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Multicentre Study of *l*-α-Glyceryl-Phosphorylcholine *vs* ST200 among Patients with Probable Senile Dementia of Alzheimer's Type

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Summary A multicentre, randomised, controlled study compared the efficacy of *l*-α-glyceryl-phosphorylcholine (αGPC) and ST200 (acetyl-*l*-carnitine) among 126 patients with probable senile dementia of Alzheimer's type (SDAT) of mild to moderate degree. Efficacy was evaluated by means of behavioural scales and psychometric tests. The results showed significant improvements in most neuropsychological parameters in the αGPC recipients. Improvements also occurred in the ST200 recipients but to a lesser extent. Tolerability was good in both groups. These positive findings require replication in larger, double-blind, longitudinal studies coupling clinical and biological determinations.

l-α-Glyceryl-phosphorylcholine (αGPC) is a semi-synthetic derivative of lecithin. After oral administration, it is converted to phosphorylcholine, which is a metabolically active form of choline able to reach cholinergic synaptic endings, thus increasing acetylcholine synthesis and release. Furthermore, αGPC contributes to anabolic processes responsible for membrane phospholipid and glycerolipid synthesis, positively influencing membrane fluidity (Spano & Trabucchi 1990).

These pharmacological properties offer a rational premise for the efficacy of αGPC in the treatment of age-related dementias (particularly senile dementia of Alzheimer's type; SDAT) since, in these disorders, there is a breakdown of cholinergic synthesis and impaired fluidity of neuronal membranes.

The efficacy of αGPC was compared with cytidine-diphospho-choline (CDP-choline) [Di Perri et al. 1991; Frattola et al. 1991] in 2 multicentre, randomised, controlled studies among patients with multi-infarct dementia (MID). Both investigations showed significant improvements in most neuropsychological and behavioural instruments in the αGPC recipients compared with CDP-choline recipients; both drugs were well tolerated.

This multicentre, randomised, controlled study was undertaken in patients with probable SDAT with mild to moderate mental deterioration to confirm the efficacy of αGPC compared with ST200

(acetyl-*l*-carnitine). ST200 was chosen as the reference drug since consistent evidence exists about its efficacy in improving cognitive functions in SDAT (Calvani & Carta 1991; Cucinotta et al. 1988; Parnetti et al. 1990; Rai et al. 1990).

Patients and Methods

126 outpatients of either sex were enrolled in 7 Italian Centres. Clinical diagnoses of dementia were made according to Diagnostic and Statistical Manual of Mental Disorders, third edition revised (DSM-III-R) criteria. All patients fulfilled National Institute of Neurological and Communicative Disorders and Stroke-Alzheimers and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease (McKhann et al. 1984) and had a clinical onset of dementia after 65 years of age (senile dementia of Alzheimer's type). The degree of mental deterioration ranged from mild to moderate (Mini Mental State Examination score: 11 to 23). Significant depression was excluded by means of a Hamilton Depression Rating Scale (HDRS) [Hamilton 1967] score ≤ 18. Other inclusion criteria included age between 65 and 85 years, 3 to 12 years of schooling, Hachinski ischaemic score ≤ 4, the absence of cerebral vascular lesions on computerised tomography scan, and a Global Deterioration Scale score of 3 to 6. Patients were excluded in the presence of major psychiatric illness (depression or major psychoses); primary central or peripheral neurological diseases; systemic or neoplastic diseases; major organ failure or severe metabolic disorders; or chronic alcohol abuse.

Patients were randomised using a balanced-block list, and after a 2-week washout from other treatments, 65 patients received oral αGPC (800mg at 8am and 400mg at 4pm) and 61 patients received oral ST200 (1000mg at 8am and 500mg at 4pm) for 6 months.

At baseline (T0), after 4 months (T4) and at the end of treatment (T6) behavioural and neuropsychological testing for assessing efficacy was carried out. Tests included: the Global Deterioration Scale (GDS) [Reisberg & Ferris 1982] for monitoring progression of the disease; the Sandoz Clinical Assessment Geriatric (SCAG) scale (Shader et al. 1974); assessment of different clinical symptoms, structured under 5 factors (cognitive dysfunction, interpersonal relationships, affective disorders, apathy, somatic functioning); the Gottfries-Bråne-Steen (GBS) Rating Scale for Dementia (Gottfries et al. 1982); an Italian version of the GBS (Parnetti et al. 1989) which quantifies motor, intellectual and emotional impairments and other symptoms common to dementing disorders, namely confusion, irritability, anxiety, fear and panic, depression and restlessness; Mini Mental State Examination (MMSE) [Folstein et al. 1975]; and Rey's 15-word test for assessment of verbal memory (Rey 1958).

Statistical Analysis

Data are presented as mean $\pm$ standard deviation. Statistical analysis was performed by means of ANOVA for repeated measures, then multiple comparison according to Dunnett's procedure. An analysis of covariance for the last values (month 6), with basal values as covariates, were also performed; centres and treatments were used as factors.

As far as GDS is concerned, data were analysed in terms of change at end of treatment. A multivariate logistic analysis was also performed to identify factors associated with the improvement in GDS stage. p-Values of less than 0.05 were considered significant.

Results

The baseline profile of the 2 groups studied (table I) disclosed no significant differences between αGPC- and acetyl carnitine–treated groups.

Significant improvements of MMSE scores were observed in both groups ($p < 0.05$) after the fourth month of treatment (table II). Between-group comparisons carried out at month 6 failed to show any significant difference.

Verbal memory, as assessed by means of Rey's 15-word test, was statistically significantly improved in αGPC recipients. Improvement occurred on both immediate and delayed recall scores

Table I. Baseline profile of *l*-α-glyceryl-phosphorylcholine (αGPC) and ST200 groups

	αGPC	ST200
No. of patients	65	61
Gender (male/female)	23/42	25/36
Age (mean ± SD) years	74.2 ± 5	74.3 ± 6
Hachinski ischaemic score	2.0 ± 1.1	2.0 ± 1.2
Mini Mental State Examination score	18.3 ± 3.4	17.4 ± 3.5
Hamilton Depression Rating Scale score	8.6 ± 4.7	8.5 ± 4.8
Sandoz Clinical Assessment Geriatrics score	49.8 ± 12.3	50.9 ± 13.5

at month 6 ($p < 0.05$); a similar improvement in delayed recall was observed in ST200 recipients (table II).

Intellectual and emotional impairments, evaluated by GBS, improved significantly after 4 and 6 months of therapy only in the αGPC group; analogous results were observed for the items 'confusion' and 'depression'. Most of the GBS scores at month 6 were statistically significantly better in αGPC versus ST200 recipients (table III).

The SCAG factors including 'affective disorders', 'apathy', 'somatic functioning', as well as the item 'overall impression', showed statistically significant improvements at month 6 in the αGPC-treated group compared with the ST200-treated group (fig. 1). Furthermore, within-group analyses (at months 4 and 6 *vs* baseline) revealed improvements in all the SCAG parameters, excepting 'interpersonal relationship', in the αGPC-treated group; similar behavioural improvements were observed in the ST200–treated group, but to a lesser extent.

It is interesting to note that GDS staging showed improvements, i.e. a decrease by at least 1 point in 29% of the αGPC-treated group and in 15% of ST200-treated group ($p < 0.05$). On the other hand, GDS staging worsened in 5% of the αGPC-treated group and 10% of ST200-treated group (table IV). Multivariate logistic regression showed that these behavioural changes were associated only with treatment, and not with other variables such as gender, age and basal values.

Both drugs were well tolerated. Adverse effects observed in the αGPC-treated group were insomnia, gastralgia and restlessness in 1 patient each. In the ST200-treated group, 3 patients reported agitation, 2 pyrosis, 2 nausea, and 1 gastralgia. These effects were of modest intensity and did not require drug withdrawal.

Discussion

The first consideration in clinical trials of pharmacological treatment of SDAT should be to improve the patients' quality of life. Up to now, practically all proposed drugs act symptomatically. This means that, although the clinical features of the disease are temporarily improved, the treatment does not influence the course of the disease itself.

Table II. Mini Mental State Examination (MMSE) and Rey's 15-word scores obtained in *l*-α-glyceryl-phosphorylcholine (αGPC)- and ST200-treated groups at baseline, and after 4 and 6 months of therapy

Test	Treatment group	Baseline	Month 4	Month 6
MMSE	αGPC	18.3 ± 3.4	19.7 ± 4.3[a]	20.2 ± 4.9[b]
	ST200	17.4 ± 3.5	18.4 ± 3.9[a]	18.5 ± 4.0[b]
Rey's 15 word:				
immediate recall	αGPC	19.3 ± 6.4	20.3 ± 7.0	22.0 ± 6.7[b]
	ST200	18.1 ± 6.7	18.5 ± 6.9	19.4 ± 8.4
delayed recall	αGPC	1.8 ± 1.8	2.1 ± 1.8	2.4 ± 1.8[b]
	ST200	1.5 ± 1.6	1.7 ± 1.8	1.9 ± 2.2[b]

a Month 4 *vs* baseline, $p < 0.05$.
b Month 6 *vs* baseline, $p < 0.05$.

Table III. Gottfries-Bråne-Steen (GBS) rating scale scores obtained in *l*-α-glyceryl-phosphorylcholine- and ST200-treated groups at baseline, after 4 and 6 months of therapy

GBS item	Treatment group	Baseline	Month 4	Month 6
Motor impairment	αGPC	0.96 ± 0.72	0.96 ± 0.73	1.00 ± 0.80
	ST200	1.00 ± 0.75	1.04 ± 0.76	1.07 ± 0.79
Intelligence impairment	αGPC	1.95 ± 0.66	1.78 ± 0.67[a]	1.72 ± 0.74[b,c]
	ST200	2.07 ± 0.79	2.05 ± 0.77	2.02 ± 0.82
Emotional impairment	αGPC	1.76 ± 0.97	1.54 ± 0.80[a]	1.50 ± 0.74[b,c]
	ST200	1.79 ± 1.06	1.75 ± 0.92	1.79 ± 0.97
Confusion	αGPC	2.2 ± 1.4	2.0 ± 1.3[a]	1.9 ± 1.2[b,c]
	ST200	2.3 ± 1.3	2.2 ± 1.3	2.3 ± 1.3
Irritability	αGPC	1.0 ± 1.3	0.9 ± 1.1	0.8 ± 1.0
	ST200	1.1 ± 1.3	1.1 ± 1.3	1.0 ± 1.2
Anxiety	αGPC	1.8 ± 1.5	1.7 ± 1.3	1.6 ± 1.3
	ST200	1.8 ± 1.2	1.9 ± 1.3	1.8 ± 1.1
Fear panic	αGPC	0.7 ± 0.9	0.5 ± 0.7	0.4 ± 0.7[c]
	ST200	0.5 ± 0.7	0.7 ± 0.9	0.7 ± 0.9
Depression	αGPC	1.7 ± 1.4	1.3 ± 1.2[a]	1.2 ± 1.2[b,c]
	ST200	1.6 ± 1.2	1.5 ± 1.2	1.4 ± 1.2
Restlessness	αGPC	1.0 ± 1.2	0.9 ± 1.0	0.9 ± 1.1[c]
	ST200	1.1 ± 1.2	1.2 ± 1.2	1.3 ± 1.3

a Month 4 *vs* baseline, $p < 0.05$.
b Month 6 *vs* baseline, $p < 0.05$.
c αGPC *vs* ST200 at month 6, $p < 0.05$.

Table IV. Variations of Global Deterioration Scale (GDS) scores observed after treatment with *l*-α-glyceryl-phosphorylcholine (αGPC) or ST200: patients showing a decrease of at least one point were judged to be improved

Initial GDS stage	Treatment group	Baseline (no. of patients)	Month 6 [no. (%) of patients]	
			improved	worsened
3	αGPC	28	6 (9%)	0
	ST200	23	2 (3%)	1 (2%)
4	GPC	23	8 (12%)	1 (2%)
	ST200	23	4 (7%)	3 (5%)
5	αGPC	14	5 (8%)	2 (3%)
	ST200	14	2 (3%)	2 (3%)
6	αGPC	0	0	0
	ST200	1	1 (2%)	0

Therefore, it is imperative to develop drugs able to correct the neurochemical deficit which contributes to the manifestation of mental deterioration.

αGPC is a precursor of acetylcholine. Experimental studies have shown that αGPC stimulates acetylcholine synthesis in different regions of rat brain, particularly in the hippocampus, frontal cortex and striatum. It also participates in anabolic processes within biological membranes, particularly neuronal membranes. Both these actions are relevant with respect to the pathophysiology of Alzheimer's type dementia, since cholinergic breakdown and alteration of membrane properties are both hallmarks of this disease.

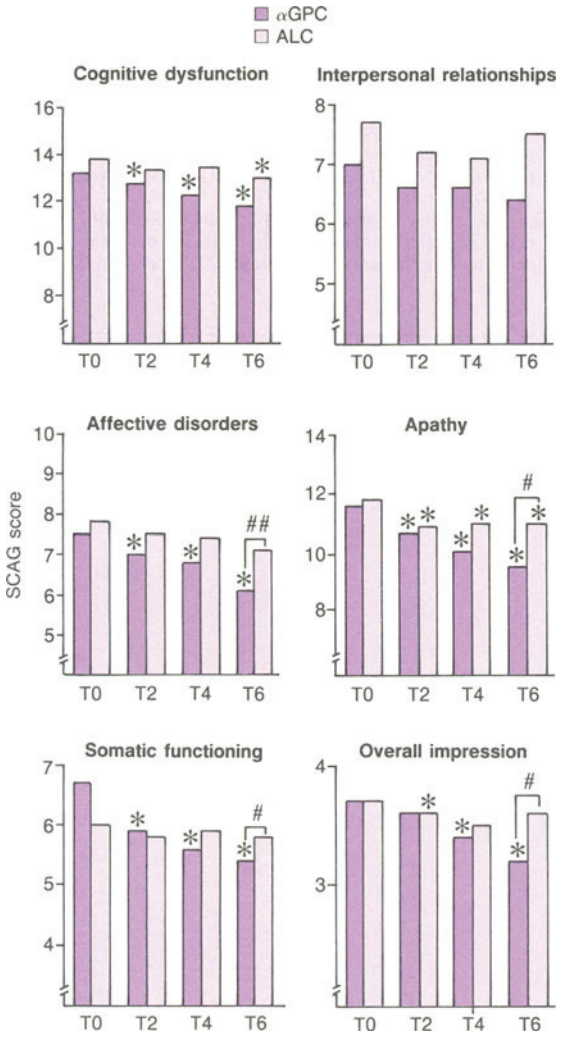

Fig. 1. Sandoz Clinical Assessment Geriatrics (SCAG) scale scores in *l*-α-glyceryl-phosphorylcholine- and ST200-treated groups at baseline (T0), after 2 (T2), 4 (T4), and 6 (T6) months of therapy; ✻ = $p < 0.05$ *vs* baseline; # = $p < 0.05$ *vs* ST200 at month 6; ## = $p < 0.01$ *vs* ST200 at month 6.

Therapeutic Implications

These therapeutic premises are consistent with the clinical efficacy demonstrated with αGPC treatment. In the present investigation, αGPC consistently showed favourable effects in improving the neuropsychological and behavioural test scores of SDAT patients. Indeed, the improved GDS scores show that αGPC induces global functional improvement, to a degree which may improve the patients' quality of life.

It will be fundamental to continue to study this problem. Future clinical investigations should be long term, involve mildly deteriorated patients, and use rating scales and psychometric tests specifically designed to quantify the global functional state of the patient. Such investigations should attempt to determine the optimal dosage regimen by assessing the different pharmaceutical dosage forms available, i.e. tablets and injectable preparations. Finally, biological measurements should be carried out before and after treatment, in order to quantify the patients' overall status. Such a structured approach would probably lead to more rational pharmacological strategies for treating dementias of old age.

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