction. The preprocessing of the planar dataset involves a number of calculations and dataset manipulations. Each frame undergoes scatter correction (using a modified low window subtraction method) and decay correction. These are employed to improve both quantitative accuracy and image contrast. The Butterworth pre-filter is used and the filter parameters of critical frequency and power factor are calculated dependent on the maximum count in the cerebellum. An attenuation correction of 0.15 is used according to the method of Chang (*13*). A reproducible reprojection through the temporal lobe can be achieved by determining the angle from the plane of the three ^{57}Co markers to the horizontal line. The average angle is calcu-

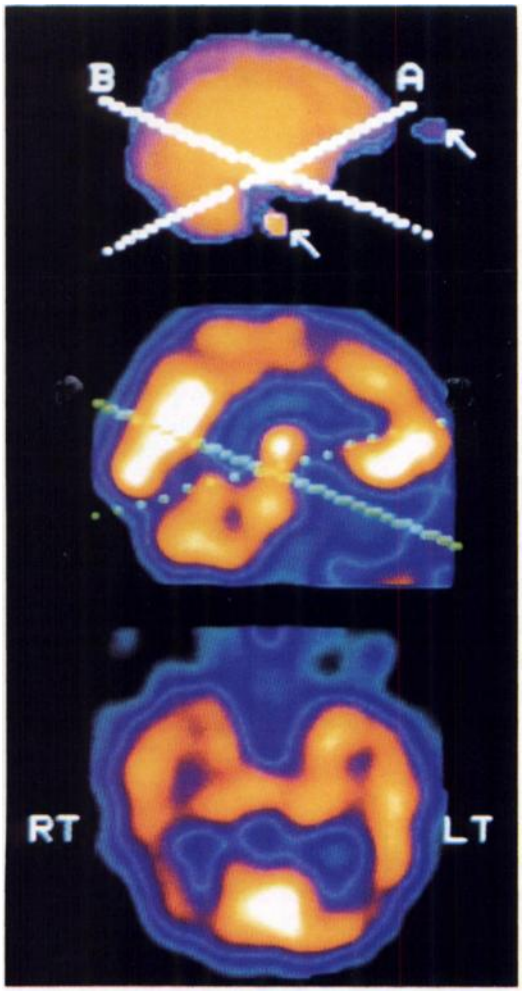

FIGURE 1. Optimal image display of temporal lobe structures. The top image shows a three-dimensional reconstruction of the brain with the ^{57}Co glabella and ear markers shown (arrows). Line A is parallel to these markers and line B is at 50° to A, along the long axis of the temporal lobe. The middle image shows lines A and B on the conventional midsagittal slice. The lower image shows the temporal dataset projected along line B.

lated using the left and right lateral frames. Slice thickness is 3 mm.

The center of the reconstruction, magnification and the limits of reconstruction were determined using a threshold edge detection algorithm. The transaxial dataset was reconstructed once these parameters were determined. The final image resolution was 12 mm at full width of half maximum (FWHM).

Image Display. The reprojection dataset is generated after production of the transaxial dataset. A single sagittal image is created through the previously calculated center of the reconstruction. In order to best display the temporal lobes, a "temporal" dataset is reprojected at an angle of 50° to the line between the glabella marker and the ear markers. A coronal dataset is then generated at 90° to the temporal dataset. This reprojection technique enables accurate image slice alignment between different studies of a particular patient or between different patients' studies. The angle of the temporal dataset is used for the optimal display of the distribution of activity throughout the mesial and lateral temporal cortex and lies at approximately 35° from the conventional orbito-meatal line (Fig. 1). This is ideal for studies of patients with temporal lobe epilepsy which is the most common focal epilepsy investigated at our unit. Other angles of reconstruction can be derived from the transaxial data, should different views be required.

Image Interpretation. The SPECT images derived from ictal or postictal HMPAO injection are interpreted only with knowledge of the type of seizure and the exact time of injection relative to the end of the seizure, as both factors determine the patterns of blood flow captured by the ligand injection. Because this information can only be obtained from video playback, this underscores the necessity of recording on video all injected seizures.

Close liaison with the clinicians reviewing the videos provides verification as to whether or not the seizure was typical of the nature of the epilepsy being investigated. Occasionally, patients on reduced medication either have partial seizures that secondarily generalize or have anticonvulsant withdrawal convulsions. These show cerebral perfusion patterns different to those of partial seizures that do not generalize. Also, an injection may be inadvertantly made during an infrequent pseudo-seizure that occurs in the monitoring suites and the identification of these will prevent time being wasted on interpretation and analysis.

The timing of injection relative to the end of the seizure determines the cerebral perfusion patterns. Interpretation of temporal lobe seizure perfusion patterns requires knowledge of the "postictal switch" (*14*) where the marked increase in anterior temporal lobe perfusion switches within 60–90 sec to a pattern of hypoperfusion of the lateral temporal cortex with relative preservation of mesial temporal perfusion (Fig. 2).

RESULTS

Quality Assurance

Table 1 shows the results of radiochemistry purity analyses on the unused portion of 242 consecutive preparations of ^{99m}Tc-HMPAO, reconstituted using our current rapid preparation technique. The chromatographic analyses were performed within a 30 min period after preparation and injection into patients. All injections were of high purity (> 80%) and resulted in good quality SPECT images.

From 1987 to 1991, we performed over 250 peri-ictal injections in the neurology ward. One minor episode of isotope spillage occurred in this period when there was a faulty connection between the syringe loaded with tracer and the intravenous cannula.

Clinical Results

From June 1987 to January 1989, 46 patients with unilateral temporal epilepsy were studied. Ictal injection was only achieved in one case (2%); the remaining cases had postictal studies. With the improved techniques described here, another 73 patients were studied (February 1989–September 1991) and ictal injections were achieved in 50 (68%).

Table 2 shows the results of SPECT localization in this consecutive series of 119 patients with unilateral tempo-

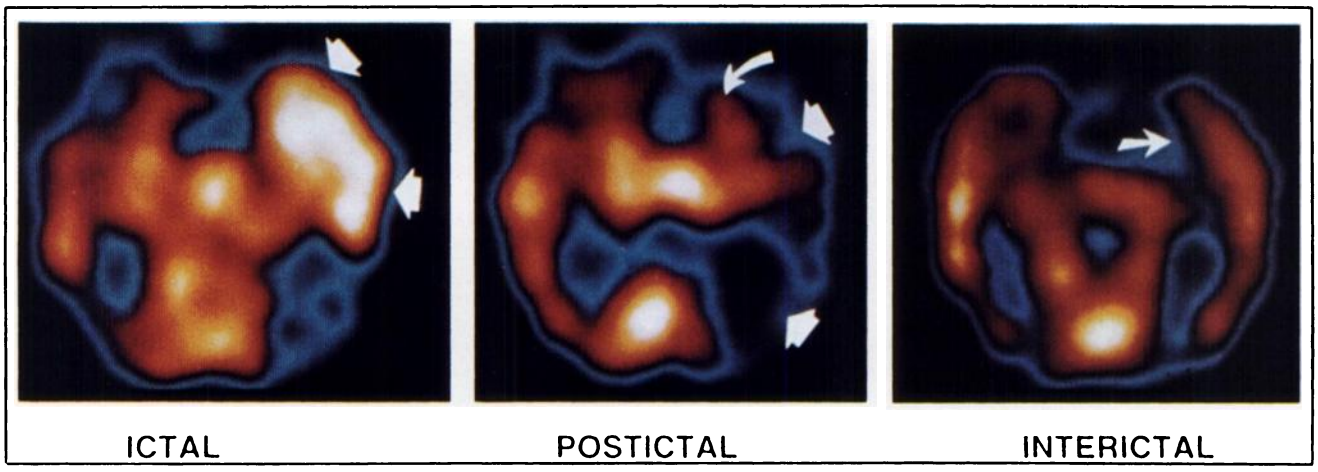

FIGURE 2. Changing perfusion patterns in one patient with left temporal lobe epilepsy shown in the temporal projection. The ictal study shows marked left temporal *hyperperfusion* involving the mesial and especially the lateral temporal regions (arrows). The postictal study shows *hyperperfusion* of the left mesial temporal region (curved arrow) with relative *hypoperfusion* of the lateral temporal cortex (short arrows). The interictal study shows relatively symmetrical temporal lobe perfusion, with a minor decrease in the left antero-mesial temporal region (arrow).

ral epilepsy read by blinded observers. The side of the seizure focus was established by video-EEG monitoring of at least three spontaneous seizures (sometimes including depth electrode studies), MRI and neuropsychological studies as previously described (*5,8,9,14,16*). Ictal SPECT scans (97% correct, 0% incorrect) were clearly superior to postictal studies (71% correct, 4% incorrect) which were more reliable than interictal examinations (48% correct, 10% incorrect).

DISCUSSION

Our data show that ^{99m}Tc-HMPAO can be rapidly, reliably and safely reconstituted adjacent to the monitoring suite. This permits the attainment of ictal scans in a high proportion of patients with refractory temporal lobe epilepsy. The essential steps involve close collaboration between neurology and nuclear medicine departments, special care in the production of ^{99m}Tc-pertechnetate and storage of isotopes close to the monitoring suite for rapid reconstitution. Designated staff are trained to respond quickly and efficiently when spontaneous seizures do occur in order to prepare and inject ^{99m}Tc-HMPAO rapidly and safely. Attention to image reconstruction details and display allow the data from the temporal lobes to be properly appreciated. Finally, knowledge of the exact timing of seizure onset, seizure termination and isotope injection is vital to allow proper interpretation of scans as the patterns of blood flow distribution change rapidly after seizures. This is only possible if seizures are recorded on video-EEG linked to a timer.

The clinical importance of the technical advances permitting ictal SPECT studies with ^{99m}Tc-HMPAO is best appreciated by comparing interictal, postictal and ictal studies. Interictal scans may show lateralized hypoperfusion. In this study, interictal scans were lateralized to the wrong side in 10% of cases, with 48% being correctly lateralized (Table 2). If interictal scans are conservatively interpreted, that is, if the interpreter attributes significance only to large areas of hypoperfusion, only one-third

TABLE 1
Radiochemical Purity in 242 Reconstitutions of ^{99m}Tc-HMPAO

Compound	Percent of total activity [mean ± s.d. (range)]
Secondary ^{99m}Tc-HMPAO complex	3.7% ± 2.5% (0%–12.6%)
Free pertechnetate	2.9% ± 2.7% (0%–13.3%)
Reduced-hydrolyzed ^{99m}Tc	2.4% ± 1.5% (0.1%–9.9%)
^{99m}Tc-HMPAO	91.1% ± 3.9% (80.9%–97.7%)

TABLE 2
Localization of Epileptic Foci Using Interictal, Postictal and Ictal SPECT in 119 Cases of Unilateral Temporal Lobe Epilepsy

SPECT lateralization*	Ictal† (n = 51)	Postictal‡ (n = 77)	Interictal (n = 119)
Correct	97%	71%	48%
Inconclusive	3%	25%	42%
Incorrect	0%	4%	10%

*The first 46 cases were interpreted independently by two blinded reviewers, and the next 73 cases by three blinded reviewers. Values shown are the percentage means for the whole series.

†Fifty-one studies in 51 cases. 49/51 cases were correctly lateralized by all three independent blinded reviewers. One case that was not lateralized by any reviewer had a repeat ictal study that showed correct lateralization. A second case was not lateralized by only one of three reviewers.

‡Seventy-seven studies in 77 patients in which 9 also had ictal studies.

of cases are correctly lateralized (although there are rare cases of incorrect lateralization (*15*). Early postictal scans show mesial hyperperfusion and/or lateral temporal hypoperfusion on the side of the focus. These abnormalities were found in 71% of cases, but the appearances can be subtle and occasional localization errors occur. In contrast, ictal studies show striking and easily interpretable hyperperfusion in virtually all cases. We have yet to encounter an example of an incorrectly lateralized ictal study.

We have shown that the unique properties of HMPAO can be exploited to capture the rapidly evolving perfusion changes of spontaneously occurring seizures on a regular basis. This enables the outstanding clinical (*3,15*) and scientific potential (*14,16*) of SPECT with ^{99m}Tc-HMPAO in epilepsy to be fully explored, thus heralding an exciting new era in functional imaging of human epilepsy.

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