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Piracetam Improves Activated Blood Flow and Facilitates Rehabilitation of Poststroke Aphasic Patients

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Background and Purpose—In a prospective, double-blind, placebo-controlled study, it was investigated whether piracetam improves language recovery in poststroke aphasia assessed by neuropsychological tests and activation PET measurement of cerebral blood flow.

Methods—Twenty-four stroke patients with aphasia were randomly allocated to 2 groups: 12 patients received 2400 mg piracetam twice daily, 12 placebo. Before and at the end of the 6-week treatment period in which both groups received intensive speech therapy, the patients were examined neuropsychologically and studied with $H_2{}^{15}O$ PET at rest and during activation with a word-repetition task. Blood flow was analyzed in 14 language-activated brain regions defined on reconstructed surface views from MRI coregistered to the PET images.

Results—Before treatment, both groups were comparable with respect to performance in language tasks and to type and severity of aphasia. In the piracetam group, increase of activation effect was significantly higher ($P<0.05$) in the left transverse temporal gyrus, left triangular part of inferior frontal gyrus, and left posterior superior temporal gyrus after the treatment period compared with the initial measures. The placebo group showed an increase of activation effect only in the left vocalization area. In the test battery, the piracetam group improved in 6 language functions, the placebo group only in 3 subtests.

Conclusions—Piracetam as an adjuvant to speech therapy improves recovery of various language functions, and this effect is accompanied by a significant increase of task-related flow activation in eloquent areas of the left hemisphere. **(*Stroke*. 2000;31:2112-2116.)**

Key Words: aphasia ■ piracetam ■ recovery of function ■ tomography, emission computed

Whether the efficacy of rehabilitative measures can be enhanced by adjuvant pharmacotherapy in patients with cerebral disorders is still controversial. Trials relevant to this question were started in the 1940s and applied various agents in different neurological disorders. Early on, this strategy was targeted to language impairment, especially poststroke aphasia, but normally only single cases or small numbers of patients were reported. Positive effects observed in a few cases with various drugs acting by diverging mechanisms[1–5] could usually not be replicated in large clinical trials.[6,7] Piracetam, a γ-aminobutyric acid derivative with a potential effect on cognitive and mnestic functions,[8] was repeatedly used in the treatment of aphasia: In small placebo-controlled trials, 4.8 g piracetam daily over 6 to 12 weeks improved the performance in subtests of the Aachen Aphasia Test,[9–11] but the mechanism by which piracetam enhances recovery from aphasia remained a matter of speculation. Because infarcted tissue cannot regenerate, recovery from poststroke aphasia must involve regions outside the morphologically damaged area that regain or take over language functions lost in acute stroke. It was repeatedly demonstrated that functional imaging modalities can follow the improvement of neurological deficits in changes of task-related activation patterns of flow or metabolism in the course after stroke.[12–15] The aim of this placebo-controlled double-blind study was to test the effect of piracetam as an adjuvant to speech therapy on 2 levels—performance in aphasia tests and task-related flow activation in eloquent brain regions—in a small group of patients with poststroke aphasia.

Subjects and Methods

Twenty-four right-handed patients (13 men, 11 women) were enrolled in the study. All patients suffered from acute aphasia of various types after ischemic stroke of the left hemisphere. All patients were native speakers, between the ages of 18 and 75 years, and without any cognitive or mnestic deficits before stroke. Diagnosis was based on neurological and medical examination, laboratory tests, EEG, Doppler ultrasonography of extracranial and large intracranial vessels, and CT early after stroke and MRI in the later course. Patients with previous ischemic events were excluded. Aphasia severity had to be mild to moderate and was measured with the Token test.[16] To ensure sufficient performance of the word-repetition task during PET measurement, the patients had to reach a score of >50 of 150. Within 14 days after stroke, the patients were included in the study. Further exclusion criteria were clinically relevant hearing or sight disturbances, neurodegenerative disorders,

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psychiatric disease, drug-induced dementia, epilepsy, renal insufficiency, and treatment with other nootropics or with blood-flow-supporting medication before baseline testing. The patients were expected to have led an independent life before stroke event. At runtime of the study, we presupposed exclusion of patients in case of a suspect adverse reaction, a subsequent stroke, illicit drug taking, or by personal request.

The study protocol was approved by the ethics committee of the university and was performed according to European Guidelines for Good Clinical Practice. All patients or their close relatives gave informed consent.

Study Design

The study was prospective, randomized, double blind, and placebo controlled. Patients received either piracetam 2×2400 mg/d or placebo for 6 weeks. The regular administration of the drug/placebo was supervised by drug counting. The randomization list was generated by a software based on the uniform pseudo variates generated by the "RANUNI" function (SAS Inc). The list was built by using blocks of 4. Treatment usually started 2 weeks after stroke. PET measurement (during a word-repetition task) and language and neuropsychological testing were usually done 2 to 3 days before. The same procedures were repeated 8 weeks after the acute stroke. Treatment together with extensive language therapy, occupational therapy, and physiotherapy was identical for all patients. Speech therapy was performed 5 times a week for 60 minutes, so that all patients had received 30 sessions of language therapy at the end of treatment.

Neuropsychological Test Battery

The test battery included the following tests: a verbal fluency task with the letters F, A, and S (1 minute for each letter),[17] Corsi's block span test,[18] a modified laterally score after Oldfield,[19] tests for apraxia,[20] progressive matrices of Raven,[21] and the Benton test.[22]

For language testing the Aachen Aphasia Test was used,[16] which consists of 6 rating scales for spontaneous speech (communicative verbal behavior, articulation and prosody, automated language, semantic structure, phonemic structure, and syntactic structure) and 5 subtests for the assessment of specific language impairments (repetition, written language, naming on confrontation, comprehension, and Token test).

Image Data Acquisition

PET studies were performed on a CTI/Siemens ECAT EXACT HR scanner in 3-dimensional mode.[23] Data acquisition started with intravenous bolus injection of 370 MBq of ^{15}O-labeled water and lasted for 90 seconds. At each PET measurement (baseline at 2 weeks and follow-up at 8 weeks), 8 subsequent scans were obtained for each patient, with an interval of approximately 8 minutes between scans. MRI scanning was performed with 1-T Magneton Impact (Siemens Medical Systems), using a fast, low-angle shot sequence (flip angle 40°, repetition time 40 ms, echo time 15 ms) that produced 64 transaxial T1-weighted slices.

Activation Paradigm

The activation paradigm comprised 2 sets with 4 replications each: a resting condition (dark room, eyes closed, and low ambient noise) and a word-repetition task (repeating nouns read aloud) presented in a balanced sequence (ABBABAAB, with A=rest and B=word repetition). Patients were instructed to repeat and pronounce simple, highly frequent German nouns aloud as quickly as possible.[24] For each run, a new list of nouns was used to avoid recognition and habituation. Presentation of stimuli started 5 seconds before tracer injection and ended 90 seconds after injection. The rate of stimuli presentation was adapted to the patient's ability to repeat the word read aloud.

Image Processing

Each MRI data volume was aligned to the anterior-posterior commissure line with an interactive 3-dimensional image registration program.[25] MRI data were segmented in brain and infarct regions on transaxial T1-weighted slices with an interactive IDL (Interactive Data Language, Research Systems Inc) and C-based image analysis system,[26] operating at a spatial resolution of 1 mm^3. After segmentation of brain and infarcted tissue, a set of 14 volumes of interest (VOI) was drawn on the MRI scans, as described in Table 1. All PET scans were matched interactively to MRI. Average images of the 4 scans belonging to each task were calculated and normalized to mean global brain activity (nCi/mL). In VOI sets transferred to the 2 average images, regional CBF changes (rΔCBF) were calculated as differences between resting and activated condition. From task-induced regional changes (rΔCBF) of each measurement before and after treatment, increase in rΔCBF from 2 to 8 weeks was computed as ($rΔCBF_{8\ weeks} - rΔ\ CBF_{\ 2\ weeks}$).

TABLE 1. Volumes of Interest

Frontal	
F3o	Opercular part of inferior frontal gyrus (BA 45)
F3t	Triangular part of inferior frontal gyrus (BA 44)
PRG3	Inferior part of precentral gyrus (primary vocalizing area)
Temporal	
H1	Transverse temporal gyrus (Heschl's gyrus)
PT	Temporal plane (BA* 41 and 42)
T1p	Posterior superior temporal gyrus (BA 22)
Other	
SMC	Supplementary motor area

*BA indicates Brodman area.

Statistical Analysis

The significance of regional increase of rΔCBF was measured for the regions across subjects in each of the 2 groups (placebo and verum) was assessed by using *t* tests. Neuropsychological and language data were analyzed with *t* tests for dependent samples.

Results

Twelve patients received piracetam and 12 received placebo. Both groups were comparable in age: the piracetam group was mean age 57.41 (SD 13.53) years, the placebo group 56.33 (9.95) years. Initial aphasia severity, as measured with the Token test, was mean 17.16 (SD 14.31) errors in the piracetam group and 17.91 (15.47) errors in the placebo group. In the piracetam group the treatment started 7.8 days after stroke, and in the placebo group it started 8.2 days after stroke. Infarct location was comparable in both groups, with 5 frontal, 3 subcortical, and 4 temporal lesions in each. Infarct volume was not significantly different in either group.

Neuropsychological Results

The results of language performance and the neuropsychological tests are summarized in Table 2. Initially, both groups had mild to moderate language impairment plus impairment in other neuropsychological functions, such as visuospatial memory, recognition memory, and reasoning,[17,21,22] but there was no difference in the neuropsychological profile. Both groups showed significant reduction in the Token test error rate from the first to the second testing. Whereas the placebo group showed improvement in written language and in comprehension, the piracetam group showed significant improvement not only in the subtests for written language,

TABLE 2. Neuropsychological Test Battery

	Piracetam		Placebo	
Test	Before	After	Before	After
FAS test	10.08 (10.60)	12.91 (11.19)	7.16 (5.42)	10.91 (11.04)
Corsi block span	4.41 (0.90)	4.83 (0.71)	4.08 (1.50)	4.50 (1.16)
Raven test	27.50 (10.54)	36.08 (22.67)	31.10 (11.12)	32.88 (13.10)
Benton test	9.16 (2.91)	10.16 (3.63)	8.66 (4.07)	9.66 (4.55)
Aachen Aphasia Test				
Spontaneous speech				
Communicative verbal behavior	3.0 (0.95)	3.5 (1.24)*	3.0 (1.0)	3.33 (1.22)
Articulation and prosody	4.58 (0.90)	4.83 (0.38)	3.88 (1.16)	3.88 (1.26)
Automatized language	4.41 (0.66)	4.75 (0.45)	4.77 (0.44)	4.88 (0.33)
Semantic structure	3.41 (0.79)	3.91 (0.66)‡	3.77 (0.44)	4.00 (0.70)
Phonemic structure	3.83 (1.02)	4.08 (0.90)	3.77 (0.83)	3.77 (1.71)
Syntactic structure	3.33 (0.88)	3.83 (0.83)*	3.11 (1.05)	3.44 (1.01)
Subtests				
Repetition	129.75 (21.62)	130.91 (35.85)	121.55 (26.32)	130 (19.15)
Written language	61.08 (25.17)	73.00 (25.20)†	60.33 (30.48)	72.44 (25.19)*
Naming on confrontation	70.66 (36.65)	93.16 (33.29)*	81.33 (23.03)	100.33 (13.21)
Comprehension	84.83 (20.45)	94.91 (19.91)‡	88.77 (11.48)	100.77 (8.65)‡
Token test (errors)	17.16 (14.31)	9.66 (12.62)‡	17.91 (15.47)	12.50 (16.88)‡

Values in parentheses are SDs.
*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

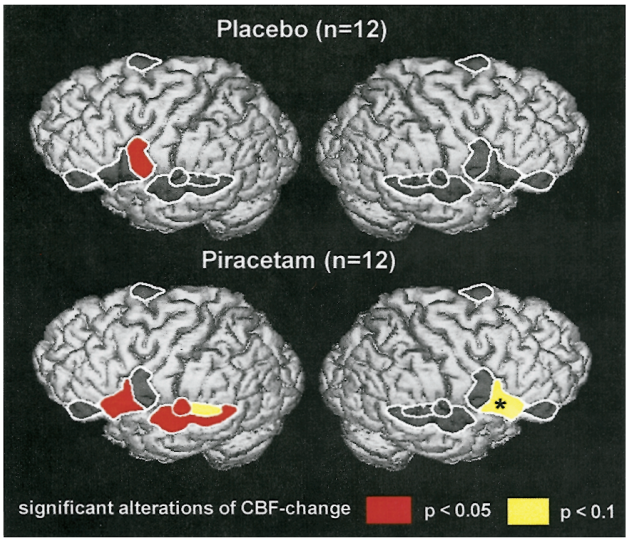
naming on confrontation, and comprehension (see Table 2), but also in spontaneous speech, especially in communicative verbal behavior, and in the semantic and syntactic structure of their speech.

PET Results

From the CBF changes at 2 and 8 weeks, relative increases of rΔCBF were calculated for the language-related areas of the left and right hemispheres (Table 1). As shown in the Figure and Table 3, activation-induced flow changes increased in several left hemisphere regions over the treatment period and reached significant levels ($P<0.05$) in the left transverse temporal gyrus (Heschl's gyrus), the left superior temporal gyrus (BA 22, Wernicke's region), and the triangular part of the left frontal gyrus (BA 44, Broca's area) in the piracetam-treated group. The placebo group showed significantly increased activation only in the inferior part of the left precentral gyrus (vocalizing area). In neither group were enhancements of the activation responses observed for right hemispheric regions. In the piracetam group, a tendency but not a significant suppression of rΔCBF in the right Broca area was observed.

Discussion

Most patients who survive the acute phase of an ischemic stroke regain some of the lost functions. In particular, the improvement of sensorimotor function is accompanied by increased blood flow and/or metabolism in impaired brain regions surrounding focal infarcts and in contralateral regions of the undamaged hemisphere,[12,13] which might be a correlate to the functional remapping of the cortex demonstrated in experimental studies.[27] Recovering from poststroke aphasia to a satisfactory level relies to a great extent on the functional reintegration of eloquent areas of the dominant hemisphere,[15,28] whereas regions of the contralateral network



A significant enhancement of blood flow change at the end of treatment was observed only in the left hemisphere. In the piracetam group, rΔCBF was significantly higher in the left transverse temporal gyrus, left triangular part of inferior frontal gyrus, and left posterior superior temporal gyrus after the treatment period compared with the initial measures. The suppression effect of the right Broca area (area with asterisk) is compatible with successful language recovery. The placebo group showed an increase of activation effect only in the left vocalization area.

TABLE 3. Increase/Decrease of Task-Related Flow Changes (mean±SD) in Language-Related Brain Regions Before and After Treatment Period

	Piracetam		Placebo	
	Left	Right	Left	Right
Frontal				
BA 44	0.49±2.91	−0.95±2.98	0.25±3.42	−0.68±3.14
BA 45	1.61±2.38*	−0.62±2.29	−1.24±2.79	−0.38±1.89
Primary vocalizing area	1.52±3.15	0.69±2.39	3.07*±4.10	−1.10±3.08
Temporal				
Heschl's gyrus	3.25±4.08*	1.31±9.72	2.51±6.04	−0.56±4.76
BA 41 and 42	3.09±5.74	1.80±5.83	2.74±7.76	−2.37±4.69
BA 22	3.51±5.34*	1.94±7.40	1.11±4.47	0.51±2.50
Other				
Supplementary motor area	1.04±7.26	1.07±7.15	0.73±2.98	1.15±4.21

*$P<0.05$.

contribute to improvement to a lesser extent and are not sufficient for recovery of full language function. Recovery after stroke is accelerated and facilitated by rehabilitation therapy, which might be supported by various drugs.[29] Whereas the effect of physiotherapy for the improvement of sensorimotor deficits is unchallenged, the efficacy of speech therapy is still controversial, with several randomized controlled trials yielding no difference in outcome between treated and nontreated groups.[7] Therefore, many trials were undertaken to enhance recovery from aphasia with use of pharmacological agents.[30–32] In this context, amphetamines were applied for enhancing vigilance by increased noradrenaline levels in the brain, bromocriptine for the selective action of dopamine on language output,[33] and cholinergic substances for the effect on naming.[34] Piracetam improves learning and memory by facilitating release of acetylcholine and excitatory amino acids, and this effect might lead to increases in flow[35] and energy metabolism.[36,37] Several controlled studies[10,11] have demonstrated a significant advantage of the piracetam-treated group in measures of aphasia, which did not persist over 24 weeks. In a large, multicenter trial, piracetam did not influence overall outcome when given within 12 hours of onset of acute ischemic stroke[38]; however, a significant improvement of language functions could be demonstrated with the Frenchay Aphasia Screening Test with piracetam in the subgroup of patients with poststroke aphasia.[39] Our double-blind study in a small group of patients with poststroke aphasia supports these results and shows for the first time an action on the capacity to respond to a specific task related to the improved language function.

The mechanisms by which piracetam supports the beneficial effect of speech therapy and the relationship of this effect to increased blood-flow response to functional activation, however, is unclear. One might speculate that the actions of piracetam on transmitter release and functions[40,41] as well as on pathologically altered neuronal membranes[42] affect morphologically intact but functionally compromised tissue surrounding ischemic lesions and thereby enhance the capacity of these areas to be reintegrated into a functional network. This hypothesis is supported by findings on the importance of the state of tissue in the vicinity of infarcts for the recovery from aphasia[43]; the ability of these cortical areas to learn from specific rehabilitative measures, eg, speech therapy, might be enhanced by piracetam.[44] Our results additionally point to the importance of the functional reactivation of temporal regions within the dominant hemisphere,[15] which might be more efficient for recovery from aphasia than facilitation of transcallosal transfer[45] and restitution of functions within a bilateral network.[46] The results also emphasize the need to select patients who can benefit from drug treatment, especially in support of rehabilitative efforts targeted at relearning lost functionality. This learning process can be activated only as long as cortical areas specific or related to the impaired functions are morphologically intact and are not disconnected from the integrative network.

Our findings indicate a mechanism of action of piracetam in poststroke aphasia and support previous results. A large-scale clinical trial is justified by these data and is needed to prove the efficacy of piracetam as an adjuvant to speech therapy in poststroke aphasia.

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