Cognitive decline in the elderly: A double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration

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ABSTRACT. This double-blind study assesses the therapeutic efficacy and the safety of oral treatment with phosphatidylserine (BC-PS) vs placebo (300 mg/day for 6 months) in a group of geriatric patients with cognitive impairment. A total of 494 elderly patients (age between 65 and 93 years), with moderate to severe cognitive decline, according to the Mini Mental State Examination and Global Deterioration Scale, were recruited in 23 Geriatric or General Medicine Units in Northeastern Italy. Sixty-nine patients dropped out within the 6-month trial period. Patients were examined just before starting therapy, and 3 and 6 months thereafter. The efficacy of treatment compared to placebo was measured on the basis of changes occurring in behavior and cognitive performance using the Plutchik Geriatric Rating Scale and the Buschke Selective Reminding Test. Statistically significant improvements in the phosphatidylserine-treated group compared to placebo were observed both in terms of behavioral and cognitive parameters. In addition, clinical evaluation and laboratory tests demonstrated that BC-PS was well tolerated. These results are clinically important since the patients were representative of the geriatric population commonly met in clinical practice.

INTRODUCTION

Physicians and researchers in the western world have to face the medical problems created by the increasing number of people reaching old age. One of them is the increase in degenerative and chronic disease leading to multiple disabilities, that may compromise the quality of life of elderly people and their relatives (1).

A deterioration in cognitive function is a common aspect of chronic diseases in the aged (2, 3). The functional decline in the central nervous system (CNS) may depend upon age-related biochemical and structural abnormalities: derangement of neuronal membrane lipid composition and enzymatic activities (4, 5), decreased neurotransmitter synthesis and metabolism (6), as well as decrement in synaptic density (7, 8).

Pharmacological research aimed at improving cognitive deficits and the behavioral disturbances that frequently accompany them, has been actively engaged in finding both clinically active and well tolerated substances. The safety of pharmacologically active substances is a particularly important problem in patients who frequently have multiple pathologies and are treated with a number of active drugs, as is the case of elderly people routinely observed in clinical practice (9).

Brain cortex-derived phosphatidylserine (BC-PS), a pharmacologically active phospholipid
(10), was shown to enhance the activities of membrane-bound enzymes involved in neurotransmitter release and signal transduction in the CNS (11). BC-PS administration stimulates catecholaminergic neurotransmission (12, 13), and acetylcholine release and synthesis in the cerebral cortex of aged rats (14, 15); furthermore, its oral administration in rodents prevented age-induced loss of dendritic spines in hippocampal pyramidal neurons (16) and atrophy of cholinergic cells in the basal forebrain (17). As a consequence, treatment with BC-PS increases learning and memory functions in aged rodents (18, 19), and improves the age-associated decay in spatial behavior (20). In addition, BC-PS in vitro reduces cell death induced by xanthine oxidase (21).

In healthy volunteers BC-PS administration counteracted the adrenocortical activation induced by physical stress (22, 23), and brought about EEG changes (such as increment of absolute power) that could be assessed quantitatively (24). Modern neuroimaging techniques (PET) further showed that BC-PS induces a significant increase in glucose metabolism of defined cortical and subcortical structures (25). Clinical trials with BC-PS evidenced positive effects on cognitive impairment and behavioral disturbances in elderly patients with mild to severe cognitive decline due to various etiologies (26-29), including Alzheimer’s disease (30, 31). These trials however, were usually conducted in small groups of patients who were selected for the presumptive presence of senile dementias.

We report the results of a double-blind, randomized, placebo-controlled multicenter trial performed in Italy (Geriatric Multicenter Italian Study - GER.M.I.S.). The aims of the study were to evaluate the efficacy of long-term treatment with BC-PS vs placebo on cognitive impairment and behavioral disturbances, and to test drug safety in a large population of elderly patients presenting a clinical picture of “moderate to severe” cognitive decline, and concomitant multiple extracerebral pathologies.

MATERIALS AND METHODS

Subjects

Four hundred and ninety-four patients with symptoms of memory impairment (151 men and 343 women) were recruited in 23 Geriatric or General Medicine Units in Northeastern Italy. Name and location of principal investigators are listed on p. 131.

Twenty-five percent of patients were living in nursing homes, while the remainder were recruited and evaluated as periodical inpatients (4 or 5 days each time) in a hospital setting (medical or geriatric wards). The patients were observed by the same clinicians at baseline and at each follow-up.

According to the Declaration of Helsinki and Good Clinical Practices, the purpose of the study was explained to the patients and their relatives, who gave oral informed consent.

Inclusion criteria

Each patient had to be over 65, with a score of 10-23 in the Mini Mental State Examination (MMSE) (32), and a clinical picture of “moderate to severe” cognitive decline, according to the Reisberg Global Deterioration Scale (GDS; stages 4-6) (33, 34). Just before starting the therapy, the patients were examined with a “symptoms evaluation scale” (made up of items from both Wells (35) and Blessed et al. (36) scales), to obtain additional information about the onset of mental decline and the current cognitive status. This instrument was used only to facilitate collection of anamnestic data.

Exclusion criteria

These comprised the presence of very severe Alzheimer’s disease, (GDS stage 7) Parkinson’s disease and other neurological disorders possible conducive to secondary dementia (such as alcoholism, trauma sequelae, etc.), psychosis, stroke in the previous six months, tumors, and severe metabolic, cardiac and pulmonary diseases non responsive to treatment. Patients with severe liver and kidney failure were also excluded.

The severity of these conditions was assessed on the basis of clinical history, physical, neurologic and neuropsychiatric examinations, instrumental and laboratory tests.

Depressed patients were excluded by setting a score limit of 3 or more in three items (depressed mood, guilt, suicidal tendencies) on the Hamilton Depression Rating Scale (37, 38). Also excluded were patients with severe visual or