Choline Alphoscerate (Alpha-Glyceryl-Phosphoryl-Choline) An Old Choline-containing Phospholipid with a Still Interesting Profile As Cognition Enhancing Agent

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Abstract: Cholinergic precursors have represented the first approach to counter cognitive impairment occurring in adult-onset dementia disorders. These compounds were early leaved because their clinical efficacy was not clearly demonstrated. This is probably not true for some choline-containing phospholipids including choline alphoscerate. Choline alphoscerate increases the release of acetylcholine in rat hippocampus, facilitates learning and memory in experimental animals, improves brain transduction mechanisms and decreases age-dependent structural changes occurring in rat brain areas involved in learning and memory. The compound exerts neuroprotective effects in models of altered cholinergic neurotransmission and of brain vascular injury. In clinical studies choline alphoscerate improved memory and attention impairment, as well as affective and somatic symptoms in dementia disorders. An ongoing trial indicates that association between the acetylcholinesterase inhibitor donepezil and choline alphoscerate is accompanied by an improvement in several cognitive tests superior to that induced by donepezil alone. It is suggested that this association may represent a therapeutic option to prolong beneficial effects of cholinergic therapies in Alzheimer’s disease patients with concomitant ischemic cerebrovascular disorders. In summary, choline alphoscerate has significant effects on cognitive function with a good safety profile and tolerability. Although limited both in terms of size of the samples investigated and of the length of treatment, preclinical and clinical results presented suggest that cognitive enhancing capabilities of choline alphoscerate merit of being further investigated in appropriate trials.

Keywords: Adult-onset dementia, choline alphoscerate, cholinergic neurotransmission, clinical trials, preclinical studies.

1. INTRODUCTION

Changes in cholinergic function are implicated in the pathogenesis of learning and memory alterations occurring in adult-onset cholinergic dysfunction including dementia disorders [1-5]. Brain cholinergic pathways are not the only neurotransmitter system affected in cognitive dysfunction common of Alzheimer’s disease or vascular dementia, but their involvement in cognition is commonly accepted [1-5].

Studies of the brain of patients suffering from Alzheimer’s disease have shown marked loss of the acetylcholine synthesizing enzyme choline acetyltransferase and of nicotinic cholinergic receptors [1-5]. Administration of the muscarinic antagonist scopolamine to healthy young subjects induces a cognitive impairment resembling that found in adult-onset dementia [6]. A correlation between the loss of cortical cholinergic synapses and between this loss and the decrease of high affinity cholinergic receptors was reported [1-5]. These findings have contributed to the development of the so called cholinergic hypothesis of geriatric memory dysfunction [3]. They served also as the conceptual basis to consider restoration of deficient cholinergic neurotransmission involving primarily the basal forebrain as a possible treatment of adult-onset dementia disorders [7].

Cholinergic precursors have represented an old approach to treat cholinergic dysfunction and cognitive decline in adult-onset dementia [8, 9]. Many of these precursors were early leaved because their efficacy was not clearly demonstrated. This is not true for some cholinergic precursors including choline alphoscerate, a cholinergic precursor available in the pharmaceutical market of several countries, which has been studied both in preclinical paradigms and in clinical trials [10].

Choline and the choline-containing phospholipid phosphatidylcholine are essential for maintaining cell membrane integrity and structure. Choline is also required to transport fats in and out of cells, and is a precursor of acetylcholine. Choline is probably one of the most basic nutrients necessary for optimal cognitive function being the precursor for acetylcholine. It is also used by cellular machinery for synthesizing phosphatidylcholine [6, 11, 12].

(Fig. 1) summarizes acetylcholine anabolic pathways [6]. As shown, the enzyme glyceryl-phosphorylcholine diesterase transforms alpha glyceryl-phosphorylcholine into a molecule of choline and another of glycerol-1-phosphate.
Choline can be used to synthesize acetylcholine, whereas glycerol-1-phosphate after being phosphorylated can enter in the pool of phospholipids [6, 13]. These pathways provide both free choline and phospholipids for preparing acetylcholine and to reorganize nerve cell membrane components. Free choline administration increases brain choline availability but it does not increase acetylcholine synthesis/or release [6]. Acetylcholine is a neurotransmitter derived from choline and acetyl coenzyme A, the biosynthesis of which is catalyzed by choline acetyltransferase. Nervous tissue is unable to synthesize choline, which derives from the diet and is delivered to neurons through the blood stream. Acetylcholine released from cholinergic synapses is hydrolyzed by acetylcholinesterase into choline and acetyl coenzyme A. Approximately 50% of choline derived from acetylcholine hydrolysis is received through a high affinity transporter. Therefore neurons require a further supply of choline for synthesizing acetylcholine [6].

Choline alphoscerate or alpha-glyceryl-phosphorylcholine (ATC code N07AX02) (GPC) (Fig. 2) is a semi-synthetic derivative of lecithin. Following oral administration, it is converted to phosphorylcholine, a metabolically active form of choline able to reach cholinergic nerve terminals where it increases acetylcholine synthesis, levels and release [6, 8].

Although choline alphoscerate is in the pharmaceutical market since 1987, the interest on it was apparently reduced after the introduction in therapy of cholinesterase inhibitors. In the last 10 years a renewed attention on the compound was seen with preclinical studies, clinical investigations and review articles published in literature [10, 14-17]. This paper summarizes the main preclinical and clinical studies documenting a cognition-enhancing activity of choline alphoscerate.

Fig. (1). Acetylcholine synthetic pathways. Interference of choline-containing compounds. Modified from [8]. Steps in which choline alphoscerate can influence neurotransmitter biosynthesis are shown. Cytidin diphosphate (CDP); Cytidin triphosphate (CTP); Glyceryl-phosphorylcholine diesterase (GPD); Choline acetyltransferase (ChAT); Choline kinase (ChK); Phosphocholine cytidyl transferase (PCT).

Fig. (2). Chemical structure of choline alphoscerate.

2. PRECLINICAL STUDIES

Choline alphoscerate interferes with brain phospholipid metabolism and increases brain choline and acetylcholine levels and release [6, 8]. Pharmacodynamic studies on choline alphoscerate during phases of development of the compound were focused primarily on its role in potentiating brain cholinergic neurotransmission and in interfering with brain phospholipid metabolism. Preclinical studies have demonstrated that choline alphoscerate increases the release of acetylcholine in rat hippocampus [9], facilitates learning and memory in experimental animals [18], improves brain transduction mechanisms [19, 20] and decreases the age-dependent structural changes occurring in the rat frontal cortex and hippocampus [21]. Moreover, the compound contributes to anabolic processes responsible for membrane phospholipid and glycerolipid synthesis, positively influencing membrane fluidity [22]. Choline alphoscerate was demonstrated to improve cognitive deficit in experimental models of aging brain [23, 24] and to reverse mnemonic deficits induced by scopolamine administration [9, 18]. Based on the above evidence, the central parasympathomimetic activity of the compound was defined, suggesting its clinical use in patients affected by cognitive decline. Consistently with the
activity of the cholinergic system was documented by studies performed in old rodents. In these investigations the compound was able to counter age-related changes in brain acetylcholine synthesizing (choline acetyltransferase) and degrading (acetylcholinesterase) enzymes [26] and of some muscarinic cholinergic receptors subtypes [27, 28]. Neurprotective effects of choline alphoscerate were also reported in a rodent model of altered cholinergic neurotransmission caused by lesioning of the Nucleus Basalis Magnocellularis which represents the main source of cholinergic innervation of cerebral neocortex [29, 30]. A positive effect of treatment with choline alphoscerate on hippocampus microanatomy and glial reaction was documented in spontaneously hypertensive rats [31]. Glial reaction represents an early sign of brain damage and spontaneously hypertensive rats model of vascular brain injury used to mimic to some extent neuropathological changes occurring in vascular dementia [32]. Among cholinergic precursors tested lecithin, cytidine 5'-diphosphocholine (CDP-choline) and choline alphoscerate, the latter elicited the most relevant stimulation on vesicular acetylcholine and choline transporters in the same model of brain vascular injury. This suggests that it represents an enhancer of central cholinergic neurotransmission [33].

Effects of choline alphoscerate were investigated not only in rodent models of aging or of lesioning of brain cholinergic nuclei, but also in Rhesus monkeys. In this species, the compound revealed general facilitatory properties on retinal neurotransmission as well as specific spatial frequency tuning effects on retinal information processing [33].

More recent studies have demonstrated that association of choline alphoscerate with (acetyl)cholinesterase inhibitor rivastigmine induced an increase of brain acetylcholine levels and of high affinity choline uptake binding sites more pronounced than single drugs alone [34]. This suggests that combination of a suitable precursor of brain acetylcholine such as choline alphoscerate and of an acetylcholinesterase inhibitor may represent an association worthwhile of being investigated as a cholinergic replacement therapy in pathologies characterized by impaired cholinergic neurotransmission [34]. This working hypothesis was supported by the demonstration of a more sustained neurprotective action by choline alphoscerate plus the acetylcholinesterase inhibitor galantamine than the two drugs administered alone [35].

Other preclinical studies published in the last few years were focused on the activity of choline alphoscerate on neurotransmitter transporter systems. Plasma membrane and vesicular transporters for acetylcholine, and monoamines (dopamine, norepinephrine, and serotonin) are specific proteins with a role in the regulation of neurotransmission and may represent a target for the action of therapeutic agents [15, 23]. Cholinergic transporters including high-affinity choline uptake and vesicular acetylcholine transporters control cellular mechanisms of acetylcholine synthesis and release at presynaptic terminals and loading of it into synaptic vesicles respectively. Treatment for 4 weeks of spontaneously hypertensive rats with choline alphoscerate increased high-affinity choline uptake and vesicular acetylcholine transporters in the frontal cortex, striatum and hippocampus as well as in peripheral blood lymphocytes considered as a marker of brain cholinergic transporters [15]. This effect of choline alphoscerate was considered consistent with the increased synthesis of acetylcholine it induces [15].

The activity of choline-containing phospholipids on brain phospholipid biosynthesis may influence brain metabolism and different neurotransmitter systems. Based on the observation that the choline-containing phospholipids CDP-choline has a monoaminergic profile, the activity of choline alphoscerate on brain dopamine, and serotonin levels and on dopamine plasma membrane transporter, vesicular monoamine transporters 1 and 2, serotonin transporter and norepinephrine transporter was investigated [17]. Administration of the compound increased dopamine levels in frontal cortex and cerebellum and serotonin levels in frontal cortex and striatum. It also stimulated dopamine plasma membrane transporter in frontal cortex and cerebellum. This investigation concluded that choline alphoscerate possesses also a monoaminergic profile and interferes to some extent with brain monoamine transporters [17].

3. PHARMACOKINETICS

The kinetics and metabolism of choline alphoscerate (GPC) were investigated in male and female rats after intravenous (10 mg/kg) and oral doses (100-300 mg/kg) of the compound labeled with [14C]-glycerol ([14G]-GPC) or [14C]-choline ([14C]-GPC). Different kinetic and metabolic profiles were observed after intravenous and oral administration. Choline alphoscerate is hydrolyzed by phosphodiesterases in the gut mucosa. The labeled metabolites have diverse kinetic properties of absorption, distribution and clearance, leading to different blood concentration-time curves of total radioactivity. Both labeled compounds gave a wide distribution of radioactivity, particularly concentrated in the liver, kidney, lung and spleen compared to blood. Brain concentrations of [14C]-GPC were comparable to ([14C]-GPC) or lower than ([14C]-GPC) total blood radioactivity. The metabolite profile in the perfused brain showed a small amount of choline and two unknown metabolites, probably the same as in blood. In addition, choline was incorporated into brain phospholipids in increasing amounts within 24 h of dosing. In all cases renal and fecal excretion of radioactivity was low and comparable for [14C]-GPC and [14C]-GPC. Mostly of the administered radioactivity was exhaled as 14CO2, this degradation being faster and more pronounced for the glycerol-labeled metabolites than for the choline-labeled metabolites for both routes of administration [36].

Plasma choline levels were higher in eight healthy volunteers after intramuscular administration of choline alphoscerate compared to placebo [37]. Mean plasma choline levels in the placebo group ranged from 10.6 to 12.0 μM. After choline alphoscerate administration, the plasma choline level reached 35.1 μM in 30 min, and then decreased gradually. Plasma choline levels became comparable in the treated and placebo groups 6-8 h after administration [37]. These pharmacokinetic data further support the view that choline alphos-
Choline Alphoscerate (Alpha-Glyceryl-Phosphoryl-Choline) increases the bioavailability of choline which is converted in acetylcholine.

An increased of brain cholinergic tone by administration of choline alphoscerate was demonstrated by the clinical pharmacology study mentioned below [38]. Growth hormone (GH) secretion is decreased in aging. This decrease may be due to increased hypothalamic somatostatin release, which is inhibited by cholinergic agonists, or to decreased secretion of GHRH. Administration of choline alphoscerate elicited a greater GH response to the GHRH compared to placebo and potentiated GH secretion more effectively in elderly subjects. These findings support the view that administration of choline alphoscerate increases cholinergic tone and results in enhanced GH release [38].

4. CLINICAL EFFICACY

As mentioned in the introduction, cholinergic precursor loading therapy was the first approach tried to relief cognitive impairment in dementia disorders. Controlled clinical trials failed to show significant improvements with choline or phosphatidylcholine (lecithin), a choline-containing phospholipid [39], alone or in association with cholinesterase inhibitors (tacrine plus choline, or physostigmine plus choline) [40]. The negative effects with choline or phosphatidylcholine [8, 40] cannot be generalized for all cholinergic precursors. It is thought that phosphatidylcholine increases brain choline and acetylcholine concentrations [40, 41]; although an effect of this precursor on neurotransmitter synthesis was not confirmed by all studies [42]. A possible reason for the lack of effectiveness of phosphatidylcholine is that it can provide choline for acetylcholine synthesis only in conditions of stimulated neurotransmitter release [43].

Other cholinergic precursors such as CDP-choline and choline alphoscerate increase acetylcholine content and release [18, 44-46]; being choline alphoscerate more effective than CDP-choline in rising plasma choline levels [44]. The reasons of the different effects of the above compounds on acetylcholine synthesis and release are unclear. It cannot be excluded that the activity observed in clinical trials with different cholinergic precursors depends from the availability of acetylcholine they induce [8].

The main clinical experiences with choline alphoscerate in adult-onset cognitive disorders are summarized below. The majority of clinical studies available on the effect of choline alphoscerate on cognitive function in neurodegenerative and cerebrovascular disorders were detailed in two review articles of our group [9, 47] and are summarized in (Table 1). Studies published before 2001 have investigated 1,570 patients, 854 of which were included in controlled trials. Patients examined were affected by dementia of degenerative, vascular or combined origin, such as dementia of the Alzheimer's type, vascular dementia and acute cerebrovascular diseases [transitory ischemic attack (TIA) and stroke] [47]. Test batteries for assessing the effect of choline alphoscerate on cognitive domains were primarily the Mini Mental State Evaluation (MMSE) in disorders of neurodegenerative origin and the Sandoz Clinical Assessment Geriatric (SCAG) scale in disorders of vascular origin (e.g. vascular dementia) [47].

Overall, 565 patients with cognitive impairment of degenerative origin of mild to moderate grade were enrolled. Three homogeneous-case trials evaluated 186 patients, whereas the three combined-case trials included 379 patients with degenerative dementia. In four trials, choline alphoscerate was given orally at the dose of 1,200 mg/day (466 patients treated for 6 months and 39 for 3 months). In the remaining studies it was administered intramuscularly at the dose of 1,000 mg/day. The duration of treatment was 3 or 6 months for oral administration and 3 months for parenteral administration. These trials documented that choline alphoscerate improved the patients’ clinical condition with particular reference to memory and attention [47]. Comparison between choline alphoscerate and acetyl-l-carnitine gave scores more favorable to choline alphoscerate [47].

<p>| Table 1. Clinical Trials on Choline alphoscerate in Cognitive Dysfunction of Neurodegenerative or Vascular Origin and in Cerebrovascular Disease |</p>
<table>
<thead>
<tr>
<th>CI of NDG Origin</th>
<th>CI of VAS Origin</th>
<th>CI of Combined NDG and VAS Origin</th>
<th>TIA or Stroke</th>
<th>Total</th>
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</thead>
<tbody>
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<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Controlled</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>826</td>
<td>789</td>
<td>216</td>
<td>2,484</td>
</tr>
<tr>
<td>Controlled</td>
<td>486</td>
<td>421</td>
<td>208</td>
<td>0</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>340</td>
<td>368</td>
<td>8</td>
<td>2,484</td>
</tr>
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</table>

Data summarized in this table were discussed critically in a previous paper of our group [9]. CI: Cognitive impairment NDG: Neurodegenerative; VAS: Vascular; TIA: Transient ischemic attack.
The activity of choline alphoscerate was also investigated in 789 patients with cognitive impairment of vascular origin. Three homogeneous-case trials evaluated 408 patients and three combined-case trials included 381 patients with vascular dementia. In four trials, choline alphoscerate was administered orally at the dose of 1,200 mg/day for 3 or 6 months, while in the other three studies it was administered by intramuscular injection at the dose of 1,000 mg/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. In these studies, investigators thoroughly assessed cognitive impairment, behavioural disturbances, and changes of interpersonal relations, affective disorders and somatic problems. Similarly as observed in degenerative dementia disorders in all trials on cognitive impairment of vascular origin, treatment with choline alphoscerate improved memory and attention, as well as affective and somatic symptoms (fatigue, vertigo). Effects of choline alphoscerate were greater than those of placebo and of the same extent or superior of those of reference compounds [47]. Comparison between choline alphoscerate and CDP-choline gave SCAG scores more favorable to choline alphoscerate [47]. Oxiracetam was reported to have an activity comparable with choline alphoscerate in two uncontrolled trials [47].

Choline alphoscerate was also investigated in three uncontrolled studies examining its activity in acute cerebrovascular disease [47]. Treatment consisted in the intramuscular administration of a daily dose of 1,000 mg/day of choline alphoscerate in the 4 weeks following the acute event. Parenteral administration was followed by a 5-month oral administration of the drug at the dose of 1,200 mg/day. In these trials, parenteral treatment with choline alphoscerate favored cognitive, functional and motor recovery in the acute phase. The subsequent oral treatment consolidated clinical results obtained in the acute phase and positively influenced the whole clinical course. Unfortunately, the typology of these studies makes them of marginal relevance [47].

A more recent trial has evaluated 261 patients aged 72.2 ± 7.5 years (132 treated for 180 days with 400 mg tablets of choline alphoscerate 3 times a day and 129 included in the placebo group) affected by mild to moderate dementia of the Alzheimer’s type [48]. In patients under active treatment, the mean decrease in Alzheimer’s Disease Assessment Scale (ADAS)-Cognition subscale (Cog) score was 2.42 points after 90 days of therapy and 3.20 points at the end of the study (day 180), whereas in the placebo group a mean increase in ADAS-Cog score of 0.36 point (p < 0.001 vs. baseline) after 90 days and of 2.90 points after 180 days of observation (p < 0.001 vs. baseline) was noticeable. Other parameters assessed [MMSE, Global Deterioration Scale (GDS), ADAS Behaviour subscale (Behav), ADAS-Total, and Clinical Global Impression (CGI)] improved after 90 and 180 days versus baseline, whereas in the placebo group they remained unchanged or worsened. Statistically significant differences were observed between treatments after 90 and 180 days in ADAS-Cog, MMSE, GDS, ADAS-Total, and CGI scores and after 180 days of treatment in ADAS-Behav and GIS scores [48]. This last investigation presents the advantage of having been conducted using a modern approach if compared with former clinical studies. On the other hand this trial, different from previous studies with choline alphoscerate [47] has used batteries of tests and time of observation comparable with studies assessing the activity of (acetyl) cholinesterase inhibitors [49-56]. A comparison of ADAS-Cog analysis from this investigation [48], with the results obtained on the same item in 4 trials with the cholinesterase inhibitor donepezil [57-60] revealed a more positive trend with the cholinergic precursor choline alphoscerate compared with donepezil (Fig. 3).

Cognitive dysfunction is also common in early Parkinson’s disease and affects attention, psychomotor function, episodic memory, executive function and category fluency [61]. An open 10-day study has assessed therapeutic activity of choline alphoscerate in Parkinson’s disease with cognitive impairments reaching the level of moderate cognitive disorder or dementia. Forty patients were treated intravenously with 1,000 mg/day compared to piracetam given to 20 patients at a dose of 2,000 mg/day [62]. Choline alphoscerate produced marked and moderate improvements on cognitive functions more frequently than piracetam (40% and 25%, respectively); while the incidence of deterioration was lower (5% and 15%, p < 0.05). Choline alphoscerate displayed a good profile of tolerability, with mild and short-term side effects only in the 15% of patients investigated [62]. Although limited both in terms of size of the sample investigated and of the length of treatment, the results of this pilot study suggest to further investigate activities of choline alphoscerate also in Parkinson’s disease accompanied by cognitive dysfunction.

Therapeutic interventions for cognitive symptoms in Parkinson’s disease are currently based on the use of (acetyl) cholinesterase inhibitors. These agents produce a modest improvement in cognitive function, as well as in psychotic symptoms, generally without an adverse effect on motor function [63]. The availability of another therapeutic option such as choline alphoscerate for these disorders could offer some alternatives primarily in patients in which (acetyl) cholinesterase inhibitors are not indicated.

Other investigations have evaluated the effects of choline alphoscerate on ischemic and hemorrhagic stroke. These studies reported regress of neurological deficit, better recovery of cognitive functions and functional status in patients actively treated with choline alphoscerate [64-67]. Stabilization of the blood-brain barrier was also observed [67]. A few studies from the same country have examined patients affected by chronic cerebrovascular disease [68, 69] and reported improvement of coordination and neurological symptoms, cognitive and emotional functions, activity and mood. Language barriers (Russian with an English abstract), the small sample of patients recruited and/or the limited time of observation do not allow a detailed evaluation of these trials.

Preclinical studies showing that association of choline alphoscerate with (acetyl)cholinesterase inhibitors potentiates effects of both drugs on cholinergic neurotransmission [34, 35], prompted the development in Italy of the independent (not supported by pharmaceutical companies) trial “Effe of association between a cholinesterase inhibitor and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular impairment” (ASCOMALVA). This controlled, randomized and double-blind multicenter (two
neurologic units in Naples and Mantua) study was designed to assess if association between the acetylcholinesterase inhibitor donepezil at the daily dose of 10 mg and choline alphoscerate at the daily dose of 1,200 mg/day was accompanied by changes in MMSE, ADAS-cog, Basic Activities of Daily Living (BADL), Instrumental Activities of Daily Living (IADL) and Neuropsychiatric Inventory (NPI). This latter included evaluation of severity (NPIF) and of caregiver stress (NPID) measures.

At the present this double-blind trial has completed the observation of 183 patients of the 210 planned [70]. Patients were aged between 56 and 91 years (mean 75 ± 10 years) and were included in the protocol with a MMSE score between 15 and 23. Patients should suffer from ischemic brain damage documented by neuroimaging (MRI and CT scan), with a score ≥ 2 in at least one subfield (white matter or basal ganglia) according to the New Rating Scale for Age-Related White Matter Changes (ARWMC) [71]. Recruited patients were then randomly allotted to an active treatment group (donepezil + choline alphoscerate) or to a reference treatment group (donepezil + placebo) and were treated for 12 months, being examined at recruitment and after 3, 6 and 9 months of treatment. Consistent with literature data, in patients allotted to the reference treatment group (donepezil + placebo) a slight time-dependent worsening of MMSE and ADAS-cog scores was found [70]. Treatment with donepezil + choline alphoscerate (active treatment) countered the decline of MMSE and ADAS-cog scores. The effect of association on psychometric tests was statistically significant after 12 months of treatment (Figs. 4A and 4B). BADL scores were unchanged between the control group and the donepezil + choline alphoscerate groups (Fig. 4C), whereas IADL scores were improved in active treatment patients compared to the reference group at 12 months of treatment (Fig. 4D) [70].

Data of choline alphoscerate are taken from [48]. Scores for donepezil and respective control groups were obtained by pooling average data obtained in 4 trials [57-60]. Data are expressed as means of the difference in the scores from baseline obtained in the ADAS-Cog test and were analyzed statistically by ANOVA. Standard error for each point was less than 5%.

Data of NPI, NPIF and NPID are shown in (Figs. 4E and 4F). At 12 months of observation there is a significant decrease of NPI severity and stress of caregiver scores in patients treated with donepezil + choline alphoscerate compared with those receiving treatment with donepezil alone [70]. The above results suggest that association of the cholinergic precursor choline alphoscerate to the standard treatment with a (acetylcholine) cholinesterase inhibitor may represent a therapeutic option to prolong beneficial effects of cholinergic therapies in Alzheimer’s disease patients with concomitant ischemic cerebrovascular disease [70].

5. TOXICOLOGY AND SAFETY

Studies on the toxicological profile and safety of choline alphoscerate were summarized in a recent review article [72]. The oral LD_{50} is equal to or greater than 10,000 mg/kg in rats and mice. In some cases deaths are preceded by convulsions. Dosing of dogs with up to 3,000 mg/kg choline alphoscerate resulted only in reduced activity. Sub-chronic and chronic oral toxicity studies in rats (up to 1,000 mg/kg/day) and beagle dogs (up to 300 mg/kg/day) produced symptomology primarily consisting of reduced activity, slight decreases in food consumption and body weight gain, slight reduction in liver weight, paralleled by significant decreases in plasma triglycerides, bilirubin, and alkaline phosphatase. These changes are no accompanied by histopathological correlates. *In vitro* and *in vivo* assays indicate that choline alphoscerate is devoid of mutagenic activity and is not genotoxic *in vitro* or *in vivo* [72]. To sum up, toxicology studies indicate that choline alphoscerate has low acute oral toxicity and, has an oral NOAEL (No Observed Adverse Effect Level) of 150 mg/kg body weight/day following 26 weeks oral exposure [72].
In clinical settings, choline alphoscerate has shown to be a safe drug and in more than 20 years of clinical experience side effects were reported only rarely. Pharmacovigilance data report a single event of moderate adverse reactions in the elapse of time from 1 January 1998 to 16 May 2011 (data not shown). Analysis of adverse reactions in controlled clinical trials revealed a slightly higher incidence of adverse events with choline alphoscerate compared to placebo. These events were mild and never required discontinuation of treatment [47, 48, 61, 70]. Comparison of the safety of choline alphoscerate with (acetyl) cholinesterase inhibitors revealed a more favorable profile for the compound under analysis. An example of it comes from the comparative evaluation of the cardiovascular side effects of (acetyl) cholinesterase inhibitors and of choline alphoscerate [73].

6. CONCLUSIONS

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

A problem with cholinergic precursors including choline alphoscerate is that the majority of clinical trials were carried out from 25 to 15 years ago. They therefore reflected diagnostic limits and cognitive function analysis tools of that time. However, the few studies comparable with trials assessing activity of more recent drugs such as (acetyl) cholinesterase inhibitors do not reveal a relevant advantage of these newer compounds compared with the safe and well tolerated choline alphoscerate. On the other hand, choline alphoscerate could represent a therapeutic resource in particular situations in which treatment with inhibitors is not tolerated or contra-
indicated. This is the case, for instance, of bradycardia, asthma, or of the cognitive impairment in the oldest old (> 85 years), a typical condition in which co-morbidity or very advanced age may contraindicate cholinesterase inhibitors use.

Therapeutic strategies for countering MCI either of degenerative and vascular origin are not established yet. There are currently no EMEA/FDA-approved therapies for MCI as no treatment trial to date has convincingly demonstrated a significant effect on cognition or symptom progression. Future trials will likely need to use strategies to define optimal treatment durations, and develop sensitive assessments and reliable outcomes to detect treatment benefit in mildly impaired subjects. In meantime, in spite of the numeric differences of patients treated with (acetyl) cholinesterase inhibitors or with choline alphoscerate, positive results obtained with this cholinergic precursor probably would justify reconsideration of its effects as well as further investigations on it in larger carefully controlled studies.

New interest on therapeutic applications of choline alphoscerate comes also from the more recent studies demonstrating an activity of the compound in relieving cognitive dysfunction occurring in early Parkinson’s disease [63] and from the ongoing ASCOMALVA trial [70]. The first of these studies [63] highlights new possible therapeutic applications of choline alphoscerate in treating an early and so far rather neglected symptomatological correlate of Parkinson’s disease. The second one [70] if the interim results will be confirmed at the conclusion of the trial, suggests that association of a (acetyl)cholinesterase inhibitor with choline alphoscerate could slow-down the progressive loss of efficacy of treatment with inhibitors so far experienced.

To sum up, in his long service choline alphoscerate has demonstrated a relevant role as a cholinergic neurotransmitter enhancing agent with a still interesting profile in cognitive dysfunctions. New possible therapeutic applications of this compound reviewed here [63, 70] could open new avenues in choline alphoscerate research worthwhile of being pursued.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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