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Piracetam in the Treatment of Cognitive Impairment in the Elderly

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ABSTRACT

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Piracetam (Nootropil, 2-oxopyrrolidone acetamide) has been extensively investigated for the treatment of cognitive impairment. Initial studies on normal subjects and patients with mild or moderate cognitive decline have been somewhat encouraging. Accordingly, we conducted a further evaluation of the effects of piracetam in the treatment of elderly outpatients 60 to 85 years of age with mild to moderate memory impairment consistent with a diagnosis of Primary Degenerative Dementia (PDD). In our first study, we examined the effects of piracetam in 20 patients. All patients received 7.2 g of piracetam and placebo for 4 weeks in accordance with a double-blind, randomized treatment order, crossover design with 1-week washout periods prior to each crossover period. Hence, the total study period for each patient was 10 weeks (1-4-1-4). An analysis of 43 psychometric measures revealed significant improvement ($P < 0.05$) in only three measures, all favoring the treatment condition. Recent findings support a rationale for examining the effects of piracetam in conjunction with cholinergic precursors in patients with cognitive decline. In our second study we conducted a 1-week open trial of 1.6 g of piracetam t.i.d. in conjunction with 3 g of choline chloride t.i.d. in 15 patients. Four patients were rated as clinically improved. These "responders" were all subjects with moderate cognitive impairment. The responders showed much higher RBC choline levels than the nonresponders, both at baseline and during treatment. We conclude that the present evidence indicates that the effects of piracetam treatment alone in elderly outpatients with mild to moderate cognitive decline are subtle and not of proven clinical significance. However, studies of longer duration and of piracetam in combination with other agents may eventually show genuine clinical utility.

Key words: piracetam, cognition, aging

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INTRODUCTION

Piracetam (Nootropil, 2-oxopyrrolidone acetamide) is a substance which was synthesized in the search for an analog of GABA which would be capable of crossing the blood brain barrier. Although piracetam apparently does not have GABA-ergic effects, it was found to exert a therapeutic effect on nystagmus of central origin and hence to have some CNS activity. Subsequently, piracetam was shown to facilitate learning in animal models [Wolthius, 1973] and increase the amplitude of transcallosal evoked potentials obtained by electrical stimulation of the associative cortex [Buresova and Bures, 1976; Giurgea, 1976]. Hence, the hypothesis has been formulated that piracetam enhances information processing. It may also have a direct metabolic effect in the brain in that it has been shown to increase the ratio of ATP to ADP [Pede et al., 1971].

These properties have resulted in piracetam being tested for value in a variety of clinical areas in which increasing brain energy and enhanced information processing seem desirable. Clinical studies have been aided by the virtual absence of any known toxic effects of piracetam. Furthermore, piracetam appears to be devoid of sedative analgesic, analeptic, or autonomic effects.

Previous studies of the effects of piracetam on the treatment of cognitive impairment have recently been reviewed [Reisberg et al., 1981]. Initial studies which have been conducted on normal subjects [Dimond and Brouwers, 1976] and on patients with mild or moderate cognitive decline [Mindus et al., 1976; Stegink, 1972] have been somewhat encouraging. Studies conducted on severely impaired and hospitalized patients have been less encouraging [Stegink, 1972; Abuzzahab et al., 1978; Trabant et al., 1977].

STUDY I: A DOUBLE-BLIND CONTROLLED EVALUATION OF PIRACETAM IN PATIENTS WITH MILD TO MODERATE PRIMARY DEGENERATIVE DEMENTIA (PDD)

Methods

We have conducted a well-controlled and systematic evaluation of piracetam treatment in mild to moderately cognitively impaired outpatients. All subjects manifested psychiatric, neurologic, clinical, and neuroradiologic findings consistent with a DSM III diagnosis of Primary Degenerative Dementia (PDD) [American Psychiatric Association, 1980].

Twenty patients were included in the study (12 women and eight men; mean age 71.5 years, range 61–85 years). The study utilized a double-blind crossover design, with an initial 1-week washout period, followed by two 4-week treatment periods (one period on piracetam and one period on placebo). The order of treatment was randomized, with a second 1-week placebo washout between treatment periods. The dosage utilized was 2.4 g t.i.d. (7.2 g/day). In addition to clinical and laboratory measures, patients were assessed on a broad range of psychometric parameters.

Results

The results for the cognitive tests are summarized in Table 1. A two-way analysis of covariance was performed using the baseline values as the covariate, treatment order as an independent measures factor, and treatment as a repeated measures factor. Of the 43 measures evaluated, the only changes which were statistically significant were in favor of piracetam. Patients on active medication made fewer errors on a test of verbal associative memory requiring a recall response (First-Last Names, $P < 0.05$ for learning trial 1, and for delayed recall); and a test of visual attention and speed (Perceptual Speed, $P < 0.01$). There were no significant changes favoring placebo.

Discussion

We conclude from the present evidence that the effects of piracetam treatment alone on patients with age-associated cognitive decline are subtle and not of proven clinical significance. However, studies of longer duration or with more potent piracetam analogs may eventually show genuine clinical utility.

TABLE 1. Double-Blind Piracetam Study: Psychometric Test Measures (N = 20)

Category	Test	Trial	Response Type	Significance	Favoring
Verbal memory	Buschke intrusions	1	Correct	NS	
		2	Correct	NS	
		3	Correct	NS	
		4	Correct	NS	
		5	Correct	NS	
		Delayed	Correct	NS	
Verbal/visual memory	Faces	1	Correct	NS	
			Incorrect	NS	
		2	Correct	NS	
			Incorrect	NS	
		3	Correct	NS	
			Incorrect	NS	
		Delayed	Correct	NS	
			Incorrect	NS	
Verbal associative memory	Names recall	1	Correct	NS	
			Incorrect	0.02[a]	Active
		2	Correct	NS	
			Incorrect	NS	
		3	Correct	NS	
			Incorrect	0.04[a]	Active
		Delayed	Correct	NS	
			Incorrect	NS	
Associative memory	Name-face	1	Correct	NS	
			Incorrect	NS	
		2	Correct	NS	
			Incorrect	NS	
		3	Correct	NS	
			Incorrect	NS	
		Delayed	Correct	NS	
			Incorrect	NS	
Perceptual speed	Number crossover	—	Correct	NS	
		—	Incorrect	0.01[b]	Active
Flexibility of closure	Hidden words	—	Correct	NS	
		—	Incorrect	NS	
Digit symbol substitution test	DSST (WAIS)	—	Correct	NS	
Continuous performance test	Respond to "X"	—	Correct	NS	
		Lat.	Correct	NS	
		—	Incorrect	NS	
		Lat.	Incorrect	NS	
	Respond to "A" followed by "X"	—	Correct	NS	
		Lat.	Correct	NS	
		—	Incorrect	NS	
		Lat.	Incorrect	NS	

[a]$P < .05$
[b]$P < .01$

STUDY II: COMBINED TREATMENT WITH CHOLINE AND PIRACETAM

Recent studies have demonstrated a selective cholinergic deficiency in the brains of persons with Alzheimer disease [Bowen et al., 1976; Davies and Maloney, 1976; White et al., 1977; Perry et al., 1977]. Based upon these findings, cholinergic precursor treatment, in particular choline chloride and lecithin, have been widely studied in the treatment of PDD [Boyd et al., 1977; Smith et al., 1978; Mohs et al., 1979; Ferris et al., 1979; Etienne et al., 1979]. To date, these precursor treatments alone do not appear to have been successful [Pomara et al., 1981]. However, recent work in our laboratory has revealed a particularly strong relationship between brain metabolism (assessed using 18F-2-deoxy-2-fluoro-D-glucose tracer in conjunction with positron emission tomography to determine the rate of glucose utilization) and progressive cognitive decline in patients with PDD [Ferris et al., 1980]. A general increase in brain metabolism may facilitate acetyl choline synthesis and drugs which enhance brain metabolism might potentiate the effects of cholinergic precursors [Reisberg, 1981]. Piracetam may also have more direct cholinergic effects, since it increases the incorporation of ^{32}P into phosphatidyl choline [Woelk, 1979], thus suggesting an increase in phosphatidyl choline turnover. Bartus et al. [1980] treated aged rats with both choline and piracetam and demonstrated a much greater effect on memory retention with combined treatment than with either compound alone. We therefore conducted an initial, open-clinical trial in dementia with combination choline/piracetam treatment.

Methods

Fifteen mildly to moderately impaired outpatients with a diagnosis of PDD completed the study. Their age range was 60–85. Diagnostic assessments included a medical history and examination, CT scan, clinical laboratory tests, psychiatric and neurological evaluations, and objective cognitive tests. Patients with cognitive impairment secondary to conditions other than PDD were excluded. The patients received 9 g/day of choline chloride (3 g t.i.d.) and 4.8 g/day of piracetam (1.6 g t.i.d.) for a period of 7 days. A short cognitive test battery was administered at baseline and following the treatment period. Plasma and RBC choline levels were also determined (gas chromatograph method), at baseline and 1 hr after the final drug administration.

Results

No patients experienced side effects. For the entire group, the cognitive measures showed small, nonsignificant improvements. Some subjects failed to improve, but none were worse. Since the study psychiatrist independently rated four patients as clinically improved, the cognitive measures for these patients were analyzed separately. The results for a selective reminding verbal learning task [Buschke and Fuld, 1974] are summarized in Table 2. Each patient showed substantial improvement in memory storage and retrieval. Several other memory measures showed similar positive changes. These "responders" were all subjects with moderate rather than very mild cognitive impairment. We have not previously observed such marked improvements in clinical trials with choline treatment or piracetam treatment alone.

The results for the blood choline assays were also encouraging. Of the ten subjects for whom blood data were available, all showed large increases in both plasma and RBC choline levels during treatment. The group means (nmol/ml $\pm$ SEM) for baseline and treatment, respectively, were 7.1 $\pm$ 0.3 versus 2.75 $\pm$ 2.1 for plasma, and 12.0 $\pm$ 3.3 versus 34.4 $\pm$ 6.3 for RBC. However, the three responders showed much higher RBC choline levels than the seven nonresponders, both at baseline (23.8 $\pm$ 8.0 versus 7.0 $\pm$ 0.8) and during treatment (56.4 $\pm$ 7.8 versus 23.4 $\pm$ 3.4). The plasma choline levels for the two groups were quite similar (6.7 $\pm$ 1.1 versus 7.1 $\pm$ 0.3 at baseline; 25.8 $\pm$ 4.9 versus 28.2 $\pm$ 2.4 during treatment).

Discussion

These interesting but preliminary findings suggest the possibility of a responder subgroup for combined choline/piracetam treatment. Furthermore, high RBC choline levels may be predictive of clinical response. Further evaluation of these possibilities by means of dose-finding studies and double-blind trials is recommended.

Table 2. Mean Scores on Selective Reminding Task of Four Patients Showing Clinical Response to 1-Wk Treatment with Choline and Piracetam

Measure	Baseline	1 Wk	% change
Storage			
Trial 1	2.25 (1.71)[a]	4.50 (1.73)	100.0
2	4.50 (3.32)	6.25 (3.30)	38.9
3	5.50 (4.20)	8.00 (2.71)	45.5
4	7.25 (2.98)	8.25 (2.22)	13.8
5	7.25 (2.99)	8.25 (2.22)	13.8
Retrieval			
Trial 1	2.25 (1.71)	4.50 (1.73)	100.0
2	3.75 (3.00)	4.25 (0.96)	13.3
3	3.50 (2.39)	5.75 (1.50)	64.3
4	4.25 (1.26)	7.25 (1.71)	70.6
5	4.25 (1.50)	4.50 (3.00)	5.9
Delayed	2.75 (2.75)	4.75 (1.26)	72.7

[a]SDs are in parentheses.

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