group were withdrawn from the study due to rash in 3 patients, or adverse events (primarily nausea). No serious sequelae were observed in patients who dropped out for adverse reactions. The clinical relevance of these findings varied considerably among patients. Doses over 80 mg/day per cent may be required in patients who can tolerate tacrine.

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**CHRONIC LOW DOSE EPTASTIGMINE IN ALZHEIMER PATIENTS: RELATIONSHIP BETWEEN ACETYLCHOLINESTERASE INHIBITION AND COGNITIVE EFFECTS. B.P. Impiombato, P.B. Lucchelli. Medical Dept., Mediolanum Farmaceutici, Milan, Italy.**

Eptastigmine is a long acting acetylcholinesterase (AChE) inhibitor. A double-blind, placebo-controlled, multicenter study was performed to assess the safety, tolerability, pharmacodynamics and preliminary efficacy of multiple oral doses of eptastigmine in 100 patients with mild to severe Alzheimer's disease. Patients were randomly assigned to eptastigmine (30-60 mg/day) or placebo for 4 weeks at a ratio of 4:1. Blood cell AChE activity was repeatedly measured from 10 L capillary blood with an automated device. Nine patients dropped out due to adverse events. No hematological adverse events occurred. Nineteen patients on eptastigmine had cholinerergic adverse events associated to peak AChE inhibition exceeding 50% after the first dose or 70% at steady-state. Four patients had a modest reversible increase in serum AChE levels. Performance on various cognitive tasks improved at the 200 mg dose compared to placebo. The predosing score on day 1 was used as the baseline. The CDR system included assessments of simple and choice reaction time, sustained vigilance, memory scanning and delayed recall recognition of words, pictures and faces. Comparison of the pre-dosing performance of this elderly population to that of young control volunteers identified a clear pattern of slowed performance on the various attentional and memory tasks. When compared to placebo, S12024 produced a dose-dependent improvement in the speed of recognition performance at the intermediate doses (50 and 100 mg t. d.) and to a lesser extent at the 200 mg dose lev.; 10 mg dose was ineffective. In conclusion, this study indicates that daily steady-state AChE inhibition showed clinical improvement. Performance on both word fluency and logical memory tasks improved at the 200 mg dose compared to placebo. The predosing score on day 1 was used as the baseline. The CDR system included assessments of simple and choice reaction time, sustained vigilance, memory scanning and delayed recall recognition of words, pictures and faces.

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**CLINICAL AND NEUROPHYSIOLOGICAL EVALUATION OF 3 DOSES OF S12042 (50, 100, 200 mg a.d.) DURING REPEATED ORAL ADMINISTRATION (7 days) IN 12 PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. S. Derouesne*, L. D€ribert, C. Dulac, E. Hesse, A. Jouvet, P. L. Mouren, N. Notte, A. Van de Ville, U. Voss, J. Van der Linden, J. Van der Linden, M. Verhey and J. Jolles.**

A great number of clinical trials have been conducted to assess the efficacy of newly developed cognition enhancers in the treatment of Alzheimer's Disease as well as age-associated memory impairment. Nevertheless, research has only shown minor effects of newly developed substances that should enhance cognition. One of the world's most widely used cognitive enhancers is caffeine. A large postal survey conducted by our department, among 2043 normal subjects divided over 13 age groups ranging from 23-85 years yielded that the subjects' reported average coffee consumption is low (mean: 1.5 cups/day) and in the two highest age groups (60 and 75 yrs) daily intake as the baseline) and 1.5 hour after the first intake at D1 and after the last intake at D7 of each period. Quantitative EEG (QEEG) was performed (ERP) during a selective auditory attention task were also performed at D7 of each period. Twelve patients (mean age: 64 years old + 10, mean MMS: 23+3) completed the study. No serious effect was observed on MMS, VDL, battery or activities of daily living scores. A significant period effect was shown in L and D between the second and the 4th period of treatment for some items in favor of a learning effect (implicit memory). CIBIC results showed a non-significant treatment effect in favor of active treatment (100-200 mg t. d.). Significant change was observed in ERP in EEG P3 and in P3 amplitude (p<0.01) in favor of nonspecific stimulation of vigilance. A significant difference (<0.05) was observed between placebo and S12024 concerning the amplitude of the ERP P3 signal (processing cognitive information including central and attention-related effect).

In summary, S12042 has shown preliminary evidence of central pharmacodynamic activity predominantly at 200 mg/day based on neurophysiological assessments results in favor of some overall improvements in vigilance or attentional functions. Clinical and biological tolerability was demonstrated by the parameter stability. The ongoing European phase IIb study on 300 AD patients treated during 3 months will provide more data.

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The cognitive potential enhancing properties of S12042, which appears to facilitate the activity of brain noradrenaline and vasopressin, have been found to enhance the acquisition and recall of information in marmoset, monkey and aged rats. In order to determine whether any evidence of similar effects could be obtained in man, the Cognitive Drug Research (CDR) computerized assessment system (CDS) included in a placebo-controlled double-blind, rising dose, tolerance and pharmacokinetic trial of the compound in 36 elderly (> 60 years) volunteers. The trial was conducted in five sequential stages, in each, 6 volunteers received active and placebo medication in random order. During the initial stages, twice daily 10, 50, 100 and 200 mg S12042 respectively. After training sessions, cognitive testing was performed prior to the morning dosing and then at 1.5, 3, 4.5 and 8 hours post-dosing on days 1 and 6. The pre-dosing score on day 1 was used as the baseline. The CDR system included assessments of simple and choice reaction time, sustained vigilance, memory scanning and delayed recognition of words, pictures and faces.

Comparison of the pre-dosing performance of this elderly population to that of young control volunteers identified a clear pattern of slowed performance on the various attentional and memory tasks. When compared to placebo, S12042 produced a dose-dependent improvement in the speed of recognition performance at the intermediate doses (50 and 100 mg t. d.) and to a lesser extent at the 200 mg dose level; 10 mg dose was ineffective. In conclusion, this study has shown preliminary evidence that S12042 is capable of correcting age related declines in human cognitive processes in a dose-dependent fashion. The study highlights the advantage of including appropriate cognitive early in the process of drug evaluation and is promising for the development of S12042 as a cognition enhancer. Further work on the compound is underway to confirm and extend these findings (e.g. Alatan et al., this conference).

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Neurotransmission studies have shown that the cholinergic system is involved in memory, learning and aging. Caffeine has been shown to enhance memory performance in young and elderly individuals. However, the mechanism of caffeine's effect has not been clarified. The current study aimed to investigate the role of cholinergic neurotransmission in memory enhancement and the effect of caffeine on it. The subjects were divided into two groups: one received caffeine (150 mg) and the other received placebo. The subjects were administered with caffeine or placebo, and then underwent various memory tasks, including free recall, recognition memory, and delayed recall memory. The results showed that caffeine significantly enhanced memory performance in both young and elderly individuals, and that this effect was more pronounced in the elderly group. The study suggests that caffeine enhances memory function by modulating cholinergic neurotransmission.
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414 THERAPY WITH A COMBINATION OF IRON, VITAMIN B6 AND COENZYME Q10 IN THE LONG TERM FOR SPORADIC ALZHEIMER'S DISEASE. Masaki Imagawa MD, Department of Neuropsychiatry, Hyogo Prefectural Amagasaki Hospital, Hyogo, Japan.

The therapy with combination of coenzyme Q10 (CoQ10), vitamin B6 and iron, two in the same family were found to have mis sense mutation of amyloid β-protein precursor gene. This therapy have been used in 20 patients with the sporadic Alzheimer's disease (AD) in the long term (one year). It is suggested that this therapy may be effective for AD. SUBJECTS AND METHODS This clinical study included 20 AD, mean±SD age, males 61.8±6.8 y.o., females 61.8±6.8 y.o., 20 patients have been suffered from AD from 1 year to 7 years. Diagnosis was based on DSM-III-R. Mental state and daily activity were evaluated with mini-mental state examination score (MMSE) and functional assessment staging (FAST). And so the clinical course was followed by the two methods. These numbers have changed according to the severity of the patient's symptoms and signs. Those scores were marked on the time scale (0, 2 weeks, 1, 3, 6 months, one year). The dose of the drugs taken by the patients was iron 50-150 mg, B6 90-180 mg, CoQ10 60-180 mg, daily. RESULTS In this therapy, each points have significantly different from zero point in scores. In MMSE, 0: 14.8±7.0 (n=20), 2W: 22.5±5.4 (n=16), 1M: 20.3±5.4 (n=18), 3M: 21.5±5.4 (n=20), 6M: 20.3±7.1 (n=20), 1Y: 21.8±6.5 (n=11)*, paired t test, p<0.001. In FAST, the stage have changed from 3 stage (zero point) to 3 stage. DISCUSSION Why dose this therapy effect in AD? In general, iron, particularly the action of Fe²⁺ have a intoxication in vivo because of free radicals. But iron is essential mineral in the body, especially, brain. Adding to CoQ10, iron dependent free radicals may be disappeared. In this therapy it is focus on the production of the neurotransmitters through the decarboxylation (B6 B6-enzyme) with ATP. B6 is acquires the biosynthesis of GABA. Neuronal cell's death said to be the hypothesis of glutamine induced cell's death. Therefore, it is importance that the action is related to related with GABA. The obtained results indicated that the severity of mental-annestic disturbances and disorientation in time and space reliably decreased after 3 and especially 6 months of treatment. There was also a trend for praxic and speech impairments to decrease from baseline. In addition, indices of orientation and awareness improved. The results of immunoenzyme analysis of NSP and AAB to them showed a decrease of NSP serum concentration and a stabilizing influence of dimethylsulfoxide on the blood-brain barrier. The action mechanism, clinical efficacy and adverse reactions will be discussed.


Potelactam (1-lypo-2-aminoadipyl-1-Leucil-prolinamide) is a synthetic neuropeptide with neurotrophic activity and modulatory effects on various neurotransmission systems. This drug is today under study in many clinical trials in Europe, according to results obtained in preliminary studies in patients suffering from dementia, either of Alzheimer type or vascular origin. This double-blind, randomized, short-term clinical trial was carried out in order to evaluate the safety profile of Potelactam on both cardiovascular and hormonal parameters.

Analysis of the performance data shows that scopolamine produced severely disturbed memory as well as psychomotor functions. Caffeine significantly reduced such disturbances and disorientaiton in time and space. Central seromnergic hyperresponsivity with a combination of iron, vitamin B6 and coenzyme Q10 in the long term for sporadic Alzheimer's Disease (AD) in the long term (one year). It is suggested that this therapy may be effective for AD. In general, iron, particularly the action of Fe²⁺ have a intoxication in vivo because of free radicals. But iron is essential mineral in the body, especially, brain. Adding to CoQ10, iron dependent free radicals may be disappeared. In this therapy it is focus on the production of the neurotransmitters through the decarboxylation (B6 B6-enzyme) with ATP. B6 is acquires the biosynthesis of GABA. Neuronal cell's death said to be the hypothesis of glutamine induced cell's death. Therefore, it is importance that the action is related to related with GABA. The obtained results indicated that the severity of mental-annestic disturbances and disorientation in time and space reliably decreased after 3 and especially 6 months of treatment. There was also a trend for praxic and speech impairments to decrease from baseline. In addition, indices of orientation and awareness improved. The results of immunoenzyme analysis of NSP and AAB to them showed a decrease of NSP serum concentration and a stabilizing influence of dimethylsulfoxide on the blood-brain barrier. The action mechanism, clinical efficacy and adverse reactions will be discussed.

417 CENTRAL SEROTONERGIC HYPERRESPONSIVITY IN THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE. D.M. McLoughlin, J.V. Lucey and T.G. Dinan. Institute of Psychiatry, London SE5 BAF, and Dept. of Psychiatry, Trinity College Medical School, Dublin 8, Ireland.

A wide range of neuroanatomical and biochemical deficits have been identified in the central serotonergic (5-HT) systems in late-onset probable AD (NINCDS-ADRDA criteria) and in an elderly healthy comparison group. PRL levels were measured hourly for 5 hours following an oral dose of 30mg of d-FEN. The PRL response to d-FEN (A PRL) was calculated by subtracting the baseline PRL from the maximum PRL level post ingestion of d-FEN. There was no significant difference in baseline PRL levels between the two groups and the peak PRL response occurred in all subjects within 300 mins. The mean ΔPRL in the AD group was 209.6 (SD=116.9) μIU/1 and 95% (μIU/1) [95%] in the comparison group, the A PRL response was significantly greater in the AD group (Z=2.04, p=0.04; Mann-Whitney U test).

This preliminary study is the first to report an enhanced 5-HT neuroendocrine responsivity in late-onset AD. 5-HT abnormalities have been implicated in depression, anxiety and impulsive, aggressive behaviour. 5-HT has also been recognised as having an influence, possibly inhibitory, on learning and memory. The findings of this study suggest that a diminished central serotonergic responsivity in late-onset AD may be a biological marker of the behavioural and cognitive symptoms in AD.

418 MANAGING PROBLEM BEHAVIORS ASSOCIATED WITH ALZHEIMER'S DISEASE: A PIAGETIAN APPROACH. M.A. Matsson, A. Linton, M.J. Lichtenstein, B. Cleary. University of Texas Health Science...