Alzheimer Type and Multi-Infract Dementia

Nicergoline (or hydergine) Treatment

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.

These alterations in brain function, evaluated initially by exploratory, and later by confirmatory statistics, reflected 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.

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 Trial-Making Test and the Digit Span Test.

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 www.healthoracle.org
the Alzheimer type (SDAT) and multi-infarct dementia type (MID), utilizing psychometric, computed tomography, EEG and ERP mapping technique.

**Clinical Findings**

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

**EEG Mapping**

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 (power) to fulfill the conditions for the MANOVA (homogeneity of variances and co-variances), as well as the symmetrical unimodal distribution. Hotelling’s T2 values were used to avoid type 1 errors, with inflated df, and were imaged in terms of brain maps. As can be seen, nicergoline induced, as compared with placebo, significant changes in brain function in both SDAT and MID patients.

**EG Maps- Univariate Analysis**

In the placebo-treated SDAT patients, absolute power increased in the delta/theta and slow alpha, as well as 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, www.healthoracle.org
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). 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.2). 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). Inter-drug differences were characterized by an attenuation of delta/theta power and augmentation of alpha-2 and beta power (P<0.05), thereby signaling an improvement of vigilance.

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.
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

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. Differences between verum and placebo were significant (P<0.05) in both sub-types of dementia. Thus, the significantly shortened latency in both sub-types of dementia suggests improved cognitive information processing under nicergoline.

Remarks

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 Clinical Global Impression (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 per cent of SDAT patients treated with nicergoline improved, while 33.3 per cent did not improve, with just the opposite findings under placebo administration (33.3 per cent improving; 66.6 per cent not improving; 33.3 per cent not improving; 66.6 per cent not improving).
improving). Very similarly, with nicergoline treatment of MID patients, 71 per cent improved, 29 per cent did not, while under placebo administration 27 per cent improved and 73 per cent did not. Other nootropic drugs have also been reported to exert similar therapeutic effects in MID and SDAT patients.

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 per cent in the nicergoline-treated patients versus 15 per cent 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 per cent in week 4 versus 4.3 per cent in week 24).

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.