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Randomized placebo-controlled trial of sodium valproate in progressive supranuclear palsy

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ABSTRACT

Objectives: Results from preclinical studies suggest that inhibition of glycogen synthase kinase (GSK-3) is a therapeutic option for tauopathies. The aim of the present study was therefore to determine the effects of sodium valproate (VPA), a GSK-3 inhibitor, on disease progression in progressive supranuclear palsy (PSP).

Patients and methods: We performed a double-blind, randomized, placebo-controlled trial, in 28 PSP patients who received VPA (1500 mg/day) or matching placebo for 24 months. The primary endpoint was the change from baseline in Progressive Supranuclear Palsy Rating Scale (PSPRS) at 12 and 24 months. Secondary endpoints evaluated the effects of VPA on cognitive and behavioral status (MMSE, Mattis Dementia Rating Scale, Wisconsin Card Sorting, Gröber and Buschke and Oral Denomination 80 tests), tolerability of treatment, and patient compliance.

Results: There were no baseline differences between active treatment and placebo groups in age and clinical rating scores. PSPRS score at 12 months was significantly higher in the VPA than in the placebo group (60.8 ± 20 versus 46.9 ± 18.6 respectively, $p = 0.01$), but was similar between the two groups at 24 months. No significant differences were observed between VPA and placebo groups for the secondary endpoints.

Conclusion: Our results suggest that VPA is not effective as a disease-modifying agent in PSP.

1. Introduction

Progressive supranuclear palsy (PSP) is an adult-onset neurodegenerative disease, characterized by postural instability, vertical supranuclear gaze palsy, dysarthria, dysphagia, frontal cognitive disturbances and levodopa-unresponsive parkinsonism [1]. The median time from disease onset to death is 5.9 years [2]. No effective symptomatic, disease-modifying or neuroprotective therapy is currently available. Neuropathologically, PSP belongs to the family of tauopathies and is therefore characterized by a widespread neuronal cell loss associated with an abnormal accumulation of intracellular microtubule-associated protein tau in specific basal ganglia and brainstem areas [3].

Under physiological conditions, unphosphorylated tau is soluble and binds reversibly to microtubules [4]. In PSP, tau is hyperphosphorylated by kinases at several serine or threonine residues [5]. Phosphorylated tau loses its affinity for microtubules and becomes resistant to proteolysis, resulting in the formation of cytotoxic tau-aggregates [6]. Two serine/threonine protein kinases, glyco-

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gen synthase kinase (GSK-3) and cyclin-dependant kinase-5 are critically involved in abnormal tau phosphorylation [7,8]. GSK-3 is involved in the formation of oligomeric tau fibrils *in vitro* [9] and associated with tau hyperphosphorylation and tangle formation in transgenic models [10,11]. It co-localizes with filamentous tau in transgenic mice [10] and with neurofibrillary tangles in the brain of patients with Alzheimer's disease or PSP [12]. These data suggest that GSK-3 inhibition might constitute a relevant strategy to tackle PSP progression [6]. Sodium valproate (VPA) has been demonstrated to inhibit the activity of both GSK-3 isoforms at clinically achievable concentrations [13]. We therefore undertook a prospective, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of VPA in slowing the rate of progression of the clinical features of PSP.

2. Patients and methods

2.1. Standard protocol approvals, registration, and patient consents

The study was conducted over a 24-month period (ClinicalTrials.gov identifier: NCT00385710) from December 2006 to July 2008 at 4 centers in France. It complied with the International Conference on Harmonization Good Clinical Practice guidelines, was approved by Ethics Committees/Institutional Review Boards of the coordinating center and conducted according to International standards of Good Clinical Practice (ICH guidelines and the Helsinki Declaration). Participants provided written informed consent before participation.

2.2. Patients

Eligible patients were men and women aged 45–75 years old with possible or probable PSP according to the NINDS-Society for Progressive Supranuclear Palsy [SPSP] diagnostic criteria [14]. Inclusion criteria also included Mini-Mental Status Examination (MMSE) score above 22, PSPRS score under 40, menopause status or contraception and negative β-HCG for women. Exclusion criteria were NINDS-SPSP exclusion criteria, positive syphilis serology test, personal or familial history of severe hepatitis, personal history of allergy to valproate, divalproate, valpromid or sodium valproate excipient, personal history of porphyry, unstable central nervous system medication for the past 3 months, unstable dopaminergic treatment for the past month as well as prohibited associated treatment (mefloquin, St.-John's-wort, anticonvulsivant, neuroleptic except clozapine, medication metabolizing to valproate such as valproate, valpromid).

2.3. Study design

This study was designed as a randomized, double-blind placebo-controlled, parallel-group, multicentric phase II trial, assessing the efficacy and safety of VPA at a single dose (1500 mg per day). Randomization was balanced by center. The 1:1 randomization sequence was produced by the statistics department from Nantes University Hospital (Nantes, France). The randomization list was sent to an independent contract research organization (LC2, Lentilly, France), which prepared and distributed identical capsules of VPA and placebo. Assignment was masked from the patients, study staff, investigators, and data analysts.

After randomization, VPA or matching placebo was administered following a weekly dose titration, beginning at one tablet (500 mg in VPA group) per day, then b.i.d (1000 mg in sodium valproate group), and up to t.i.d (1500 mg in VPA group) the third week, a dose that was maintained during the entire study duration. Patients were contacted by phone 15 days after treatment initiation to check for treatment tolerability and the occurrence of potential adverse effects. Treatments were delivered at inclusion, at 1 month, 3 months, and then every 3 months until the end of the study. After a 24-month period, treatment was gradually tapered to a stop following a one tablet (500 mg in VPA group) weekly dose decrease.

2.4. Evaluation

MMSE was completed during selection visit. Demographic data, initial symptoms, date of onset, disease duration, diagnostic classification according NINDS-SPSP criteria, personal medical history, actual and past month treatment, general and neurological clinical examination including PSPRS score, were completed during inclusion visit. Biological analysis were done at inclusion, including full blood count, electrolytes, kidney and liver functions, TPHA-VDRL syphilis serology, and β-HCG level.

The primary endpoint evaluated the effect of VPA on disease clinical progression as assessed by the PSPRS score at 12 and 24 months. Secondary endpoints evaluated the effects of VPA on cognitive and behavioral status, the tolerability of the treatment, and patient compliance to treatment.

The PSPRS score was assessed at inclusion, at 1 month, at 3 month, and then every 3 months until 24 months after inclusion and after treatment discontinuation at 25 months [15]. Neuropsychological and behavioral statuses were evaluated at inclusion, 12 months and 24 months after inclusion. Neuropsychological tests included a global cognitive evaluation (MMSE, Mattis Dementia Rating Scale MDRS), an evaluation of executive functions (Wisconsin Card Sorting Test, verbal fluency), verbal episodic memory (Gröber and Buschke test) and language (Oral Denomination 80 test), behavioral impairment was rated by Neuropsychiatric Inventory (NPI).

Clinical and biological tolerability was evaluated at each following visit. Clinical examination comprised weight, blood pressure and pulse rate. Biological tests consisted in full blood count, electrolytes, and kidney and liver analyses. Most frequent expected adverse events under treatment were gastrointestinal symptoms, weight gain, dizziness or sleepiness, tremor and hair loss.

2.5. Statistical analyses

Continuous data were expressed as the mean ± standard deviation and categorical data were expressed as numbers and percentage. PSPRS score, MDRS score, NPI score at 12 months and 24 months and weight at 24 months were compared between VPA and placebo group with rank analysis of covariance after adjusting for baseline value. Number of adverse events, number of severe adverse events and observance were compared between groups with Wilcoxon tests. Overall survivals were compared between the two groups using Log-Rank test. SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina). For all statistical tests $p < 0.05$ was deemed significant.

3. Results

3.1. Study population

Thirty-six patients were assessed for eligibility (Fig. 1). Eight were not eligible. Twenty-eight met the inclusion and exclusion criteria and were therefore randomized. Fourteen were assigned to receive placebo and 14 to VPA. One patient allocated to VPA discontinued the study before follow-up, because of early interruption of treatment. Twenty-seven patients entered the study. Baseline