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Clinical evidence of the effectiveness of vinpocetine in the treatment of organic psychosyndrome

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This study was multi-center, double-blind, placebo controlled, and involved random assignment of patients. It was carried out in the ambulances of general practitioners and internists. The aim of the study was to evaluate the efficacy and tolerance of vinpocetine in patients with a mild to moderate severe organic psychosyndrome caused by cerebral blood supply disorders and/or metabolic disturbance. Dosage of 5, 10 and 20 mg vinpocetine or placebo t.i.d. were examined over a treatment period of 12 weeks with 282 patients.

The study design required a programmed, standardized investigator training. In addition, a pre-study test was used to ensure correct and uniform execution of study control.

The Clinical Global Impression (CGI) and the performance test SKT showed statistically significant differences between the verum groups and placebo. Self-assessment of mood and performance capability (EDS), and life satisfaction (LZ) confirmed these outcomes. The results of the Hachinski Ischaemia Scores did not permit an unequivocal classification of patients into primary degenerative and multi-infarct dementia types. The higher dosage groups experienced a greater therapeutic advantage than did the 5 mg t.i.d vinpocetine dosage group. Only a few side effects were observed.

KEY WORDS—Vinpocetin, organic, psycho syndrome, clinical efficacy, therapeutic relevance.

INTRODUCTION

The rising number of elderly people in the community is accompanied by an equally strong increase in the incidence of behavioural and cognitive impairments due to cerebral pathology (organic psychosyndrome). Most common types of pathology concern disturbances in cerebral blood supply, metabolic disorders and progressively degenerating processes, which in more advanced stages most frequently become diagnosed as dementia of Alzheimer's type or multi-infarct dementia (Hoyer, 1984). In less advanced stages of impairment, a reliable diagnosis is often difficult to make, however the opportunities for favourable therapeutic intervention may be maximal in these early stages of mental deterioration, while there is very probably still no severe loss of neural functioning. On the basis of its interesting pharmacological characteristics in animals and humans the present study investigated the therapeutical possibilities as well as the safety of the eburnamenine derivative vinpocetine in the treatment of patients with mild to moderately severe organic psychosyndrome (OPS). In animals and humans vinpocetine leads to a reduction of cerebral vascular resistance (Imamoto *et al.*, 1984). This effect is accompanied by an increase in the c-GMP content in the vascular smooth musculature, which is brought about through the selective inhibition of Ca^{++}Calmodulin-dependent phosphiesterase (Hagiwara *et al.*, 1984). The increase in the arteriovenous oxygen balance demonstrates an increase in the oxygen utilization in the brain's blood supply (Kárpáti and Szporny, 1976). Furthermore, glucose uptake (Shibota *et al.*, 1982), percentage of cyclic nucleotides (Lapis *et al.*, 1984). as well as content and turnover of biogenic amines such as serotonin, noradrenalin, and dopamine in the brain are increased by vinpocetine (Kiss *et al.*, 1982). Optimizing or improving brain metabolism leads to an increase in the tolerance of neurons for hypoxidoses (Kakihana *et al.*, 1982). The effects of vinpocetine on memory performance were demonstrated in a

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placebo controlled study with normal healthy volunteers (Subhan and Hindmarch, 1985).

This study was designed to examine the clinical aspects of vinpocetine's therapeutic efficacy. Because patients with organic brain performance deficiencies normally visit an ambulatory general practitioner first, a clinical trial was designed for this setting. Patients to be examined should be suffering from a mild to moderately severe organic psychosyndrome (OPS), arising from cerebral blood supply and/or metabolic disturbances.

The aim of the study was to answer the following questions:

- Does vinpocetine demonstrate a therapeutic efficacy in patients suffering from a mild to moderately severe OPS in comparison to placebo treatment?
- Are there signs of undesired drug effects related to vinpocetine treatment?

MATERIALS AND METHODS

Pre-study: In order to create the most comparable trial conditions, 61 physicians were informed on course and procedure of the study on the occasion of four briefing conferences in München, Berlin, Hamburg, and Singen. Special emphasis was placed on instructions and test procedures.

The main issue was the training with SKT (Syndrom-Kurztest), which is designed to measure attention and memory disturbances (Erzigkeit, 1986). In the course of a pre-study, each physician examined 10 patients within his or her practice using the parallel forms A and B of the SKT. This served to provide further practice with the SKT and to increase the objectivity of the data collection. Through validity control, eventual testing irregularities could be discovered and discussed. 49 physicians finally participated in the main study.

Study design

The multi-center study was double-blind, placebo controlled and involved random assignment of patients. Four independent patient groups were created for the following dosages: 5, 10, or 20 mg vinpocetine or placebo t.i.d. The treatment phase lasted 12 weeks following a 14-day placebo wash-out phase.

Patient selection and diagnostic classification

The study called for patients with clinically evaluated mild to moderately severe organic psychosyndrome. The degree of severity was determined by scores of the SKT. Only patients with a total score of more than 8 SKT-points –

Table 1: Time schedule

	Two-week wash-out phase	Beginning of treatment phase after two weeks: 12 weeks duration						
Week	0.	2.	4.	6.	8.	10.	12.	14
Personal Data, Anamnesis, Psychiatric Anamnesis, Physical Examination, Differential Diagnosis	X							
Hachinski Ischaemia Score	X							
Clinical Global Impression (CGI)		X	X	X		X		X
SKT	X	X	X	X		X		X
form:	A	B	A	B		A		
Multiple Choice Vocabulary Test (MWT-B)	X							
Erlangen Depression Scale (EDS)	X	X						X
Life Satisfaction Scale (LZ)		X						X
Activity Index (AI)	X	X	X	X		X		X
Side Effects		X	X	X		X		X
Laboratory Tests	X							X
Compliance Control		X	X	X	X	X	X	X

which in clinical terms represents the minimal degree of disturbance of a mild 'Durchgangs-syndrom' which can be regarded as a synonym for OPS according to Wieck and Blaha (1981) and a mild morbidity intelligence level was evaluated with the help of the Multiple Choice Vocabulary Test (MWT-B) (Lehrl, 1977). Patients with a below average intelligence level (i.e., IQ under 86, which corresponds to less than 18 points on the MWT-b) were excluded from the study. The Hachinski-Score (Hachinski *et al.*, 1975, was used for differentiation of the diagnostic groups multi-infact type (MID) and primary degenerative dementia (Alzheimer's type).

In addition to the clinical exclusion criteria such as severe decompensated organic diseases, medication allergies, drug abuse, and pathological laboratory values, patients under concomitant treatment with anit-depressive agents, neuropleptics, hypnotics, and narcotics were excluded. Also patients with brain diseases with focal symptomatics or extra-cranially caused cerebral metabolic and/or circulatory disturbances were not admitted.

Test Variables and Time Schedule

Indicator variables for the proof of efficacy were the Clinical Global Impression (CGI) (CIPS, 1986) and the results of the attention and memory performance in the SKT. As further examinations the Erlangen Depression Scale (EDS) (Lehrl and Gallwitz, 1977), the Life Satisfaction Scale (LZ) (Löhr and Walter, 1974). and an Activity Index (AI), were used. Side effects were documented as well as laboratory data. Time points for the evaluation of the various parameters can be taken from Table 1.

Statistics

For the statistical inference evaluation of the various target parameters, each parametric and non-parametric comparison of the experimental groups was performed on the basis of scale size and distribution structure of the variable. The SKT was evaluated on raw values as well as on total score. In order to have analogous statistical test models for the raw values and the intelligence and age-dependent total score values, an analysis of variance comparison of the total score values was made parallelly to a multivariate analysis of variance of the raw values with the co-variants age and intelligence.

For the multi-factor analysis of variance and for the individual group comparisons, the identified probabilities of error were always shown in a two-sided analysis.

Ethical Considerations

The study protocol is in conformity with German Drug Law (AMG 2 §§ 40, 41) and with the general principles of the Revised Declaration of Helsinki.

Table 2: Patient characteristics at inclusion

	Placebo	5 mg Vp	10 mg Vp	20 mg VP
Number of patients	56	52	56	53
Age: <70 years	8	11	13	12
70–75	24	22	19	22
>75	24	19	24	19
Mean age (SD)	74·8 ± 5·2	74·5 ± 5·8	75·0 ± 7·1	73·3 ± 6·1
Age range	65–87	66–91	58–90	59–86
Sex: male	22	20	21	27
female	34	32	35	26
Severity of OPS*				
mild	40	41	38	39
moderately severe	15	11	17	13
SKT-Score				
9–13	40 71%	43 83%	43 77%	37 70%
>13	16 29%	9 17%	13 23%	16 30%
MWT-B Score				
mean (SD)	23·9 ± 4·5	24·3 ± 4·4	25·6 ± 4·7	24·1 ± 4·6

*For three patients no information was available.

RESULTS

Twenty-two of the 282 patients who were examined dropped out before the study was completed; seven due to side effects. Data on 43 patients were excluded from the statistical analysis due to deviations from the protocol. Thus, case record forms of a total of 217 patients were available for evaluation.

As shown in Table 2 the population in the study consisted of elderly patients with a mean age around 74 years (range 58–91), while there were somewhat less males than females. On the basis of the investigator's judgement the severity of the organic psychosyndrome was mild in about three-quarter of the patients, and was moderately severe in the others (see p.o.). These judgements are confirmed by the performance-scores on the SKT, in which 75% achieved a score of 9–13, while the remaining 25% got higher scores (range 14–18). The index for the pre-morbid level of intelligence, the score on the MWT-B test reached an average of 24.5. The tests for the four treatment groups did not reveal any significant differences in these parameters as determined at the start of the wash-out period of the study.

A discrimination of the patients into diagnostic groups of primary degenerative dementia and multi-infarct dementia was not possible with the help of the Hachinski Ischaemia Score. The results (Figure 1) showed that about 50% of the patients could not be categorized with sufficient assurance into either of the two types since most of the patients were scored between 4 and 7 points. Therefore, it was decided not to perform a separate statistical evaluation of the two diagnostic groups.

Clinical global impression

The CGI was chosen to evaluate the investigators' assessment. For each factor of the CGI seven

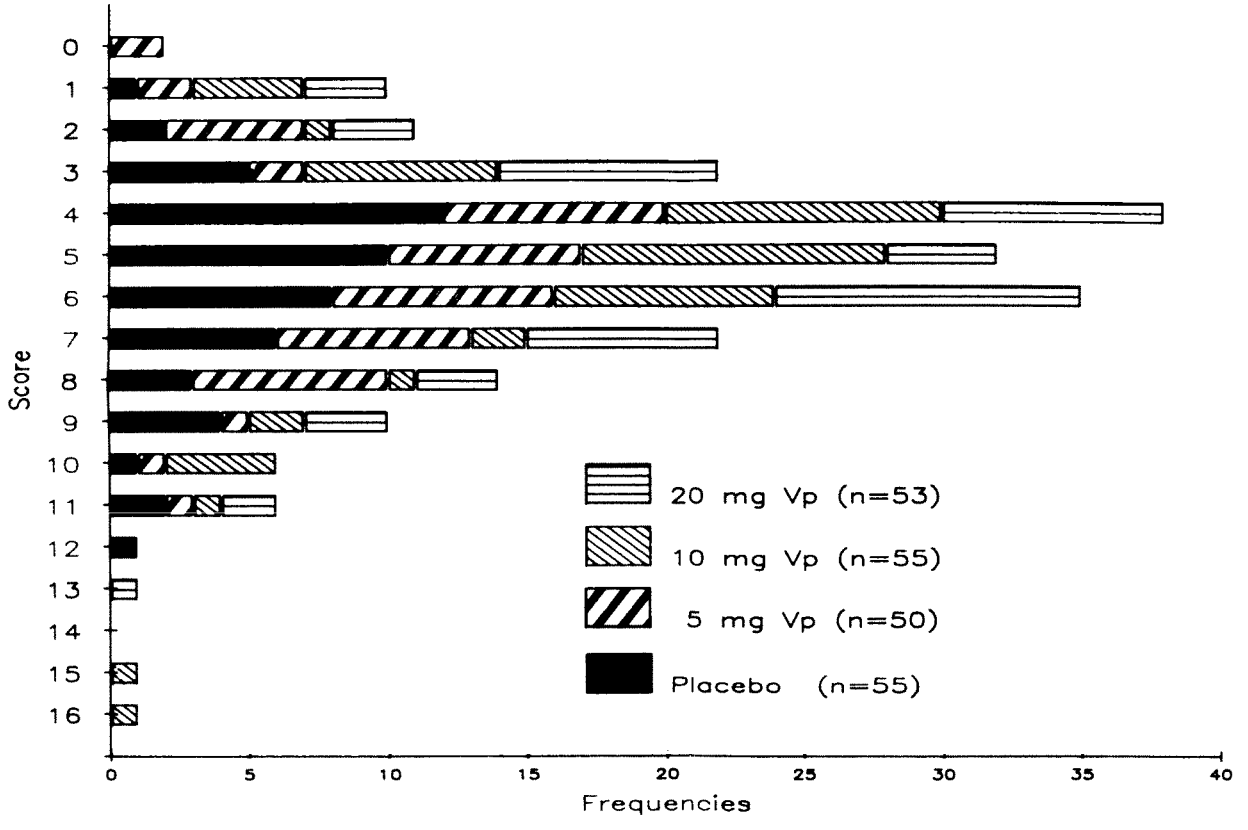

Figure 1.

Table 3. CGI a): Degree of Severity of Disease after the placebo wash-out/after 12 weeks of treatment; "Extremely severely ill": no mentions.

	Placebo	5 mg Vp	10 mg Vp	20 mg Vp
None at all	0/1	0/3	0/4	0/6
Borderline case	4/8	2/13	5/13	2/17
Mildly ill	20/30	18/27	21/26	25/19
Moderately ill	21/14	28/6	21/11	17/11
Clearly ill	11/3	4/3	8/2	9/0
Severely ill	–	–	1/0	–
p-values		0·04	0·10	0·01

possibilities of categorization were offered. The factors to be assessed were: a) degree of severity of disease and b) change in condition.

CGI a) Degree of severity of disease

At the time of baseline (after the two-week placebo wash-out), no statistically significant differences in the evaluation of severity were found between the groups. At the end of treatment, there was a significant improvement in the assessment for the 5 mg and 20 mg vinpocetine sample groups compared to placebo (U-test) (Table 3). A p-value of 0·10 was achieved for the 10 mg vinpocetine group.

CGI b) Change in condition

The assessment of the change in condition related to the beginning of treatment is shown in Table 4. At baseline, no stastically significant difference existed (U-test).

In the verum groups, a general improvement was more often indicated than in the placebo group. At treatment end, the U-test showed a significant advantage in the 10 and 20 mg vinpocetine groups compared to placebo.

SKT: Evaluation of attention and memory disturbances

Statistical evaluation of initial and baseline examinations documents homogeneity. Mean and standard deviations showed that the majority of patients could be classified in the scope of 'mild OPS' (9–13 SKI points) as to the degree of disturbance. This corresponds to the investigators' assessments (Table 2).

The SKT was not only used for the categorization of the organic psychosyndrome but also as process control of the twelve weeks active treatment.

A multivariate analysis of covariance performed on raw values, with age and MWT-B score as covariants, for each of the sub-test groups 1, 3, 4, 5, 6, 7 (seconds) and 2, 8, 9 (rank numbers) justified a rejection of the null-hypothesis.

In order to specify existing differences in treatment, following the analysis of variance, individual comparisons of the total scores of the

Table 4. CGI b): Change in Condition after 12 weeks of treatment; "Very much deteriorated": no mentions.

	Placebo	5 mg Vp	10 mg Vp	20 mg Vp
Very much improved	1	11	6	13
Improved	23	14	31	24
Barely improved	14	14	9	8
No change	13	12	10	7
Mildly deteriorated	4	1	–	1
Much deteriorated	1	–	–	–
p-values		0·10	0·01	0·01

Table 5. SKT; attention and memory performance through the course of the study

			Placebo n = 56	5 mg Vp n = 52	10 mg Vp n = 56	20 mg Vp n = 53
T_1	At time of	$\bar{x}$	11·9	11·5	11·8	11·8
	enrollment	s	2·5	2·0	2·8	2·4
	Control after:					
T_2	2 weeks	$\bar{x}$	11·9	11·5	11·6	11·9
	(Baseline)	s	2·8	2·2	2·9	2·3
T_3	4 weeks	$\bar{x}$	10·7	9·6	9·9	10·0
		s	3·0	2·7	3·4	2·1
T_4	6 weeks	$\bar{x}$	9·9	9·2	9·1	9·1
		s	3·2	2·4	3·0	2·5
T_6	10 weeks	$\bar{x}$	9·3	8·3	8·4	8·5
		s	3·3	2·5	3·1	2·5
T_8	14 weeks	$\bar{x}$	9·2	7·9	7·8	8·0
		s	3·1	2·8	2·7	2·6
	p-values			0·025	0·008	0·013
	Difference 14	$\bar{x}$	−2·7	−3·6	−3·8	−3·9
	weeks Baseline	s	2·6	2·7	2·6	2·2

SKT for the three verum groups, corrected for age and MWT-B total scores, were performed for the final examination. The t-tests yielded the error probabilities displayed in Table 5 in comparison of the verum groups with placebo. A statistical significant advantage was found for each vinpocetine dosage.

Erlangen Depression Scale (EDS)

In the EDS all four groups showed score changes during treatment, and the verum groups showed more marked improvements than the placebo group (Table 6).

In the two individual factors 'depressive mood' and 'limited expansiveness', significant differences to placebo could be observed. In total score comparisons of the verum groups with placebo, after 12 weeks of treatment, significant differences were observed in the 10 mg and 20 mg samples (Table 6).

Life satisfaction scale (LZ)

The baseline values of all treatment groups were clearly below the standard values described by Erzigkeit (1978). In the course of treatment, an improvement of all total scores was recorded in all verum groups. In the 20 mg vinpocetine sample, the total value after 12 weeks corresponded to the standard value for 'normal people' (Table 7).

Activity index

Data indicated a positive effect on the factors 'sleep behaviour' and 'daily activity' (carrying out household activities) under treatment with vinpocetine.

Table 6. Results of the EDS after the placebo wash-out/after 12 weeks of treatment

	Placebo	5 mg Vp	10 mg Vp	20 mg Vp
Depressiveness	10·0/8·2	8·5/6·7	8·8/6·5	9·3/6·3
Expansiveness	7·0/5·6	6·5/5·0	5·9/4·7	6·6/4·3
Total Score	17·0/14·0	15·0/11·7	14·7/11·2	16·0/10·2
p-values		0·09	0·025	0·009

Table 7. Results of the LZ

Total-Index		Placebo	5 mg VP	10 mg VP	20 mg VP
After 2	$\bar{x}$	7·7	8·3	7·5	7·4
Weeks	s	5·2	5·5	5·0	5·0
Baseline					
After 14	$\bar{x}$	8·6	11·9	11··4	13·0
Weeks	s	5·6	6·2	5·8	5·2
p-values			0·008	0·015	0·000

Standard values:
Resident of home for the aged ($\bar{x}$ 61 years) $\bar{x}$ = 10·0; s = 5·3
Resident of apartment for the aged ($\bar{x}$ 61 years) $\bar{x}$ = 12·5; s = 5·2
'normal persons' ($\bar{x}$ 48 years) $\bar{x}$ = 13·0; s = 5·0

Side effects

All accompanying symptoms reported by patients during treatment were recorded under the category of side effects. Patients in the verum groups reported side effects somewhat more often than patients in the placebo group (Tables 8 and 9).

Virtually all complaints were transitory; most reports occured after ten weeks (Table 9). Because of low frequencies and multiple reports, a statistical evaluation was not performed.

DISCUSSION

The tests used in the study comprised both clinical and psychometric viewpoints. As a differential diagnostic method, a German version of the

Table 8. Reports on side effects in the treatment phase

Side Effects	Number of Reports* Placebo	5 mg Vp	10 mg Vp	20 mg Vp
Stomach disorders	1	2	5	4
Nausea	1	–	–	2
Headache and head pressure	4	1	2	1
Sleep disturbances	1	4	5	4
Dizziness	1	1	3	–
Red marks on face	1	–	–	–
Increase in leg oedema	1	–	–	–
Being "wound-up", hyper-reactive	–	1	1	–
like cold water over the back	–	1	–	–
Trembling	–	1	–	1
Internal restlessness	–	1	1	3
"Ants walking in my extremities"	–	1	1	–
Stabbing chest pains	–	–	1	–
Tinnitus	–	–	2	–
General weakness and feeling drained	–	–	1	–
Heavy sweating	–	–	1	–
Weight gain/feeling of fullness after eating	–	–	1	–
Upper stomach pains/Ulcus Ventriculi	–	–	1	–
Confusion	–	–	–	2

*Several reports per patient possible

Table 9. Number of patients with side effects

	Placebo	5 mg Vp	10 mg Vp	20 mg Vp
after 2 weeks	2	2	3	1
after 4 weeks	–	1	3	3
after 6 weeks	1	2	4	3
after 10 weeks	3	5	7	6
after 14 weeks	2	3	3	4

Hachinski Ischaemia Score was used in order to classify patients into primary degenerative or multi-infarct dementia types. The desired discrimination into these two groups was not possible. The frequency distribution of the Hachinski Score had its peak just in the transition range between 4 and 7 points. Therefore, a separate statistical evaluation of whether vinpocetine is more efficient primary in degenerative or multi-infarct dementia was not done. It appears that there are still uncertainties, which are the most reliable point levels for the discrimination of these both types of dementia (Harrison *et al.*, 1979; Rosen *et al.*, 1980).

When drafting the study design, it was presumed from the conception that the choice of the Clinical Global Impression (CGI) and the performance process aspects of the clinical profile, the CGI could be used to record those characteristics of the illness profile that indicate to the physician changes in the condition of the patient, which cannot be objectified or standardized by a performance test. Therefore, the SKT is appropriate for recording in a relatively sensitive way, certain aspects of the therapeutic efficacy, while the CGI is needed to evaluate its clinical relevance. With both approaches, the proof of vinpocetine's efficacy in comparison to placebo was statistically demonstrated.

The results of the Erlangen Depression Scale (EDS) and the Life Satisfaction Scale (LZ) also demonstrated that patient's subjective condition and life satisfaction 'normalized' under vinpocetine treatment. However, it must be said, that – given these diagnostic groups – results of the self-assessment scales often cannot clearly be interpreted because monotone or even linear relationships with the degree of severity of the organic psychosyndrome cannot be assumed (Burkard and Blaha, 1980). Often it could be observed, that some patients showed increased complaint-scores with objectively measurable diminished disturbances. Objective and subjective assessments of severity degree of the illness (Arnold and Herrklotz, 1980) obviously follow no system which would permit correlative predictions. A further reason for this may be the loss of validity of self-assessment scales with patients suffering from intellectual disturbances – such as they are also caused by organic psychosyndrome (Röth, 1971).

The study results lead to the presumption that the higher dosages of the cerebral anti-hypoxidotic vinpocetine in comparison with the 5 mg t.i.d. dosage, have a greater therapeutic efficacy. Attention and memory disturbances, subjective assessment of emotional state, performance capability, and the physicians' opinion on the course of treatment demonstrates the therapeutic efficacy of vinpocetine significantly.

Review of results within the vinpocetine group shows thats, when comparing baseline and final values, about 80% of the patients experienced improvement in their illness profile in the assessment of the investigator. This is confirmed by the SKT performance tests, in which the mean values of the initial stage correspond to a mild organic psychosyndrome; whereas these values at the end can only be classified in the range of a 'questionable' disturbance. Given these findings, one must go beyond the statistically proven efficacy and acknowledge the clinically relevant efficacy of vinpocetine. Thus, vinpocetine is recommended as therapy for patients with organic psychosyndrome.

Tolerance of vinpocetine was good in all three dosage groups; however, the incidence of side effects was somewhat higher than in the placebo group. Because the responses 'stomach disorders', 'internal restlessness', and 'sleep disturbances' were more frequent with vinpocetine treatment, but cannot be statistically demonstrated, these could be considered to be caused by the substance. However, one could also discuss 'internal restlessness' and 'sleep disturbances' as positive effects in the sense of an activation brought about by vinpocetine.

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