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The Effects of Oxiracetam (ISF 2522) in Patients With Organic Brain Syndrome (A Double-Blind Controlled Study With Piracetam)

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ABSTRACT

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In a double-blind controlled trial, the clinical effects of oxiracetam, a new "nootropic" compound, were investigated in a group of 60 elderly patients with organic mental disorders (DSM-III). The starting dose of both oxiracetam and the control drug, piracetam, was 400 mg. The dosage was increased by 400 mg at weekly intervals up to 2,400 mg daily (sixth week). During the following 6 weeks the administered dose was fixed at 2,400 mg daily. Most of the important target symptoms improved significantly over time, both subjectively (i.e., rating scales) and objectively (i.e., psychological tests), after administration of either oxiracetam or piracetam. In comparison to piracetam, oxiracetam exhibited more statistically significant improvement in the memory factor, whereas piracetam showed more improvement than oxiracetam in factors of paranoid ideation and agitation. Both drugs were tolerable and did not elicit any significant side effects. It was postulated that "nootropics" may represent a new group of CNS effective compounds, and thus be a "second generation" of psychotropics, which have more direct effects on the central target organs than are presently found in the "classical" psychotropics.

Key words: oxiracetam (ISF-2522), piracetam, organic mental disorder, memory, computer EEG, vigilance-enhancing drugs, alpha-enhancing drugs

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INTRODUCTION

Organic brain syndrome (OBS) without established cause is frequently associated with the "physiological" aging process. It has a variety of irreversible symptoms. The treatment of any of these symptoms has significant impact on the life of the aging person. Recently, therapeutic effects of piracetam, a GABA-GABOB derivative, on organic brain syndrome have been reported (1,2,3). Double-blind controlled clinical trials have confirmed the therapeutic effects of piracetam on some of the symptoms of OBS (as hypothesized by animal model (4)) including confusion, disturbances of memory, lack of concentration, and difficulties with attention (5,6). Based on animal studies similar but even more potent therapeutic effects have been predicted with oxiracetam (oxiracetam was kindly supplied by ISF S.p.a., Milan, Italy), an analog of piracetam (7,8). The quantitative pharmaco-EEG (9) study with different dosages of oxiracetam confirmed the predictions of animal pharmacology: The mode of action of oxiracetam on human brain function was found to be very similar to piracetam (10). Oxiracetam belongs to the group of drugs which possess alpha-enhancing effects in human electroencephalogram (EEG). In addition to the "classical" psychostimulants, such as dextroamphetamine and caffeine, some of the MAO inhibitors and "antigeriatric" drugs also belong to this group (11).

The aim of the present study was to determine whether oxiracetam, administered orally over a period of 12 weeks, is safe and effective in a group of elderly patients who belong to the diagnostic group of organic mental disorders and whether these effects are similar to those induced by piracetam.

REVIEW OF PREVIOUS STUDIES OF ISF-2522

Preclinical Studies

Oxiracetam was selected from among a series of GABA-GABOB derivatives which may be classed as nootropic drugs (Fig. 1). The first compound reported to belong to this class was piracetam.

A series of pharmacological tests were carried out on oxiracetam, comparing the results with those of piracetam. Oxiracetam has been studied in a series of biochemical tests, both in vitro and in vivo, to evaluate its effects on the metabolism of brain tissue and possible evidence of a biochemical activity that might lie at the basis of its mechanism of action as a "nootropic" drug.

All the tests were performed on rats or on preparations of rat brain tissue. Piracetam was also tested either in parallel or in separate experiments for all the parameters investigated. The doses and concentrations of the two compounds were chosen in the light of the results obtained during the pharmacological investigation in the learning tests. Oxiracetam, like piracetam, stimulates the turnover of lecitine and phosphatidylethanolamine, as demonstrated by the in vivo tests on the synthesis of the two phospholipids and by the in vivo-vitro tests on phospholipase activity (12). Oxiracetam is markedly more active than piracetam on phospholipase A_1 and in particular on the synthesis of the two phospholipids in vivo. A positive action of piracetam on brain phospholipid synthesis has already been reported in the literature.

To speculate on possible correlations between this action of the two compounds on a biochemical level and their activity on learning and memory in animals, a more active renewal of important components of the cell membranes could be a consequence or a premise for increased nervous activity.

The differing behavior of oxiracetam in vitro and in vivo-vitro tests for certain parameters (Pt-choline and Pt-ethanolamine synthesis, phospholipases and phospholipid base exchange) indicates that the drug is probably metabolized in the organism, giving origin to a metabolite which is generally considered the active compound. This evidence does not occur for piracetam, which has the same activity in vitro and in vivo-vitro.

The stimulating effect of oxiracetam on glycolysis could also be of marked interest, especially if it is demonstrated that it is not accompanied by a negative action on respiration, and if this effect should prove to be potentiated during particular conditions involving a distress of cerebral tissue (anoxia, atherosclerosis, old age, etc.).

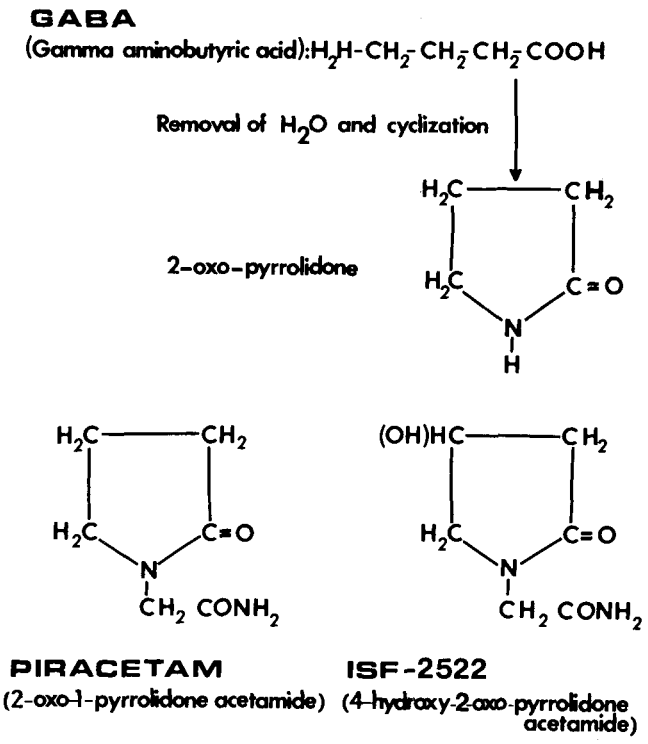

Fig. 1. Chemical structures of piracetam and ISF-2522 (oxiracetam).

A positive action of piracetam on the energetic balance, i.e., on the ATP/ADP ratio, especially during recovery from anoxia, has been reported in the literature.

The results of the animal investigations showed that oxiracetam and piracetam are inactive, at least in adult rats under normal conditions on brain protein synthesis, a parameter which, on the basis of current knowledge and hypotheses concerning the mechanism of memory process, could conceivably be correlated to an effect on learning and memory (13). Both compounds are also inactive on phosphatidylinositol synthesis, a phospholipid assigned an important functional role at the level of the cell membrane, whose turnover seems to be influenced by numerous physiological and pharmacological stimuli.

Unlike piracetam, oxiracetam is also active in vivo-vitro on the last step, not "rate-limiting" of the phosphatidylcholine and phosphatidylethanolamine synthetic pathway (CDP-choline or CDP-ethanolamine + diglyceride → Pt-choline or Pt-ethanolamine + CMP). Perhaps even more interesting is the fact that the compound inhibits, always in vivo-vitro, the exchange of phospholipid bases; this could be interpreted in terms of a stabilization or maintenance of the structural and especially functional characteristics of the membrane and could thus be correlated to the "fixing" of a trace or a nervous circuit. Piracetam is inactive on this parameter.

According to the investigations, oxiracetam was shown to be nontoxic and nonactive on classical pharmacological tests (nonsedative, nonstimulant, nonanalgesic, nonactive on the cardiovascular system, nonactive on autonomous nervous system, etc.). It is active only on those tests in which learning and memory processes are involved or, as in the case of curare-induced lethality, in which central nervous system function is impaired (anorexia in this specific case). Compared with piracetam, oxiracetam is two to three times more active, depending on the type of test (12).

Oxiracetam is active against the cerebral deficit amnesis induced by the edema and by electrocardioshock. Oxiracetam has also been shown to be active in a further test for the study of learning, i.e., the water maze. The effect of the product is seen on young as well as old animals.

Oxiracetam does not antagonize the anticonvulsive effect of diazepam, while in the past a positive effect was observed on amnesia provoked by the tranquilizer (positive avoidance test and maze test in mice).

Clinical Studies

A single rising dose tolerance, safety, and dose finding study was conducted in seven healthy male volunteers and one female volunteer, using quantitative pharmaco-EEG and quantitative pharmaco-psychology measurements. The effects of different dosages (200, 400, 800, 1,200, and 2,400 mg) of oxiracetam and control compounds (15 mg dextroamphetamine, 1,200 mg piracetam and placebo) were investigated in a single blind study.

The results of the *safety* data indicated that oxiracetam can be orally administered in humans up to 2,400 mg without any noticeable clinical or laboratory (blood chemistry, hematology, EKG, urinalysis) side effects (10). The most frequent side effects were observed after 15 mg dextroamphetamine. Oxiracetam-induced side effects were, in quantity and quality, similar to those seen after placebo. The insignificant side effects, even after 2,400 mg oxiracetam was administered, included an increase of headaches (two subjects), increase of tremor (two subjects), sleepy behavior (two subjects), nausea (one subject), and dry mouth (one subject). Nausea was also observed after 400 mg oxiracetam, but also after placebo.

The results of the CNS *efficacy* information, based on quantitative EEG measurements, indicated that oxiracetam, in dosages of 200 mg, 1,200 mg, and 2,400 mg, could be statistically differentiated from placebo (multivariate randomized T^2 statistics). Certain CEEG measurements suggested dose-related and time-related effects on human brain function (regression analysis). The dose-response curves demonstrated that the effect of oxiracetam is linear up to 1,200 mg.

The results of the CEEG analysis concerning the mode of action of oxiracetam indicated that oxiracetam produces alpha-enhancing effects on human brain function (Fig. 2). Thus, the computer EEG data base classified oxiracetam, in dosages of 200 mg, 400 mg, 1,200 mg, and 2,400 mg, with a group of "vigilance-enhancing" drugs (Fig. 3). Also, the active control compounds, 15 mg dextroamphetamine and 1,200 mg piracetam, were classified as "vigilance enhancing" ("psychostimulant").

MATERIALS AND METHODS

A total of 63 female and male subjects were included in the study but only 60 were statistically evaluated (11 female and 19 male in the oxiracetam group, and 19 male and 11 female in the piracetam group). The age range was 50–87 years (ranges 50–77 years, mean: 63.5 in oxiracetam group; ranges 50–87, mean: 61.1 in piracetam group). Subjects were diagnosed as "Organic Mental Disorder" (DSM-III, Section I), which included different types of dementia [Progressive Idiopathic Dementia with senile onset (290.0) or presenile onset (290.1) or multiinfarct dementia (290.4)]. However, according to the global evaluation, organic brain syndrome was not severe, chronic, and in "irreversible" degree. Only subjects who exhibited a moderate to marked degree of memory impairment (especially recent memory, recall, and retention, disturbed concentration, and problems of mental activity and mobility), and accompanied by any of the two following symptoms, were included in the program: (1) lack of energy and drive; (2) psychomotor retardation; (3) lack of activity, general fatigue; (4) impaired attention and concentration; (5) lack of general interest, withdrawal; and (6) unstable emotional behavior.

Subjects with the following criteria were excluded from the study: (1) subjects with severe, known neurological problems (subjects with severe acute and subacute brain syndrome); (2) subjects with severe dementia; (3) subjects who were being treated (and could not maintain a 1-week drug-free period) with major or minor tranquilizers, antidepressants, and/or psychostimulant drugs; (4) subjects with an acute infectious disease, or severe metabolic, endocrinal, hepatic, renal, or hematopoietic disorders (because of the age of the population, patients with "borderline" and even "abnormal" laboratory, EEG, and EKG findings were included in the program providing they were not considered "severe "); (5) subjects with a recent history of alcoholism and drug abuse problems; (6) subjects exhibiting psychotic behavior; and (7) pregnant females and females able to have children.

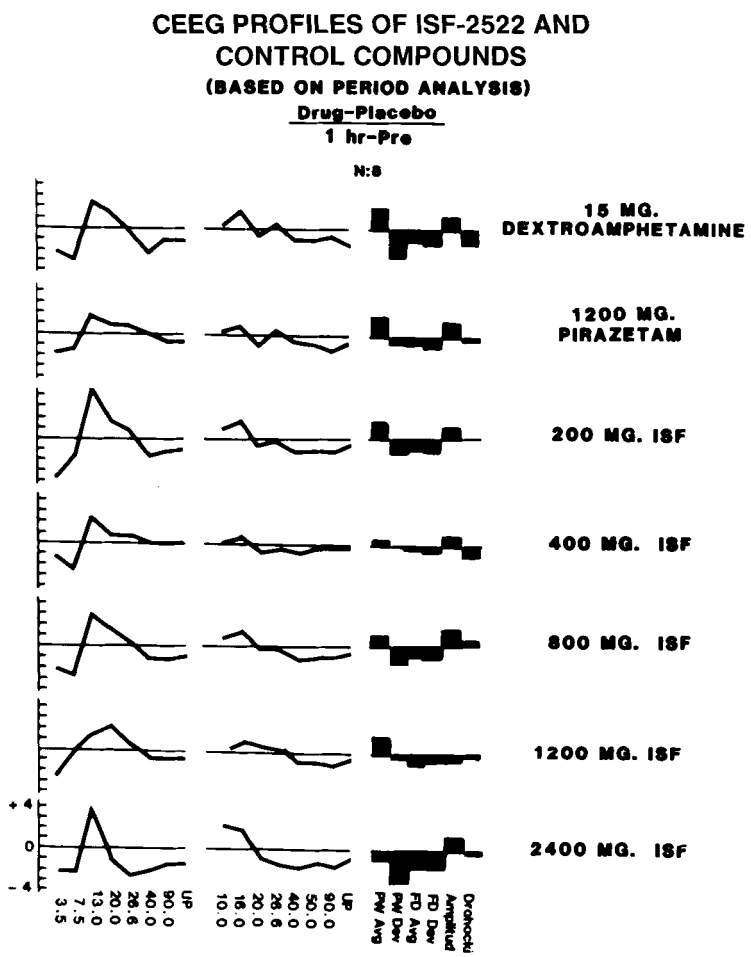

Fig. 2. CEEG profiles of ISF-2522 and control compounds. In the abscissa, computer EEG measurements, and in the ordinate, the changes from pre-1 hr after drug administration minus placebo administration. As seen, the CEEG profiles of different dosages of ISF-2522 show very similar shape to control compounds, dextroamphetamine, and piracetam.

This study was designed as double-blind with an active control compound (piracetam). Preferably, the subjects who were not receiving medical treatment were included in the study. If a patient received any medication other than psychotropic drugs (hypertension drugs, cardiac drugs, etc.) for a minor illness, he/she could be included in the study. If any subject was receiving heavy doses of a psychotropic compound, he (she) had at least a 1-week drug-free period. During the drug-free period, only an occasional anxiolytic (Valium) or hypnotic (Mogadon or Dalmane) could be given (no more than 3 consecutive days). Subjects were randomly assigned to either drug A (oxiracetam) or drug B (piracetam) treatment groups. The treatment for each subject was separately coded.

Patients were treated with a "fixed" and a "rising" dose order. The initial starting daily dose was 400 mg of oxiracetam or piracetam. At weekly intervals, the dosage of oxiracetam or piracetam was increased by 400 mg (week 2 = 800, week 3 = 1,200 mg, week 4 = 1,600 mg, week 5 = 2,000 mg, week 6 = 2,400 mg of oxiracetam or piracetam). Weeks 7–12, the dosage was kept at 2,400 mg. Because of side effects, dosage was changed in three patients of the ISF group and in two patients of the piracetam group. In each of these cases, the dosage was decreased back to the previous dosage schedule.

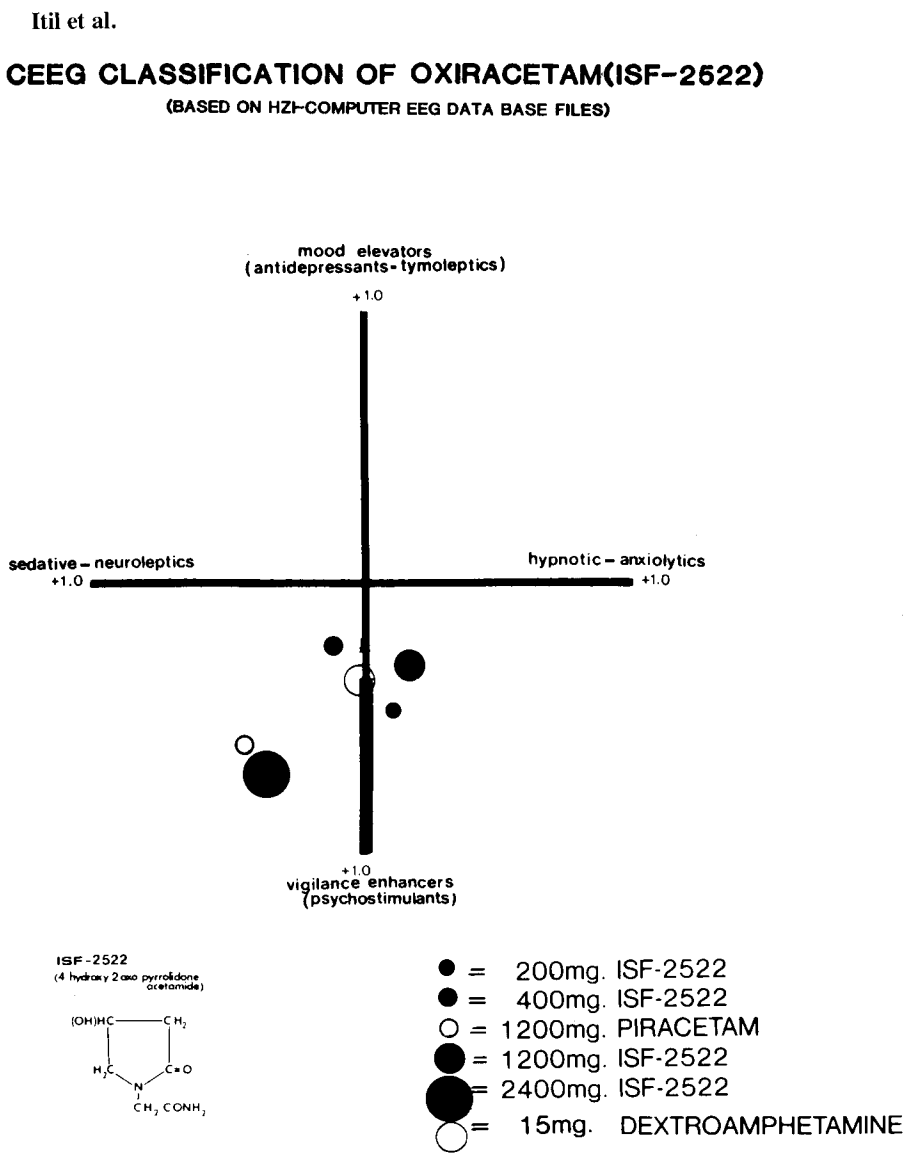

Fig. 3. Two-dimensional classification of different dosages, ISF-2522, and control compounds. In the two-dimensional classification system, the computer data base groups are shown in two axes. If the CEEG profile of a new drug is 100% similar to one of the drug groups of the computer data base by correlation statistics it is shown in that axis as plus 1.0. The two highest correlations with two drug groups will be shown accordingly. As seen, 15 mg dextroamphetamine was correlated only with psychostimulants with the correlation coefficients as 0.40 piracetam at 1,200 mg, and ISF-2522 at 2,400 mg did show highest similarity to psychostimulants with the second highest similarity to sedative neuroleptic drugs.

Out of a total of 63 patients, 21 did not complete 12 weeks of the study period (14 from oxiracetam and seven from the piracetam group). Three patients who were dropped for personal reasons were replaced with new patients. Five patients from the oxiracetam group (two with blurred vision, one with diarrhea, one with pressure in the head, one with recurrence of hypertension), and one patient from the piracetam group (diarrhea) were dropped from the program because of persistent side effects. The other patients dropped from the program because of intercurrent illness

or worsening symptomatology, or they showed marked improvement and refused further treatment. Sixty patients were included in the statistical evaluation.

The following ratings and evaluations were conducted prestudy, second, fourth, eighth and twelfth weeks of the study: (1) ABNP, Abnormal Psychosomatic Findings rating scale; (2) IPSC-E, Inventory of Psychic and Somatic Complaints; (3) SQQ, Sleep Quality scale; (4) CGI, Clinical Global Impressions scale; (5) SIEL, (Short well-being self rating scale); and (6) TWIS, Treatment Emergent Signs and Symptoms scale (applied whenever side effects occurred).

As experimental psychological tests (1) Benton Visual Motor Retention Task and (2) Pauli Performance Task were completed prestudy and at the fourth and eighth weeks of the study. The Benton Visual Motor Retention test is designed to measure immediate memory in two separate tests with ten designs each. The four variables derived here are "total correct" and "total error" in each of the two trials.

Two different psychometric tests are conducted in the Pauli Performance test. In the "simple" version two numbers are presented which must be added, and the last digit of the answer depressed on a special keyboard. The "complex" version required that one of the numbers be remembered from the last trial. There are four variables for each version. Ten trials are presented of 30-sec duration. The variables are (1) mean number of problems attempted, (2) standard deviation of problems attempted, (3) mean number of correct responses, and (4) standard deviation of correct responses.

Electrocardiogram, blood chemistry (including alkaline phosphatase, SGOT, SGPT, hematology (WBC and RBC and differential)), and complete urinalysis were completed prior to weeks 4 and 12, and/or at the time of the study whenever the subjects were dropped from the program.

Except aspirin, chloral hydrate, vitamins, and drugs without CNS effects, no concomitant medication was allowed to be taken by the patients during this study. Patients who needed a psychotropic drug and/or drugs with possible CNS effects on more than 3 consecutive days were dropped from the program.

RESULTS

A clinical subsidiary analysis of the dropout rate (a life table analysis) indicated that there is a significant difference between the groups. Examination of the reasons for termination showed no consistent reason, or common subject characteristics. Because of this dropout rate, the analysis of covariance at each period used a different sample size (N). The repeated measures analysis used only the patients with complete results.

The results of the demographic data indicated that, according to the age, number of offspring, race, episode of illness, duration of episode, and history of allergy, two groups of patients were very similar. The results of the physical and neurological examinations indicated that the population of the oxiracetam group resembles the piracetam group. The "abnormal" physical and neurological findings before treatment were not severe and were within the acceptable ranges. Over time, the results of the physical examination changed in some subjects. However, these changes were not serious nor systematic for any of the drug groups. None of the subjects were dropped from the program because of changes in physical examinations. The results of neurological examinations, which changed over time, did not show any characteristic patterns for any of the drug groups. The statistical evaluation of vital signs indicated that the oxiracetam group showed a decrease in supine and standing systolic blood pressure at 12 and 2 weeks, respectively, a decrease in supine and standing diastolic (2 weeks), and a decrease in supine (4 weeks) and standing pulse rate (2, 4, and 12 weeks) at the $P = 0.1$ level of statistical significance. The piracetam group showed a significant decrease in supine and standing systolic blood pressure (12 weeks) and respiration (4 and 8 weeks).

The oxiracetam group had significantly lower diastolic supine blood pressure than piracetam at 2 weeks (both the t and ANCOVA), and at 4 weeks (ANCOVA alone), as well as an overall difference over time according to the repeated measures results (Table 1). The systolic standing showed an overall strong time decrease, but no group difference. The standing diastolic blood pressure showed a difference between the two groups with the oxiracetam group having a signif-

TABLE 1. Changes in Vital Signs[a]

Variable	Period	Ancova *P* level	Adjusted means (diffs) ISF-2522	Adjusted means (diffs) Piracetam
Systolic	W-2	0.29	141.68(−9.10)	145.14(−5.04)
supine	W-4	1.00	148.53(−2.88)	147.32(−4.09)
	W-8	1.00	144.82(− 4.97)	146.30(−3.49)
	W-12	1.00	137.84(−12.6)	146.30(−10.7)
RM.		*P*(grp)<1.00	*P*(time)<0.07	*P*(grp × time)<0.14
Diastolic	W-2	XX		
supine	W-4	X		
RM.		*P*(grp)<X (0.06)		
Pulse				
supine				
Respir				
Temper				
Systolic				
standing				
Diastolic	W-2	X		
standing	*P*(time)	X		
Pulse				
standing	W-4	XX		
RM.		*P*(grp)<X		
Weight				
(kg)				

[a]RM = Repeated measures. XXX = $P<0.0001$; XX = $P<0.01$; X = $P<0.05$.

icantly lower value at 2 weeks. The oxiracetam group showed similar differences from piracetam, with a significantly lower standing pulse rate at 4 weeks (t test and ANCOVA) and over time according to the repeated measures results.

Temperature showed a decrease with both drugs over time (no statistically significant decrease with any drug and no difference between the two drugs). Weight did not show any statistically significant change over time with any of the drugs. There were no significant differences in the two drug groups.

The analysis of the Clinical Global Impressions scale (CGI) indicated that the overall illness of patients decreased with both compounds over time (improvement was faster with oxiracetam than with piracetam). However, there were no statistically significant differences. Also, changes over time did not show any difference between the two groups. The therapeutic index also showed an increase with both drugs, but without significant differences.

The Inventory of Psychic and Somatic Complaints-Elderly (IPSC-E) consists of 80 symptoms graded from 1 (not at all) to 5 (extreme). The scores are grouped into 16 factors (Table 2).

According to this scale, there were many significant time responses. The piracetam group showed significant time responses in all variables except hallucination, motor coordination, and sex. The oxiracetam group showed significant time responses in all variables except confusion, disorientation, hallucination, manic behavior, motor coordination, and sex. The group comparison (t test) showed strong group differences in memory, concentration, and paranoid ideation (disorientation only in screening). The analysis of covariance results kept the group difference in memory (oxiracetam) with significance over the entire time period, and at 8 weeks (Fig. 4). Also, disturbed concentration seemed to be more improved with oxiracetam than with piracetam. However, piracetam was more therapeutically effective on paranoid ideation and agitation.

The results of the statistical evaluations of the Abnormal Psychosomatic Finding Scale (ABNP) (48 symptoms are rated for severity: 0 = absent, 1 = light, 2 = moderate, and 3 = marked) indicated that both groups showed a significant decrease in total symptom scores over

TABLE 2. Changes in the Inventory of Psychic and Somatic Complaints in Elderly (IPSC-E)[a]

Factors	Periods	ANCOVA *P* level	Adjusted means (diffs)	
			ISF-2522	Piracetam
Energy loss	W-2	1.00	1.91 (−0.27)	1.98 (−0.20)
	W-4	0.23	1.67	
	W-8	1.00	1.53	
	W-12	1.00	1.48	
RM		*P*(grp)<0.27	*P*(time)<0.0001	*P*(grp × time)<1.00
Depression			*P* (time)	*P*(grp × time)
RM			XXX	
Sleep distur				
Anxiety			XXX	
RM				
Hostility			XXX	
RM				
Memory	W-8	XX	XXX	
RM		*P*(grp) 0.05		
Concent.			XXX	
RM				
Confusion			XX	XX
RM				
Disorient.				
Paranoid ID.	W-2	X	XXX	
RM	W-8	X		
Hallucinat.				
Agitation	W-12	X	X	X
RM				
Manic behav.				
Motor coor.				
Somatic comp.			X	XX
RM				
Sex				

RM, Repeated measures. XXX = *P*(grp)<0.001; XX = *P*(time)<0.01; X = *P*(time)<0.05.

time and in every evaluation period (paired t-test ANCOVA and the repeated measures time response). However, there were no group differences.

The SIEL (Short Form) consists of ten items and is a self-administered questionnaire. The patient rates himself from −5 to +5 on the following dimensions: tired (−5) versus alert (+5), sick versus healthy, nervous versus calm, tense versus relaxed, insecure versus secure, unhappy versus happy, anxious versus carefree, indifferent versus interested, passive versus active, depressed versus euphoric.

The statistical evaluation indicates that total scores showed an improvement over time with both drugs. The oxiracetam group showed temporal changes across all variables except sick-healthy, disinterested-interested, and passive-active (paired t-test and repeated measures). The piracetam group showed temporal changes across all variables except disinterested-interested and passive-active. The repeated measures results showed significant changes over time in all variables except tired-alert, sick-healthy, tense-relaxed, and passive-active. There was no group difference based on ANCOVA or repeated measures during any of the treatment periods.

Sleep Quality Questionnaire (SQQ) is also a self-rating 4-point scale, which is meant to measure four different dimensions of the subject's sleep and includes four questions: (1) Do you have difficulty in falling asleep? (2) Did you sleep comfortably? (3) Did you wake up earlier than usual? (4) Did you feel tired after you woke up?

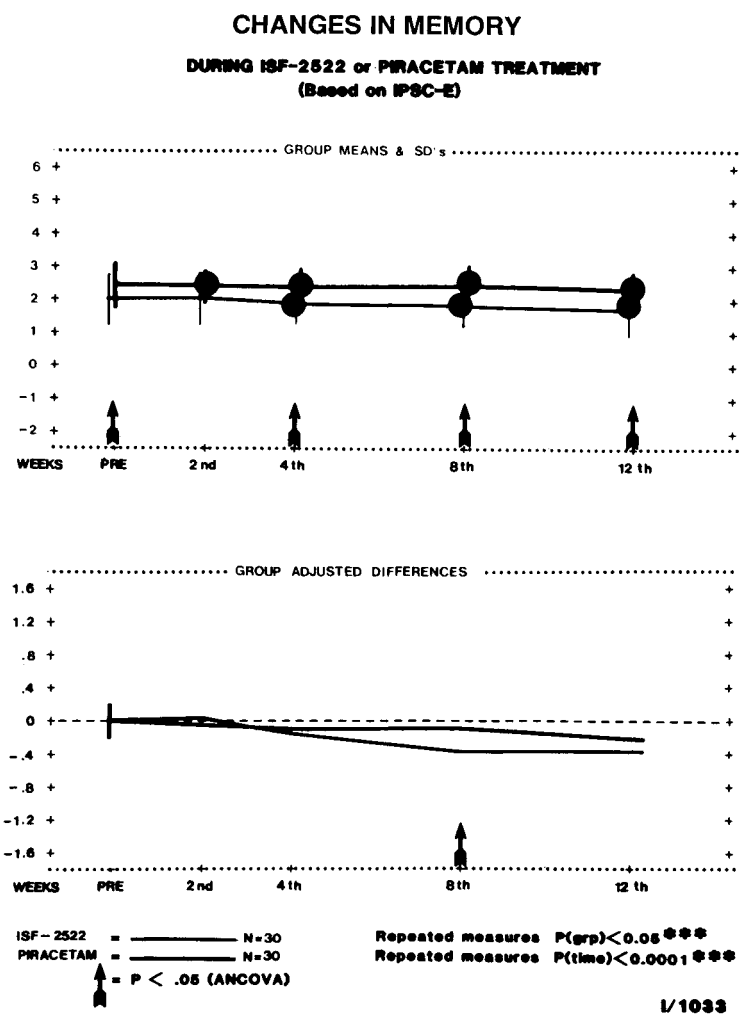

Fig. 4. Changes in memory. In the abscissa, the treatment period is shown and in the ordinate the group means and standard deviations (above) and group-adjusted differences (below) are shown. As seen, both ISF-2522 and piracetam groups show significant improvement in memory scores. ISF-2522 produced significantly more improvement than piracetam during 8 weeks of treatment.

Both groups showed very strong time response (t test and repeated measures). Indeed, two groups appear significantly different only at 2 weeks, where the piracetam improved disturbance in falling asleep and early waking more quickly than the oxiracetam group.

Side Effects

Treatment Emergence Symptom Scale (TWIS) is completed as necessary when patients complain of side effects. The data recorded are the symptom, name, intensity, relationship to the drug, and action taken. Twenty-four of the subjects reported symptoms at some time compared with 20 of the piracetam group. None of the symptoms are really consistent across either of the drug groups, and only a few patients reported any one symptom. The number of symptoms reported in any of the time periods, by any of the subjects, was not different between the two groups (for oxiracetam, 67 and for piracetam, 65). The most reported symptoms were sleep disturbance (nine

times with oxiracetam and eight times with piracetam); headache (ten times with oxiracetam and six times with piracetam); blurred vision (seven times with piracetam and three times with oxiracetam); nausea (four times with both compounds); dry mouth (five times with piracetam, and twice with oxiracetam); head pressure (four times with piracetam and three times with oxiracetam). An increase in urinary frequency and hand tremor were seen only after piracetam, whereas hearing impairment and hypertension were seen with oxiracetam.

In conclusion both drugs seemed to produce sleep disturbance, nausea, and head pressure. The symptoms seen predominantly with oxiracetam included headache, hearing impairment, hypertension, constipation, diarrhea. The symptoms seen with piracetam were dizziness, increased urinary frequency, blurred vision, tremor in hands, dry mouth.

Psychoexperimental Test Results

There was a statistically significant improvement of Pauli Performance test scores over time with both compounds, more frequently with oxiracetam than piracetam. There is a very strong time response in mean number attempted and mean number corrected in both tasks, as seen in repeated measures and matched t results. There was no group difference during treatment with both drugs.

According to evaluation of Benton Visual Motor Retention test significant changes from pretreatment to treatment periods with oxiracetam were observed. However, none of the results indicated any group differences. The oxiracetam group showed significant time response in all four variables, with generally poorer performance at 4 weeks and better performance at 8 weeks in comparison to screening. The piracetam group showed a similar pattern, but no significance. The repeated measures results also showed a very strong time response.

Laboratory Findings

The most frequently occurring values before treatment were found in the urinalyses results. These included high albumin, urobilinogen, oxalate crystals, and rare RBC, WBC, and epith cells (14 of 33 subjects). There was no significant increase or decrease in blood chemistry, hematology, or urinalysis by the end of the piracetam treatment program.

Sixteen subjects of oxiracetam group had high and low values in their urinalyses before treatment. These values included albumin, RBC cells, urobilinogen, WBC cells, oxalate crystals, and epith cells. By the end of the treatment week, only eight subjects had similar values.

No severe abnormal EEG findings were observed during both drug treatments. All electrocardiograms were within acceptable limits before, during, and at the end of piracetam treatment. One subject's EKG (week 8) had coronersclerose and one subject's EKG had a branch block before, during, and at the end of oxiracetam treatment.

Fifteen subjects out of 33 had eye changes before piracetam treatment. These included arteriosclerotic changes in vessels, venous enlargement in both fundus, anemia in both fundus, and slight senile cataracts. By the end of the treatment period, only four subjects had eye changes. Fourteen subjects out of 30 had eye changes before oxiracetam treatment. These included blurred edges, venous engorgement in both fundus, senile cataracts, slight anemic fundus, and anemic retina. At the end of the treatment period, eye changes were observed in only five subjects. The changes in any of the subjects (improvement or worsening) were not serious or systematic enough to be considered.

DISCUSSION

Chronic organic brain syndrome is a progressive disorder of higher mental functions, personality, and affect. It is usually attributed to senile brain disease or cerebral atherosclerosis. Autopsy reports indicate that these two processes frequently coexist. Drug therapy is part of a general program in managing these disorders.

In alleviating psychotic symptomatology of chronic OBS and in controlling agitation and irritability, the neuroleptic drugs were found to be effective; in the treatment of depressive features,

tricyclic antidepressants were found very helpful. The treatment of the cardinal symptoms of organic brain syndrome, such as impaired intellectual function and memory, is far more difficult. Among others, cerebral vasodilators, ergot alkaloids, anticoagulants, vitamins, nutrition, hormones, and analeptics have been tried to prevent the progression and to reverse the pathological process (14). Except for some direct-acting vasodilators and dihyrogenated ergot alkaloids, most other treatments were found useless in controlled trials. Even the results of the dihydrogenated ergot alkaloids or the vasodilators have not been consistent in terms of the particular symptoms relieved. Up to now, there is no evidence that any chemical agent can prevent progression of atherosclerotic or organic brain disease, or reverse the pathologic process (15).

Piracetam is the first compound reported to be effective on the symptoms of chronic brain syndrome without having the "typical" pharmacological profile of well-known psychotropic drugs or ergot alkaloids or cerebral vasodilators. It has facilitory effects in several learning models, protection from various disturbances caused in those learning models, facilitation of inter- and intrahemispheric transfer, and increased cortical control over subcortical structures (16). Piracetam does not fit into any known classes of psychotropic drugs. It is inactive on limbic system, and partially inactive (it inhibits central nystagmus) on reticular activating system. Giurgea (17) postulated that piracetam has selective effects on the "noetic" functions, and suggested that piracetam represents a new group of centrally effective compounds, nootropics (noos = mind, tropic = toward). In contrast to the usual psychotropics which "act" essentially indirectly upon higher telencephalic structures, piracetam's main function in fact is the telencephalic, higher brain integrative activity: it enhances its efficacy and compensates, at least partially, for its deficits (18). Because of these properties, the therapeutic effects of piracetam were predicted on the impaired memory and disturbed learning of patients with organic brain syndromes (19).

Oxiracetam, a GABA-GABOB derivative, exhibits pharmacological effects qualitatively similar to piracetam. However, a given dosage of oxiracetam is more potent than the same dosage of piracetam (7). Despite some minor differences in some of the tests [see detailed information in the chapter of Prof Nicolaus in this book], oxiracetam resembles piracetam more closely than psychotropic drugs. Thus, it can be included in the group of "nootropics." The studies in hypertensive rats demonstrated that learning speed was significantly reduced when they developed cerebral lesions. Oxiracetam is active in these animals, both intraperitoneally and orally in improving the learning speed (20).

In the present study, most of the important target symptoms of the patients with organic brain syndrome improved significantly over time in subjective (rating scale) and objective (experimental psychological tests) evaluations after both oxiracetam and piracetam. In comparison to piracetam, oxiracetam exhibited more statistically significant improvement in the memory factor (at 8 weeks and overall time), whereas piracetam showed statistically significant greater improvement than oxiracetam in factors of paranoid ideation and agitation.

The improvement of the symptoms of chronic organic brain syndromes due to aging or by other causes was demonstrated with piracetam in a variety of double-blind controlled trials (5,6,21,22). It was postulated that the therapeutic effects of piracetam may be related, among others, to the acceleration of turnover of cerebral energy available in the form of ATP (23), to the increase in the consumption of glucose, and to the enhancement in the biosynthesis of macromolecules, such as lipids, protein, and RNA (24). The clinical improvement is well correlated with the "specific" animal pharmacology profile of piracetam (16).

Electrophysiological tests in animals without computer evaluation did not provide significant effects of piracetam. However, the investigations in man demonstrated that piracetam has significant effects on human brain function where quantitative EEG was applied (25).

In our study using quantitative pharmaco-EEG, piracetam reduced slow waves and increased alpha waves. The computer EEG data base of psychotropic drugs (26) classified the effects of different dosages of oxiracetam and piracetam in the group of "vigilance-enhancing" drugs, such as some of the classical psycho-stimulants, MAO inhibitors, and stimulant antidepressants (10). Also, some of the cerebral vascular compounds such as hydergine were classified by the computer

EEG data base in the same group. Thus, we have hypothesized that "antigeriatric" drugs reduce slow waves and have significant alpha-enhancing properties on human EEG (11).

The EEG of an adult person is characterized by a predominant alpha activity. In the process of aging, a significant slowing of alpha activity with decrease of alpha waves and increase of slower potentials has been reported (27,28,29). It is interesting that most of the other clinical conditions (cerebrovascular accidents, posttraumatic syndromes, acute alcohol intoxication delirium tremens, and comas with different etiology), which reported having therapeutic benefits from piracetam treatment, are also characterized by a decrease of alpha and increase of slow potentials. Also, children with mental retardation and learning deficiencies, who show good therapeutic response to piracetam (30,31), have significantly less alpha activity and more slow waves than control groups. These findings suggest that the abnormal clinical conditions which are associated with a slow EEG and poor alpha activity respond to piracetam and piracetamlike "alpha-enhancing" and slow wave reducing compounds such as oxiracetam. The improvement of clinical conditions during piracetam treatment was found to be correlated with the "normalization" (decrease of slow waves) of EEG pattern (32).

The therapeutic effects of piracetam in psychotic symptomatology, particularly on paranoid ideation, is an important phenomenon. Recent studies on brain monoamine metabolism and serum prolactin levels in rats indicated that piracetam seemed to accelerate brain catecholamine turnover via a blockade of catecholamine receptors. In these experiments, piracetam acts similarly to the neuroleptic drugs, but significantly differently from dextroamphetaminelike compounds (33). In the human electroencephalogram there are also some similarities between neuroleptics and "nootropics" (piracetam and oxiracetam). Both groups of drugs show alpha-enhancing properties. However, neuroleptics produce slower alpha waves, increase slow waves, and decrease fast activity (34), whereas piracetam and oxiracetam decrease slower potentials. Increase of alpha activity in schizophrenics during neuroleptic treatment is significantly correlated with the decrease of acute psychotic symptomatology (35).

According to these findings, the improvement of symptoms of organic brain syndrome may be related to the biochemical changes in the brain, which are responsive to the EEG alpha-enhancing and slow wave-reducing properties of oxiracetam and piracetam. According to this hypothesis, one could postulate that the greater the increase of alpha activity during piracetam or oxiracetam treatment, the more clinical improvement will be seen. Thus, the lesser alpha waves in a patient with an organic brain syndrome the more therapeutic response to piracetam or oxiracetam treatment is expected. A prospective controlled double-blind study is required to test this hypothesis.

The clinical and experimental investigation with oxiracetam, piracetam and similar compounds suggests that, in the near future, one may be able to discover psychotropic drugs with completely new pharmacological profiles. These compounds, which we could call a "second generation" of psychotropics, may not have any clinically noticeable central or peripheral nervous system "side effects." Thus they would be effective predominantly on special receptors which are directly or indirectly responsible in the psychiatric disease process. As demonstrated by the discovery of psychotropic hormones (36,37), studies with peptides (38,39) and nootropics (10,11) the computer-analyzed EEG can be an integral part in the development of a second generation of psychotropic drugs.

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