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ORIGINAL INVESTIGATION

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Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study

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Abstract In a double-blind, placebo-controlled study on the therapeutic efficacy and central effects of nicergoline, an ergot alkaloid with metabolic, antithrombotic and vasoactive action, 112 patients with mild to moderate dementia, diagnosed according to DSM III-R criteria (MMS 13–25), living in pensioners' homes, were included. Fifty-six were subdiagnosed as senile dementia of the Alzheimer type (SDAT), 56 as multi-infarct dementia (MID), based on computed tomography and Hachinski scores (≤49 SDAT, ≥7 MID). They received, after 2 weeks' run-in period (placebo), randomized for 8 weeks either 2×30 mg nicergoline (NIC) or 2×1 placebo (PLAC) orally. The four subgroups (SDAT/NIC, SDAT/PLAC, MID/NIC, MID/PLAC; 4×28 patients) were comparable in regard to age and sex. Only four, four, four and two patients of the respective groups did not finish the study for minor reasons. Confirmatory statistical analysis demonstrated in the target variable – the Clinical Global Impression (CGI) – a significant superiority of NIC over PLAC in both the SDAT and MID groups. Global improvement (CGI item 2) was seen in both nicergoline subgroups (3 and 3), while no changes occurred under placebo (4 and 4, respectively). The responder versus non-responder ratio was in the SDAT/NIC group 16/8, versus 8/16 in the SDAT/PLAC group ($\chi^2 = 4.1$, $P = 0.04$); in the MID/NIC group 17/7, versus 7/19 in the MID/PLAC group ($\chi^2 = 7.96$, $P < 0.005$). Furthermore, there was a significant improvement of the Mini-Mental State and the SCAG score in both the MID and SDAT group after 8 weeks of nicergoline, which was significantly superior to the minimal improvement or no change in placebo-treated SDAT and MID patients. EEG mapping demonstrated in NIC-treated SDAT and MID patients a significant decrease in delta and theta, increase in alpha 2 and beta activity and an acceleration of the centroid of the total power spectrum as compared with pretreatment, while opposite changes occurred in PLAC-treated SDAT and MID patients. The differences between PLAC and NIC reached the level of statistical significance. Event-related potential (ERP) recordings demonstrated a significantly shortened P300 latency under NIC treatment in both SDAT and MID patients, while there was a trend towards lengthening under PLAC. Thus, nicergoline improved vigilance and information processing at the neurophysiological level, which leads at the behavioural level to clinical improvement both in degenerative and vascular dementia.

Key words Senile dementia of the Alzheimer type
Multi-infarct dementia · Nicergoline
Clinical findings · EEG mapping
Event-related potentials
Gerontopsychopharmacology · Nootropics

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Introduction

In earlier studies involving clinical and quantitative electroencephalographic (EEG) investigations in dementia patients, we could demonstrate that both senile dementia of the Alzheimer type (SDAT) and multi-infarct dementia (MID) patients demonstrated increased delta/theta and decreased alpha and beta activity, as well as slowing of the dominant frequency and the centroid of the total power spectrum, as

compared with normally ageing controls (Saletu et al. 1988, 1991a, 1992; Saletu 1994). These alterations in brain function, evaluated initially by exploratory, and later by confirmatory statistics, reflected a deterioration in vigilance, as defined first by Head in 1923 as the availability and grade of organization of man's adaptive behaviour, which is dependent upon the dynamic state of the neuronal network. This vigilance decrement results noopsychically in deterioration of intellectual performance and memory, and thymopsychically in decreased drive and affect, which constitute the axial syndrome of dementia, as described in several psychiatric classification systems (Berner 1977; American Psychiatric Association 1987). Indeed, utilizing correlation maps, we could demonstrate that EEG slowing is correlated both to radiological and to psychopathological and psychometric data: the more pronounced the atrophy in computed tomography, the more delta and theta was evident at the neurophysiological level, which in turn was correlated to higher SCAG and lower Mini-Mental State scores at the clinical level, and to a poorer psychometric performance, seen in several tests such as the Digit-Symbol Substitution Test, the Trail-Making Test and the Digit Span Test (Saletu et al. 1991a, b).

Thus, a drug which should be therapeutically effective in dementia has to induce exactly the opposite changes in brain function found during normal and pathological ageing. Indeed, several nootropic drugs induced such changes (Saletu and Grünberger 1980, 1985; Saletu 1981, 1993, 1994; Itil et al. 1985; Herrmann et al. 1986; Saletu et al. 1987, 1990a–d). As early as the 1970s, we identified nicergoline as one of these compounds (Saletu et al. 1979a,b). Nicergoline (10-alpha-methoxy-1,6-dimethylergoline-8-beta-methyl-(5-bromnicotinate) is an ergot alkaloid, which was initially thought to act as a vaso-dilator due to its alpha-1 receptor blocking effects, proven by various animal studies (Le Poncin-Lafitte et al. 1984), as well as in man by an increase in the average cerebral hemispheric blood flow (Iliff et al. 1979). However, further investigations demonstrated that the metabolic effects are of far greater importance, as under hypoxia, ischaemia or intoxication, nicergoline improves glucose uptake and utilization (Benzi et al. 1972; Le Poncin-Lafitte et al. 1984), protein and RNA synthesis (Paul and Chandra 1979; Chandra and Paul 1985; Rossi et al. 1988), oxygen utilization (Maiolo et al. 1972), and cerebral cytochromoxidase activity (Shintomi et al. 1986). Benzi et al. (1979) also described a nicergoline-induced improvement in ATP and intermediary products of the glycolytic pathway, the Krebs cycle and the electron transfer chain. Indeed, utilizing experimentally-induced hypoxic hypoxidosis in man, we could demonstrate that nicergoline exerted brain protective properties, as the hypoxia-induced performance decrement of 43% under placebo was reduced to 24% after 30 mg (Saletu et al. 1990d). Further experimental and clinical pharmacological studies demonstrated a dopaminergic effect (Moretti et al. 1985, 1988; Borromei 1989; Rossi et al. 1990), antithrombotic action (Pogliani et al. 1975; Lagarde et al. 1980), positive haemorheologic properties (Ehrly and Landgraf 1985) and certain calcium antagonist activities (Heitz et al. 1986). Finally, an action on the cholinergic system was demonstrated with biochemical and behavioural methods: inhibition of rat synaptosomal fraction AChE activity and a significant increase in Ach levels in the striatum were shown after acute oral dosing. After chronic treatment in aged rats, nicergoline significantly diminished the reduction in Ach levels in the cortex and striatum and the animals showed a significant and linear improvement in the radial arm learning test (McArthur et al. 1993).

With regard to therapeutic efficacy in dementia of the Alzheimer type and vascular dementia, several double-blind studies have been carried out, partly with placebo, partly with active reference substances (Arrigo et al. 1982; Granata et al. 1984; Dolce et al. 1985; Italian Cooperative Group 1985; Jori et al. 1985; Martucci et al. 1985; Kugler 1988; Zappoli et al. 1988; Battaglia et al. 1989; Moglia and Arrigo 1989; Nicergoline Cooperative Study Group 1990). However, as some of these early studies have methodological shortcomings in our present scientific methodological understanding, the present study was carried out with a prospective allocation to a degenerative (SDAT) and vascular aetiology (MID), and subsequent randomization of these dementia sub-groups to placebo or verum. The aim of this double-blind, placebo-controlled, parallel-group design study was to assess efficacy, safety and neurophysiological effects of 30 mg nicergoline b.i.d. in mild to moderate dementia of the Alzheimer type (SDAT) and multi-infarct dementia type (MID), utilizing psychometric, computed tomography, EEG and ERP mapping techniques.

Materials and methods

Design and patients

In the double-blind, placebo-controlled, parallel-group design study, 112 patients (56 MID and 56 SDAT) were included. Inclusion criteria called for male or female patients over the age of 60 years, residing in nursing homes for the elderly, who were diagnosed according to DSM-III-R criteria for dementia (SDAT/MID). The degree of illness should have been mild to moderate, the Mini-Mental State (MMS) ranging from 13 to 25. They had to be able to complete the Labyrinth Test. Allocation to the sub-group SDAT or MID was based on the Hachinski Ischaemic Score (Hachinski et al. 1975) (SDAT ≤ 4; MID ≥ 7) and CT (Meese et al. 1980).

Exclusion criteria were in keeping with the recommendations for nootropic drug trials. They included among others: pseudo-dementia due to depression; psychosis; aphasia, hemiplegia or other clinical neurological deficits that could interfere with cognitive and psychometric tests; stroke within the last 3 months; cardiac

insufficiency stage III or IV; other serious diseases (renal insufficiency, hepatic insufficiency, malignant tumours, etc.) that would interfere with an evaluation of the efficacy criteria; allergy to nicergoline or severe allergy to other medication; alcohol or drug abuse; chronic intake of psychotropic medication (antidepressants, neuroleptics, sedatives, hypnotics, CNS stimulants) which had not been withdrawn at the beginning of the wash-out period and that could interfere with the evaluation; other nootropics; treatment of peripheral or central ischaemic disturbances with substances such as naftidrofuryl, pentoxifylline, cinnarizin, flunarizine and nimodipine.

After a 2-week wash-out period, the patients received, randomized for 8 weeks, either 2×30 mg nicergoline (Sermion) per day or 2×1 tablet placebo per day, orally. The resulting four sub-groups (4×28 patients) were comparable in age and sex (SDAT/NIC: 23 females (f), 5 males (m), age 78±7; SDAT/PLAC: 21 f, 7 m, age 77±10; MID/NIC: 22 f, 6 m, age 81±7; MID/PLAC: 19 f, 9 m, age 79±7). Only four, four, four and two patients of the four respective groups did not finish the study for minor reasons, which will be described later. The study was performed in accordance with the Declaration of Helsinki, revised in 1975 (Tokyo) and amended in 1983 (Venice). The approval of an ethical committee was obtained, as was the patients' informed consent.

Evaluation

Clinical evaluation

The clinical global impression (CGI) score (CIPS 1981), selected for confirmatory statistics, was completed at weeks 0 and 8; the Sandoz Clinical Assessment-Geriatric (SCAG) Scale (Shader et al. 1974) and the Hamilton Depression Scale (HAMD) for 21 items (Hamilton 1967) as well as the Dosage Record and Treatment Emergent Symptom Scale (DOTES) were completed at weeks -2, 0, 2, 4, 6 and 8. The Mini-Mental State (MMS; Folstein et al. 1975) was done at weeks −2, 0, 4 and 8, the Nurses' Observation Scale for In-Patient Evaluation (NOSIE) (Honigfeld 1974) was completed at weeks 0, 4 and 8. Medical history was performed at week −2, the CT within the wash-out period. Laboratory tests were scheduled for pre- and post-treatment.

EEG / ERP mapping

For EEG mapping, a 3-min vigilance-controlled EEG (V-EEG) was recorded by means of a 21-channel Nihon Kohden 4321 F polygraph at weeks 0 and 8. Nineteen EEG leads (referenced to averaged mastoids), vertical and horizontal EOG were digitized on-line by a Hewlett Packard Vectra system with a sampling frequency of 102.4 Hz (Anderer et al. 1987; Saletu et al. 1987). Artifact-free epochs were selected using a two-step analysis for automatic minimization and rejection of artifacts (Anderer et al. 1992). Subsequently, a common average reference was calculated. Spectral analysis was performed using the fast Fourier transform technique for 5-s epochs.

Target variables (absolute and relative delta and theta, alpha-1, alpha-2 and beta power, centroids of the delta and theta, alpha, beta and total activity) at the 19 leads before and 8 weeks after drug administration were compared. Results of this exploratory process were expressed in *t*-scores and displayed as SPMs (Bartels and Subach 1976; Duffy et al. 1981; Saletu et al. 1987). The same method was utilized to demonstrate differences between nicergoline-induced and placebo-induced alterations ("pharmaco-EEG maps").

Event-related potentials (ERP) were investigated in a two-tone auditory odd-ball paradigm (Semlitsch et al. 1989). In the present paper, the latency changes in P300 from pre- to 8 weeks' treatment will be reported. A detailed description will be given elsewhere (Semlitsch et al., in preparation).

Statistics

Sample size determination was based on the CGI (Global Clinical Impression) data of a previous study in MID and SDAT patients. On the basis of an alpha-error of 5% and a beta-error of 20%, and under the assumption of minimal relevant differences (verum minus placebo) of 0.81 for SDAT, and 0.74 for MID patients, a sample size of 112 patients was calculated.

Statistical analysis was based on the concept of descriptive data analysis with confirmatory statements as proposed by Abt (1988) for controlled studies. The pre-selected null hypothesis for confirmatory testing was: there is no difference between nicergoline-induced and placebo-induced changes (8 weeks' treatment as compared with pre-treatment) in the CGI (maximal error probability = 0.05). Alpha adjustment by Bonferroni-Holme led to individual error probabilities of P (1) < 0.0125, P (2) < 0.0167, P (3) < 0.025 and P (4) < 0.05. All other variables were tested descriptively. Normal distribution was tested by means of one Kalmogorov-Smirnov test. A responder analysis was carried out, based on item 2 of the CGI.

With regard to the EEG data, a multi-variate test was performed first, followed by univariate analyses. MANOVAs were performed for each of the 21 electrodes, considering group (drug, placebo), time (pre-drug, post-drug) and absolute power values in all nine absolute power and nine frequency measures. Hotelling T^2 values were used to avoid type I errors, with inflated degree of freedom.

Results

Clinical Findings

Of the 112 demented patients included in the study, only 14 dropped out prematurely. In the SDAT/NIC sub-group (n = 28) four patients dropped out after week 2 (two patients because they found the study too troublesome, one because she required an antidepressant and one because she moved to live with her daughter in another city). In the SDAT/PLAC sub-group (n = 28) four patients left the study in the wash-out period (one because of a venous thrombosis in her legs, two because they found the investigations too troublesome and one because she rejected the idea of taking more pills). In the MID/NIC sub-group (n = 28) four patients withdrew from the study (two in the wash-out period, one in week 2 and one in week 4 because they found the study too troublesome). In the MID/PLAC sub-group (n = 28), two patients withdrew in the wash-out period because they found it too tiresome to participate.

The *CGI-item 1* demonstrated a significant improvement by −0.79 after 8 weeks in the nicergoline-treated SDAT patients (P< 0.001), while the placebo-treated SDAT patients showed only minimal changes (−0.25, P < 0.05, Wilcoxon). Both treated groups remained moderately ill (Table 1). Inter-group differences reached the level of statistical significance in confirmatory testing. The nicergoline-treated MID patients also showed significant improvement at the P < 0.001 level (Wilcoxon Test), while the placebo-treated ones showed only minimal changes (Table 1). Both patient groups remained

Table 1 Severity of illness (item 1) and global improvement (item 2) based on CGI (clinical global impression) before and after 8 weeks treatment with nicergoline (2×30 mg/day) and placebo in SDAT and MID

	SDAT/NIC ($n=24$)		SDAT/PLAC ($n=24$)		MID/NIC ($n=24$)		MID/PLAC ($n=26$)	
	Pre	Week 8	Pre	Week 8	Pre	Week 8	Pre	Week 8
Severity of illness								
Mean	4.33	3.54	4.29	4.04	4.42	3.83	4.23	4.00
SD	1.01	0.88	0.95	0.95	1.02	1.09	1.03	1.17
Median	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Change		−0.79***		−0.25*		−0.59***		−0.23*
Wilcoxon, p-value		0.001		0.046		0.001		0.029
Inter-drug difference U-test, p_C-value			0.01 < 0.025				0.034 < 0.05	
Global improvement								
Mean	3.21		3.75		3.29		3.81	
SD	0.78		0.61		0.62		0.57	
Median	3.00		4.00		3.00		4.00	
Inter-drug difference U-test, P-value			0.001				0.04	

moderately ill. The inter-drug difference was, however, significant in confirmatory testing (Table 1).

The *CGI-item 2* on global improvement after 8 weeks' therapy also showed significant differences between the nicergoline- and placebo-treated patients, both in the SDAT and MID sub-groups (Table 1). While the nicergoline-treated SDAT and MID patients revealed, on average, a minimal improvement, the placebo-treated ones showed no changes. Nicergoline was significantly superior to placebo in both sub-types of dementia. A *responder analysis* was performed based on CGI-item 2. If one divides the patients into responders (CGI-2 ≤ 3, i.e. patients showing improvement) and non-responders (CGI-2 ≥ 4, i.e. patients showing no changes or worsening), the SDAT group showed under nicergoline 16 responders and 8 non-responders, while the placebo group showed 8 responders and 16 non-responders, with the χ^2 Test being significant at $P = 0.041$. The MID group showed under nicergoline 17 responders and 7 non-responders, while under placebo 7 responders and 19 non-responders (χ^2 Test, $P = 0.005$).

If one calculates the *percentage of responders and non-responders* in all four sub-groups, 66.6% of nicergoline-treated SDAT patients showed improvement and 33.3% a non-response, while the placebo-treated SDAT patients exhibited just the opposite findings (Fig. 1). Similarly, 70.83% of the nicergoline-treated MID patients were responders, 29.17% non-responders, while of the placebo-treated MID patients 73.08% were non-responders and 26.92% responders. The differences between the groups were significant.

The *Mini-Mental State (MMS)* showed at week -2 no significant differences between the four sub-groups (medians for SDAT/NIC: 22.0; SDAT/PLAC: 21.0; MID/NIC: 22.0; MID/PLAC 21.0) or significant changes to week 0 (22.0, 23.0, 23.0, 21.0, respectively). In SDAT patients, nicergoline treatment resulted in a slight but significant improvement by 2.7 or 4.2 points in weeks 4 and 8, respectively, while placebo induced only an increase of 0.9 and 2.2 (Fig. 2). Similarly, MID patients improved significantly under NIC by 2.4 and 3.7 points in weeks 4 and 8, while placebo induced only minimal and non-significant changes by 0.8 and 0.9 points, respectively. NIC was significantly superior to PLAC in both the SDAT ($P < 0.01$ in week 4 and 8, Mann Whitney U-Test) and MID group ($P < 0.05$ in week 4, $P < 0.01$ in week 8).

The *Sandoz Clinical Assessment – Geriatric (SCAG)* demonstrated no significant inter-group differences before the start of the treatment (medians for SDAT/NIC: 55.0; SDAT/PLAC: 57.5; MID/NIC: 55.5; MID/PLAC: 53.5) or significant changes from week −2

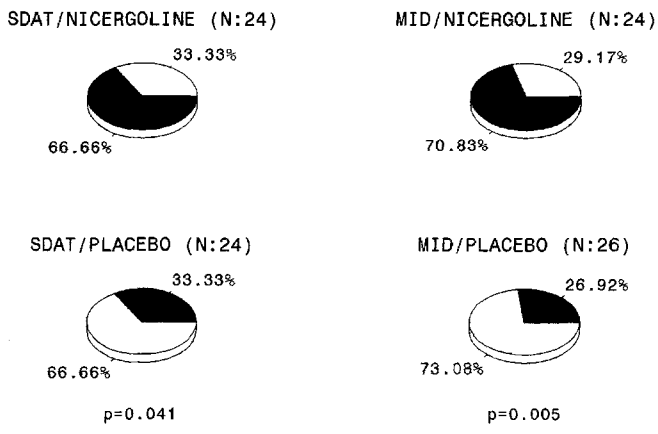


Fig. 1 Responder-analysis (χ^2 Test) after 8 weeks' therapy with nicergoline (2×30 mg/day) and placebo in SDAT and MID (responder: CGI-2 ≤ 3; non-responder: CGI-2 ≥ 4). While in the nicergoline-treated SDAT patients there are 66.66% responders and 33.33% non-responders, just the opposite is seen in placebo-treated SDAT patients. In MID patients, the findings are very similar. CGI-2: Responder ■ ≤ 3; non responder □ ≥ 4

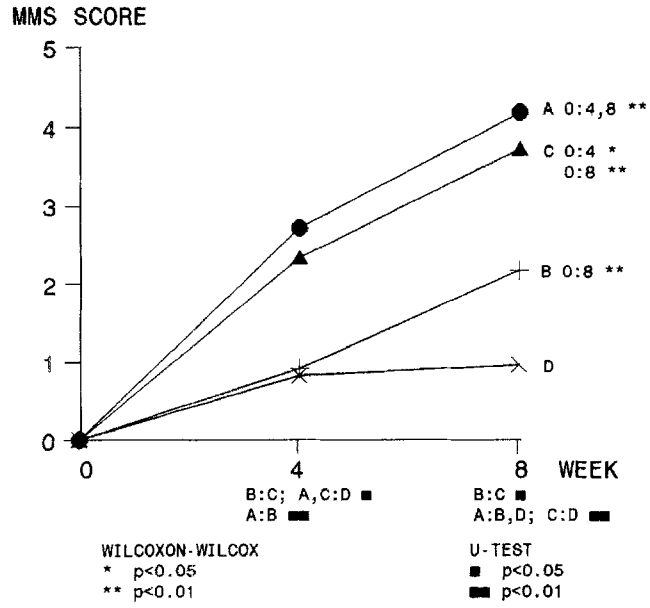


Fig. 2 Changes in Mini-Mental State (MMS) scores during 8 weeks with nicergoline (2 × 30 mg/day) and placebo in SDAT and MID. Baseline scores did not differ between the four groups at week 0 (SDAT/NIC: 21.5 ± 3.1, Md 22.0; SDAT/PLAC: 21.8 ± 4.8, Md 23.0; MID/NIC: 21.1 ± 3, Md 23.0; MID/PLAC: 22.0 ± 3.4, Md 21.0). While nicergoline induces a significant improvement in both the SDAT and MID patients in weeks 4 and 8 of therapy (approximately 4 points at the end of 8 weeks therapy), there are only slight improvements in placebo-treated SDAT and MID patients. Nicergoline is superior to placebo in both sub-types of dementia in weeks 4 and 8 of therapy. –●– A SDAT/NIC (N:24); + B SDAT/PLAC (N: 23); –▲– C MID/NIC (N:24); –×– DMID/PLAC (N:24)

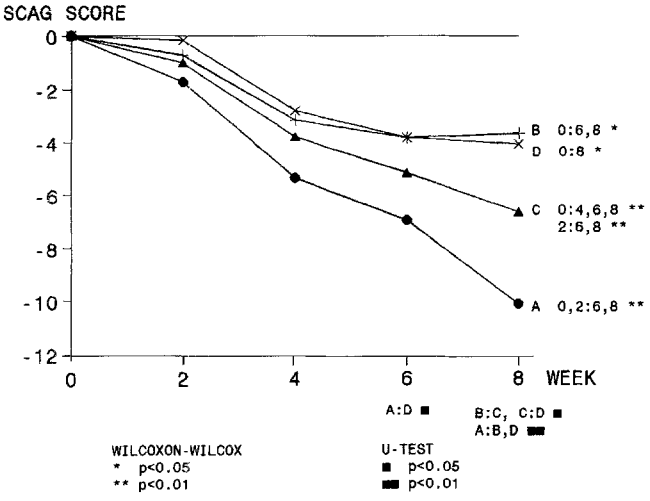


Fig. 3 Changes in SCAG scores during 8 weeks' therapy with nicergoline (2 × 30 mg/day) and placebo in SDAT and MID. Baseline values did not differ between the four sub-groups (SDAT/NIC: 56.8 ± 15.5, Md 55.0; SDAT/PLAC: 55.2 ± 13.4, Md 56.0; MID/NIC: 55.8 ± 16.1, Md 57.0; MID/PLAC: 54.3 ± 13.8, Md 55.0). A significant improvement in the SCAG score was noted in weeks 4, 6 and 8 in the MID/NIC group and in weeks 6 and 8 in the SDAT/NIC group, as compared with baseline. Although there was also a slight improvement with placebo in week 8 in both MID and SDAT patients, nicergoline was significantly superior to placebo in both sub-types of dementia in the 8 weeks of treatment. –●– A SDAT/NIC (N:24); + B SDAT/PLAC (N:24); –▲– C MID/NIC (N:24); –×– DMID/PLAC (N:20)

to baseline (55.0, 56.0, 57.0 and 55.0, respectively). SDAT patients, treated with nicergoline, showed a significant improvement in weeks 6 and 8, as compared with baseline, while after placebo a slight improvement occurred only in week 8 (Fig. 3). Also in nicergoline-treated MID patients a significant improvement was seen in weeks 6 and 8, while under placebo non-significant changes occurred. Nicergoline was significantly superior to placebo in both the SDAT patients ($P < 0.01$, U-Test) and MID patients ($P < 0.05$) at the end of 8 weeks' treatment.

The *Hamilton Depression Score* (24 items) was low in all four sub-groups, both before and during treatment (medians in week 0: 6.0, 6.5, 8.5 and 7.0, respectively; week 8: 5.0, 5.0, 7.0 and 5.5, respectively), thereby reflecting that the exclusion criteria were met. There were no clinically relevant changes, as compared with baseline, in any of the groups, nor relevant inter-group differences.

The *NOSIE index* did not show any significant changes or inter-drug differences, either.

Evaluation of the *Treatment Emergent Symptom Scale* showed side-effects in 7 out of 24 nicergoline-treated SDAT patients, which were mild itching, blocked nose, sweating, dry mouth, diarrhoea, weight loss and constipation in one patient each; mild or marked headaches in two patients and mild tachycardia in two patients. In placebo-treated SDAT patients, four patients complained of emergent symptoms, which were mild sweating, diarrhoea and weight loss and moderate dizziness in one patient each and mild dry mouth in two patients. In the MID groups, only two nicergoline-treated patients reported emergent symptoms, which were mild or marked insomnia in two patients and moderate rigor in one, while three placebo-treated MID patients complained of mild headache, sweating and depressed mood (one case each). There were no clinically relevant changes in laboratory findings.

EEG mapping

EEG maps – multi-variate analysis

In order to obtain an answer to the question of whether or not the investigational drug exerted a significant effect on the human brain, as compared with placebo, MANOVAs were performed (for each of the 21 electrodes) considering drugs (nicergoline, placebo), times (weeks 0 and 8) and variates (nine absolute power and nine frequency measures). Absolute power values were transformed in ln(power) to fulfil the conditions for the MANOVA (homogeneity of variances and co-variances), as well as the symmetrical unimodal distribution (Gasser et al. 1982). Hotelling's T^2 values were used to avoid type 1 errors, with inflated *df*, and were

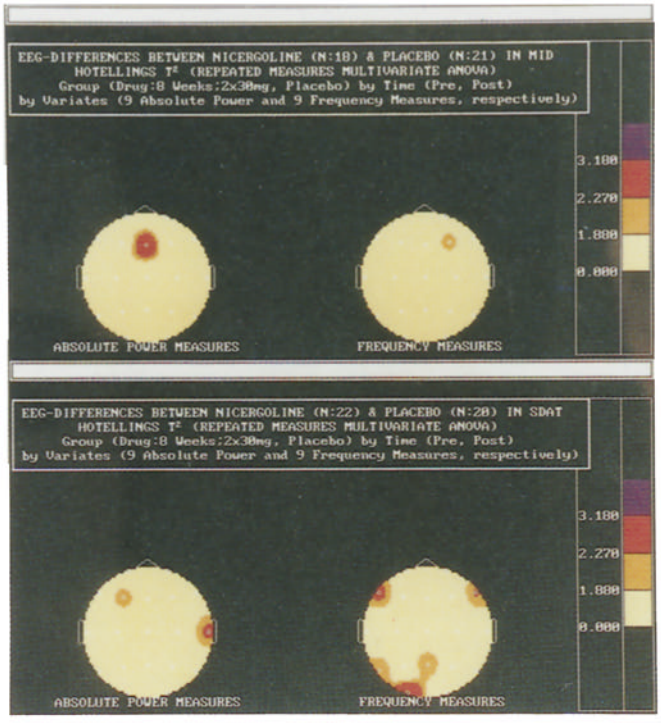
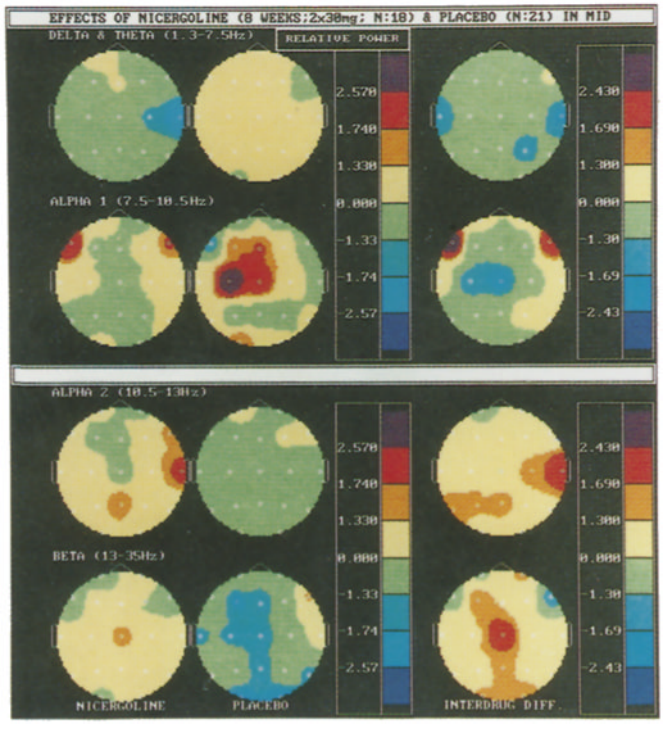


Fig. 4 EEG maps depicting global EEG differences between nicergoline and placebo in MID patients (*upper part* of the figure) and SDAT patients (*lower part* of the figure), based on Hotelling's T^2 maps, derived by repeated measures multi-variate ANOVA. The multi-variate analyses consider group (drug, placebo) by time (pre, 8 weeks post) by variates (nine absolute power and nine frequency measures, respectively). Hot colours represent significant differences between nicergoline and placebo; significant $T^2 > 1.88$, $P < 0.10$; > 2.27, $P < 0.05$; > 3.81, $P < 0.01$. Nicergoline induces significant changes, as compared with placebo in MID patients mostly over the frontal region, while in SDAT patients mostly over both fronto-temporal and occipito-temporal to parietal regions



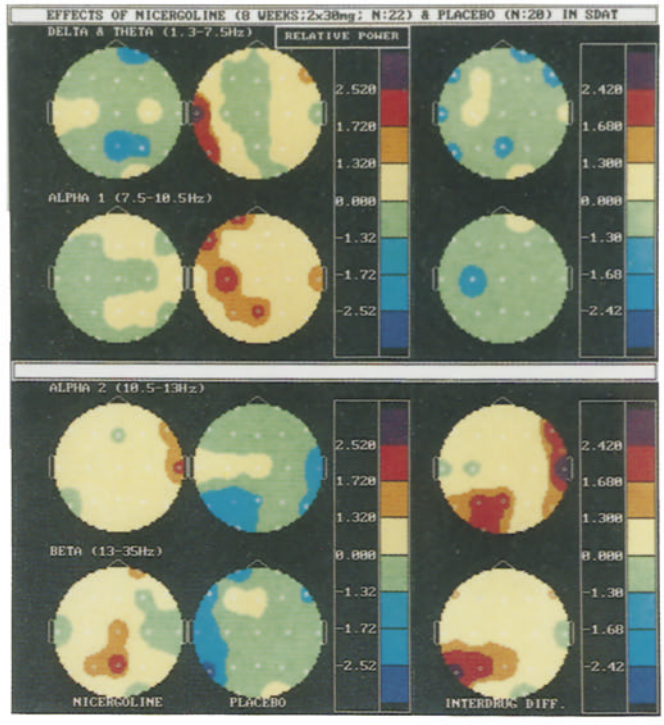


Fig. 5 Maps on the effects of nicergoline (8 weeks, 2 × 30 mg/day; $n = 22$) and placebo ($n = 20$) in different EEG frequency bands in SDAT patients. Changes in relative delta/theta, alpha-1, alpha-2 and beta power (*top to bottom row*) after nicergoline and placebo, as compared with baseline, are shown in the left and middle column, respectively, inter-drug differences in the right column. The colour key shows *t*-values; hot colours represent an increase (purple $P < 0.01$, red $P < 0.05$, ochre $P < 0.10$), cold colours a decrease (dark blue $P < 0.01$, medium blue $P < 0.05$, green-blue $P < 0.10$). Nicergoline induces a decrease in delta/theta and an increase in alpha-2 and beta activity, while after placebo an increase in delta/theta and alpha-1 activity and a decrease in alpha-2 and beta activity can be seen over various brain regions. Thus, inter-drug comparison shows that nicergoline produces, as compared with placebo, an attenuation of delta/theta and alpha-1 activity and an augmentation of alpha-2 and beta activity, thereby improving vigilance

imaged in terms of brain maps (Fig. 4). As can be seen, nicergoline induced, as compared with placebo, significant changes in brain function in both SDAT and MID patients.

EEG maps – univariate analysis

In the placebo-treated SDAT patients, absolute power increased in the delta/theta and slow alpha, as well as

Fig. 6 Maps on the effects of nicergoline (8 weeks, 2 × 30 mg/day; $n = 18$) and placebo ($n = 22$) in different EEG frequency bands in MID patients. For technical description of the maps and the colour key, see Fig. 5. While nicergoline decreases delta/theta power and increases alpha-1 and alpha-2 power, after placebo administration there is usually an increase in slow alpha and decrease in beta power. Thus, inter-drug comparison shows that nicergoline produces a decrease of delta/theta and an increase of alpha-2 and beta power, thereby improving vigilance

in the superimposed beta frequency range, while opposite changes as well as a decrease of alpha-2 activity occurred in the nicergoline-treated patients ($P < 0.05$, t-test). Thus, inter-drug differences revealed a significant attenuation of delta/theta, alpha-1, but also alpha-2 and beta power, after nicergoline, as compared with placebo ($P < 0.05$, t-test).

Relative power increased in the delta/theta and alpha-1 frequency bands of placebo-treated SDAT patients, along with a decrease of alpha-2 and beta activity, while nicergoline-treated patients showed exactly the opposite ($P < 0.05$) (Fig. 5). Thus, nicergoline induced, as compared with placebo, an attenuation of delta/theta and slow alpha and an augmentation of alpha-2 and beta activity ($P < 0.05$) (Fig. 5). These alterations, reflecting an improvement in vigilance, were most pronounced over the right temporal to fronto-temporal and left parietal and temporo-occipital regions.

The centroids became faster in the delta/theta and slower in the alpha, beta and total frequency bands after 8 weeks' placebo in SDAT patients, while an alpha acceleration and acceleration of the total centroid occurred after nicergoline treatment ($P < 0.05$–0.01). Thus, inter-drug differences were characterized by an acceleration of the alpha, beta and total centroid after nicergoline, as compared with placebo, while the delta/theta centroid slowed down ($P < 0.05$).

In MID patients, a decrease in absolute power occurred in the beta band after placebo ($P < 0.05$), while a trend towards an attenuation of delta/theta power was observed after nicergoline. There were no significant inter-drug differences.

Relative power showed an increase in the alpha-1 and decrease in the beta range after placebo administration, while after nicergoline delta/theta attenuation and alpha-1 and -2 augmentation occurred ($P < 0.05$) (Fig. 6). Inter-drug differences were characterized by an attenuation of delta/theta power and augmentation of alpha-2 and beta power ($P < 0.05$), thereby signalling an improvement of vigilance (Fig. 6).

The centroids showed a slowing in the alpha, beta and total frequency range after placebo ($P < 0.05$), while an opposite trend occurred after nicergoline. Thus, nicergoline induced, as compared with placebo, an acceleration of the alpha centroid and total centroid, while in regard to the beta centroid there was an acceleration over the left parietal and occipito-temporal region and a slowing over the right fronto-temporal region ($P < 0.05$).

Event-related potential findings (P300)

While in both SDAT and MID patients nicergoline induced a significant ($P < 0.05$, t-test) shortening of latency of the P300, a trend towards lengthening occurred after 8 weeks of placebo treatment (Fig. 7). Differences between verum and placebo were significant ($P < 0.05$) in both sub-types of dementia (Fig. 7). Thus, the significantly shortened latency in both sub-types of dementia suggests an improved cognitive information processing under nicergoline.

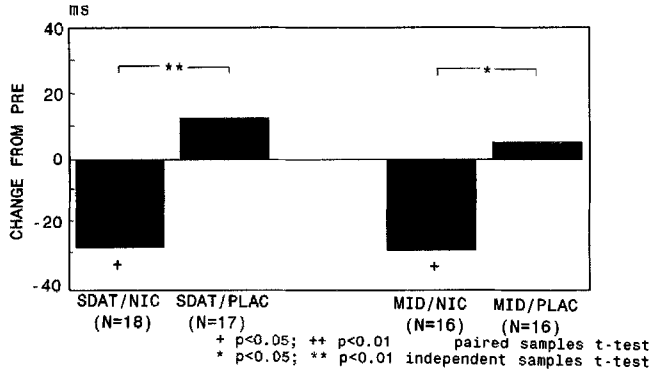


Fig. 7 Effects of nicergoline (8 weeks, 2×30 mg/day) and placebo on P300 latency in SDAT patients (N:35) and MID patients ($n = 32$). Groups are shown on the *abscissa*, changes from pre-treatment in ms are indicated in the *ordinate*. While nicergoline induces both in the SDAT and MID patients a significant shortening of P300 latency, a trend towards lengthening occurrs after 8 weeks of placebo therapy. The differences between nicergoline and placebo are significant in both sub-types of dementia

Discussion

This double-blind, placebo-controlled study demonstrated that nicergoline improved the clinical symptomatology of both SDAT and MID patients, as compared with placebo. The superior therapeutic efficacy of nicergoline after 8 weeks of treatment with 30 mg b.i.d. over placebo was clearly demonstrated in the confirmatory statistical analysis for the target variable, the clinical global impression, with the clinical relevance of this outcome underlined by the results of the descriptive statistics in the other investigated variables, further by the responder analysis, as well as by the neurophysiological findings underlying the psychopathological changes.

The CGI changes were, of course, of small magnitude, with the patients remaining still moderately ill, as far as the severity of illness was concerned. However, item 2 of the CGI showed, on average, a slight improvement in the nicergoline-treated SDAT and MID patients, while there was no change on average after placebo. Moreover, the responder analysis demonstrated that 66.6% of SDAT patients treated with nicergoline improved, while 33.3% did not improve, with just the opposite findings under placebo administration (33.3% improving; 66.6% not improving). Very similarly, with nicergoline treatment of MID patients, 71% improved, 29% did not, while under placebo

administration 27% improved and 73% did not. Other nootropic drugs have also been reported to exert similar therapeutic effects in MID and SDAT patients (Saletu et al. 1988, 1992; Fischhof et al. 1989, 1992).

Our MMS data demonstrated that nicergoline indeed improved cognitive function, as the nicergoline-treated SDAT group showed an improvement by 4 points versus 2 in the placebo group and the nicergoline-treated MID patients showed similarly an improvement by almost 4 points versus 1 point, seen in the placebo-treated patients. Our results in the MID patients are in agreement with the recent findings of Herrmann (1993), who reported that nicergoline-treated MID patients improved by an average of 4 points, and the placebo patients by 1 point, after 6 months of drug administration.

In our present study, the SCAG score also showed significant superiority of nicergoline over placebo after 8 weeks of treatment, as in the nicergoline-treated SDAT patients there was a drop of 10 points versus 4 points observed in placebo-treated SDAT patients, while the nicergoline-treated MID patients showed a drop of 7 points, as compared with 4 points improvement in MID patients under placebo. Again, these results are in agreement with those of Herrmann (1993), who also reported a significant improvement after 30 mg nicergoline b.i.d. in MID patients, with the latter showing an improvement by 9 points versus 3 points under placebo, after 6 months of therapy. The fact that, in regard to the SCAG score, we found significant superiority of nicergoline only after 2 months of treatment, supports the idea that nootropic drug treatment should be continued over a long period of time. The extent of the improvement is also in line with the average improvement of 15–35% in the SCAG scale, as reported by Herrschaft (1992), based on various published studies. Herrschaft also pointed out that the onset of therapeutic effect in regard to dementia symptoms is rather slow (10–12 weeks), while, in contrast, tinnitus and vertigo are sometimes already improved under acute infusion therapy. Arrigo et al. (1982) found an overall improvement in the SCAG of 20% in 20 patients with mild to moderate senile dementia, treated with 60 mg for 12 weeks, daily.

Nicergoline was very well tolerated, as mild side-effects, such as itching, blocked nose, headaches, tachycardia, sweating, insomnia, dry mouth, diarrhoea, constipation and weight loss were mostly observed only in single patients. Overall, they were of transient nature and did not warrant any treatment. This low incidence (19% in the nicergoline-treated patients versus 15% in the placebo-treated ones) is in agreement with open-field studies, which also showed a decrease in frequency in virtually all categories of complaints with time (13% in week 4 versus 4.3% in week 24) (Saletu 1991).

Our EEG mapping demonstrated in nicergoline-treated SDAT patients a significant decrease of delta and theta activity, an increase of fast alpha and beta activity, and an acceleration of the alpha centroid and of the total centroid, which reflects improvement of vigilance. These changes after the ergotalkaloid were exactly opposite to the findings observed in placebo-treated SDAT patients. The differences between the nicergoline-induced and the alterations seen after placebo were also statistically significant. Nicergoline-treated MID patients also showed a decrease of delta/theta and increase of fast alpha and beta activity, as well as an acceleration of the centroid of the alpha and total activity, as compared with placebo-treated ones, thereby also demonstrating the vigilance-promoting effect of nicergoline. These present EEG mapping data support our earlier placebo-controlled findings after nicergoline, obtained still with single-lead analysis in normally ageing subjects (Saletu et al. 1979a, b), our later EEG mapping results after oral administration of 30 and 60 mg nicergoline, as compared with placebo also in normally ageing subjects (Saletu et al. 1990b), and the EEG mapping data on brain protection of nicergoline against hypoxia (Saletu et al. 1990d). Other authors, such as Bente et al. (1979), Gessner et al. (1979), Arrigo et al. (1982) and Moglia et al. (1985), demonstrated vigilance-promoting effects by means of EEG evaluation as well.

Finally, in the light of the significant nicergoline-induced improvement observed in the Mini-Mental State in regard to cognition, it seems of interest that the cognitive evoked potential – the P300 – showed a significantly shortened latency in nicergoline-treated SDAT and MID patients, while placebo-treated ones exhibited a trend towards lengthening. Several authors such as Squires et al. (1980), Semlitsch et al. (1990, 1992) and Polich (1991) pointed out that the P300 can provide useful information on individual cognitive function. It may possibly be more than a coincidence that the shortening of the P300 latency under nicergoline in SDAT and MID patients (in ms) is the same as the amount by which the latency of the untreated dementia patients deviates from that of normal aged subjects (Saletu 1994). Thus, nicergoline significantly improved stimulus evaluation time of cognitive information processing, thereby tending to normalize the former in both SDAT and MID patients.

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