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Research Article

Efficacy of Ultramicronized Palmitoylethanolamide on the Clinical Symptoms of Charcot-Marie-Tooth Neuropathy

Giovanni Antioco Putzu*[1]

[1] Neurology and Clinical Neurophysiology, Casa di Cura Polispecialistica Sant'Elena, Viale Marconi 160, 09045 Quartu S'Elena, Cagliari, Italy

Abstract

This study investigates the efficacy of ultramicronized palmitoyletanolamide (PEA-um) in treating the clinical symptoms of Charcot-Marie-Tooth (CMT) Neuropathy. 22 CMT patients were assessed with Visual Analogue Scale (VAS) for pain, fatigue and cramps, at baseline (T0), and following 20 (T1) and 80 days (T2) treatment with 1200 mg/day of PEA-um. Electromyographic examination was performed both at baseline (T0) and at end of study treatment (T2). None of the patients received an add-on treatment for these symptoms. A significant improvement of pain, fatigue and cramps was observed in VAS scores after 20 days of treatment with PEA-um microgranules (T1). Mean values of VAS score for pain decreased from 5.9 ± 2.1 to 3.9 ± 1.7, VAS score for fatigue decreased from 6.3 ± 2.4 to 3.4 ± 1.6 whereas VAS score for cramps diminished from 5.4 ± 1.2 to 3.8 ± 1.3. Further clinical improvement was observed also after 80 days (T2) of treatment with the same dosage of PEA-um tablets. Muscle strength, vibratory sensation and motor / sensory nerve conduction velocities did not display any significant modification. Although obviously limited as an open study, the data strongly suggest an efficacy of PEA-um in improving the clinical symptoms of CMT neuropathy.

Keywords: *Charcot-Marie-Tooth Neuropathy, Open Trial, Palmytoilethanolamide-um, pain, cramps, fatigue.*

Introduction

Charcot-Marie-Tooth disease (CMT) is one of the most commonly inherited neuromuscular diseases, with a prevalence of approximately 1 in 2,500 persons. It represents a genetically heterogeneous group of inherited neuropathies, clinically characterised by prevalent distal muscle atrophy, sensory impairment, muscle pain, sensation of fatigue and painful muscle cramps [1]. Although treatment with high doses of vitamin C was effective in an animal model of CMT, studies in humans failed to confirm a benefit of this treatment [2,3]. Progesterone antagonists and subcutaneous neurotrophin-3 injections were also ineffective in humans [4,5]. Recent advances suggest that neuroinflammation may play a role in the pathophysiology of peripheral nerve damage in CMT [6,7]. P2X7 inhibition has recently shown tolerability and efficacy in an animal model of CMT, thus confirming the active role of neuro-inflammation in CMT [8]. Palmitoylethanolamide (PEA), an endogenous lipid signalling molecule, can inhibit the release of proinflammatory mediators from activated mast cells, thereby reducing the recruitment and activation of mast cells in peripheral nerve [9-11]. This study was therefore carried out to evaluate the clinical efficacy of ultramicronized PEA (PEA-um) treatment in a cohort of patients affected by the most common form of CMT.

Middle section

Patients and Experimental MethodsTwenty-two patients from four families suffering from CMT neuropathy received PEA-um at dosage of 1200 mg/day for 80 days (Normast 600 mg, Epitech Group Srl, Saccolongo, Italy). PEA-um was administered as follows: microgranules 600 mg/BID by the sublingual route for 20 days followed by tablets 600 mg/BID for a further 60 days. Patients with diabetes or diseases that potentially cause neuropathy (for example, alcoholism, chronic renal failure, chronic hepatitis or cancer treatment) were excluded from the study. The main clinical complains included muscle pain (22 patients), painful cramps (9 patients) and sensation of fatigue (22 patients); symptoms intensity was evaluated by Visual Analogue Scale (VAS). None of the patients received treatment for these clinical symptoms in the 90 days before study onset. Neurological examination including deep tendon reflexes, measurement of vibratory sensation at both upper and lower limbs, segmental muscle strength (Medical Research Council scale – MRC, 1978) was performed at baseline (T0), T1 (20th day) and T2 (80th day) in all patients. All patients were tested with DN4 questionnaire. Electromyographic study included measurement of motor and sensory nerve conduction velocities at baseline (T0) and at T2. Room and skin temperatures were maintained stable in all measurements (T0 and T2). Only 12 patients underwent a complete electromyographic study. The other patients experienced discomfort due to needle examination and electric stimuli, and refused to undergo a further examination at T2. Statistical analysis of pain, fatigue and cramps at T0, T1 and T2 was performed using the Tukey-Krammer test. MRC data, vibratory sensation and electromyographic results were processed by means of Friedman rank sum test.

Results and Discussion

The clinical status, along with gender, age range and genotype characteristics of CMT patients are summarised in Table 1. One patient dropped out of the study because of a previous history of alcoholism that emerged after T0. Complete clinical data were available for 22 patients (7 males and 15 females), mean age 53.5± 13.49 years. Mean disease progression was 31.6± 12.44 years. Fourteen patients were affected by CMT IA, the most common genotype, which

Corresponding author: Giovanni Antioco Putzu, Neurology and Clinical Neurophysiology, Casa di Cura Polispecialistica Sant'Elena, Viale Marconi 160, 09045 Quartu S'Elena, Cagliari, Italy, Tel: ; Fax: ; Email: puzzugio@gmail.com

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Table 1: Clinical status, demographic and genetic data of CMT patients included in the study.

CMT form	Gene anomalie	Number of patients	Gender	Age range	Clinical status range
CMT IA	Duplication 17.11.2	14	9 females and 5 males	26-61 years	Moderate to severe
CMT IB	Point mutation Myelin Protein Zero gene chromosome 1	8	7 females and 1 male	46-79 years	Moderate to severe

is characterised by duplication of chromosome 17p11.2. Eight patients were classified as CMT IB due to a point mutation of P0 located on chromosome 1. Results of VAS scores for pain, fatigue and cramps at T0, T1 and T2 are summarised in Figures 1-3.

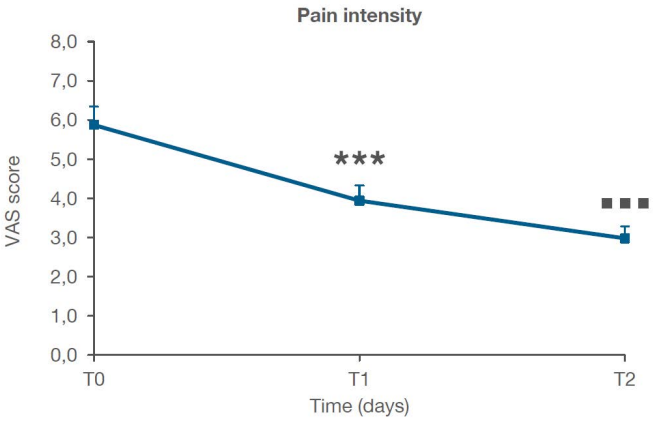
A significant improvement of pain, fatigue and painful cramps was observed in VAS scores after 20 days of treatment (T1). Mean values of VAS for pain decreased from 5.9 ± 2.1 to 3.9 ± 1.7 ($p<0.0001$); VAS for fatigue decreased from 6.3 ± 2.4 to 3.4 ± 1.6 ($p<0.0001$) whereas VAS for painful cramps diminished from 5.4 ± 1.2 to 3.8 ± 1.3 ($p<0.0001$). Further clinical improvement was observed also at T2, after another 60 days of treatment with PEA-um tablets maintaining the same dosage. Means values of VAS for pain decreased from 3.9 ± 1.7 to 3.0 ± 1.4 ($p<0.0059$); VAS score for fatigue diminished from 3.4 ± 1.6 to 3.0 ± 1.3 (ns) and VAS score for cramps decreased from 3.8 ± 1.3 to 2.9 ± 1.3 ($p<0.0395$). Statistical analysis of

MRC score, vibratory sensation measurements and sensory and motor nerve conduction velocities did not display any significant modification. DN4 score was under the cut-off value of 4 in all patients. There were no adverse events related to treatment at any time during the course of the study.

CMT neuropathy is one of the most commonly inherited neuromuscular disorders, characterised by prevalent myelin loss in the demyelinating forms and prevalent axonal damage in axonal ones [12]. Both demyelinating and axonal forms progressively reduce motor performance and the patient quality-of-life [13]. Pain and muscle cramps are frequent, even in pediatric patients affected by CMT [14-16]. CMT patients are also more prone to develop psychiatric disturbances than non-affected individuals [13]. No treatment has proven to be clinically efficacious until now, although high doses of vitamin C, anti-progesterone and neurotrophin-3, and recently P2X7 inhibition, have demonstrated some effects in animal models [2, 3, 8]. Anti-progesterone therapy has potential side effects in women and children, whereas subcutaneous neurotrophin-3 has a very short half-life. The P2X7 inhibition, although tolerable and experimentally effective, must be tested on humans yet.

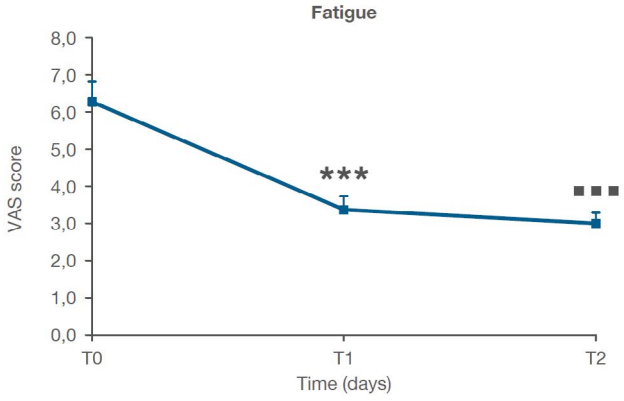
Conclusions

The present open-label study was performed in patients affected by the most common demyelinating forms of CMT (CMT 1). Fifteen patients suffered from CMT 1A (duplication of 17p 11.2) and 7 patients from CMT 1B (point mutation of P0 gene on chromosome 1). Clinical symptoms such as pain, fatigue and painful muscle cramps dramatically improved after 20 days (T1) of treatment with 1200 mg/day of PEA-um microgranules. Further improvement was observed also after a further 60 days (T2) with the same dosage of PEA-um tablets. All patients included in the study were in an advanced phase of the neuropathy, in fact, mean disease progression was 31.6 ± 12.44 years. Nonetheless, a statistically significant clinical improvement was observed in a relatively short period of observation. Modification of other parameters such as muscle strength, vibratory sensation and electomyographic data is obviously limited by the years of disease progression. In fact, the longer the disease history the greater is peripheral nerve damage, especially axonal loss [12]. It might be of utility as well to obtain data in the future from chronic treatment with PEA-um at the time of diagnosis or in the early phase of the disease, i.e childhood. Based on these encouraging, albeit preliminary data, a double-blind multicenter study seems warranted to confirm



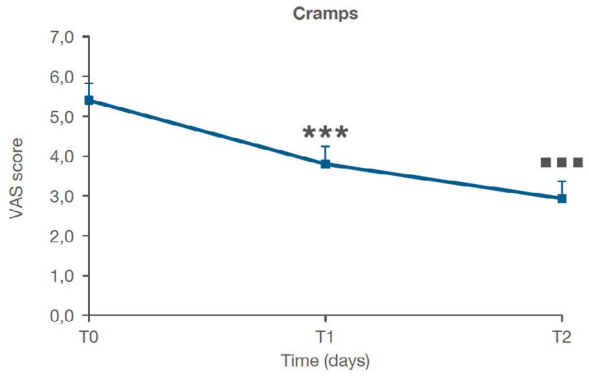
T0 =baseline, T1 and T2 = 20th and 80th day respectively.
***p<0.0001 vs T0; ▪▪▪p<0.0059 vs T2.

Figure 1: Reduction in pain intensity over time in the patients treated with PEA-um. Values are expressed as mean ± SE.



T0 =baseline, T1 and T2 = 20th and 80th day respectively.
*** p<0.0001 vs T0; ▪▪▪ p = 0.1813 vs T2

Figure 2: Reduction in fatigue over time in the patients treated with PEA-um. Values are expressed as mean ± SE.



T0 =baseline, T1=20th and T2 =80th day.
*** p<0.0001 vs T0; ▪▪▪p<0.0395 vs T2

Figure 3: Reduction in muscle cramps over time in the patients treated with PEA-um. Values are expressed as mean ± SE.

the efficacy of PEA- um in treating the clinical symptoms of CMT neuropathy.

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Conflict of Interest

The author declares no conflict of interests.

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