

Choline alfoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data

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Abstract

This paper has reviewed the documentation on the clinical efficacy of choline alfoscerate, a cholinergic precursor, considered as a centrally acting parasymphomimetic drug in dementia disorders and in acute cerebrovascular disease. Thirteen published clinical trials, examining in total 4054 patients, have evaluated the use of choline alfoscerate in various forms of dementia disorders of degenerative, vascular or combined origin, such as senile dementia of the Alzheimer's type (SDAT) or vascular dementia (VaD) and in acute cerebrovascular diseases, such as transitory ischemic attack (TIA) and stroke. Analysis has assessed the design of each study, in particular with respect to experimental design, number of cases, duration of treatment and tests used to evaluate drug clinical efficacy. Most of the ten studies performed in dementia disorders were controlled trials versus a reference drug or placebo. Overall, 1570 patients were assessed in these studies, 854 of which in controlled trials. As detected by validated and appropriate tests, such as Mini Mental State Evaluation (MMSE) in SDAT and Sandoz Clinical Assessment Geriatric (SCAG) in VaD, administration of choline alfoscerate significantly improved patient clinical condition. Clinical results obtained with choline alfoscerate were superior or equivalent to those observed in control groups under active treatment and superior to the results observed in placebo groups. Analysis stresses the clear internal consistency of clinical data gathered by different experimental situations on the drug effect, especially with regard to the cognitive symptoms (memory, attention) characterising the clinical picture of adult-onset dementia disorders. The therapeutic usefulness of choline alfoscerate in relieving cognitive symptoms of chronic

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cerebral deterioration differentiates this drug from cholinergic precursors used in the past, such as choline and lecithin. Three uncontrolled trials were performed with choline alfoscerate in acute cerebrovascular stroke and TIA, totalling 2484 patients. The results of these trials suggest that this drug might favour functional recovery of patients with cerebral stroke and should be confirmed in future investigations aimed at establish the efficacy of the drug in achieving functional recovery of patients with acute cerebrovascular disease. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Choline alfoscerate; Cholinergic precursors; Central parasymphomimetic drugs; Cognitive decline; SDAT; VaD; TIA; Stroke

1. Introduction

Aging brain is characterized by a range of disorders involving local metabolism, regional blood supply and neurotransmitter availability (Bartus et al., 1982) that lead to progressive deterioration of memory formation and retention. This mental decay, which can be compensated for through experience and culture, can be worsened by concurrent pathologic situations, such as Alzheimer's disease (AD) and vascular dementia (VaD). A definite relationship is known to exist between the completeness of the cholinergic transmission and memory and cognitive abilities (Bartus et al., 1982). A correlation between acetylcholine, memory and cognition was confirmed by neurochemical evidence proving a severe central cholinergic deficiency in patients affected by AD. Studies in AD or VaD patients have shown that learning and memory deficits are associated with disorders in cholinergic transmission in the central nervous system (Carlsson, 1987), in general characterized by reduced availability of acetylcholine. Significant loss of forebrain cholinergic neurons accompanied by decreased neocortical choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activities, the major anabolic and catabolic enzymes for acetylcholine, respectively, was commonly reported in brains of demented subjects (Davies and Maloney, 1976; Whitehouse et al., 1981, 1982). Reduction in ChAT and AChE activity is related with the degree of dementia and neuropathological hallmarks of AD, confirming a close association between cholinergic biochemical abnormalities and the disease (Perry et al., 1978). These findings form the basis for the most widely accepted neurochemical hypothesis for cognitive deficits accompanying AD (Bartus et al., 1982).

The experimental observation that, under conditions of reduced cholinergic synthesis and increased neuronal demand, neurons increase their ability to incorporate exogenous choline (Wecker and Schmidt, 1979), suggested that the systemic administration of a choline precursor should antagonize biochemical disorders of cholinergic system, thereby improving cognitive function. In other words, it was suggested that replacement of lost cholinergic functions might provide palliative therapy for cognitive deficits. Several approaches to cholinergic replacement have been tried in cognitive decline. Clinical studies with muscarinic acetylcholine receptor agonists, AChE inhibitors and acetylcholine-releasing agents have shown significant albeit weak activity (Davis et al., 1993).

Initial attempts to enhance brain cholinergic function in AD focused on precursor loading were based on the successful use of neurotransmitter precursors in other neurodegenerative diseases (i.e. L-DOPA for Parkinson's disease). Despite encouraging early results (Brinkman et al., 1982a,b), well-controlled clinical trials failed to show significant improvement of treatment with choline or lecithin (Etienne et al., 1981; Thal et al., 1981; Pomara et al., 1983; Smith et al., 1984; Samorajski et al., 1985; Little et al., 1985; Growdon et al., 1986; Heyman et al., 1987) and therefore, the clinical value of these drugs, if any, is controversial. The development of central inhibitors of AChE, whose therapeutic role in the treatment of AD symptoms is suggested (Mayeux and Sano, 1999), prompted scientists to re-focus their attention on the role of cholinergic loss as responsible for cognitive impairment which is a trait of the disease (Ehrenstein, 1997; Kasa, 1997).

Choline alfoscerate (L- α -glycerylphosphorylcholine), a semi-synthetic derivative of phosphatidylcholine, is a relatively new cholinergic drug. Pre-clinical studies have demonstrated that it increases the release of acetylcholine in rat hippocampus (Sigala et al., 1992), facilitates learning and memory in experimental animals (Govoni et al., 1990), improves brain transduction mechanisms (Schettini et al., 1990) and decreases the age-dependent structural changes occurring in the rat frontal cortex and hippocampus (Amenta et al., 1993). The compound also contributes to anabolic processes responsible for membrane phospholipid and glycerolipid synthesis, positively influencing membrane fluidity (Aleppo et al., 1994). From a functional point of view, choline alfoscerate improves cognitive deficit in experimental models of aging brain (Canonica et al., 1990; Drago et al., 1990) and reverses mnemonic deficits induced by scopolamine administration (Govoni et al., 1990; Sigala et al., 1992). Based on the above evidence, the central parasymphomimetic activity of choline alfoscerate was defined, suggesting its clinical use in patients affected by cognitive decline. Consistently with the activity profile, choline alfoscerate was classified as a centrally acting parasymphomimetic drugs both in international pharmacopoeias (Reynolds, 1996) and in the Chemical Therapeutical Anatomical Classification.

Choline alfoscerate finds also a rationale for a possible role in acute cerebrovascular diseases by antagonising the biochemical-functional deficiency of the cholinergic system damaged by ischemia (Bergamaschi, 1995). A neuroprotective activity of carriers of exogenous choline with respect to ischemic damage has already been demonstrated for other choline carriers, both in pre-clinical (Casamenti, 1979; Jope, 1982; Secades, 1995) and clinical studies (Tazaki, 1988; Clark, 1997).

This paper has evaluated published studies on choline alfoscerate in the treatment of dementia disorders and acute cerebrovascular disease, in order to prove its clinical usefulness. The main purpose of this work was to establish whether the drug gained data of clinical efficacy adequate to differentiate it from other cholinergic precursors used in the past, such as choline and lecithin (or phosphatidylcholine).

2. Materials and methods

Thirteen clinical trials were published on choline alfoscerate (Table 1). These studies evaluated the use of choline alfoscerate in dementia disorders of degenerative, vascular and combined origin, and in acute cerebrovascular diseases, such as transitory ischemic attack (TIA) and stroke. In this analysis, each study was extensively examined, in particular with respect to experimental design, number of cases, duration of treatment and tests used to assess drug clinical efficacy.

2.1. Studies in dementia disorders (SDAT, VaD or mixed forms)

Table 2 shows the characteristics of the six clinical trials including patients with dementia disorders of degenerative or vascular origin. To obtain the most objective and homogeneous overall evaluation of the efficacy of choline alfoscerate in studies on dementia disorders of degenerative origin, the results of Mini Mental State Evaluation (MMSE) (Folstein et al., 1975) in these trials were evaluated. The choice of MMSE was made by applying the criteria to select, among the various tests used by investigators, an instrument of clinical examination that is:

1. highly indicative under the clinical profile, widely validated and of established use;
2. appropriate to thoroughly assess cognitive domains (memory, attention, etc.) of mental functions;
3. constantly used in all trials considered.

The MMSE is a simple test developed to evaluate cognitive disorders in the elderly. The examination, with its 11 items, analyses the patient's ability of orientation, recent memory, attention, calculus and language. The result of the test

Table 1

Clinical trials on choline alfoscerate in dementia disorders of neurodegenerative or vascular origin and in acute cerebrovascular disease

	(1) Neurodegenerative dementia disorders	(2) Vascular dementia	(3) Combined neurodegenerative and vascular forms	(4) TIA or stroke	(5) Total
Total No. of trials	3	4	3	3	13
Controlled	3	4	1	0	8
Uncontrolled	0	0	2	3	5
Total No. of patients	565	789	216	2484	4054
Controlled	225	421	208	0	854
Uncontrolled	340	368	8	2484	3200

Table 2

Clinical trials with choline alphoscerate in patients with neurodegenerative dementia disorders or mixed degenerative or vascular forms

First author	Indication	Design	No. of patients	AR	Reference drug	Duration of therapy (months)	Tests used
Abbati	Mild cognitive impairment	Controlled	40	IM	Oxiracetam	3	MMSE; Barthel index
Parnetti	SDAT	Controlled	126	Oral	Acetyl-L-carnitine	6	MMSE; GDS; SCAG; GRS; Rey 15 words test
Schettini	AD	Controlled (blind)	20	IM	Placebo	3	MMSE; SCAG; Raven Wechsler memory; Word repetition; Word fluency
Ban	VaD; mixed forms	Open	350 VaD; 173 mixed forms	Oral		6	MMSE; SCAG; GDS; CGRS
Palleschi	Mild cognitive impairment	Open	46 DEG; 18 VaD; 35 mixed forms	Oral		6	MMSE; SCAG; Digit Span; Digit Symbol; Rey 15 words test
Vezzetti	Mild cognitive impairment	Controlled (blind)	39 DEG; 13 VaD; 8 mixed forms	Oral	Placebo	3	MMSE; ECAI; RTI

AR, administration route; DEG, degenerative; ECAI, Echelle clinique d'aptitude intellectuelle; GRS, Gottfries Rating Scale; IM, intramuscular; RTI, Neurotest Reaction Times Scale. The significance of other abbreviations is indicated in the text.

Table 3
Clinical trials with choline alfoscerate in patients with vascular dementia

First author	Indication	Design	No. of patients	AR	Reference drug	Duration of therapy (months)	Tests used
Di Perri	VaD	Controlled	120	IM	Citicholine	3	SCAG; Parkside BRS; Word fluency test; Wechsler memory (subtest)
Frattola	VaD	Controlled	126	IM	Citicholine	3	SCAG; Parkside BRS; Word fluency test; Wechsler memory (subtest)
Muratorio	VaD	Controlled	112	IM	Citicholine	3	SCAG; Blessed Dementia Scale; Wechsler Memory Scale; Rapid Disability Rating Scale; Token test; Word fluency test; Simple Drawing Copy
Paciaroni	VaD	Controlled	50	Oral	Oxiracetam	6	SCAG; Birren test; Digit Span; Digit Symbol; Rey 15 word test
Ban	VaD; mixed forms	Open	350 VaD; 173 mixed forms	Oral		6	MMSE; SCAG; GDS; CGRS
Palleschi	Mild cognitive impairment	Open	46 DEG; 18 VaD; 35 mixed forms	Oral		6	MMSE; SCAG; Digit Span; Digit Symbol; Rey 15 word test
Vezzetti	Mild cognitive impairment	Controlled (blind)	39 DEG; 13 VaD; 8 mixed forms	Oral	Placebo	3	MMSE; ECAI; RTI

AR, administration route; DEG, degenerative; ECAI, Echelle clinique d'aptitude intellectuelle; IM, intramuscular; RTI, Neurotest Reaction Times Scale. The significance of other abbreviations is indicated in the text.

Table 4
Clinical trials with choline alfoscerate in patients with acute cerebrovascular disease

First author	Indication	Design	No. of patients	Administration route	Duration of therapy (months)	Tests used
Aguglia	Stroke/TIA	Open	425	Intramuscular, oral	1 i.m.; 5 os	Mathew/MMSE; GDS; CGRS
Barbagallo Sangiorgi	Stroke/TIA	Open	2044	Intramuscular, oral	1 i.m.; 5 os	Mathew/MMSE; GDS; CGRS
Tomasina	Stroke	Open	15	Intramuscular, oral	1 i.m.; 5 os	Mathew/MMSE; SCAG; Psychological Evaluation Scale

The significance of abbreviations is indicated in the text.

is expressed in a score ranging from 0 to 30, where the lower limit of the ‘normality’ of cognitive functions is 23. The results of this largely validated test consistently describe the clinical condition of patients affected by cognitive decline. The MMSE results obtained in the various trials at the beginning and at the end of treatment with choline alfoscerate and with any reference treatment (active or placebo) were analysed.

Table 3 shows the characteristics of six clinical trials carried out with choline alfoscerate including patients affected by chronic cerebrovascular disease. In these trials, the Sandoz Clinical Assessment Geriatric (SCAG) scale meets the three criteria mentioned above for MMSE and was therefore selected for analysis in this review. Similarly, as with MMSE in degenerative dementia, the SCAG results obtained in the various trials on VaD were taken at the beginning and at the end of treatment with choline alfoscerate and with any reference treatment (active or placebo). The SCAG is an instrument for assessing the patient’s clinical condition, developed for use in trials of geriatric psychopharmacology (Venn, 1983). It investigates, in an articulate manner, various aspects of cognitive decline, the emotional–affective disorders and problems faced in the interpersonal relations by elderly patients. The results of this test, similar to the MMSE results, are considered as a good indicator of the patient’s clinical condition.

Clinical results obtained with choline alfoscerate were evaluated by analysing the results of these two tests in the different situations relating to the two main types of chronic cerebral deterioration (degenerative and vascular). Each of these diseases was assessed separately and the relative results are described in the following sections.

2.2. Studies in acute cerebrovascular diseases (TIA, stroke)

Table 4 shows the characteristics of the three clinical trials on choline alfoscerate including a total of 2484 patients with acute cerebrovascular disease. To assess

the functional recovery in the acute post-stroke phase, all investigators used the Mathew's scale (Mathew et al., 1972), whereas the efficacy of the subsequent oral treatment was evaluated by the MMSE (three trials), the Global Deterioration Scale (GDS) (Reisberg et al., 1982) (two trials) or the Crichton Geriatric Rating Scale (CGRS) (Guy, 1976) (two trials).

The Mathew's scale was developed to analyse the functional status of a patient after an acute cerebrovascular event (Mathew et al., 1972). It carefully assesses both cognitive domains (awareness level, orientation) and neurological domains (language, cranial nerve function, motor and sensitive function). The GDS (Reisberg et al., 1982) was developed to quantify by a 1–7 score, the overall seriousness of cognitive decline in the elderly. The CGRS (Guy, 1976) is an 11-item instrument to assess behavioural functions. Each item is attributed a variable score, depending on the patient's conditions, from 1 (normal) to 5 (loss of function).

3. Results

3.1. *Studies in cognitive decline*

The numeric distribution of the trials with respect to various pathologies was quite homogeneous. Most of the studies were controlled trials versus a reference drug or placebo. Overall, 1570 patients were assessed in these trials, 854 of which in controlled trials (Table 1). The numeric distribution of patients both in the controlled and in the uncontrolled clinical trials on choline alfoscerate in the two main chronic diseases (degenerative dementias and VaD) was also quite homogeneous (Table 1).

3.1.1. *Degenerative dementia disorders*

Three of these trials (Abbati et al., 1991; Parnetti et al., 1993; Schettini et al., 1993) considered homogeneous cases and were controlled versus a reference drug or placebo (Table 1, column 1). The remaining three trials considered cases with combined degenerative and vascular forms (Ban et al., 1991; Palleschi and Zuccaro, 1992; Vezzetti and Bettini, 1992), being two open studies and one blind controlled versus placebo (Table 1, column 3). Overall, 565 patients with degenerative dementia disorders—generally mild to moderate—were enrolled in the trials. The three homogeneous-case trials evaluated 186 patients, whereas the three combined-case trials included 379 patients with degenerative dementia disorders. In four trials, choline alfoscerate was administered orally at the dose of 1200 mg per day, while in the remaining studies it was administered intramuscularly at the dose of 1000 mg per day. The duration of the treatment was 3 or 6 months for oral administration and 3 months for parenteral administration. Overall, 505 patients were treated orally (466 for 6 months and 39 for 3 months) and 60 patients were treated intramuscularly. By means of various diagnostic instruments and tests, the trials assessed different aspects of mental deterioration, such as cognitive impairment, behavioural disturbances, changes of interpersonal relations, affective disorders and

somatic problems. In general, in all trials treatment with choline alphoscerate proved to improve the patients' clinical condition, especially regarding memory and attention impairment. Such improvement, measured by tests administered at the beginning and at the end of treatment, recorded marked variations of results obtained at the end of the treatment period, with statistical significance compared to baseline data. In comparative studies, clinical results of choline alphoscerate were superior or equivalent to those observed in the control group under active treatment and consistently superior to the results observed in the placebo group.

Table 5 summarises the results of the MMSE test (average scores) recorded in the various trials at the beginning and at the end of treatment with choline alphoscerate and, if present, with reference treatment (active or placebo). On analysing data of Table 5, the comments detailed below can be made.

1. in all trials, the average MMSE score increased during treatment with choline alphoscerate, indicating a marked improvement of cognitive functions (orientation, memory, attention, language, etc.)
2. in the four controlled studies (Abbati et al., 1991; Ban et al., 1991; Vezzetti and Bettini, 1992; Parnetti et al., 1993; Schettini et al., 1993), the percent increases in the MMSE scores recorded during the treatment with choline alphoscerate varied between 26 and 10%, in a relatively small range. These results were similar to those observed in one trial (Abbati et al., 1991), in which the reference treatment was oxiracetam and superior to those obtained in the other three studies carried out against acetyl-L-carnitine (Parnetti et al., 1993) or placebo (Vezzetti and Bettini, 1992; Schettini et al., 1993);
3. in the two uncontrolled trials (Ban et al., 1991; Palleschi and Zuccaro, 1992) the increases of score observed with choline alphoscerate varied around 18–20% and were therefore at the centre of the variability interval observed in controlled studies. This confirms the role and value of results obtained in uncontrolled trials;
4. in controlled trials, placebo gave hardly ascertainable therapeutic results. In one of the two studies (Schettini et al., 1993) the negative results observed with placebo are consistent with the progressive nature of dementia disorders examined.

3.1.2. *VaD*

Four of these trials (Di Perri et al., 1991; Frattola et al., 1991; Muratorio et al., 1992; Paciaroni and Tomassini, 1993) considered homogeneous cases and were controlled versus reference drug (see Table 1, column 2). Three trials considered cases with combined forms (Ban et al., 1991; Palleschi and Zuccaro, 1992; Vezzetti and Bettini, 1992). Cases of dementia disorders included in these last three trials have been considered in Section 3.1.1. As already mentioned, two of these studies were open and one was blind controlled versus placebo (Table 1, column 3). Overall, 789 patients with VaD were enrolled in the trials. The three homogeneous-case trials evaluated 408 patients, whereas the three combined-case trials included 381 patients with VaD. In four trials, choline alphoscerate was administered orally at the dose of 1200 mg per day for 3 or 6 months, while in the other three studies

Table 5

Results of the MMSE or SCAG tests carried out in patients with neurodegenerative dementia disorders and vascular dementia, respectively

First author	No. of patients	Choline alfoscerate			Reference treatment ^{a,b}		
		Baseline mean ± S.E. (S.D.)	Final mean ± S.E. (S.D.)	Δ%	Baseline mean ± S.E. (S.D.)	Final mean ± S.E. (S.D.)	Δ%
<i>MMSE—neurodegenerative dementia disorders</i>							
<i>Controlled trials</i>							
Abbate	40	23.0 ± 1.2	28.4 ± 2.4	+23.5**	22.3 ± 1.1	27.4 ± 1.2	+22.9**
Parnetti	126	18.3 ± 3.4	20.2 ± 4.9	+10.4*	17.4 ± 3.5	18.5 ± 4.0	+6.3*
Schettini	20	17.9 ± 1.2	20.7 ± 1.4	+15.6*	19.2 ± 1.5	17.6 ± 2.1	-8.3*
Vezzetti	39	23.1	29.2	+26.4	24	25.1	+4.6
<i>Uncontrolled trials</i>							
Ban	294	16.7	19.8	+18.9**			
Palleschi	46	20	24	+20**			
<i>SCAG-vascular dementia</i>							
<i>Controlled trials</i>							
Di Perri	120	56.9	43.1	-24.2*	60.3	48.1	-20.2*
Frattola	126	52.07 ± (10.7)	42.56 ± (12.2)	-18.3*	53.22 ± (10.4)	48.33 ± (13.9)	-9.2*
Muratorio	112	43.44 ± (13.6)	39.98 ± (12.1)	-7.9**	43.08 ± (14.4)	41.65 ± (13.9)	-3.3
Paciaroni	50	54 ± 1.3	38 ± 1.4	-29.6**	53 ± 1.7	43 ± 1.1	-18.9**
<i>Uncontrolled trials</i>							
Ban	350	60.6	46.4	-23.4**			
Palleschi	18	54	43	-20.4**			

^a Neurodegenerative dementia disorders: in Abbate: oxiracetam; in Parnetti: acetyl-L-carnitine; in Schettini and Vezzetti: placebo.

^b VaD: in Di Perri, Frattola, Muratorio: citicholine; in Paciaroni: oxiracetam; * $P < 0.05$; ** $P < 0.01$.

it was administered by intramuscular injection at the dose of 1000 mg per day for 3 months. Of the 431 orally-treated patients, 418 received the drug over 6 months and 13 over 3 months. A total of 358 were treated intramuscularly over 3 months.

For VaD, the investigators assessed by various diagnostic instruments and tests, the different aspects of mental deterioration already mentioned in the preceding section: cognitive impairment, behavioural disturbances, changes of interpersonal relations, affective disorders and somatic problems. Similarly, as observed in degenerative dementia disorders, treatment with choline alfoscerate improved overall clinical symptoms, such as memory and attention impairment, affective disorders and somatic symptoms (fatigue, dizziness) in all trials on VaD.

The results of various tests administered before and at the end of the treatment confirmed statistically the extent of this improvement. Moreover, in controlled

Table 6

Percent decrease in the SCAG scores of patients with vascular dementia treated intramuscularly for 3 months with choline alfoscerate or citicholine

First author	No of patients	Choline alfoscerate	Citicholine	Δ	<i>P</i>
Di Perri	120	-24.2	-20.2	2	n.s
Frattola	126	-18.3	-9.2	9.1	0.05
Muratorio	112	-7.9	-3.3	4.6	n.s

Table 7
Results of tests carried out in patients with TIA or stroke treated with choline alfoscerate

First author	No of patients	Baseline mean	Final mean	$\Delta\%$	<i>P</i>
<i>1st month—intramuscular treatment</i>					
<i>Mathew's Scale</i>					
Aguglia	425	62.02	73.53	+18.56	0.001
Barbagallo Sangiorgi	2044	58.7	74.6	+27.1	0.001
Tomasina	15	61.55	73.4	+19.2	–
<i>2nd to 6th month—oral treatment</i>					
<i>MMSE</i>					
Aguglia	425	21.53	24.19	+12.35	0.001
Barbagallo Sangiorgi	2044	21	24.3	+15.7	0.001
Tomasina	15	22.13	25.5	+15.2	0.05
<i>Global deterioration scale</i>					
Aguglia	425	2.63	2.10	–20.15	0.001
Barbagallo Sangiorgi	2044	2.72	2.16	–20.6	0.001
<i>Crichton geriatric rating scale</i>					
Aguglia	425	19.31	15.63	–19.06	0.001
Barbagallo Sangiorgi	2044	20.2	15.9	–21.3	0.001

trials, choline alfoscerate gave clinical efficacy results equal or superior to those observed in the control group under active treatment and superior to the results obtained with placebo. Analysis of SCAG results on VaD before and at the end of the treatment reported in Table 5, raises comments similar to the above comments on MMSE in degenerative dementia disorders.

1. in all trials, the average SCAG score decreased during treatment with choline alfoscerate, indicating a marked clinical improvement of symptoms assessed by SCAG scale, such as disorientation, irritability, emotional lability and indifference to surroundings;
2. in the four controlled studies (Frattola et al., 1991; Di Perri et al., 1991; Muratorio et al., 1992; Paciaroni and Tomassini, 1993), the percent decreases in the overall SCAG score recorded during the treatment with choline alfoscerate vary between 30 and 8%. Comparison between choline alfoscerate and citicholine gave SCAG scores more favourable to choline alfoscerate, whereas in all trials the two treatment groups record average decreases of similar extent (Table 6). This suggests that compared groups were substantially balanced as regards the clinical variables. Oxiracetam showed a clinical efficacy comparable with the average results obtained with choline alfoscerate;
3. in the two uncontrolled trials (Ban et al., 1991; Palleschi and Zuccaro, 1992), the decreases observed varied from 20 to 23%, in a range at the centre of the variability interval observed in controlled studies. Similarly, as mentioned above for dementia disorders, these data suggest the value of uncontrolled clinical observations as well.

One of the controlled trials (Muratorio et al., 1992) included a follow-up period of 3 months. In patients treated with choline alfoscerate, but not in the reference group, improvement of SCAG score persisted at the end of this period. Authors have put in relationship these findings with a neuroprotective activity of choline alfoscerate on nervous structures involved in the cognitive processes (Muratorio et al., 1992). The neuroprotective activity of choline alfoscerate, probably related to its property of restoring membrane phospholipid fluidity suggests that treatment could be suspended for some time without affecting clinical results obtained. This may have obvious favourable effects on patients' compliance and on treatment cost.

3.2. *Studies in acute cerebrovascular diseases*

The treatment protocol was identical in the three trials (Tomasina et al., 1991; Aguglia et al., 1993; Barbagallo Sangiorgi et al., 1994). It consisted in intramuscular treatment with a daily dose of 1000 mg per day choline alfoscerate in the 4 weeks following the acute event. This parenteral administration was followed by a 5-month oral administration of the drug at the dose of 1200 mg per day. In all three trials, parenteral treatment with choline alfoscerate favoured cognitive, functional and motor recovery in the acute phase, while the subsequent oral treatment consolidated the clinical results obtained in the acute phase and positively influenced the whole clinical course. In Table 7, the results of the Mathew's scale regarding the parenteral therapy in the acute phase (first month) and the results of the three assessments (MMSE, GDS, CGRS) carried out in at least two of the three trials at the beginning and at the end of the oral treatment (second to sixth month) were reported.

Data in Table 7 suggest the following observations:

1. in the 4 weeks of parenteral treatment with choline alfoscerate, the extent of the recovery of neurological functions was clinically relevant and varied around 20–30% in the three trials;
2. the subsequent phase of oral treatment gave relevant results as well. Moreover, each of the three tests used to evaluate the extent of the clinical improvement (MMSE, GDS, CGRS) gave comparable clinical results in the different experimental situations where they were used: + 15/12% for MMSE, – 20% for GDS, – 19/21% for the CGRS scale;
3. in spite of limits deriving from the absence of control groups treated with reference drugs or placebo, the extent and the consistency of clinical results observed in the three trials suggests the existence of a therapeutic effect of choline alfoscerate, both when administered parenterally in the post-stroke phase or in the subsequent long term oral treatment.

4. Conclusions

The clinical efficacy of choline alfoscerate in controlling the symptoms of cognitive decline associated with dementia disorders, both of degenerative and vascular origin, were verified in a large number of patients treated with the drug in

controlled trials versus reference drugs or placebo. The significant improvement observed makes choline alfoscerate different from other cholinergic precursors, such as choline or lecithin, that although extensively tested in clinical trials in the past, both alone or in association with AChE inhibitors, did not provide evidence of improving cognitive impairment typical of dementia disorders (Davis et al., 1993; Mayeux and Sano, 1999).

The extent of improvement of cognitive functions observed with choline alfoscerate in the various case reports was generally high. Clinical results obtained with choline alfoscerate were superior or equivalent to those observed in the control groups under active treatment and superior to the results observed in placebo groups. Among data gathered up to date in different situations in which the drug was tested, it was noticeable a significant activity of choline alfoscerate on cognitive symptoms, such as memory and attention, that characterize the clinical picture of dementia disorders.

To sum up, controlled clinical trials reviewed in this paper have demonstrated the efficacy of choline alfoscerate in clinical situations associated with cognitive impairment characteristic of dementia disorders, both of degenerative and vascular origin. The stated therapeutic usefulness of choline alfoscerate in the relief of cognitive symptoms, such as memory and attention impairment, differentiates the drug from cholinergic precursors used in former clinical trials. Also, the results of uncontrolled trials carried out in the treatment of TIA or stroke suggest that choline alfoscerate might favour functional recovery of patients with acute cerebrovascular event. Although these findings need to be confirmed by controlled trials, published clinical data collectively suggest a clinical efficacy of this cholinergic precursor in cognitive impairment occurring in dementia disorders.

References

- Abbati, C., Rondi, G., Rosola, R., Vavassori, F., Bosio, A., 1991. Nootropic therapy of cerebral aging. *Adv. Ther.* 8, 268–276.
- Aguglia, E., Ban, T.A., Panzarasa, R.M., Borra, S., Fjetland, O.K., 1993. Choline alfoscerate in the treatment of mental pathology following acute cerebrovascular accident. *Funct. Neurol. (Suppl.)* 8, 5–24.
- Aleppo, G., Nicoletti, F., Sortino, M.A., Casabona, G., Scapagnini, U., Canonico, P.L., 1994. Chronic L- α -glycerylphosphorylcholine increases inositol phosphate formation in brain slices and neuronal cultures. *Pharmacol. Toxicol.* 74, 95–100.
- Amenta, F., Franch, F., Ricci, A., Vega, J.A., 1993. Cholinergic neurotransmission in the hippocampus of aged rats: influence of L- α -glycerylphosphorylcholine treatment. *Ann. N.Y. Acad. Sci.* 695, 311–313.
- Ban, T.A., Panzarasa, R.M., Borra, S., Del Duchetto, D., Fjetland, O.K., 1991. Choline alfoscerate in elderly patients with cognitive decline due to dementing illness. *New Trends Clin. Neuropharmacol.* 5, 1–35.
- Barbagallo Sangiorgi, G., Barbagallo, M., Giordano, M., Meli, M., Panzarasa, R., 1994. Glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial. *Ann. N.Y. Acad. Sci.* 717, 253–269.
- Bartus, R., Dean, R.I., Beer, B., Lippa, A., 1982. The cholinergic hypothesis of geriatric memory dysfunction. *Science* 217, 408–414.

- Bergamaschi, M., 1995. Deacylated phospholipids: chemistry and therapeutic potential. In: Cvec, G., Paltauf, F. (Eds.), *Phospholipids: Characterization, Metabolism, and Novel Biological Applications*. AOCS Press, USA, pp. 228–247.
- Brinkman, S.D., Smith, R.C., Meyer, J.S., Vroulis, G., Shaw, T., Gordon, J.R., Allen, R.H., 1982a. Lecithin and memory training in suspected Alzheimer's disease. *J. Gerontol.* 37, 4–9.
- Brinkman, S.D., Pomara, N., Goodnick, P.J., Barnett, N., Domino, E.F., 1982b. A dose-ranging study of lecithin in the treatment of primary degenerative dementia (Alzheimer disease). *J. Clin. Psychopharmacol.* 2, 281–285.
- Canonico, P.L., Nicoletti, F., Scapagnini, U., 1990. Effetti neurochimici e comportamentali di α -GFC (colina alfoscerato). *Basi. Raz. Ter.* 20, 53–54.
- Carlsson, A., 1987. Brain neurotransmitters in ageing and dementia: similar changes across diagnostic dementia groups. *Gerontology* 33, 159–167.
- Casamenti, F., 1979. Effect of phosphatidylserine on Ach output from the cerebral cortex of the rat. *J. Neurochem.* 32, 529–533.
- Clark, W.M., 1997. A randomized dose–response trial of citicholine in acute ischemic stroke patients. *Neurology* 49, 671–678.
- Davies, P., Maloney, A., 1976. Selective loss for central cholinergic neurons in Alzheimer's disease. *Lancet* 2, 1403.
- Davis, E.R., Emmerling, M.R., Jaen, J.C., Moos, W.H., Spiegel, K., 1993. Therapeutic intervention in dementia. *Crit. Rev. Neurobiol.* 7, 41–83.
- Di Perri, R., Coppola, G., Ambrosio, L.A., Grasso, A., Puca, F.M., Rizzo, M., 1991. A multicentre trial to evaluate the efficacy and tolerability of α -glycerylphosphoryl-choline versus cytidine diphosphocholine in patients with vascular dementia. *J. Int. Med. Res.* 19, 330–341.
- Drago, F., Nardo, L., Freni, V., Spadaro, F., Valerio, C., 1990. Effetti comportamentali di α -GFC in modelli di invecchiamento cerebrale patologico. *Basi. Raz. Ter.* 20, 65–68.
- Ehrenstein, G., 1997. The choline-leakage hypothesis for the loss of acetylcholine in Alzheimer's disease. *Biophys. J.* 73, 1276–1280.
- Etienne, P., Dastoor, D., Gauthier, S., Ludwick, R., Collier, B., 1981. Alzheimer disease: lack of effect of lecithin treatment for 3 months. *Neurology* 31, 1552–1554.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini Mental State—a practical method for grading the cognitive state of patients for the clinician. *Psychiatry Res.* 12, 189–198.
- Fratolla, L., Piolti, R., Bassi, S., Albizzati, M.G., Galetti, G., Grumelli, B., 1991. Colina alfoscerato (α -GFC) nel trattamento della demenza multifattoriale. Studio clinico multicentrico comparativo vs CDP-colina. *Giorn. It. Ric. Clin. Ter.* 12, 159–166.
- Govoni, S., Lopez, C., Battaini, F., Longoni, A., Trabucchi, M., 1990. Effetti di α GFC sul comportamento di evitamento passivo del ratto e sui livelli di acetilcolina. *Basi. Raz. Ter.* 20, 55–60.
- Growdon, J.H., Corkin, S., Huff, F.J., Rosen, T.J., 1986. Piracetam combined with lecithin in the treatment of Alzheimer's disease. *Neurobiol. Aging* 7, 269–276.
- Guy, W., 1976. *ECDEU Assessment Manual for Psychopharmacology*. DPKEW (ADM) Bethesda, 76–338.
- Heyman, A., Schmechel, D., Wilkinson, W., Rogers, H., Krishnan, R., Holloway, D., Schultz, K., Gwyther, L., Peoples, R., Utley, C., 1987. Failure of long term high-dose lecithin to retard progression of early-onset Alzheimer's disease. *J. Neural. Transm. Suppl.* 24, 279–286.
- Jope, R.S., 1982. Effects of phosphatidylcholine administration to rats on choline in blood and choline and Ach in brain. *J. Pharmacol. Exp. Ther.* 220, 322–328.
- Kasa, P., 1997. The cholinergic system in Alzheimer's disease. *Prog. Neurobiol.* 52, 511–535.
- Little, A., Levy, R., Chuaqui, K.P., Hand, D., 1985. A double-blind, placebo controlled trial of high-dose lecithin in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 48, 736–742.
- Mayeux, R., Sano, M., 1999. Drug therapy: treatment of Alzheimer disease. *New Engl. J. Med.* 341, 1670–1679.
- Mathew, N.T., Mayer, J.S., Rivera, V.M., 1972. Double-blind evaluation of glycerol therapy in acute cerebral infarction. *Lancet* 1, 1227–1231.
- Muratorio, A., Bonuccelli, U., Nuti, A., Battistini, N., Passero, S., 1992. A neurotropic approach to the treatment of multi-infarct dementia using L- α -glyceryl-phosphorylcholine. *Curr. Ther. Res.* 52, 741–751.

- Paciaroni, E., Tomassini, P.F., 1993. Studio clinico di efficacia e tollerabilità di α -GFC (colina alfoscerato), controllato vs oxiracetam in pazienti affetti da declino cognitivo di grado lieve-moderato su base vascolare. *Giorn. It. Ric. Clin. Ter.* 14, 29–34.
- Palleschi, M., Zuccaro, S.M., 1992. Valutazione di efficacia e tollerabilità di α -GFC (colina alfoscerato) in pazienti affetti da declino cognitivo di grado lieve-moderato. *Geriatrics* 4, 61–65.
- Parnetti, L., Abate, G., Bartorelli, L., Cucinotta, D., Cuzzupoli, M., Maggioni, M., Villardita, C., Senin, U., 1993. Multicentre study of L- α -glyceryl-phosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's type. *Drugs Aging* 3, 159–164.
- Perry, E.K., Tomlinson, B.E., Blessed, G., Bergmann, K., Gibson, P., Perry, R.H., 1978. Correlation of cholinergic abnormalities with senile plaques and mental test scores in dementia. *Br. Med. J.* 2, 1457–1459.
- Pomara, N., Domino, E.F., Yoon, H., Brinkman, S., Tamminga, C.A., Gershon, S., 1983. Failure of single-dose lecithin to alter aspects of central cholinergic activity in Alzheimer's disease. *J. Clin. Psychiatry* 44, 293–295.
- Reynolds J.E.F. (Eds.), 1996. Parasympathomimetics. In: Martindale—The Extra Pharmacopoeia, thirty-first ed. Royal Pharmaceutical Society, London, pp. 1413–1428.
- Reisberg, B., Ferris, S.H., De Leon, M.J., 1982. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am. J. Psychiatry* 139, 1136–1139.
- Samorajski, T., Vroulis, G.A., Smith, R.C., 1985. Piracetam plus lecithin trials in senile dementia of the Alzheimer type. *Ann. N.Y. Acad. Sci.* 444, 478–481.
- Schettini, G., Florio, T., Ventra, C., Grimaldi, M., Meucci, O., Landolfi, E., 1990. Effetto del trattamento in vivo con α -GFC (colina alfoscerato) sull'attività dei sistemi di trasduzione a livello cerebrale. *Basi. Raz. Ter.* 20, 23–30.
- Schettini, G., Cicerano, U., Pellegrino, G., Soricelli, A., Postiglione, A., 1993. Effetto della colina alfoscerato in pazienti anziani affetti da demenza degenerativa primaria. *Basi. Raz. Ter.* 23, 108–116.
- Secades, J.J., 1995. CDP-choline; pharmacological and clinical review. *Methods Find. Exp. Clin. Pharmacol. (Suppl. B)* 17, 2–54.
- Sigala, S., Imperato, A., Rizzonelli, P., Casolini, P., Missale, C., Spano, P.F., 1992. L-alpha-glycerylphosphorylcholine antagonizes scopolamine-induced amnesia and enhances hippocampal cholinergic transmission in the rat. *Eur. J. Pharmacol.* 21, 351–358.
- Smith, R.C., Vroulis, G., Johnson, R., Morgan, R., 1984. Comparison of therapeutic response to long-term treatment with lecithin versus piracetam plus lecithin in patients with Alzheimer's disease. *Psychopharmacol. Bull.* 20, 542–545.
- Tazaki, Y., 1988. Treatment of acute cerebral infarction with a choline precursor in a multicenter double blind placebo-controlled study. *Stroke* 19, 211–215.
- Thal, L.J., Rosen, W., Sharpless, N.S., Crystal, H., 1981. Choline chloride fails to improve cognition of Alzheimer's disease. *Neurobiol. Aging* 2, 205–258.
- Tomasina, C., Manzino, M., Novello, P., Pastorino, P., 1991. Studio clinico dell'efficacia terapeutica e della tollerabilità della colina alfoscerato in 15 soggetti con compromissione delle funzioni cognitive successiva ad ischemia cerebrale focale acuta. *Riv. Neuropsichiatria Sci. Affini.* 37, 21–28.
- Venn, R.D., 1983. The Sandoz Clinical Assessment Geriatric (SCAG) Scale—a general purpose psychogeriatric rating scale. *Gerontology* 29, 185–198.
- Vezzetti, V., Bettini, R., 1992. Valutazione clinica e strumentale dell'effetto della colina alfoscerato sul decadimento cerebrale. *Presse Med. It.* 5, 141–144.
- Wecker, L., Schmidt, D.E., 1979. Central cholinergic function in the rat relationship to choline administration. *Life Sci.* 25, 375–384.
- Whitehouse, P., Price, D.L., Clark, A.W., Coyle, J.T., DeLong, M.R., 1981. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann. Neurol.* 10, 122–126.
- Whitehouse, P., Price, D., Struble, R., Clark, A., Coyle, J., DeLong, M., 1982. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 215, 1237–1239.