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AJNR Am J Neuroradiol 1992, 13 (1) 249-253
http://www.ajnr.org/content/13/1/249

Evaluation of Focal Epilepsy: A SPECT Scanning Comparison of 123-I-Iomazenil versus HM-PAO

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Purpose: To establish whether regional disturbances of the benzodiazepine receptor distribution in focal epilepsies can be detected by SPECT using 123-I-Iomazenil. **Patients and Methods:** Benzodiazepine receptor imaging was carried out in 10 patients interictally. To be eligible for this study the patients had to have a history of focal seizures and no evidence of routine imaging abnormalities as in CT or MR. The patients were selected on the basis of a regional decreased blood flow in HMPAO SPECT that correlated with the site of a stable unifocal EEG abnormality. Benzodiazepine receptor imaging was performed after intravenous administration of approximately 110 MBq 123-I-Iomazenil using SPECT. **Results:** A regional reduced activity was found on sequential SPECT series after 30 and 90 min post injection in the receptor study. The brain region with a reduced receptor density was concordant to the pathologic finding in HMPAO SPECT in all patients. **Conclusion:** For the evaluation of patients with focal epilepsies Iomazenil SPECT offers several advantages over HMPAO SPECT. Iomazenil binds specifically to the benzodiazepine receptor complex whereas the exact binding sites of HMPAO are still unknown. In contrast to HMPAO, Iomazenil can be used for sequential SPECT examinations that may detect dynamic changes of the receptor complex. For the purpose of benzodiazepine receptor imaging, Iomazenil is a suitable ligand in patients with focal epilepsies.

Index terms: Seizures, focal; Single photon emission computed tomography (SPECT); Cerebral blood flow

AJNR 13:249–253, January/February 1992

Benzodiazepine (BZ) receptor antagonists like flumazenil and similar ligands have been extensively investigated by positron emission tomography since they can be labeled by either C11 or F18. (1–3).

It has been shown that in focal epilepsies the receptor density is decreased whereas the receptor affinity for the ligand is unaffected in the presumed epileptogenic focus (4). Altered receptor sites have also been found in Alzheimer disease, Huntington disease, and other central nervous system disorders (5).

Recently Iomazenil, a flumazenil analog that can be labeled with 123-iodine, has been synthesized. Preclinical trials have shown that this ligand is capable of visualizing the gamma-aminobutyric acid/benzodiazepine receptor complex in vitro and in vivo because of its high affinity to the binding sites (6).

The purpose of this study is to establish whether regional disturbances of the BZ receptor distribution in focal epilepsies can be detected by single photon emission computed tomography (SPECT) using 123-I-Iomazenil (IMZ). All the results of Iomazenil SPECT (IMZ SPECT) were compared with hexamethyl-propyleneamine oximae (HMPAO)SPECT in the same patients.

Received January 22, 1991; accepted contingent on revision April 8; revision received July 11, final acceptance July 15.

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AJNR 13:249–253, Jan/Feb 1992 0195-6108/92/1301-0249

Patients and Methods

Patients

Ten patients (seven women, three men) between 19 and 59 years-of-age were investigated. The patients were diagnosed as suffering from active focal epilepsy as demonstrated by electroencephalogram (EEG) and were selected by a pathologic HMPAO SPECT finding

Seven patients were on antiepileptic medication either by carbamazepine or phenytoin alone or in combination. Focal lesions in these patients had been excluded by computed tomography (CT) or magnetic resonance (MR) imaging. In each patient HMPAO and IMZ SPECT were performed interictally with a time interval of 48 to 72 hr. The clinical and EEG data are shown in Table 1.

Radioligands

For the SPECT examination of the BZ receptor distribution, patients received IMZ labeled with 123-iodine with a specific activity of approximately 0.2–1.5 TBq/mg resulting in a total amount of 1–5 μg 123-I-Ro 16–154. Two SPECT series were performed, the first was started 30 min (IMZ SPECT (30′)), the second 90 min (IMZ SPECT (90′)) after injection.

The SPECT examination of regional cerebral blood flow (rCBF) was carried out using 555 MBq 99mTc HMPAO that was administered intravenously and was started 10 min thereafter. Prior to both IMZ or HMPAO SPECT patients received 500 mg sodium perchlorate orally to avoid thyroid contamination with the administered radioactivity.

Imaging

Intracerebral distribution of the radioactive ligands was measured with a rotating gamma camera connected to an electronic data processing unit (APEX 409, Elscint). The camera rotated through 360° with a radius of less than 30 cm. The patients were supine and positioned with the orbitomeatal line perpendicular to the axis of rotation.

Their heads were held motionless in the center of the field of view by using a head restraint and an adhesive band. A low-energy all-purpose collimator (APC 3, Elscint) was used for both IMZ and HMPAO SPECT. Sixty projections with a zoom of 1.5 were done in the step and shoot mode. For each projection 2/3 of the maximum matrix depth, eg 255 counts/pixel, were acquired to avoid overflow. The data were recorded on a 64 × 64 matrix. The raw data were first corrected for inhomogeneity and then for noise reduction. For IMZ SPECT, a Butterworth filter with cut off = 0.5 Ny and order = 2, and for HMPAO SPECT a Hanning filter with a resolution recovery parameter = 0 and a cut-off frequency = 1 were used. Each reconstructed image was corrected for tissue absorption by a constant attenuation coefficient of 0.125 cm^{-1}. The images were reconstructed into axial sections with a slice thickness of 9 mm. Coronal and sagittal slices were also reconstructed so as to avoid the risk of misinterpreting focal lesions in the inferior temporal lobes.

The SPECT images were evaluated qualitatively and quantitatively. By visual means, an increased tracer accumulation was interpreted as increased receptor density or increased blood flow, and decreased accumulation as decreased receptor density or decreased blood flow, respectively. For quantitative evaluation a rectangular region of interest was placed in the area with disturbed tracer accumulation and mirrored to the contralateral side for both IMZ SPECT and HMPAO SPECT. In addition, an irregular region of interest that outlined the cerebellum and a rectangular region of approximately 100 $pixel^2$ (reference region) frontal medial outside the cortex in the fourth slice above the cantomeatal level were placed for IMZ SPECT. Counts per pixel were calculated for all regions of interest. The statistical analysis was performed using Student's *t*-test for paired samples.

Physics

The radiation dose for 123-I-IMZ has been determined to be 25 μGy/MBq for the brain, 4.7 for the thyroid gland, 5.6 for the kidneys, 48 for the intestine, 1.9 for the lungs, 11.0 for the ovaries, 5.2 for the bone marrow, and 3.7 for the whole body. These values are about in the range of other routine nuclear-medicine procedures (bone scan, brain perfusion scan). Since 123-I is produced by the (p, 5n) reaction from 127-I, there is no detectable contamination by 124-I.

TABLE 1: Individual data (clinical diagnosis, medication, EEG focus) of 10 patients with active focal epilepsy

Case No.	Age (years)	Sex	Clinical Diagnosis	Medication	EEG
1	31	M	TLE	Carbamazepine	Left temporal
2	31	F	TLE	Carbamazepine	Left temporal
3	19	F	FLE	Carbamazepine	Left temporal
4	24	F	TLE	Carbamazepine, phenytoine	Left temporal
5	27	M	TLE	Carbamazepine	Right temporal
6	28	F	TLE	Phenytoine	Right temporal
7	42	F	TLE	Carbamazepine	Left temporal
8	40	F	TLE	Untreated	Right temporal
9	19	F	TLE	Untreated	Right temporal
10	59	M	TLE	Untreated	Left temporal

Note.—TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy.

Results

By visual evaluation, all patients (n = 10) had a single region of reduced HMPAO uptake in the temporal lobe. In 9/10 patients the pathologic region was found on the left, in 1/10 patients on the right side. Quantitative evaluation of HMPAO SPECT revealed a mean count density of 156 ± 19 counts/pixel (median ± SD) for the ipsilateral and 176 ± 18 (median ± SD) for the contralateral

TABLE 2: Quantitative evaluation of the count densities in different regions for IMZ SPECT (30′). IMZ SPECT (90′) and HMPAO SPECT values for counts/pixel expressed as mean SD, minimum, maximum, and range

	Counts per Pixel				
	Mean	SD	Minimum	Maximum	Range
IMZ SPECT (30′)					
Ipsilateral	131	26	81	176	95
Contralateral	143	25	93	188	95
Reference	110	14	90	134	44
Cerebellum	123	33	66	165	99
IMZ SPECT (90′)					
Ipsilateral	129	23	81	155	74
Contralateral	146	21	99	168	69
Reference	97	17	54	114	60
Cerebellum	119	23	70	154	84
HMPAO SPECT					
Ipsilateral	156	19	124	189	65
Contralateral	176	18	146	198	52

side ($P < .001$). Qualitative assessment of IMZ SPECT revealed a reduced tracer uptake in all cases for both IMZ SPECT (30′) and IMZ SPECT (90′) in the corresponding regions of HMPAO SPECT. IMZ SPECT (30′) appeared to show deeper structures of the brain like the basal ganglias whereas IMZ SPECT (90′) demonstrated the cortical pattern of BZ receptor distribution. Quantitative analysis of IMZ SPECT (30′) showed a mean count density of 131 ± 26 (counts/pixel) for the ipsilateral and 143 ± 25 (counts/pixel) for the contralateral side ($P < .000$). Values for the cerebellum and the reference region were 123 ± 33 (counts/pixel) and 110 ± 14 (counts/pixel), respectively. Quantitative analysis of IMZ SPECT (90′) showed a mean count density of 129 ± 23 (counts/pixel) for the ipsilateral and 146 ± 21 (counts/pixel) for the contralateral side ($P < .000$). Values for the cerebellum and the reference region were 119 ± 23 (counts/pixel) and 97 ± 17, respectively. Results are shown in Table 2 and Figures 1 and 2. IMZ SPECT (30′) revealed no significant difference of the count densities in the ipsilateral and contralateral region compared with the cerebellum ($P = .460$ and $P = .084$, respectively, whereas IMZ SPECT (90′) showed a significant difference for the contralateral side and the cerebellum ($P = .006$) but not for the ipsilateral side and the cerebellum ($P = .239$).

Discussion

Several reports have described the usefulness of HMPAO SPECT in the evaluation of functional disturbances in focal epilepsies (7), although the exact biokinetic and binding mechanism of this substance is unknown. Recently IMZ (RO 16-0154), which acts as a BZ receptor antagonist, has been developed. It has been shown that this ligand binds tightly to specific BZ receptors without having any intrinsic activity (6). Positron emission tomography studies have shown that the BZ receptor density is reduced in the epileptic foci whereas the affinity of the ligand for the receptor is undisturbed (9, 10).

In this study, 10 patients with active focal epilepsy were selected for interictal SPECT examinations. Inclusion criteria for these patients were focal seizures and a pathologic HMPAO SPECT finding whose site correlated with a stable unifocal spike and wave and/or sharp wave activity in the EEG recordings. Our data show that IMZ SPECT was able to demonstrate areas with reduced tracer uptake whose locations were concordant to those of the HMPAO SPECT in all cases. For the functional evaluation of patients with focal epilepsies, IMZ SPECT might be advantageous over HMPAO SPECT, in our opinion. For regulating cerebral function, the gamma-aminobutyric acid/benzodiazepine receptor complex plays an essential role as the main mediator of inhibition. IMZ binds specifically to this receptor complex whereas the exact binding sites of HMPAO are still unknown. IMZ SPECT can be performed together with noninvasive procedures in patients with focal epilepsies as part of presurgical evaluation.

The pathologic tracer uptake area could be identified on IMZ SPECT (30′) as well as IMZ SPECT (90′) in every case. Phantom studies have shown that the smallest detectable lesion has a diameter of 12 mm using the described acquisition protocol. Other investigators have found more pathologic results on late images compared with early images that are dominated by blood flow (4). Early images do not reveal a significant difference of the count densities of the ipsilateral or contralateral region compared with the cerebellum since blood pool probably dominates the receptor bound activity. On late images, however, contralateral and cerebellum activity is different whereas the activity in the foci is as low as in the cerebellum since the cerebellum contains only a minute amount of specific bound radioactivity and the washout of unspecific bound radioactivity is fast.

Since the biochemical behavior of IMZ is suitable for sequential SPECT measurements it

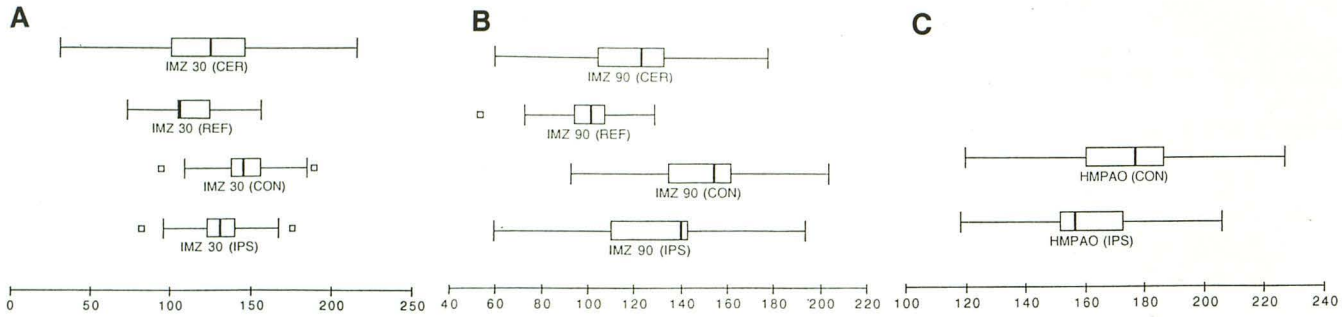

Fig. 1. "Box and whisker" plots of the count densities. *Vertical lines* represent medians, *boxes* values of the second and third quartile (interquartile range). Horizontal lines ("whiskers") extend to values within 1 interquartile range below or above the second or third quartile. Unusual values of 1.0 to 1.5 times the interquartile range below or above the first or third quartile are plotted as squares.

A, Count densities in the ipsi-(*IPS*) or contralateral cortical region (*CON*) cerebellum (*CER*) and reference region (*REF*) for IMZ SPECT (30′).

B, Count densities in the ipsi- or contralateral cortical region, cerebellum and reference region for IMZ SPECT (90′).

C, Count densities in the ipsi- or contralateral region for HMPAO SPECT.

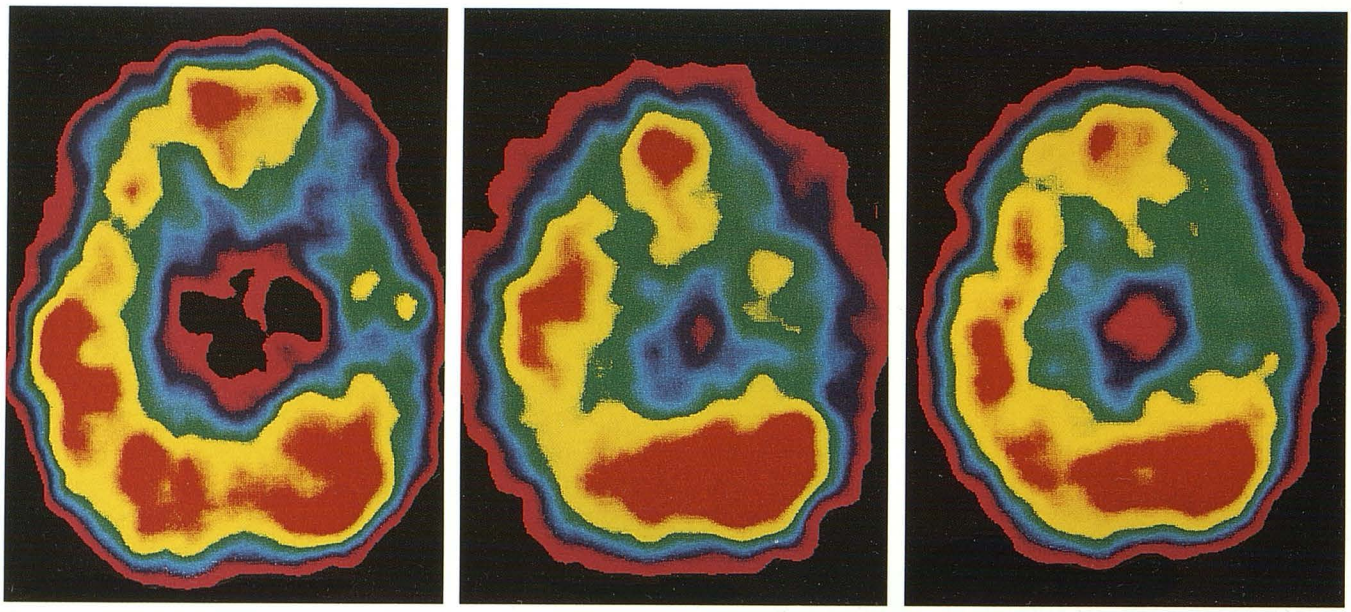

Fig. 2. *A*, 31-year-old woman with partial seizures originating from the left temporal lobe that shows a reduced rCBF in HMPAO SPECT.

B, the Tracer accumulation is also decreased in IMZ SPECT (30′), which may be due to either reduced rCBF or decreased BZ receptor density.

C, IMZ SPECT (90′) shows the cortical distribution pattern of the BZ receptor that is decreased in the left temporal lobe.

seems possible to demonstrate dynamic changes of the ligand receptor complex. While on IMZ SPECT (30′) the deeper structures of the brain (eg, white matter and basal ganglia) and the cerebellum are clearly delineated, IMZ SPECT (90′) shows a more cortical distribution pattern of the BZ receptor with lowest density in the cerebellum.

We conclude that these preliminary results make IMZ suitable as a ligand for evalutation of epileptogenic areas in focal epilepsies. With faster imaging modalities, it seems promising to record a multiple data set for better receptor kinetics and displacement studies.

Acknowledgment

The authors like to appreciate the support of Ingo Peter and the preparation of the manuscript by Brigitte Seit, both of the Institut für Diagnostikforschung. We thank the nuclear medicine technologists, especially Heidemarie Ewaldt and Bernhild Wiese, for performing the studies.

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