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Placebo-Controlled, Double-Blind, Crossover Study to Investigate the Hypoxia-Protective Effect of Vinpocetine by Psychophysiological Methodology in Healthy Volunteers

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ABSTRACT

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Vinpocetine positively influences cerebral vascular resistance (>CBF), as well as O_2-extraction (>A/V-O_2-difference) and the brain's glucose and neurotransmitter turnover, as has been shown in other experimental and clinical studies. Therefore, a hypoxia-protective effect of vinpocetine should be expected in an experimental simulatory approach using hypoxic hypoxidosis.

Key words: encephalotrophic drugs, pathophysiological conditions, senile dimentia

INTRODUCTION

The demonstration of objective data on the efficacy of so-called encephalotropic drugs, especially with respect to everyday tasks, is often frustrating in early investigational drug phases. This can be attributed to a lack of reliable and valid clinical tools and to difficulties in setting up homogeneous groups of patients with respect to a sufficient approach in statistical procedures.

To overcome these problems, an experimental human model was developed [Schaffler et al., 1981] to demonstrate the effects of encephalotropic drugs on performance. Specifically, we employed partial simulation of pathophysiological conditions in senile dementia by

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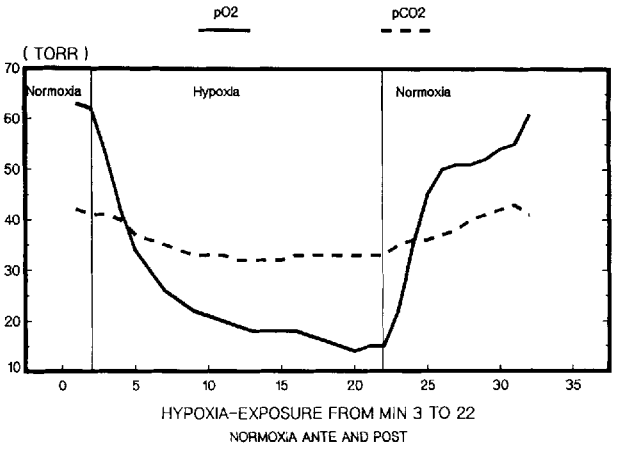

Fig. 1: Monitoring of transcutaneous blood gas analysis under hypoxia exposure (10.5% inspiratory with resulting hyperventilation and respiratory alkalosis) to demonstrate time course of O_2 and CO_2 concentrations during assessment.

hypoxic hypoxidosis with a concomitant respiratory alkalosis (!) in healthy male volunteers (Fig. 1). For the present study, the drug vinpocetine was investigated.

MATERIALS AND METHODS

Subjects were exposed to repeated hypoxic hypoxidosis (10.5% oxygen, 89.5% nitrogen inspiratory) each assessment day. The multiple hypoxic impact induces a reproducible intratest and intradiurnal impairment in performance, monitored by oculomotor and choice reaction phenomena in the so-called Oculodynamic Test (ODT) [Meyer-Delius and Schaffler, 1975; Schaffler, 1977, 1981] and by unspecific fluctuations of vigilance, measured via electroencephalographic parameters (computer-EEG analysis). This experimental set-up has already demonstrated its validity and reliability with encephalotropic drugs as: piracetam, aniracetam, ginkgo-flavonglycosides, cyclandelate and other experimental drugs of nootropic type [Schaffler et al., 1981; Schaffler 1983, 1984, 1986; Schaffler and Reeh, 1985a,b].

The study was run in a placebo-controlled, double-blind, crossover mode after a short premedication period of 2 days (intraindividual control). Intradiurnal design consisted of three sequential 20-min test periods of ODT with an evaluation of about 1,000 binocularily measured saccadic eye movements and choice reactions per assessment, and in two subsequent resting or vigilance-controlled computer-EEG sessions (prevalue normoxia, prevalue hypoxia, 1 hr post-assessment value) for each of the randomized drug or placebo periods. All assessments were run in 10 healthy, male volunteers (mean body weight 72.5 kg, mean age: 27.9 years) with a 2-day pretreatment period (40 mg vinpocetine three times daily) and a single administration (40 mg) on the assessment day. Between each medication period, there was a sufficient washout period.

RESULTS

Oculodynamic (ODT)

In several relevant parameters of the ODT, a hypoxia-protective effect of the three times daily vinpocetine premedication (day 1+2) could be demonstrated. There was with a

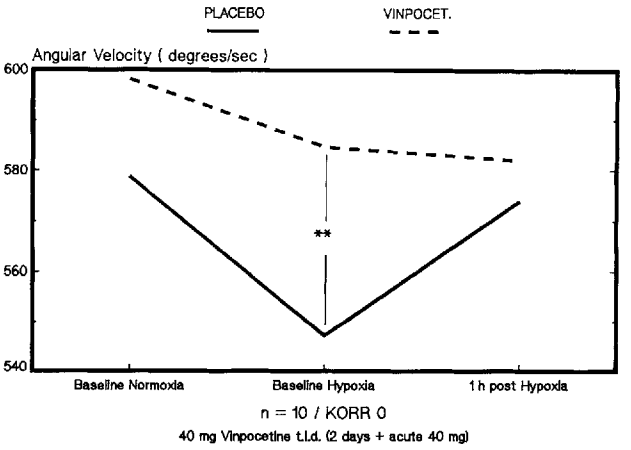

Fig. 2: General improvement of angular velocity of saccadic eye movement (a myogenic component of Oculodynamic Test = ODT) after multiple dosing of vinpocetine under normoxia and hypoxic exposure.

preference on the second daily hypoxia assessment producing a "residual" effect, thus excluding the existence of any clinically important steal-phenomena produced by drug with a resulting impairment of the daily performance level.

The main effects produced by vinpocetine on the ODT are as follows:

1. Polysynaptic retino-ponto-muscular reflex time was reduced at assessment 2 (non-significant trend).
2. Angular velocity (a dynamometric/myogenic saccadic eye-movement parameter) was significantly reduced at assessment 2 (1%-level) for the verum, (Fig. 2);
3. Complex choice reaction time (an overall performance and speed parameter of signal detection procedure) was significantly reduced at all assessments after vinpocetine (5%-, 1%- and 1%-level), (Fig. 3);
4. Respiratory rate was significantly reduced at assessment 2 (1%-level) as an antihypoxidotic effect of vinpocetine.

Subjective Well-Being

There was a subjective improvement in the tolerance of hypoxia in vinpocetine-treated subjects.

EEG

There was a variety of consistent and typical changes in the EEG pattern comparing normoxic and hypoxic conditions, with a significant increase in the total power, as well as in the absolute power of slow- and fast-wave components. However, no significant differences in the EEG for vinpocetine vs. placebo were seen.

CONCLUSIONS

In summary, antihypoxidotic and encephalotropic effects of vinpocetine could be expected for therapeutic use from the ODT-results.

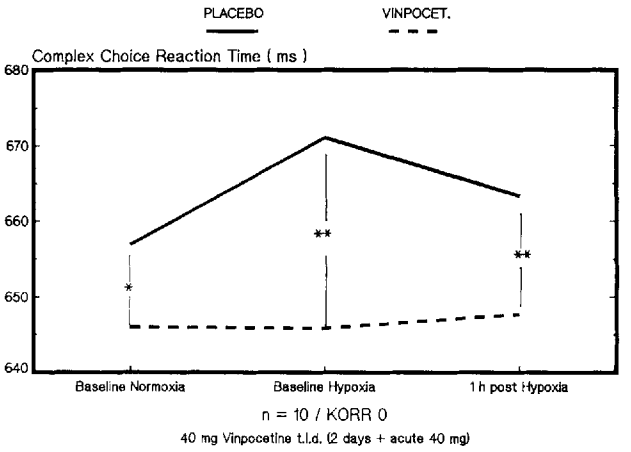

Fig. 3: Global improvement of complex choice reaction time in Oculodynamic Test (ODT) after vinpocetine under normoxic and hypoxic conditions.

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