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Safety and efficacy of valproic acid treatment in SCA3/MJD patients

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ABSTRACT

Background: Spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD) is one of 10 known polyglutamine (polyQ) diseases. In Drosophila and rat models of polyQ diseases, histone deacetylation (HDAC) inhibitors improved locomotor function and survival time by increasing histone acetylation levels and modulating gene expression. Valproic acid (VPA) is a pan-HDAC inhibitor used clinically to treat bipolar and seizure disorders. We evaluated the clinical safety and efficacy of VPA treatment for SCA3/MJD patients.

Methods: First, a randomized, open-label, dose-escalation method was used to evaluate tolerance to single-dose VPA administration in 12 SCA3/MJD patients. Patients were randomly assigned to three groups of four subjects, each with an oral dosage of 400 mg, 600 mg, or 800 mg (twice daily (bid) for one day). VPA was well-tolerated for one-dose by all patient groups. Second, a randomized, double-blind, placebo-controlled, dose-controlled study evaluated the safety and efficacy of multi-dose VPA (oral administration, twice daily (bid) for 12 weeks) in 36 SCA3/MJD patients. Patients received either low-dose VPA (800 mg/day), high-dose VPA (1200 mg/day), or placebo (n = 12 subjects per group). Symptoms were evaluated using the Scale for Assessment and Rating of Ataxia (SARA).

Results: Multi-dose VPA treatment improved SARA measures of locomotor function. Major adverse effects included dizziness and loss of appetite.

Conclusions: VPA is a potentially beneficial agent for the treatment of SCA3/MJD. These results also provide insight into possible future therapeutics for polyQ diseases.

1. Introduction

Hereditary spinocerebellar ataxias (SCAs) are a group of common neurodegenerative disorders characterized by ataxia as well as a broad range of symptomatology such as Parkinsonism, dystonia, cognitive deficits, sleep disorder, cramp and hyposmia. To date, more than 30 SCA genotypes have been reported [1]. Spinocerebellar ataxia type 3 (SCA3)—also called Machado-Joseph disease (MJD)—is the most common subtype and accounts for about 60% of SCA cases in China [2]. Recent studies found that nine polyQ diseases, including SCA3/MJD, show common characteristics. First, their pathological features are caused by an expansion of a CAG trinucleotide repeat within the pathogenic gene exon. Second, the expanded CAG trinucleotide repeats encode mutant protein with a polyQ chain that, in turn, causes cellular toxicity. Third, the mutant protein accumulates in the nuclei of neurons termed neuronal inclusions (NIs), contributing to cytotoxicity [3–5].

The extant literature suggests that transcriptional dysregulation plays a central role in the pathogenesis and pathophysiology of polyQ diseases. In general, increased histone acetylation levels allow chromatin to exist in a structurally more relaxed state that favors transcriptional activation [6]. Conversely, loss of histone acetylation yields a more compact and rigid chromatin structure,

Abbreviations: DLT, dose limiting toxicity; MTD, maximum tolerated dose.

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causing transcriptional suppression. It has been reported that an expanded polyQ tract within the mutant target disease proteins can interact with and impair neuroprotective transcription factors and histone acetyltransferases, resulting in histone hypoacetylation and transcriptional defects [7–10]. In Drosophila and rodent models of polyQ diseases, treatment with histone deacetylase (HDAC) inhibitors initially increased histone acetylation levels; this, in turn, alleviated disease phenotypes, improved locomotor function, reduced cell degeneration, and prolonged survival time [11–16].

The anticonvulsant valproic acid (VPA) has a long history of safe use in the treatment of both bipolar and seizure disorders, although mechanisms underlying the clinical efficacy are still unclear. It is known that VPA can enhance γ-amino butyric acid (GABA) neurotransmission, which is contributed by inhibition of enzymes involved in GABA metabolism such as GABA transaminase, and might be involved in the clinical efficacy for bipolar disorder [17]. VPA also inhibits voltage-gated sodium channels and T-type sodium channels and these actions have been proposed to mediate the anticonvulsive action [18]. In addition, VPA is an HDAC inhibitor affecting class I and class IIa HDAC isoforms. In preclinical models of diverse neurodegenerative and neurological disorders—including polyQ diseases—VPA exhibited robust neuroprotective and anti-inflammatory properties, promoted neurogenesis and angiogenesis, and improved behavioral performance, all via HDAC inhibition [18]. Recent research from our laboratory has explored the beneficial effects of VPA in cellular and Drosophila models of SCA3/MJD [19]. VPA inhibited the cytotoxicity of polyQ expanded mutant ataxin-3, thereby reducing the rate of early apoptotic cells in the SCA3/MJD transgenic cell model. In the SCA3/MJD Drosophila model, VPA prevented eye depigmentation, alleviated climbing disability, and extended life span. Notably, these effects were associated with restoration of histone H3 and H4 hypoacetylation.

Despite these advances, no studies have explored the effects of VPA on SCA3/MJD patients. The current study used a randomized, open-label, dose-escalation method to evaluate tolerance to a single-dose VPA administration in patients with SCA3/MJD. Subsequently, we conducted a randomized, double-blind, placebo-controlled, dose-controlled study to evaluate the safety and efficacy of multi-dose VPA for the treatment of SCA3/MJD patients.

2. Methods

2.1. Patients

Thirty-six subjects were recruited from the Department of Neurology in Xiangya Hospital, Xiangya 2nd Hospital and Xiangya 3rd Hospital of China Central South University. Twelve subjects participated in the preliminary single-dose administration tolerance study, then repeated participation with an additional 24 subjects in the multi-dose administration trial. All patients underwent a set of standardized neurological examinations by two or three neurologists who specialized in movement disorders. SCA3/MJD diagnosis was made in accordance with the classical consensus criteria established by Harding [20], and abnormal CAG expansion over 51 repeat of *ATXN3* gene. Participants were between 18 and 50 years old with body mass index (BMI) between 19 and 25 kg/m^2. Gait score, as assessed by the Scale for Assessment and Rating of Ataxia (SARA), ranged from 2 to 5. Mini-mental state examination (MMSE) produced a score of ≥21. Participants could not be taking anticonvulsant agents, traditional Chinese medicine, or any food affecting the uptake of VPA within one month of entry into the study. Exclusion criteria included pregnancy or nursing, allergy to VPA, abnormal hemopathy or blood counts, the presence of liver disease or a liver enzyme index exceeding the upper limits of normal, kidney disease or a renal function index exceeding the upper limits of normal, and/or other distinct disease symptoms and signs except those caused by SCA3/MJD. Written informed consent was obtained from each participant. The study was approved by the ethics committee of Central South University Xiangya 3rd Hospital IRB (ethical approval number: No. 0949), and was recorded in the Chinese Clinical Trial Register (registration number: ChiCTR-TRC-10000754).

2.2. Trial design

First, a randomized, open-label, dose-escalation study was conducted to evaluate tolerance to single-dose VPA administration in SCA3/MJD patients. Twelve eligible SCA3/MJD patients were screened and randomly assigned to three groups receiving oral VPA dosages of either 400 mg, 600 mg, or 800 mg (four subjects per group). VPA was well-tolerated with one dose twice daily for one day in all patient groups.

Based on the preliminary results from the tolerance study, we then conducted a randomized, double-blind, placebo-controlled, dose-controlled study to evaluate the safety and efficacy of multi-dose VPA (oral administration, twice daily (bid) for 12 weeks) in 36 eligible SCA3/MJD patients; this patient group included the 12 patients who had previously participated in the tolerance study. Patients were randomly assigned to receive low-dose VPA (800 mg/day), high-dose VPA (1200 mg/day), or placebo (n = 12 subjects per group).

2.3. Trial process

Fig. 1 illustrates the designs for single-dose tolerance study and melt-dose clinical trial.

2.4. Single-dose tolerance study

Within 48 h before drug treatment, patients underwent a general physical examination (body temperature, pulse, blood pressure, breathing rate, and other vital signs), electrocardiogram, routine blood analysis (e.g., platelet count), routine urinalysis, and tests for blood sugar, blood fat, coagulation function, electrolyte levels, liver function, and renal function. The 12 eligible patients were then hospitalized one day before drug administration and remained hospitalized under observation for 72 h. During the observation period, participants underwent the above-mentioned examinations twice: at day one and at day three post-admission.

2.5. Multi-dose randomized clinical trial

Within 48 h before drug treatment, patients underwent a general physical examination (body temperature, pulse, blood pressure, breathing rate, and other vital signs), electrocardiogram, routine blood analysis (e.g., platelet count), routine urinalysis, and tests for blood sugar, blood fat, coagulation function, electrolyte levels, liver function, and renal function. The eligible patients were hospitalized one day before drug administration, and remained hospitalized for seven days under observation. Follow-up visits were conducted on Days 28, 56, and 84 after admission into the study. At follow-up visits, medications were dispensed, compliance was evaluated, SARA evaluations were conducted, and a medical examination that included routine blood testing and tests for liver function and renal function among others was conducted. In addition, assessments were performed to assess the manifestation and severity of adverse reactions in treated subjects.

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