J. Simeon, M.D.*, B. Waters, M.D.*, M. Saxton, M.D.*
C. Fiedorowicz, HBA*, R. Trites, M.D.*
J. Volavka, M.D.** and S. Simeon, M.A.*

*Department of Psychiatry, Faculty of Medicine,
University of Ottawa
Royal Ottawa Hospital
1145 Carling Avenue
Ottawa, Ontario

and

**Missouri Institute of Psychiatry, St. Louis, Mo.
EFFECTS OF PIRACETAM IN CHILDREN WITH LEARNING DISORDERS

Piracetam (2-pyrrolidone acetamide), has been reported to facilitate learning in animals, limit the decline in human performance associated with cerebral hypoxia, and improve cognitive performance, alertness, fatigue and psychomotor agitation in aged subjects (1). The drug presumably has a direct integrative effect on the telencephalon, and as it has no apparent stimulant or sedative properties, has been defined as "neutropic." In studies of children with behavior, psychiatric, developmental, neurological, speech and hearing disorders, cerebral palsy, epilepsy and mental retardation, improvements have been reported of global behavior, mood, attention, alertness, memory, cognitive capacity, mental performance, enuresis, incontinence, spasticity and post-moratal recovery (3). Few of these studies have used controls and an appropriate experimental design. In a review of 25 pediatric trials by one of the authors (JS), there were 3 published double-blind studies of children with epilepsy (4), cerebral palsy (5) and mental retardation (6). The results of the psychogeriatric and pediatric trials are difficult to interpret and still inconclusive, and more precise indications remain to be established. In the daily dosages used in children (2.4g to 10g) the drug has been apparently safe, with minimal adverse effects reported.

In the present study, the efficacy and safety of piracetam were assessed in children with learning disorders.
In a double-blind cross-over study, piracetam was compared to placebo. After a three-week drug washout, fifteen patients were treated in a sequence with placebo-piracetam-placebo for four weeks each, while the remaining fourteen patients, the reversed sequence of placebo-piracetam-placebo was administered. Piracetam was given in a fixed daily dose of 800 mg. daily, in divided doses. Boys, 8 to 14 years old, were classified into three groups (Table 1): 1) verbal IQ ≤ 105 at least 15 points lower than the performance IQ (N=10); 2) the difference between verbal and performance IQ no greater than 10 points (N=10); 3) performance IQ at least 15 points lower than the verbal IQ (N=9). All the patients were at least one grade placement behind age expectation in reading, spelling or arithmetic on the Wide Range Achievement Test, and their full scale IQ (WISC-R) was at least 85. Their selection for the trial was made from children referred to the neuropsychology laboratory for an evaluation of learning disabilities.

At baseline and after each four week treatment phase the following evaluations were undertaken: 1) pediatric history and examinations including vital signs, weight, and clinical laboratory tests; 2) EEGs; 3) psychiatric evaluations including Clinical Global Impressions and Children's Psychiatric Rating Scale (ECDEU) (7); 4) Questionnaires including Conners' Parent's Questionnaire and School Report (7); and Myklebust Pupil Rating Scale (8); 5) A battery of neuropsychological tests for verbal, nonverbal, sensory and motor tasks.

RESULTS

A. Clinical

Parent's ratings (Conners' Questionnaire) indicated significant and consistent improvements of all eight factors with piracetam and worsening with placebo (Anova, p 0.05) (Fig. 1 and 2). The group of patients with
the low performance IQ showed most of the improvement with piracetam and
deterioration with placebo.

Ten children were judged by the neuropsychologist as improved with
piracetam on tests of memory, attention span, concentration, and eye-hand
coordination (Table 2). Four of these patients were rated as improved by
their parents.

The Clinical Global Impressions (CGI) scale of behavioral, social and
learning performance did not indicate significant differences between
piracetam and placebo (Table 3). Improvement with piracetam and dete-
rioration with placebo was suggestive for the presence of patients with small
VIQ-PIQ differences ("equal IQs") (Fig. 3).

There were no statistically significant changes of the teachers'ratings and on any of the learning, memory, attention span or reaction time
tasks with piracetam as compared to placebo.

The clinical findings, vital signs and laboratory tests indicated that
piracetam is a safe and well tolerated drug in the dosage and population
used in this trial. In only one child a deterioration of behavior was
associated with piracetam administration.

B. EEG
The results indicate that piracetam caused certain EEG changes while placebo effects seemed to be random (Fig. 4). Both occipital derivations showed a decrease of the power in the 0.5-3.5 Hz activity and an increase of power at 12-51 Hz with piracetam (Fig. 5). Piracetam was associated with significantly more power than placebo in the frequency bands 12-18 Hz, 18-24 Hz, and 24-35 Hz (p<0.05, 0.01, and 0.05, respectively) in the left occipital area (Mann-Whitney Test). In the right occipital area, the piracetam group showed significantly more power in the 18-24 Hz band both at baseline and after treatment (p<0.05).

Discriminant function analysis suggested that piracetam effects in the EEG were different from that of placebo over the left occipital area as well as the right (p<0.05) occipital area. Piracetam compared to placebo seemed to decrease the general EEG amplitude, as reflected by the power coefficients over the entire frequency range (0.5 - 51 Hz); over the left occipital area this difference is significant (p<0.05, Wilcoxon Test), while a similar trend occurs over the right occipital area (Fig. 6).

The EEG data obtained are not sufficient for any conclusive statements for the following reasons: the effects are neither particularly strong, nor consistently significant in the various statistical analyses; it is not known how reliable are these findings in individual subjects, as the cross-over data were not analysed; there were significant EEG differences between the placebo and the piracetam groups at baseline, that is before treatment was started.
In summary, partial results of power spectral EEG analyses of the first four weeks of treatment suggest significant differences between piracetam and placebo, consisting of a relative increase of power at frequencies between 12 and 35Hz - consistent with the increase of the average EEG frequency - and a general decrease of amplitude. The analysis of additional EEG data presently underway may better define the EEG effects of piracetam and its classification among psychoactive compounds.

CONCLUSION

In a double-blind cross-over trial, the efficacy of piracetam was compared to that of placebo in 29 boys (8 to 14 years old) with learning disabilities. The parents' ratings and neuropsychological tests showed significant trends in favor of piracetam. These changes were attributed to greater variability with piracetam. In teacher ratings, neuropsychological tests showed no statistical differences between piracetam and placebo. The EEG results suggest psychoactive properties. While the clinical effects of piracetam and the EEG changes reported also by others (9) suggest that this drug has psychostimulant properties similar to amphetamine (10), the absence of anorexia and insomnia indicate important clinical differences.

The short duration of each treatment phase, and possible withdrawal and/or carry-over effects may have resulted in the masking of differences between piracetam and placebo. The small number of patients in the various subgroups made statistical analyses difficult to interpret. To determine whether any subgroups of patients are responsive to piracetam, controlled trials of longer duration are needed.
1. **UNION CHIMIQUE BELGE. Piracetam. Brussels: UCB, 1976.**


9. **BENTE, D. Vigilance: psychophysiological aspects.** Paper read at the 83rd meeting of the German Soc. of Internal Medicine, Wiesbaden, April 17-21, 1977.