

A Multicentre Trial to Evaluate the Efficacy and Tolerability of α -Glycerylphosphorylcholine versus Cytosine Diphosphocholine in Patients with Vascular Dementia

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An open clinical trial was carried out to compare the efficacy and the tolerability of 1 g/day α -glycerylphosphorylcholine (α -GPC) with 1 g/day cytosine diphosphocholine (CDP) both given intramuscularly for 90 days in 120 patients with mild to moderate vascular dementia. The clinical evaluation, carried out at the start as well as halfway through (45 days) and at the end of treatment (90 days), was expressed by psychometric tests (modified Parkside behaviour rating scale, Sandoz clinical assessment geriatric scale, word fluency test, Hamilton's rating scale of depression, narration subtest of Wechsler memory scale). Both treatments produced a definite symptomatic improvement and showed a very good tolerability. The results suggest that in most tests α -GPC possessed a statistical higher efficacy and an overall more satisfactory activity assessed by both patients and investigators compared with CDP.

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E' stato effettuato uno studio clinico in aperto per confrontare l'efficacia e la tollerabilità di α -glicerilfosforilcolina (α -GFC) alla dose di 1 g al giorno verso citosina difosfocolina (CDP) sempre alla dose di 1 g al giorno, somministrate entrambe per via intramuscolare per 90 giorni in 120 pazienti affetti da demenza vascolare di grado da lieve a medio. La valutazione clinica, effettuata all'inizio, a metà (45 giorni) e al termine del trattamento (90 giorni), è stata effettuata con test psicometrici (modified Parkside behaviour rating scale, Sandoz clinical assessment geriatric scale, word fluency test, Hamilton rating scale per la depressione ed subtest del racconto della Wechsler memory scale). Entrambi i trattamenti hanno indotto un miglioramento della sintomatologia e hanno presentato una buona tollerabilità. I risultati mostrano che, nella maggior parte dei test, α -GFC ha presentato una più elevata efficacia, a confronto con CDP, come confermato anche dalle valutazioni soggettive espresse dai pazienti e dagli esaminatori.

KEY WORDS: α -Glycerylphosphorylcholine; cytosine diphosphocholine; cholinergic drugs; vascular dementia; neurotransmission; neuronal membrane function.

INTRODUCTION

In recent decades more cases of dementia have emerged possibly due to the ever-increasing number of elderly people. According to some investigators,¹ the incidence of dementia appears to be increasing and now occurs in about 10% of the population over 65 years of age. The number of people over 65 years will be growing still more in the near future and the human, social, public health and economic implications of dementia will become extremely important, stimulating medical research into the nature of the problem and the development of new therapeutic agents.

Vascular dementia, that is a dementia caused by thrombo-embolic cerebrovascular pathology, which was called multi-infarct dementia by Hachinski *et al.*² because of multiple ischaemic lesions in the grey matter, has been re-examined in the light of growing evidence that there are also lesions in the subcortical white matter (Binswanger's disease, haemodynamic

vascular dementia) and amyloid angiopathy.³ At present vascular dementia is considered to be a compound, multifactorial entity. In spite of its complexity and the doubts about interpretation, vascular dementia is still included in the most recent international classifications^{4,5} and is considered to be one of the major causes of dementia, second only to the degenerative form.^{1,6}

A possible approach to the treatment of vascular dementia may be to apply preventive measures for subjects at risk and thus to prevent the appearance or development of the disease. Alternatively, several drugs, among them cholinergic agents, are widely used.⁷ There is evidence that the pathogenesis of dementia involves several mechanisms and that the stepwise progression of the symptomatic pattern of vascular dementia results from the combined effects of a deficit of the neurotransmitter systems and the multifocal ischaemic lesions.^{8,9}

α -Glycerylphosphorylcholine (α -GPC, Delecit®), or choline alphoscerate, is a new drug that has been shown in animal studies to exert an integrated effect on

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neuronal function.¹⁰ Once α -GPC has crossed the blood – brain barrier,¹¹ it directly increases both the synthesis and the release of acetylcholine,^{12,13} and serves as a precursor for membrane phospholipids improving the fluidity and functionality of the neuronal membrane.^{14,15} In animals α -GPC facilitates learning and memory,^{16,17} and in healthy human volunteers it has been shown to prevent the memory deficit produced by scopolamine.¹⁸

Of the most frequently used drugs, cytosine diphosphocholine (CDP) has been shown in some studies to improve the symptoms of cognitive deficit in vascular dementia.^{19–25} In the present trial a comparison was made of the ability of α -GPC and CDP to improve some parameters of cognitive function and their possible improvement in the quality of daily life. In addition, the tolerabilities of α -GPC and CDP were compared.

PATIENTS AND METHODS

Patients

An open trial was carried out on 120 patients with vascular dementia enrolled at six university or hospital centres in southern Italy. The patients were of either sex, aged between 50 and 80 years, and had been attending the centres for at least 3 years. The patients' diagnoses were based on the criteria for multi-infarct dementia in the DSM-III R.⁵

Criteria for inclusion were as follows: Hachinski ischaemia scoring scale,²⁶ > 6 ; mini-mental state evaluation of Folstein *et al.*,²⁷ $10–23$; global deterioration scale of Reisberg *et al.*,²⁸ $3–5$; and Hamilton's rating scale of depression (HRSD),²⁹ < 32 . The diagnoses were confirmed by computerized tomography and/or nuclear magnetic resonance. Patients were excluded if the computerized tomography scan was positive for Binswanger's disease, or in the case of a recent (less than 2 months earlier) stroke or reversible secondary dementia, epilepsy, Parkinson's

disease, or psychosis.

Patients with stabilized diseases that should not influence the trial, e.g. arthritis, and those patients taking drugs not affecting the central nervous system were not excluded.

Study design

Histories of all the patients were obtained and they were given a clinical examination with special attention to the neurological examination. The biochemical screening included all the usual blood and urine laboratory tests.

After a 15-day washout period during which any drugs with effects on cognitive function were excluded, the patients were assigned to treatment, according to a randomization list, with 1 g/day α -GPC or CDP administered intramuscularly in the morning for 90 days. Any other treatment already being given was continued if it was thought unlikely to interfere with cognitive function.

Assessment of treatment

The patients were assessed using the following evaluations: modified Parkside behaviour rating scale (PBRs);³⁰ the Sandoz clinical assessment geriatric scale (SCAG)³¹ both used as a whole and for individual areas as recommended by Hamot *et al.*³² (Table 1), considering separately item 19 (global evaluation of the symptomatology); the word fluency test;³³ and the narration subtest of the Wechsler memory scale.³⁴ The HRSD,²⁹ which had been used as a criterion for inclusion, was also employed as a criterion for evaluation.

All of the tests were given by a single investigator at each centre at the start of treatment, after 45 days and at the end of treatment (90 days). Patients who did not complete the first 45 days of treatment were not included in the evaluation of efficacy but were observed for the entire treatment period to detect any possible side-effects.

Table 1
Subdivision into areas from the Sandoz clinical assessment geriatric scale according to Hamot *et al.*³²

Area	Item
Cognitive dysfunction	Impaired mental alertness Confusion Impairment of recent memory Disorientation
Interpersonal relationships	Uncooperativeness Irritability Bothersome Hostility
Affect	Mood depression Emotional lability Anxiety
Apathy	Lack of motivation/initiative Unsociability Indifference to surroundings Impaired self-care
Somatic dysfunction	Anorexia Fatigue Dizziness

The tolerability at the injection sites was assessed after 90 days as optimal, good, fair, mild, or scarce and at the end of treatment the investigator and the patient expressed their overall opinions about the efficacy of treatment as optimal, good, fair, mild, or nil.

Statistical analysis

Differences between the two treatment groups were analysed by non-parametric tests and the results for SCAG (overall and for the different areas) and for PBRs were analysed by the procedure of O'Brien.³⁵ The other neuropsychological data were analysed by the Wilcoxon test and the between-times differences were analysed by the Friedman test. *P*-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Table 2 lists the personal data of the patients included in the trial; there were no statistically significant differences between patients in the two treatment groups. The most frequently encountered diseases were hypertension, diabetes mellitus, chronic obstructive bronchopneumopathy and arthritis with similar frequency in both treatment groups; other diseases were seen only occasionally. Table 3 summarizes the psychometric characteristics for the two treatment groups of patients prior to commencing the study; there were no statistically significant differences between patients in the two treatment groups. Of the 120 patients who entered the trial, five did not complete it: four in the α -GPC treatment group and one in the CDP treatment group. The reason for withdrawing

Table 2

Summary of characteristics of patients with vascular dementia before treatment with α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP)

Physical characteristic	CDP	α -GPC	Overall
No. of patients			
Male	36	35	71
Female	24	25	49
Hospitalized	33	34	67
Ambulatory	27	26	53
Mean ($\pm$ SE) age (years)	69.9 $\pm$ 0.9	70.9 $\pm$ 0.7	70.4 $\pm$ 0.7
Mean ($\pm$ SE) weight (kg)	69.2 $\pm$ 1.1	71.5 $\pm$ 1.1	70.3 $\pm$ 0.7
Mean ($\pm$ SE) height (cm)	162.9 $\pm$ 0.9	163.5 $\pm$ 1.1	163.3 $\pm$ 0.7

treatment for two α -GPC-treated patients and one CDP-treated patient was occurrence of another stroke. A fourth patient moved to another town and could not,

consequently, be further followed up; another one stopped treatment after 15 days because of side-effects (headache and flushing).

Table 3

Psychometric characteristics of patients with vascular dementia before treatment with α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP)

Psychometric characteristics	α -GPC	CDP
Hachinski ischaemia scoring scale	10.8 $\pm$ 0.3	10.8 $\pm$ 0.3
Mini-mental state evaluation	17.8 $\pm$ 0.6	18.1 $\pm$ 0.5
Hamilton depression rating scale	16.4 $\pm$ 1.0	18.1 $\pm$ 0.9
Global deterioration scale	3.8 $\pm$ 0.1	3.9 $\pm$ 0.1
Parkside behaviour rating scale	39.8 $\pm$ 1.0	41.4 $\pm$ 0.9
Sandoz clinical assessment geriatric scale	60.9 $\pm$ 1.5	64.2 $\pm$ 1.3
Word fluency test	8.1 $\pm$ 0.9	6.9 $\pm$ 0.7
Narration subtest of the Wechsler memory test	3.6 $\pm$ 0.4	3.0 $\pm$ 0.3

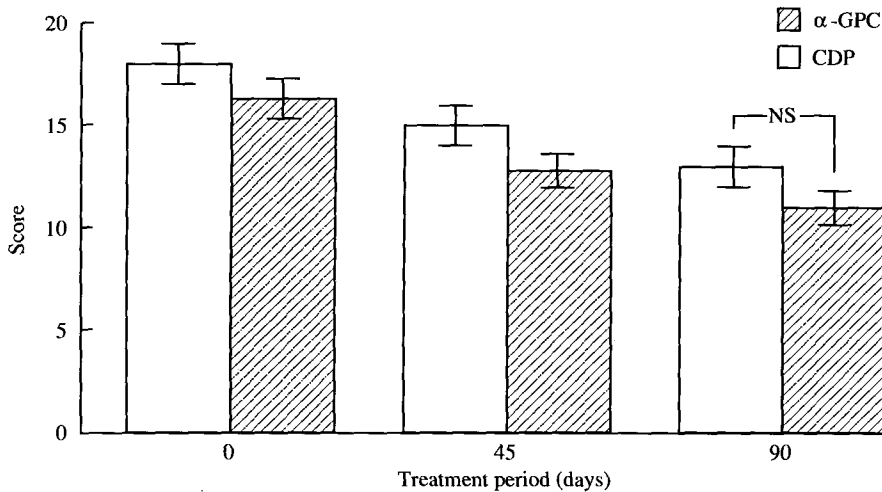


Fig. 1. Hamilton's rating scale of depression scores in patients with vascular dementia treated intramuscularly with 1 g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 45 or 90 days.

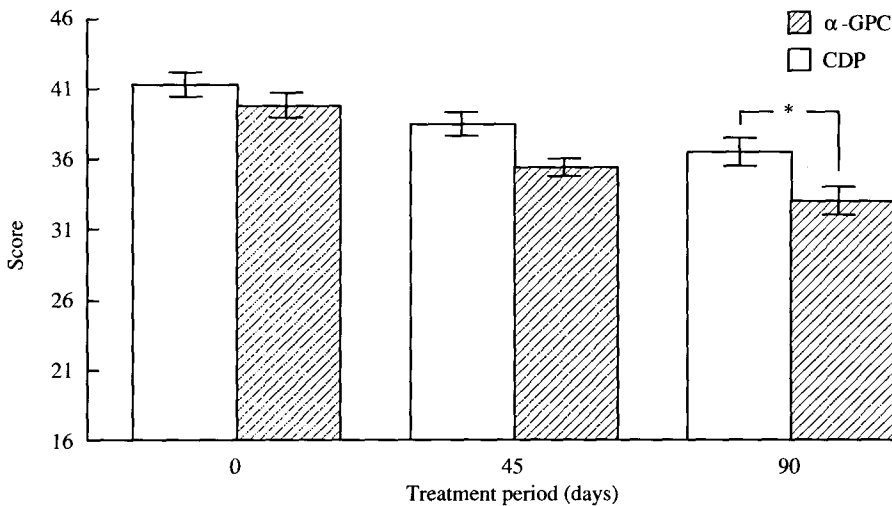


Fig. 2. Parkside behaviour rating scale scores in patients with vascular dementia treated intramuscularly with 1 g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 45 or 90 days; * $P < 0.05$.

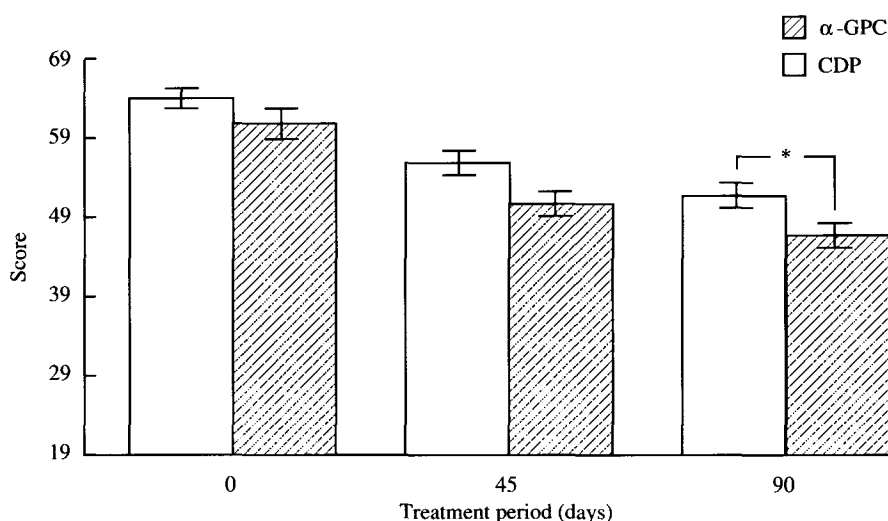


Fig. 3. Sandoz clinical assessment geriatric scale scores in patients with vascular dementia treated intramuscularly with 1g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 45 or 90 days; $*P < 0.05$.

There was a significant ($P < 0.05$) improvement in HRSD in both patient groups after treatment for 45 or 90 days (Fig. 1). The PBRs (Fig. 2), global SCAG scores (Fig. 3) and SCAG scores for the individual areas (Table 4) were also significantly improved ($P < 0.05$) after 45 and 90 days. The scores for the word fluency test (Fig. 4) and Wechsler memory scale (Fig. 5) were significantly ($P < 0.05$) improved by both α -GPC and CDP between the start of treatment and mid-treatment (45 days) but not between mid-treatment and the end of treatment (90 days, Fig. 5).

The efficacy of α -GPC was significantly ($P < 0.05$) greater than that of CDP in the Wechsler memory scale, PBRs, SCAG global score and, specifically within the SCAG evaluation, in cognitive dysfunction and item 19. There were no significant differences between α -GPC and CDP in effects on the scores for HRSD, word fluency

or the other areas of SCAG. The global assessments of the investigators and patients are given in Table 5 and their local tolerability evaluations are given in Table 6.

During treatment five side-effects were reported (headache and flushing, erythema, headache, flushing, nicturia); nicturia was not deemed treatment-related according to the investigator's opinion. The side-effects all occurred in α -GPC-treated patients, four during the first half of the study (0–45 days) and one during the second half (46–90 days).

DISCUSSION

The causes of dementia are still not sufficiently understood to be able to treat it rationally. In dementia due to circulatory problems, removal of the risk factors is important and treatment with drugs that improve the symptoms may be useful as a

Table 4
Mean (± SE) scores for individual areas of the Sandoz clinical assessment geriatric scale for patients with vascular dementia before and after treatment with 1g/day α-glycerylphosphorylcholine (α-GPC) or cytosine diphosphocholine (CDP) given intramuscularly for 45 or 90 days

Area	Baseline		45 days		90 days	
	α-GPC	CDP	α-GPC	CDP	αGPC	CDP
Cognitive dysfunction	14.5 ± 0.3	15.1 ± 0.3	12.0 ± 0.3	13.5 ± 0.4	10.6 ± 0.4	12.4 ± 0.4
Interpersonal relationships	10.1 ± 0.6	11.2 ± 0.6	8.6 ± 0.5	9.8 ± 0.5	7.9 ± 0.4	9.0 ± 0.5
Affect	10.1 ± 0.2	10.8 ± 0.2	8.3 ± 0.3	9.0 ± 0.3	7.5 ± 0.3	8.00 ± 0.3
Apathy	13.2 ± 0.5	14.4 ± 0.5	10.7 ± 0.4	12.3 ± 0.4	10.1 ± 0.4	11.5 ± 0.4
Somatic dysfunction	9.0 ± 0.4	8.8 ± 0.3	7.6 ± 0.3	7.5 ± 0.3	7.0 ± 0.3	7.2 ± 0.3

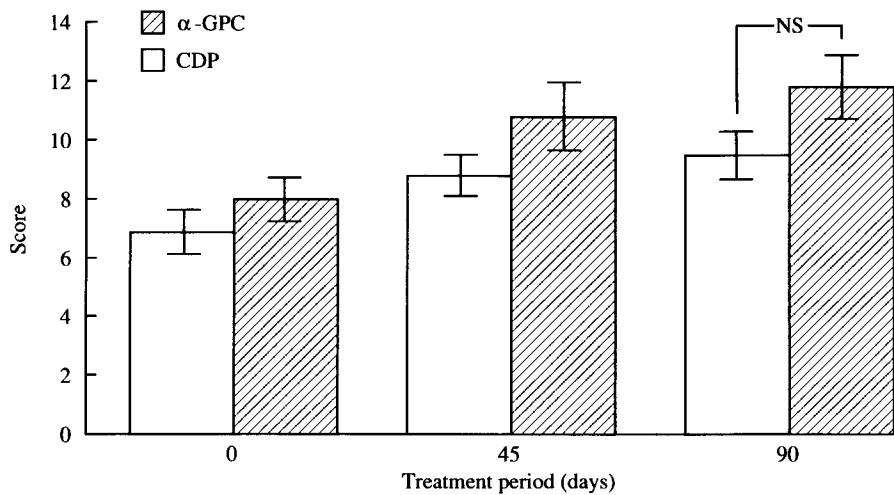


Fig. 4. Word fluency test scores in patients with vascular dementia treated intramuscularly with 1 g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 45 or 90 days.

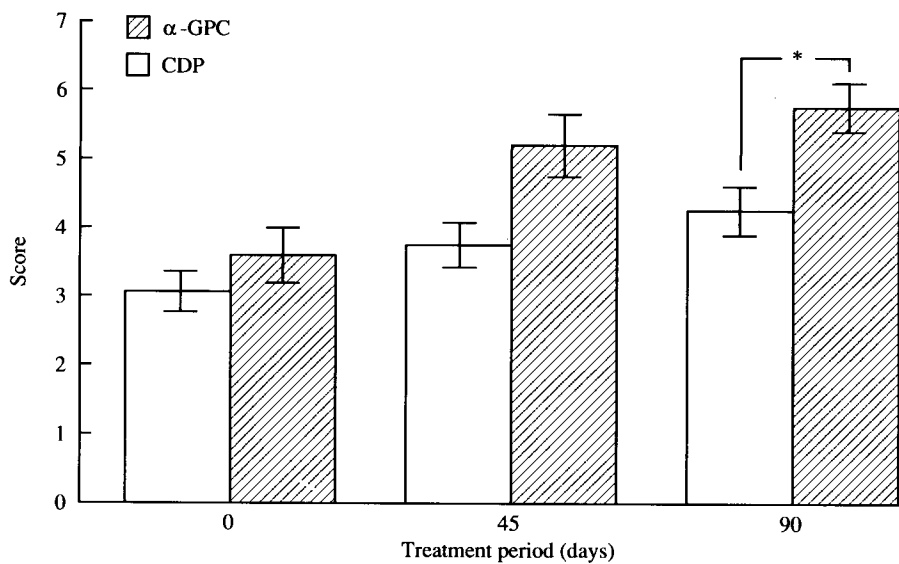


Fig. 5. Narration subtest score of the Wechsler memory scale in patients with vascular dementia treated intramuscularly with 1 g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 45 or 90 days; * $P < 0.05$.

Table 5

Global evaluation of efficacy expressed by investigators and patients with vascular dementia treated intramuscularly with 1 g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 90 days

Evaluation	Investigators		Patients	
	α -GPC	CDP	α -GPC	CDP
Optimal/good	39 ^a	25	38 ^a	30
Fair/mild	14 ^a	27	14 ^a	19
Nil	1 ^a	6	2 ^a	9
Not expressed	6	2	6	2
Total	60	60	60	60

^a $P < 0.05$ vs CDP (χ^2 -test).

Table 6

Evaluation of tolerability by patients with vascular dementia treated intramuscularly with 1 g/day α -glycerylphosphorylcholine (α -GPC) or cytosine diphosphocholine (CDP) for 90 days

Evaluation	α -GPC	CDP
Optimal	31	29
Good	25	24
Fair	1	7
Mild	1	0
Scarce	0	0
Not expressed	2	0
Total	60	60

supportive measure.⁷ In particular, cholinergic drugs, which have been introduced to correct the neurochemical abnormalities present in vascular dementia, have been shown to improve the symptoms of several patients.⁷

In the present study, the efficacy of α -GPC was compared with that of CDP, which is the drug that has been most widely

studied in the treatment of dementia.^{10,16}

The study, unfortunately, had to be carried out as an open trial because it was not possible to perform a double-blind one without manipulating the reference drug. Furthermore, a double-dummy trial would be handicapped by problems of compliance.

The patients included in the study had vascular dementia in the classical sense of the disease due to multi-infarctions of the grey matter; subjects with Binswanger's disease were excluded on the basis of computerized tomography. In addition, the patients had slight to moderate cognitive deficits, as shown by the scores for the mini-mental state evaluation²⁷ and the global deterioration scale.²⁸ There were more men than women included in the trial, as would be expected for vascular pathology.

Both treatments were effective on the basis of the parameters tested. That the effects of word fluency and Wechsler memory scale were only significant in the first 45 days of the study indicates that the treatments acted rapidly on monodimensional parameters (factors regarding

precise cognitive functions, such as fluidity of oral language and memory). The effects of the two test drugs on more complex parameters, such as SCAG and PBRs, which examine physical, mental and social functions simultaneously, became apparent more slowly and continued over a longer time. The improvement in the HRSD may indicate that both α -GPC and CDP can improve mood rather than resolving depression; the patients included in the study were not depressed by definition. The study showed that α -GPC was more effective than CDP in improving memory functions and had a more positive effect on the multidimensional parameters. It is interesting to note that the greater benefit on the SCAG scores was principally associated with effects on the areas of cognitive function.

The greater efficacy of α -GPC compared with CDP seen in the psychometric tests was confirmed by the opinions expressed at the end of treatment by both the investigators and patients, indicating an overall improvement of the symptomatology.

The tolerability of both treatments was good and similar, both systemically and locally, in spite of the long period of treatment by intramuscular injection; treatment had to be withdrawn because of side-effects in only one patient. The recording by the investigators of all side-effects including those that they did not consider to be related to treatment indicates that in an open trial the investigator gave greater attention to a new drug.

In conclusion, both drugs were found to improve some of the simple and complex symptoms of patients with vascular dementia. Although the observation period was relatively short and, therefore, additional developments may be seen with longer therapy, the results indicated that both α -GPC and CDP, if given according to adequate rules for prevention of problems and with adequate attention to daily hygiene, may improve both the specific and general

functions of the patients. This is even more important when one takes into consideration that vascular dementia has a poor prognosis and has consequences for the patients, and leads to his or her progressive exclusion from the family and social environment. The present clinical trial appears to confirm the preclinical studies that α -GPC has more complete activity than CDP.

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