Is $^{11}$C-flumazenil PET superior to $^{18}$FDG PET and $^{123}$I-iomazenil SPECT in presurgical evaluation of temporal lobe epilepsy?

R M Chr Debets, B Sadzot, J W van Isselt, G J F Brekelmans, L C Meiners, A C van Huffelen, G Franck, C W M van Veelen

Abstract

Objectives—To determine the contribution of $^{18}$FDG PET, $^{11}$C-flumazenil PET, and $^{123}$I-iomazenil SPECT to the presurgical evaluation of patients with medically intractable complex partial seizures.

Methods—Presurgical evaluation was performed in 23 patients, who were considered candidates for temporal lobe resective surgery (14 females and nine males, with a median age of 34 (range 13 to 50) years). The presurgical diagnosis was based on seizure semiology as demonstrated with ictal video recording, ictal and interictal scalp EEG recordings, and MRI.

Results—Eighteen patients had convergent findings in clinical semiology, interictal and ictal EEG with scalp and sphenoidal electrodes, and MRI that warranted surgery without depth EEG (DEEG). In five patients with insufficient precision of localisation, DEEG with intracerebral and subdural electrodes was performed. MRI showed abnormalities in 22 out of 23 patients. Of these 22, 18 had mesial temporal sclerosis. This was limited to the mesial temporal lobe in four and more widespread in the temporal lobe in 14 patients. In one patient only enlargement of the temporal horn was found and in three others only white matter lesions were detected. $^{18}$FDG PET showed a large area of glucose hypometabolism in the epileptogenic temporal lobe, with an extension outside the temporal lobe in 10 of 23 patients. Only in one of these patients DEEG showed extratemporal abnormalities that were concordant with a significant extratemporal extension of hypometabolism in $^{18}$FDG PET. $^{18}$FDG PET was compared with the results of scalp EEG: in none of the patients was an anterior temporal ictal onset in scalp EEG related to a maximum hypometabolism in the mesial temporal area. By contrast, the region of abnormality indicated by $^{11}$C-flumazenil PET was much more restricted, also when compared with DEEG findings. Extension of abnormality outside the lobe of surgery was seen in only two patients with $^{11}$C-flumazenil and was less pronounced compared with the intratemporal abnormality. Both $^{18}$FDG PET and $^{11}$C-flumazenil PET reliably indicated the epileptogenic temporal lobe. Thus these techniques provide valuable support for the presurgical diagnosis, especially in patients with non-lesional MRI or non-lateralising or localising scalp EEG recordings. In those patients in whom phase 1 presurgical evaluation on the basis of classic methods does not allow a localisation of the epileptogenic area, PET studies may provide valuable information for the strategy of the implantation of intracranial electrodes for DEEG. Previous studies have suggested that $^{11}$C-flumazenil binding has a closer spatial relationship with the zone of ictal onset than the area of glucose hypometabolism, but this study suggests rather that the decrease in the $^{11}$C-flumazenil binding simply reflects a loss of neurons expressing the benzodiazepine-GABA receptor. $^{11}$C-flumazenil PET did not prove to be superior to $^{18}$FDG PET.

Conclusion—In 21 patients sufficient material was obtained at surgery for a pathological examination. In 17 mesial temporal sclerosis, in one an oligodendroglioma grade B, in another a vascular malformation and in two patients no abnormalities were found. Although all 21 patients with pathological abnormality showed hypometabolic zones with $^{18}$FDG PET and a decreased uptake in $^{11}$C-flumazenil binding, there was no strong correlation between pathological diagnosis and functional abnormal areas in PET. Grading of medial temporal sclerosis according to the Wyler criteria showed no correlation with the degree of hypometabolism in either $^{18}$FDG or $^{11}$C-flumazenil PET.

The interictal $^{123}$I-iomazenil SPECT technique was highly inaccurate in localising the lobe of surgery.

Keywords: FDG PET; flumazenil PET; iomazenil SPECT; temporal epilepsy; epilepsy surgery

In patients with medically refractory epileptic seizures of temporal lobe origin who are candidates for epilepsy surgery, a careful presurgical evaluation is necessary for a precise definition of the zone of ictal onset. Diagnostic procedures should be limited both in number and in invasiveness. In the first investigative phase of the Dutch Epilepsy Surgery Programme, in accordance with international consensus, only non-invasive examinations are carried out.1
At present in most patients a satisfactory precision of localisation can be obtained with the use of non-invasive techniques which comprise interictal and ictal EEG-CCTV monitoring with scalp and sphenoidal electrodes, CT, MRI, and neuropsychological examination. Consequently a decreasing number of patients require a second (invasive) phase of investigation comprising recordings with subdural and intracerebral EEG (DEEG) electrodes. \footnote{Brekelmans, Meiners, Brekelmans, van Huffelen, et al.}

In the programme special attention has been given to the contribution of \textsuperscript{18}FDG PET and \textsuperscript{123}I-iomazenil SPECT. \footnote{Debets, Sadzot, van Iselt, Brekelmans, Meiners, van Huffelen, et al.} Recently \textsuperscript{11}C-flumazenil PET was added to the phase 1 studies in the context of medical technology assessment.

It has been suggested that the area of reduced benzodiazepine (BZ) receptor binding in \textsuperscript{11}C-flumazenil PET is smaller and correlates more closely with the clinical symptomatogenic zone and the EEG localisation than the area of reduced cerebral metabolic rate of glucose (CMRGl) in \textsuperscript{18}F-fluoro-deoxy-D-glucose (\textsuperscript{18}FDG) PET. \footnote{Debets, Sadzot, van Iselt, Brekelmans, Meiners, van Huffelen, et al.} As comparative data on these two techniques are limited, it is not yet clear whether they are complementary or whether one technique yields superior results.

\textsuperscript{123}I-Iomazenil, a flumazenil derivative, is a radioligand for BZ receptors which can be used with SPECT. \footnote{Debets, Sadzot, van Iselt, Brekelmans, Meiners, van Huffelen, et al.} SPECT is less expensive and more widely available than PET.

Here we consider the question of whether, and to what extent, there is evidence of a contribution of \textsuperscript{18}FDG PET, \textsuperscript{11}C-flumazenil PET, and \textsuperscript{123}I-iomazenil SPECT to the presurgical evaluation in 23 patients with medically intractable complex partial seizures. The answer to this question will indicate which method could be considered redundant. This is important to prevent excessive radiation exposure.

### Table 1 Patients, history, and seizure type

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SP = Simple partial seizures; CP = complex partial seizures; TC = generalised tonic-clonic seizures; Febr conv = febrile convulsions.

### Table 2 Presurgical evaluation phase 1 and phase 2

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T = True; W = white matter lesion; R = right; L = left; MRI = medical temporal sclerosis; ant = anterior; no lat/loc = no lateralisation or localisation; temp = temporal.

1 High signal intensity in the hippocampus.
2 Smaller size of the hippocampus.
3 Hippocampal collateral white matter atrophy.
4 Enlarged temporal horn.
5 Diminished grey and white matter demarcation.
6 Smaller temporal lobe.
electrodes (DEEG) was performed. 18FDG PET and 11C-flumazenil PET were performed in all of these patients. Nineteen patients were investigated with 123I-lomazenil SPECT. Although all 23 patients were considered candidates for temporal lobe resective surgery, temporal surgery was carried out in 22; one patient was operated on in the temporal as well as the frontal lobe. The PET and SPECT studies have not been taken into consideration with respect to the presurgical diagnosis.

NEUROPHYSIOLOGICAL EXAMINATIONS

Scalp EEG
All patients were studied with long term interictal as well as ictal EEG-CCTV monitoring with conventional scalp electrodes, and anterior temporal and sphenoidal electrodes. The data were first assessed by one neurophysiologist. A final diagnosis was reached in a consensus meeting of the clinical neurophysiologists of the programme. Eighteen patients (6–23) had convergent findings in seizure semiology, ictal scalp EEG, and MRI that warranted surgery without DEEG.

Depth EEG
DEEG was carried out in five patients (1–5), according to the DEEG technique as described by van Veenen et al.2 DEEG indicated a unilateral mesial temporal onset in one patient (5), a unilateral combined mesial and neocortical temporal onset in two patients (1,3), and a neocortical temporal onset in one other patient (2), whereas DEEG in the fifth patient (4) disclosed that epileptic seizures originated from the mesial and the neocortical temporal areas as well as the ipsilateral orbitofrontal region.

MRI
MR images were from a Philips Gyroscan 1.5 Tesla system with a regular headcoil. A protocol especially designed to visualise the temporal lobes was used.10 The MR images were reviewed by at least two radiologists blinded for the EEG lateralisation.

Abnormalities were detected in 22 of 23 patients (table 2). These were located in the temporal lobe in 20 and extratemporal lobe in three (6, 18, 23), including one patient (6) with combined temporal and extratemporal abnormality. One patient (1) showed no MRI abnormality.

In 18 patients the temporal lobe displayed the abnormalities characteristic of mesial temporal sclerosis. These abnormalities consisted of increased signal intensity of the hippocampus, atrophy of the hippocampus, and atrophy of the hippocampal white matter. In addition to these signs restricted to the mesial area of the temporal lobe, more widespread, medial temporal sclerosis related temporal abnormalities were detected—namely, an enlarged temporal horn, diminished grey and white matter demarcation, and a smaller temporal lobe.

In four patients (2, 5, 6, 7), only mesial temporal abnormalities were present. In these patients, three showed atrophy and increased signal intensity of the hippocampus. The fourth patient had only increased signal inten-

sity of the hippocampus. In 14 patients, in addition to mesial temporal abnormalities one of the signs of widespread temporal abnormality were seen. In two patients (4, 17), signs of widespread temporal abnormality other than medial temporal sclerosis were encountered. One patient (2) had a small calcified mesial temporal lesion, probably a small vascular malformation, which was detected in addition to medial temporal sclerosis.

Extratemporal abnormalities seen in three patients (6, 8, 23), were described as white matter abnormalities in all the patients concerned, probably without specific relevance. In one patient (6) abnormalities of white matter were combined with medial temporal sclerosis.

PRESURGICAL DIAGNOSIS

In 18 patients the presurgical diagnosis was reached on the base of non-invasive phase 1 studies (table 2). In patients with the epileptogenic area located “anterior temporally” the onset of the seizures was recorded on the sphenoidal electrode. In patients in whom the ictal onset was considered “temporal” a combined mesial and neocortical onset was recorded in the ictal scalp EEG. The results of the EEG and the MRI were combined to reach a phase 1 conclusion. In three patients (8, 11, 16) in whom ictal EEG localisation alone was insufficiently diagnostic, a combination of ictal EEG and MRI data warranted surgery without DEEG.

In patients 1–5 DEEG was performed because MRI and scalp EEG were not sufficiently concordant. After DEEG a final presurgical diagnosis was reached. In four patients DEEG showed a temporal onset. A fifth patient showed a combined temporal and ipsilateral orbitofrontal seizure onset. In patients with a temporal onset this was primarily mesiolimbic in one, combined mesiolimbic/neocortical in two, and only neocortical in one.

SURGERY AND POSTSURGICAL EVALUATION

Surgery included amygdalohippocampectomy and neocortical resection in all patients. Neocortical resection was guided by electrocorticography performed with a subdural subtemporal multicontact electrode forwarded to the hippocampal area in addition to the classic corticography. One patient (4) had a combined temporal and frontal resection. None of these patients, except patient 5, were considered candidates for a selective amygdalohippocampectomy only.

The seizure outcome after surgery was determined according to the criteria of Engel11 in outcome class 1–4. Follow up ranged from 0–5–2–5 years (mean one year).

A pathological diagnosis of the resected mesial and neocortical temporal lobe was feasible in 21 of the 23 patients. In three patients the paucity of material did not allow a complete pathological diagnosis. Medial temporal sclerosis diagnosed in 15 patients was severe in most patients, according to the criteria proposed by Wyler.12 Of these, only one patient (15) showed slight gliosis in the mesial tempo-
reral region. In two remaining patients; one (12) had a small mesial arteriovenous malformation (AVM), another (2) disclosed a mesial oligodendroglioma grade B (oligo B; table 3).

PET

Radiochemistry—18F-Fluorodeoxyglucose (18FDG) was prepared by the nucleophilic reaction and the method of Hamacher et al. It yields no carrier added FDG without any contamination with 18F-fluorodeoxyamphetamine.

11C-Flumazenil (11C-Ro15–1788) was prepared by methylation of the nor-derivative (Ro 15–5528) by 11CH, L. About 130 mCi of the product were obtained within 40 minutes from the end of the bombardment. The radiochemical purity of the radiopharmaceutical was found to exceed 98% by thin layer and high pressure liquid chromatography. The specific activity at the time of injection was 895 (range 337–1721) mCi/μmol. The equipment was designed to carry out the radiosynthesis automatically.

PET data acquisition—In the patients who used BZ medication this drug was withdrawn at least two weeks before the PET investigation. Before the start of the PET study, a thermodable plastic face mask (Runtech, Liège) was moulded on the face of the patient. This mask ensures reproducible and stable positioning of the head in the desired position during the PET study. The patients were positioned into the gantry of a 951 CTI/Siemens tomograph. This scanner acquires 31 contiguous transaxial planes, 5 mm in thickness, with a 3-4 mm slice separation (centre to centre), simultaneously covering 11 cm of axial field of view.

The patient’s head was placed in such a way that the most inferior plane of image acquisition passed through the orbitomeatal plane. The bed of the tomograph was then moved 1 cm more caudally in order to be certain to have all the tip of the temporal lobe in the field of view. Finally, the gantry of the tomograph was tilted —10° to —15°, so that the transverse planes were acquired parallel to the long axis of the temporal lobe.

Firstly, a 20 minute transmission scan was obtained for photon attenuation correction with three retractable rod sources containing 2.5 mCi 68Ge each. Patients were then given a 10 ml solution with 20 mCi of 11C-flumazenil intravenously in one minute. Dynamic scanning was started immediately with consecutive scans of increasing duration: 3 × 2, 3 × 3, 5 × 6, and 2 × 11 minutes, total 11C-flumazenil scanning time 75 minutes. At the end of this scan, 7.5 mCi 18FDG were given intravenously. A static PET study was obtained from 30 to 60 minutes after injection. The total time needed for both PET studies was about 2-5 hours. The start of 11C-flumazenil and 18FDG scans was separated by 100 minutes or five half lives of 11C-flumazenil. With the radioactive decay and without considering the biological washout, only 3-25% of the 11C-flumazenil activity should be remaining when the 18FDG scan started.

In this study no kinetic modelling was performed, to reduce the burden for the patient as much as possible. A kinetic study would require at least two 11C-flumazenil injections at two different specific activities. The radiation exposure would not allow an additional third injection. The protocol of this combined study was approved by the University Hospital ethics committee of the University of Liège.

Images were reconstructed with a Hanning filter with a cut off frequency set at 0.5. The smoothing effect of this filter is about 3 mm and this degrades the transverse resolution to 9 mm. A software algorithm allows for the reslicing of the study into coronal cuts.

PET was carried out in patients during the interictal state. Surface EEG could not be monitored during the PET acquisition period for technical reasons; however, all patients were continuously observed during the PET study by one of the investigators and none showed signs of clinical seizures. At the end of the study, each patient was asked whether any particular symptoms had occurred during the scanning period; none reported any sensation possibly corresponding with an aura or other seizure symptoms.

During both studies, blood samples were taken by the arterial catheter previously inserted in the radial or brachial artery under local anaesthesia. To characterise the plasma time-activity curves, a 2 ml arterial blood sample was obtained every 10 seconds during the first two minutes, every 15 seconds between two and three minutes, and then at 4, 5, 7, 5, 10, 20, 30, 40, 50, and 60 minutes. The blood was centrifuged for about five minutes and 500 μl plasma counted with a Nal well counter.

PET data analysis

Cerebral metabolic rates for glucose were calculated pixel by pixel, using the operational equation of Phelps et al. as well as the rate and the lumped constants proposed by these authors for the adult man. Parametric images of glucose consumption were obtained.

The attenuation corrected 11C-flumazenil images were decay corrected, transformed into maps of mCi/mCi using the appropriate calibration factor, and summed for the interval 17-5 to 55 minutes to enhance the anatomical details and to improve the statistical quality of the images. The summed 11C-flumazenil and the 18FDG parametric images were then reviewed independently by two authors of which one was blinded for the clinical data of the patient.

The analysis of the PET data was performed by visual and semiquantitative assessment of the metabolic images for the symmetry of glucose consumption and 11C-flumazenil binding between homologous regions of the two hemispheres. A PET study was considered abnormal if an area of relative decrease in glucose metabolism or 11C-flumazenil uptake could be seen on at least two contiguous PET slices. There was no disagreement between the investigators on which side the brain was affected.

The mesial temporal region was best identified on the 11C-flumazenil scans. We therefore selected the transverse and the coronal planes passing through the hippocampus in the 11C-
flumazenil scan and isolated the corresponding
18FDG slices. Regions of interest were then placed on the medial and lateral cortex of the
temporal lobe on the transverse slices, on the
mesial, basal, and lateral part of the temporal
lobe on the coronal slices. Asymmetry between
homologous regions was calculated as
(right−left)/(right+left) *200 and the asym-
metry was rated as slight (5 to 14.9%), moderate
(15 to 29.9%), or severe (> 30%) (table 3). No
region of interest was placed on the extratempo-
ral areas.

SPECT
SPECT was performed during the interictal
state with the central BZ antagonist 123I-iomaze-
nil, derived from flumazenil (Paul Scherrer
Institute, Würenlingen, Switzerland).
Retention within the brain at specific binding
sites is about 7% of the administered dose at 80
minutes after intravenous injection. 123I decays
by electron capture and emits γ rays with an
energy of 159 keV. In the patients who used BZ
medication this drug was withdrawn at least
two weeks before the SPECT investigation.

During the investigation ambient noise and
light were reduced. A catheter was inserted into
the antecubital vein allowing the injection of
4–5 mCi 123I-iomazenil.

Data acquisition started 75–80 minutes after
injection with a Picker Prism 3000 three-
detector rotating gamma camera, equipped
with ultra high resolution fan-beam collimators,
acquisition matrix 128 × 128 pixels, zoom fac-
tor 1, step and shoot acquisition; 3 × 20 steps,
6°/step, 20 s/view. The typical number of
counts in a total study was about 3*106.

SPECT data were reconstructed by a filtered
back projection algorithm, using a Butterworth
filter (5th order, 40% window). Attenuation
correction was applied (0-12/cm). Transaxial
slices were filtered (Ramp filter) and reoriented to
“sagittal” (parallel to the midsagittal plane),
“oblique transaxial” (parallel to the base of the
brain), and “oblique coronal” (perpendicular to
the two aforementioned directions) slice oriien-
tations. Slice thickness was 2 pixels, effective
slice thickness 7-6 mm. Spatial resolution was
7 mm at FWHM.

The typical number of counts in the transa-
xial oblique slice at the level of the midtemporal
gyrus was 100 k.

SPECT images were visually assessed by two
independent examiners. In cases of disagree-
ment a third interpreter was asked. The images
were assessed for major focal or regional asym-
metries. No such asymmetries were found in a
control population consisting of nine subjects
(age 22–33, mean 27 years).

Results

18FDG PET

18FDG PET was abnormal in all 23 patients. The
hypometabolism, expressed in degree of
abnormality 1, 2, or 3, was always unilateral
and in agreement with the lateralisation and
lobe of surgery (table 3). With these degrees of
abnormality the area with maximum hypo-
metabolism could be indicated.

Hypometabolism was restricted to the tem-
poral areas in 13 patients. In addition to
temporal hypometabolism extratemporal
hypometabolism was detected in 10; although
in eight of these the maximum abnormality
was intratemporal. In two patients (4,21) the
abnormality was equally pronounced in tem-
poral and frontal areas; one with a frontal and
temporal focus, another with a single focus in the
temporal lobe.

In 21 patients with maximum hypometabo-
лизm in the temporal lobe, this maximum was
mesial in one and neocortical temporal in
nine, whereas in most (11 patients) the
hypometabolism was equal in mesial and neo-
cortical areas. In none of the 23 patients an
anterior temporal ictal onset in scalp EEG,
characterised by initial ictal changes on the
ipsilateral sphenoidal electrode, was related to a
maximum hypometabolism in the mesial tem-
poral area.

11C-FLUMAZENIL PET

All 11C-flumazenil PET scans showed unilat-
eral decreased BZ receptor binding. It was
restricted to the temporal lobe in 21 of 23
patients. Extratemporal abnormality was
detected in two patients (15,17) but the
abnormality was always maximal in the tem-
poral lobe. The temporal lobe indicated by
11C-flumazenil PET as abnormal was identical
with the lobe of surgery in all cases.

Transverse scans disclosed a predominantly
or exclusively decreased BZ receptor binding
in the mesial temporal area in all patients
except one, who was the only one who had a
tumour (an oligodendrogloma in the mesial
temporal lobe).

Coronal 11C-flumazenil PET scans, which
provided a more detailed view of subdivisions
of the temporal lobe, were abnormal in 21
patients, whereas two were normal.
Abnormality seen in the 21 patients was maxi-
mal in the mesial temporal region in 18. Of
these 18, 13 demonstrated abnormality
restricted to the mesial temporal region. In
general the extension of decreased receptor
binding was less in coronal scans compared with
transverse sections. There proved to be no
consistent relation between mesiocortical or
neocortical temporal PET findings and
anterior temporal EEG onset. Nine patients
with an anterior temporal onset in scalp EEG,
characterised by initial ictal changes on the
ipsilateral sphenoidal electrode, demonstrated
a maximum of abnormality in the mesial tem-
poral area. This mesial temporal abnormality
was not specific for this group of patients and
was often seen in patients with a more wide-
spread ictal onset in the temporal lobe.

123I-IOMAZENIL SPECT

SPECT was performed in 19 patients (table
3). A minority of patients had a SPECT
abnormality of which the localisation was
related to the side of the lesion as established
by the methods indicated above. This corre-
lation was correct in only six of 19 patients.
In another three of these 19 patients SPECT
indicated the epileptogenic lobe as abnormal;
however these three had an equal expression of ipsilateral extratemporal abnormality (correct lateralisation: lat+, table 3) as well. In nine patients the lateralisation was incorrect and in one patient SPECT indicated no abnormality.

**COMPARISON OF 18FDG PET, 11C-FLUMAZENIL PET, 11I-OMAZENIL SPECT, AND OUTCOME AFTER SURGERY**

By contrast with the accuracy demonstrated by 18FDG PET and 11C-flumazenil PET in localising the side and lobe where the epileptogenic zone was found, 11I-omazenil SPECT was inaccurate in this respect as described in the previous section.

These conclusions are supported by the outcome data: 87% were seizure free. This seizure outcome indicated that surgery was correctly performed in the epileptogenic region in these patients. In three of the 23 patients (13%) with minor or no improvement, analysis allowed no definite conclusions why surgery was ineffective, except for patient 4, in whom the postsurgical MRI disclosed an incomplete resection of the amygdalo-hippocampal complex. The relation between outcome and the extent of amygdalo-hippocampal resection could not be analysed in detail as no volumetric MRI studies after surgery were performed.

**COMPARISON OF IMAGING TECHNIQUES AND DEEG**

DEEG was performed in five patients. In these patients the relation between area of seizure onset and results of PET techniques was analysed in detail (table 4). The area of seizure onset was described as mesial temporal, neocortical temporal, or extratemporal. Hypometabolism in 18FDG PET proved to be more extensive than the epileptogenic region indicated by DEEG in two patients, was equally extensive in two, and was more restricted in one. In 11C-flumazenil PET the abnormal region was more extensive in two, equal in one, and less extensive in two patients.

Extratemporal hypometabolism detected with 18FDG PET was not detected by 11C-flumazenil PET in these five patients.

Although the number of patients examined with DEEG was limited, no clear differences between the results obtained with this method compared with those of 11C-flumazenil PET and 18FDG PET were encountered.

**18FDG PET, 11C-FLUMAZENIL PET, AND PATHOLOGY**

A pathological diagnosis was obtained in 21 patients; in 17 mesial temporal sclerosis, in one an oligodendroglioma grade B, in another a vascular malformation, and in two patients no abnormalities were found (table 3).

In six patients with mesial temporal sclerosis, 18FDG PET demonstrated additional extra-

---

**Table 3** Functional imaging, seizure outcome, and pathology

<table>
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<th>Patient no</th>
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</tr>
</tbody>
</table>

Degree of abnormality in PET: 1 = slight (5-14%), 2 = moderate (15-29%), 3 = severe (>30%). Seizure outcome class: 1 = seizure free; 2 = sporadic seizures; 3 = >90% improved; 4 = not improved. Pathology MTS class: 1 = slight; 2 = mild; 3 = moderate; 4 = severe. trans = transverse plane; cor = coronal plane; R = right; L = left; T = true; temp = temporal; lat+ = correct lateralisation; lat = = incorrect lateralisation; MTS diagnosis MTS not confirmed due to insufficient material; abn = abnormality.

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**Table 4** Comparison of DEEG and PET localisation

<table>
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<tr>
<th>Patient No</th>
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<td>Noc</td>
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T = Temporal; abn = abnormal area.
Is $^{11}$C-flumazenil PET superior to $^{18}$FDG PET and $^{123}$I-iomazenil SPECT in presurgical evaluation of temporal epilepsy?

Figure 1 $^{18}$FDG PET, $^{11}$C-flumazenil PET, and $^{123}$I-iomazenil SPECT studies in patient 23, demonstrating the abnormality in the coronal plane of the left temporal lobe; the abnormality in $^{11}$C-flumazenil PET was restricted to the mesial temporal (hippocampal) area.

temporal hypometabolism. The maximum hypometabolism was in the temporal lobe in five, but in one patient it was equally present in the frontal and temporal lobes.

In two patients with mesial temporal sclerosis, areas with decreased benzodiazepine receptor binding were located in the mesial and neocortical part of the temporal lobe and extended to extratemporal areas as well. In two patients without abnormality in the pathological examination $^{11}$C-flumazenil PET showed areas with reduced benzodiazepine binding maximally in the mesiotemporal area. Although all 21 patients with pathological abnormality showed hypometabolic zones with $^{18}$FDG PET and a decreased uptake in $^{11}$C-flumazenil binding, there was no direct relation between pathological diagnosis and functional abnormality in PET. Presence and classification of mesial temporal sclerosis in the pathological specimen could not be predicted from the results of functional imaging. In two patients without pathological abnormality PET techniques indicated areas of abnormal function.

Discussion

GENERAL ASPECTS: CONCLUSIONS OF MRI AND EEG AND OF PET AND SPECT IN RELATION TO THE ASSESSMENT OF AN EPILEPTOGENIC REGION

A prerequisite for resective surgery in partial epilepsy is the precise identification of the zone of ictal onset. Recording DEEG is considered to be the most reliable method of
achieving this goal. However, due to the invasive character of this method, various less invasive evaluation techniques have been pursued to provide a suitable alternative. These methods are included in the non-invasive phase of the presurgical evaluation. Abnormalities on MRI, especially signs of medial temporal sclerosis, combined with concomitant ictal seizure onset in EEG monitoring, is considered an excellent predictor of good outcome after surgery. Combination of these MRI and EEG variables warranted surgery without DEEG in a group of 18 out of 23 patients in the present study. In five patients, DEEG was performed because the ictal scalp EEG was not sufficiently localising, despite the presence of a localised temporal abnormality in the MRI.

The present study enables us to give an answer to the question of whether and to what extent imaging methods $^{18}$FDG PET, $^{11}$C-flumazenil PET, and $^{123}$I-Iomazenil SPECT can contribute to the presurgical evaluation in patients with medically intractable complex partial seizures. The starting point for this comparative analysis is the assessment of phase 1 based on MRI and on ictal EEG recordings (table 2). In all cases the $^{18}$FDG PET yielded the concordant result in respect to the side of the abnormality (table 3). The same applies to the $^{11}$C-flumazenil PET but not to the $^{123}$I-Iomazenil SPECT. Concerning the lobe of onset: $^{18}$FDG PET localised incorrectly in one patient (21) and in $^{11}$C-flumazenil PET in none. In SPECT the lobe of onset correlated with the other methods in only nine of the 23 patients; in the others the localisation was the opposite in six, inconclusive due to a bilateral abnormality in three, and in one no abnormality was detected. Therefore we conclude that the present SPECT technology using $^{123}$I-Iomazenil as ligand does not contribute to the presurgical evaluation in this group of patients.

A detailed comparison between the conclusions of phase 1 (MRI and EEG) and the results obtained using the two PET methods is not simple as it cannot be specified whether the lesion was mainly mesial, neocortical (basal or lateral), or temporal. Considering all cases jointly $^{18}$FDG PET tends to detect a more extensive area of abnormality than $^{11}$C-flumazenil PET; this occurred in 17 of the 23 patients, whereas in five both detected roughly equal areas and in one (5) only $^{11}$C-flumazenil PET indicated a more extensive abnormality. In none of the patients with an anterior temporal ictal onset in scalp EEG did $^{18}$FDG PET show a maximal hypometabolism in the mesial temporal area. The mesial abnormality with $^{11}$C-flumazenil PET correlated in these patients with an anterior temporal onset in scalp EEG but was not specific, because this was also seen in patients with a more widespread ictal onset in the temporal lobe.

**PERFORMANCE OF IMAGING METHODS IN COMPARISON WITH DEEG**

A more detailed analysis is possible in those patients in whom DEEG analysis was carried out (table 4). A perfect coincidence existed between areas detected as abnormal by the $^{18}$FDG PET and those obtained by DEEG methods in only two patients (1,2). In two patients (3,5) the areas detected by $^{18}$FDG PET were more extensive than those indicated as abnormal by DEEG and in one too limited. The $^{11}$C-flumazenil PET areas detected as abnormal were the same as with DEEG in one, more extensive in two, and less extensive in two patients. In the five patients in whom DEEG was performed the $^{11}$C-flumazenil PET was not more restricted than with $^{18}$FDG PET. The results of these DEEG studies also indicate that an evaluation of functional imaging methods based on scalp EEG results alone is unreliable. Scalp EEG could not indicate the lobe of onset in three of these five patients.
In the two other patients the localisation with scalp EEG was insufficient and indicated a possible multifocal or posterior temporal onset. For all patients presented, five of 23 (22%) needed DEEG recordings to bypass filtering by structures covering the brain and to enable recording in the vicinity of the focus.

**COMPARISON BETWEEN PET AND SPECT**

With $^{18}$FDG PET, areas of decreased CMRGlu, consistent with the lateralisation or even the localisation of the primary epileptic focus have been demonstrated.$^{17-20}$ However, the hypometabolism is often widespread, which limits the localising capacity of this technique.

Flumazenil is a benzodiazepine receptor antagonist, blocking the effect of both agonists and inverse agonists at benzodiazepine receptors while having little pharmacological effect on its own. Labelled with $^{11}$C it is an excellent radiolabel to image benzodiazepine receptors in vivo with PET.$^{21}$ A comparison between PET and SPECT techniques using related ligands is necessary to establish the effectiveness of these techniques in presurgical evaluation. PET has several drawbacks compared with SPECT, such as higher costs and restricted accessibility due to limited facilities. The SPECT technique, more widely available, might enhance selection of candidates for epilepsy surgery. $^{119}$I-Iomazenil SPECT was equally effective as $^{18}$FDG PET or $^{11}$C-flumazenil PET. Comparative studies of $^{18}$FDG PET and $^{11}$C-flumazenil PET in patients with complex partial seizures have been limited so far.$^{19,24}$ In a comparison between $^{18}$FDG PET, $^{119}$I-Iomazenil SPECT, and DEEG, van Huffelen et al.$^{5}$ found that, in a study limited to eight patients, SPECT showed a correct localisation in 87.5% (seven of eight), whereas PET always demonstrated ipsilateral hypofunction. Due to its limited spatial resolution or the extent of the abnormality concerned, $^{119}$I-Iomazenil SPECT was considered primarily useful in identifying the side of epileptic focus.

PET as well as SPECT techniques have been improved recently by the introduction of second generation technology. Besides the use of $^{18}$FDG PET, direct comparison of two methods, $^{11}$C-flumazenil PET and $^{11}$I-Iomazenil SPECT, which are based on the hypothesis that changes in identical BZ receptor sites are displayed, became feasible.

In this study of 23 patients hypometabolism of $^{18}$FDG PET was found to be more extensive, with abnormality outside the lobe of surgery in nine patients. This is by contrast with the abnormal region indicated by $^{11}$C-flumazenil PET, which was topographically more restricted. Extension of abnormality outside the lobe of surgery was seen in only two of the 23 patients with this technique and turned out to be less severe compared with the temporal abnormality. DEEG studies indicate that a localised onset in the mesial or neocortical temporal region of seizures cannot be predicted in a reliable way by functional imaging with $^{18}$FDG or $^{11}$C-flumazenil PET.

It is worthwhile noting that in the only patient (4) with a temporal as well as a frontal focus the correlation with $^{18}$FDG PET was accurate whereas $^{11}$C-flumazenil PET only correlated with the temporal and not with the frontal epileptogenic area. This may indicate that the results of $^{11}$C-flumazenil PET might be less valuable in patients with an extratemporal origin of their seizures. The sensitivity of this method in extratemporal epilepsy remains to be evaluated.

The results obtained in the present study show partial agreement with previous studies,$^{7,8}$ which stated that the area of decreased uptake in $^{11}$C-flumazenil binding is more restricted and has a closer spatial relation with the zone of ictal onset than the area of glucose hypometabolism. In five patients of our study in which DEEG was performed the $^{11}$C-flumazenil PET was not more restrictive as regards the detection of abnormality in DEEG in comparison with $^{18}$FDG PET.

$^{123}$I-Iomazenil SPECT was highly inaccurate in localising the lobe of surgery. Despite introduction of second generation technology the insufficient localising capacity of interictal $^{123}$I-Iomazenil SPECT clearly restricts the applicability in presurgical evaluation of epileptic patients.

The difference in localising capacity in this limited group of patients between $^{11}$C-flumazenil PET and $^{119}$I-Iomazenil SPECT is striking, because both methods apply BZ receptor ligands. Actually, there is no definite explanation for this phenomenon, although several interpretations are conceivable. Possible factors for incongruent results are: (a) differences in molecular structure of ligands caused by adherence of different elements, a small F molecule compared with a larger I molecule, that results in divergent BZ receptor binding; (b) differences in activity level or acquisition. Activity dose administered in $^{119}$I-Iomazenil SPECT is lower compared with activity dose in the $^{11}$C-flumazenil PET technique. Onset of scanning after injection of the ligand is later in $^{123}$I-Iomazenil SPECT compared with $^{11}$C-flumazenil PET. Furthermore, the PET technique is characterised by a more efficient data acquisition system, resulting in a better signal to noise ratio than SPECT, which necessitates the use of collimators. Attenuation correction is considered a major problem in SPECT compared with PET. A question is whether future research with an improved interictal $^{119}$I-Iomazenil SPECT technique or the application of ictal $^{119}$I-Iomazenil SPECT, will show results more similar to $^{11}$C-flumazenil PET. The reduced level of costs and the relatively easy access to SPECT facilities will activate this research.

Our results suggest that the decrease in $^{11}$C-flumazenil binding seems related to the neuronal loss accompanying the epileptic focus rather than to the epileptogenicity of the involved area. These results are in line with autoradiographic studies showing a decrease of 3H-Ro 15-1788 that correlated with neuronal loss in resected tissue of patients with temporal lobe epilepsy.$^{22,23}$
Conclusions

This study illustrates that single methods as part of non-invasive presurgical evaluation may have limited localising capacity. Convergence of the results of different methods can improve the ability to indicate the localisation of the focus with more precision. In the Dutch programme only the convergence of EEG and MRI techniques was used in clinical practice. Although Engel has indicated that 18FDG PET and 11C-flumazenil PET turned out to be reliable for localisation of epileptogenic temporal lobe, which supports the presurgical diagnosis in patients with non-lesional MRI or non-lateralising/localising scalp EEG recordings. In those patients whose phase 1 presurgical evaluation allows no localisation of the epileptogenic area, PET studies may provide topographical information for the planning of the implantation of intracranial electrodes for DEEG. Further application of both PET techniques in combination with DEEG is required to elucidate the discrepancy between transverse and coronal scans and to evaluate the abnormalities in patients with extratemporal epileptic seizures.

We express our gratitude to Professor FN Lopes da Silva for his suggestions to improve the text of this article. This study was supported by a grant from the National Medical Foundation Reine Elisabeth of Belgium.
Is 11C-flumazenil PET superior to 18FDG PET and 123I-iomazenil SPECT in presurgical evaluation of temporal lobe epilepsy?

R M Debets, B Sadzot, J W van Isselt, G J Brekelmans, L C Meiners, A O van Huffelen, G Franck and C W van Veelen

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