EFFECT OF CARBAMAZEPINE THERAPY ON CEREBRAL BLOOD FLOW IN CHILDREN WITH PARTIAL EPILEPSY(*)

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ABSTRACT

Objective: The effect of chronic carbamazepine (CBZ) therapy on regional blood flow (rCBF) was evaluated using single photon emission computed tomography (SPECT) with technetium-99m hexamethylpropyleneamineoxime.

Methods: Interictal SPECT scans and electroencephalography (EEG) examinations in 13 (8 males, 5 females) children with partial epilepsy were performed twice before administering CBZ and between 4-12 months (8.00±2.23 months) after starting the therapy.

Results: Visual assessment of interictal SPECT images showed stable perfusion abnormalities in 9 of 11 cases who had regions of hypoperfusion in the first scans. Before CBZ therapy, EEG correlated well with SPECT in 9/11 patients in localizing focal abnormality and the rate of correlation was 7/11 during the therapy. By quantitative evaluation, no significant change of rCBF in all cerebral cortical regions except right inferior frontal ($p<0.03$) was found after initiation of CBZ therapy. Repeated SPECT scans done in 6 healthy volunteers at intervals of 6 to 10 months (7.20±3.45 months) demonstrated no significant change of rCBF.

Conclusion: Our results suggest that chronic CBZ therapy does not affect blood flow of the epileptogenic zone nor of the other parts of cerebral cortex. The absence of any effect due to chronic CBZ therapy may be related to the partial clinical improvement.

Key Words: Regional cerebral blood flow, carbamazepine, chronic antiepileptic drug therapy.

INTRODUCTION

Functional brain imaging in partial epilepsy has been focused on the investigation of focal abnormalities corresponding to the epileptic foci determined by electroencephalography (EEG). Using single photon emission computed tomography (SPECT), epileptic foci were usually visualised as a hypofixation zone due to a decreased regional cerebral blood flow (rCBF) during the interictal state (1-3) and a hyperfixation zone due to an increased rCBF during the ictal state (2,4-8).

The effects of antiepileptic drugs (AEDs) on cerebral metabolism and perfusion have not been investigated extensively. Using positron emission tomography with (18-F)-2-deoxyglucose, Theodore et al. (9) demonstrated that chronic barbiturate therapy reduces cerebral glucose metabolism whereas phenytoin (PHT) causes a mild decrease (10). The difference between the functional effects of phenobarbital and PHT might be related to the differences In drug mechanisms of action. Carbamazepine (CBZ) slightly reduces cerebral glucose metabolism because it has similar mechanism of action as PHT (11,12). A few studies have investigated the effect of CBZ therapy on cerebral blood flow only in adults. To our knowledge, no data concerning hemodynamic influence of chronic CBZ therapy in epileptic children is yet available. The present study was planned to investigate the effect of long-term CBZ treatment on cerebral blood flow.

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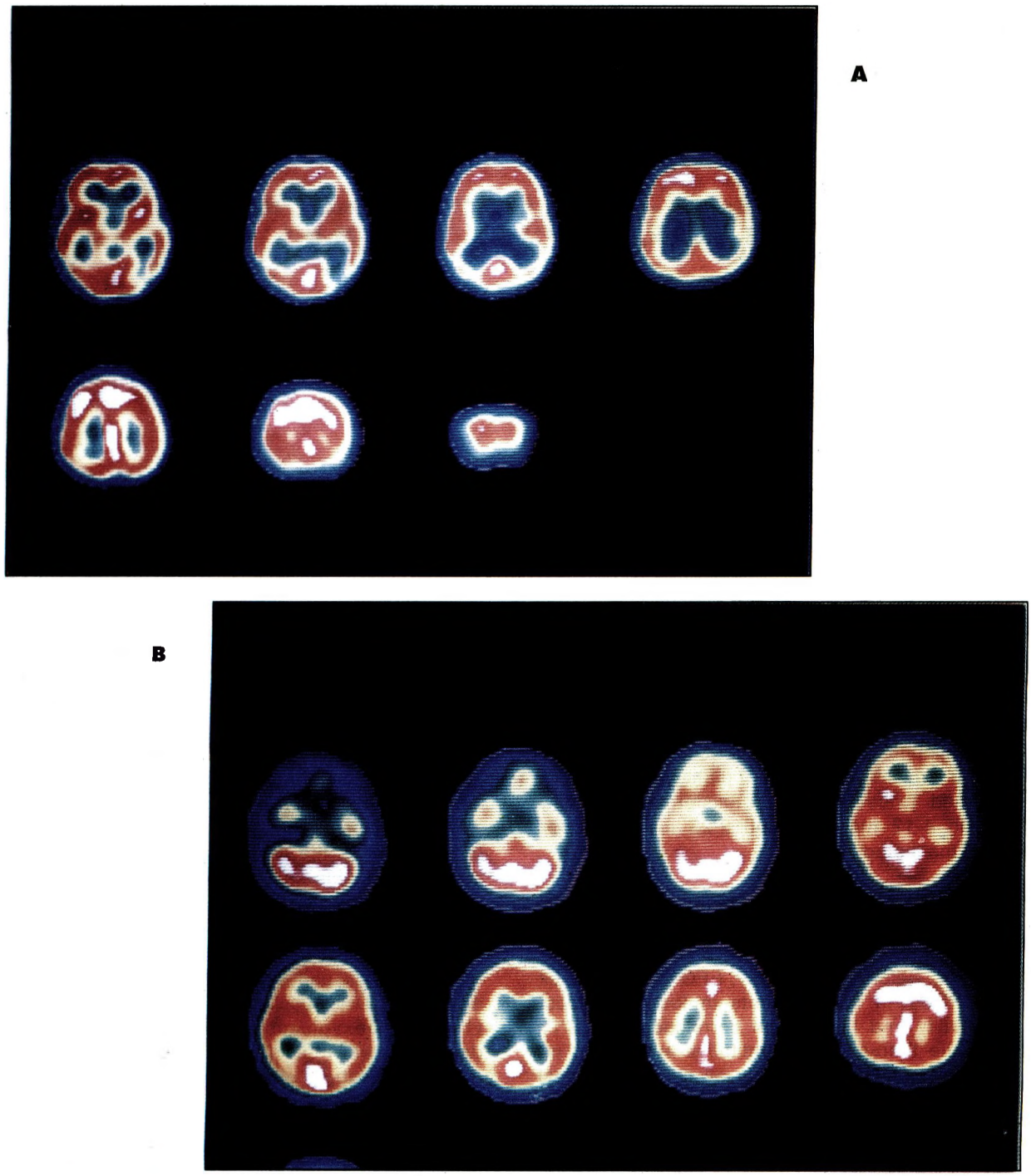

Fig. 1: A. Reduced perfusion in the left parieto-occipital region before starting therapy (patient number 12). B. After CBZ therapy normalization of the perfusion abnormality in the same patient.

MATERIALS AND METHODS

The patient group consisted of 13 children (8 males, 5 females) who had partial seizure disorders within the previous 2-24 months (mean 12.20±10.36 months) before the admission. They were not receiving any medication (Table I). Their ages ranged from 4 to 13 years (mean age 8.30±2.62 years). Clinical diagnosis of partial seizure disorder in each patient was based on the 1989 ILAE (13). Neurological examinations were normal in all patients. No structural abnormality had been determined in MRI examinations.

After informed parental consents were obtained, technetium-99m hexamethylpropyleneamineoxime (HMPAO) SPECT scans at interictal states were performed twice at intervals of 4 to 12 months (mean 8.00±2.23 months). All patients received CBZ monotherapy (15-25mg/kg per day) between the two scans. CBZ plasma level remained in the 4-10 μgr/L range.

As the control group, 6 volunteers (3 males, 3 females) who had no history of neurological or behavioral illness were investigated by serial scans. Their ages ranged from 5 to 14 years (mean age 7.80±2.72 years). The interval between the two measurements was 6 to 10 months (mean 7.20±3.45 months).

During CBZ therapy the rate of reduction in seizure frequency was less than 60% in all cases except 3 cases with a rate of 82%, 80% and 78%, respectively (patients 2, 12 and 13) (Table I).

An interictal electroencephalography (EEG) was obtained a few hours after each SPECT scan.

SPECT Studies
The scans were performed on subjects who were seizure-free for at least 4 days. Using a previously inserted and fixed butterfly needle 5-15 mCi (185-555 MBq) Tc-99m HMPAO (Ceretec, Amersham International, Amersham, UK) was injected to the patients who were in the resting state (supine, eyes closed and silent, with a minimum background noise). Scanning was started within 15-60 minutes of injection using a large field of view, single head rotating camera (Siemens Orbiter ZLC/7500, Des Plaines, IL, US) fitted with a high resolution parallel hole collimator. 128 views, each of 15 sec, were acquired on a circular, step and shoot mode at 360°. Uniformity and center of rotation (COR) corrections were performed and followed by a transverse plane reconstruction via the standard backprojection algorithm using a Butterworth filter (0.45 Nyquistic frequency and 10th order). Each slice was 6.5 mm thick. After applying an attenuation correction using Chang's methods with a coefficient of 0.12/cm, transaxial slices were reoriented parallel to orbitomeatal axis.

Visual Analysis of SPECT Images
All SPECT scans were interpreted visually by two nuclear medicine physicians without having any knowledge about the clinical data, both independently and together.

Semiquantitative Analysis of SPECT Images
Twelve contiguous transverse slices on and over the orbitomeatal line were combined to obtain six 13 mm thick slices. Symmetric regions of interest (ROIs) were manually drawn over the following regions on the composite 6 slices: mesial, inferior, lateral and anterior frontal, mesial, inferior and superior temporal, parietal and occipital cortical areas, basal ganglia, thalamus and cerebellar hemispheres. For each ROI, a cerebral cortex / cerebellum ratio (CC) was acquired by dividing the mean counts per pixel in the ipsilateral cerebellar hemisphere. This ratio was used as a measure of rCBF.

EEG Recordings
The examinations were performed with scalp recordings using both mono- and bipolar montages according to the International 10/20 system.

Statistical Analysis
Significance was assessed by a 2-tailed t test. A p-value<0.05 was considered statistically significant.

RESULTS

SPECT Findings
By visual assessment of interictal SPECT images, stable perfusion abnormalities were found in 9 of 11 patients who had hypoperfused regions in the first scans (Table II). The initial focal perfusion abnormalities in 2 patients changed to normal (patients 12 and 13) (Fig 1). Both first and second SPECT scans had no perfusion abnormality in 2 patients (patients 1 and 4).

Similar to visual evaluation, semi quantitative analysis demonstrated no significant change of CC ratio in all regions except right inferior frontal ($p<0.03$) (Table III). Both visual and semi quantitative evaluation of consecutive scans in healthy cases showed no significant change.

EEG Findings
All of the patients had epileptic foci (spike and/or spike-wave) in the first recordings and 10 of them showed the same foci in the second examinations (Table II). Epileptic foci normalized in 3 patients (patients 10,12 and 13).

Comparison of SPECT Data with EEG Results:
Comparing the findings of the first EEG findings and SPECT scans, 11 of 13 patients with EEG foci also had focal hypoperfused regions on the SPECT scans and SPECT correlated well with EEG in the localization of the foci in 9/11 patients. After initiation of CBZ therapy, 7/11 cases had stable epileptic foci and hypoperfused regions (Table II).

Table I. Clinical data of epileptic patients

Patient No/ Gender	Age (Year)	Duration of seizures before therapy (Month)	Interval between scans (Month)	Reduction of seizure frequency (%)
1/M	4	6	10	46
2/M	8	2	4	82
3/M	8	7	12	55
4/M	12	12	7	58
5/F	13	5	9	53
6/M	8	18	9	59
7/M	9	24	8	44
8/M	7	6	11	41
9/F	7	3	7	54
10/M	8	24	8	60
11/F	6	12	7	55
12/F	12	24	8	80
13/M	6	4	5	78
MEAN:	8.30	12.20	8.00	
SD:	2.62	10.36	2.23	

Table II. Localization of abnormal perfusion area (SPECT) or abnormal electrical activity (EEG)

Patient No.	EEG		SPECT	
	Off CBZ	On CBZ	Off CBZ	On CBZ
1	L-T.	L-T.	N	N
2	R-T.P.	R-T.P.	R-T.	R-T.P.
3	L-T.P.	L-T.P.	L-T.P.	L-T.P.
4	L-T.P.	L-T.P.	N	N
5	R-F.T.	R-F.T.	R-T.	R-T.
6	R-T.	R-T.	R-F.T.	R-T.
7	L-T.	L-T.	L-F.T.	L-F.T.
8	B-P.O.	B-P.O.	R-P.O.	R-P.O.
9	L-F.T.	L-F.T.	L-F.T.	L.T.
10	B-P.O.	N	R-P.O.	R-P.O.
11	R-F.T.	R-F.T.	R-F.	R-F.
12	L-P.O.	N	L-P.O.	N
13	L-T.P.	N	L-T.P.	N

L: Left, R: Right, B: Bilateral, F: Frontal, T: Temporal, P:Parietal, O: Occipital, N: Normal.

DISCUSSION

The present study indicated that CBZ did not affect cortical blood flow in children with partial epilepsy after 8.00±2.62 months of treatment. This finding confirmed the data of a few clinical studies concerning the metabolic and hemodynamic effects of CBZ. Both induction and withdrawal effects of CBZ therapy on cerebral glucose metabolism have been investigated in small study populations and no significant change has been found (11,12,14). Similarly, a SPECT study with Xenon 133 inhalation in 5 partial epileptic children showed that rCBF did not change following 4-6 months of CBZ monotherapy in spite of initial slight increase at the end of the first month of the treatment (15). Contrary

Table III. Semiquantitative Analysis of rCBF

Region of Interest	Cerebrocerebellar Ratio			
	Epileptic patients		Control patients	
	Before CBZ	On CBZ	First scan	Second scan
Inferior Frontal				
right	0.91±0.09	0.97±0.06*	1.04±0.03	1.02±0.05
left	0.91±0.10	0.95±0.07	1.06±0.09	1.04±0.08
Mesial Frontal				
right	0.96±0.10	0.99±0.06	0.98±0.01	0.98±0.02
left	0.96±0.11	0.98±0.07	0.98±0.09	0.95±0.04
Lateral Frontal				
right	1.02±0.11	1.01±0.05	1.04±0.08	1.03±0.05
left	1.00±0.13	1.01±0.06	1.03±0.11	0.94±0.06
Anterior Frontal				
right	1.00±0.11	1.03±0.07	1.17±0.14	1.06±0.07
left	1.02±0.13	1.04±0.08	1.04±0.05	1.07±0.12
Inferior Temporal				
right	0.95±0.14	0.94±0.05	1.02±0.04	1.03±0.05
left	0.96±0.15	0.94±0.06	1.01±0.06	0.99±0.01
Mesial Temporal				
right	0.95±0.10	0.97±0.04	0.98±0.01	0.97±0.02
left	0.96±0.10	0.97±0.05	0.98±0.04	0.96±0.05
Superior Temporal				
right	0.96±0.09	0.97±0.04	0.98±0.01	0.98±0.02
left	0.94±0.09	0.98±0.05	0.99±0.04	0.99±0.05
Parietal				
right	0.96±0.10	0.98±0.04	0.97±0.02	0.99±0.05
left	0.95±0.09	0.99±0.03	0.98±0.02	0.96±0.02
Occipital				
right	1.05±0.09	1.05±0.06	1.05±0.04	1.06±0.05
left	1.06±0.09	1.06±0.07	1.07±0.04	1.07±0.07
Basal ganglia				
right	1.01±0.06	1.04±0.06	1.08±0.04	0.99±0.03
left	0.98±0.10	1.03±0.08	1.03±0.10	1.03±0.12
Thalamus				
right	0.98±0.09	1.03±0.08	1.03±0.06	1.02±0.04
left	0.96±0.14	1.02±0.07	1.02±0.04	1.01±0.03

* $p < 0.03$

to the suggestion of more depressive effect of chronic CBZ therapy than acute administration on local cerebral metabolism (14), our study with a larger sample size and longer follow-up period than the previous studies did not show any change on rCBF induced by CBZ.

In this study the high number of cases with a stable focal perfusion abnormality and the high correlation rate of those SPECT findings with EEG foci indicate that chronic CBZ therapy has no effect on the epileptogenic area blood flow. The stable flow in the epileptogenic region may be related to the incomplete reduction of the seizure frequency. The positive relationship between the improvement of clinical findings and perfusion abnormalities was shown in the studies concerning the effects of CBZ or PHT (15-17). Further follow-up studies may provide more accurate information about the effect of chronic CBZ therapy on cerebral perfusion.

REFERENCES

1. *Ryding E, Rosen I, Elmquist D, Ingvar DH. SPECT measurement with 99m-Tc-HM-PAO in focal epilepsy. J Cereb Blood Flow Metab 1988;8:595-601.*
2. *Rowe CC, Berkovic SF, Austin MC, McKay WJ, Bladin PF. Patterns of postictal cerebral blood flow in temporal epilepsy: qualitative and quantitative analysis. Neurology 1991;41:1096-1103.*
3. *Dietrich ME, Bergen D, Smith MC, Fariello R, Ali A. Correlation of abnormalities of interictal n-isopropyl-p-iodoamphetamine single photon emission computed tomography with focus of seizure onset in complex partial seizure onset in complex partial seizure disorders. Epilepsia 1991;32:187-194.*
4. *Shen W, Lee BI, Park HM, Siddiqui AR, Wellman HN, Markand ON. HIPDM-SPECT brain imaging in evaluation of intractable epilepsy for temporal lobectomy. Neurology 1989;39 (suppl 1):132.*

5. Harvey AS, Bowe JM, Hopkins IJ, Shield LK, Cook DJ, Berkovic SF. Ictal 99mTc-HMPAO single photon emission computed tomography in children with temporal epilepsy. Epilepsia 1993;34:869-877.
6. Marks DA, Katz A, Hoffer P, Spencer SS. Localization of extratemporal epileptic foci during ictal single photon emission computed tomography. Ann Neurol 1992;31:250-255.
7. Harvey AS, Hopkins IJ, Bowe JM, Cook DJ, Shield LK, Berkovic SF. Frontal lobe epilepsy: clinical seizure characteristics and localization with ictal 99mTc-HMPAO SPECT. Neurology 1993;43:1966-1980.
8. Duncan R, Patterson J, Roberts R, Hadley DM, Bore I. Ictal/postictal SPECT in the presurgical localization of complex partial seizures. J Neurol Neurosurg Psychiatry 1993;56:148-158.
9. Theodore WH, Di Chiro G, Margolin R, Fishbein D, Porter RJ, Brooks A. Barbiturates reduce human cerebral glucose metabolism. Neurology 1986;36:60-64.
10. Theodore WH, Bairamian D, Newmark ME, et al. The effect of phenytoin on human cerebral glucose metabolism. J Cereb Blood Flow Metab 1986;6:315-329.
11. Theodore WH. Antiepileptic drugs and cerebral glucose metabolism. Epilepsia 1988;29(suppl 2):S48-S55.
12. Theodore WH, Ito B, Devinsky O, Porter RJ, Jacobs G. Carbamazepine and cerebral glucose metabolism. Neurology 1987;37(Suppl 1):S104.
13. Comission on Classification and Terminology of the International League Against Epilepsy:Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-399.
14. Theodore WH, Bromfield E, Onorati L. The effect of carbamazepine on cerebral glucose metabolism. Ann Neurol 1989;25:516-520.
15. Valmier J, Touchon J, Blayac JP, Baldy-Moulinier M. Initiation of carbamazepine therapy in partial epilepsy:a regional cerebral blood flow study. Epilepsy Res 1990;5:229-234.
16. Ell PJ, Lui D, Cullum I, Jaritt PH, Donaghy M, Harrison MJG. Cerebral blood flow studies with 123iodine-labelled amines. Lancet 1983;I:1348-1352.
17. Holman BL, Hill TC, Magistretti PL. Brain imaging with emission computerized tomography and radiolabeled amines. Invest Radiol 1982;17:206-215.