ORIGINAL

DOLOR. 2010;25:35-42

Palmitoylethanolamide (Normast) in chronic neuropathic pain caused by compressive-type lumbar sciatica: a multicenter clinical trial

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ABSTRACT

Six hundred and thirty-six patients (336 men and 300 women) affected by lumbosciatic algias due to radicular and/or core compression of the sciatic nerve and discopathy, in both acute and chronic phases participated in a double blind, controlled, randomized multi-center clinical study with two doses of Normast® against a placebo, in nine hospital and university departments distributed in various Italian regions. Both Normast® and the placebo were administered orally for 21 days. The effectiveness of the treatments was evaluated by the visual analog scale (VAS) to quantify the intensity of the pain, and by the Rolant-Morris disability questionnaire (RDQ) to evaluate the quality of life. Seventeen patients abandoned the study: 12 belonging to the group treated with placebo, four to the group treated with Normast® 300mg and only one to the group treated with Normast® 600mg. At the end of the treatment period both the pain reduction and the quality of life were significantly different between the three treatment groups (ANOVA; $p < 0.001$), and the daily dose of 600mg was significantly more effective than the dose of 300mg/day (Scheffé test; $p<0.05$). Both doses of Normast® were significantly more effective than the placebo (Scheffé test; $p<0.05$). In effect, in patients treated with Normast® the pain and incapacity reduced much more evidently than in the patients of the placebo group, who received the classical treatments used for this condition. The results obtained demonstrate that palmitoylethanolamide (PEA) in micronized form, the active principle of Normast®, is a new molecule, effective and safe, for the treatment of chronic neuropathy pain associated with peripheral neuropathies.

Key words: Palmitoylethanolamide. Chronic neuropathy pain. Lumbosciatic algias.

INTRODUCTION

PEA, the active ingredient in Normast (where it is present in micronized form) is an endogenous substance found in almost all cells[1]. PEA levels, as well as those of other N-acylethanolamines, are altered during tissue damage, suggesting a role in specific pathophysiological processes[2-5]. Of particular interest is the reduction in PEA levels seen in the spinal cord and thalamic nuclei, implicated in pain sensation, due to compression of the sciatic nerve[6]. This evidence suggests a role for PEA in spinal and supraspinal pain modulation. This hypothesis is supported by various experiments demonstrating that exogenous administration of PEA reduces hyperalgesia and allodynia induced experimentally via acute inflammatory stimuli or peripheral nerve injury[7-11].

Data shows that the effects of PEA are largely attributed to its ability to modulate activated mast cells via autacoid local injury antagonism (ALIA)[12-14]. Mast cells are immune cells that orchestrate both the initiation and persistence of tissue inflammatory responses[15], Mast cell mediators, secreted in response to noxious stimuli, play a fundamental role in the origin of peripheral pain. Some of these mediators, such as histamine and serotonin, act on the basal epithelium to induce vasodilation, which is quickly followed by the extravasation of protein-rich fluid and immune cells, and tissue edema. In the peripheral nerve, mast cells are localized to the endoneurium, a compartment contiguous with nerve fibers and the vasa nervorum of the microcirculation[16]. Tissue edema that develops in the endoneurial channel (a confined, functionally non-dilatable, space) causes a progressive increase in endoneurial fluid pressure that in turn significantly impairs intrafascicular capillary flow and induces ischemia in the nerve segment (defined by Lundborg et al as 'miniature compartment syndrome', MCS)[17-19]. Among the many mast cell mediators implicated in chronic pain, nerve growth factor (NGF) seems to be the most important due to its ability to alter neuronal excitability, which in turn contributes to allodynia and hyperalgesia[20]. In peripheral tissues, mast cells synthesize, store, and secrete NGF21; dysregulated secretion of NGF from mast cells results in hyperalgesia and allodynia, first by an increase in the synthesis of neurotransmitters (e.g., substance P and CGRP), and later by excessive arborization of sensory and sympathetic dendrites that occur as a result of continuously-elevated levels of NGF at the point of insult/injury. The effects of PEA are not limited to the peripheral nervous system; it was recently shown that PEA can reduce inflammation and tissue injury from spinal compression[23], as well as exert neuroprotective effects in animal models of multiple sclerosis[24-26] and ictus[27].

The wealth of experimental evidence that demonstrates the efficacy of PEA in reducing acute inflammatory processes and the neuronal hypersensitivity that develops following neuropathy[11,14,28,29] support the use of PEA in the clinical management of neuropathic pain. Based on the ability of PEA to modulate activated mast cells and evidence linking excessive mast cell activation to the pathophysiology of chronic pain[17-19], we set out to evaluate the clinical efficacy of PEA in the treatment of chronic neuropathic pain. In this multicenter clinical study, we looked at the tolerability of Normast and its ability to reduce both pain intensity and motor dysfunction in patients with lumbosciatalgia caused by radicular compression and/or discopathy.

Materials and Methods

Patient selection

We enrolled 636 patients (336 men and 300 women) with lumbosciatalgia caused by truncal and/or radicular compression of the sciatic nerve or discopathy at nine hospitals and universities in Italy. Patients enrolled in the study presented in the outpatient departments of the nine centers with either acute or chronic compression-type lumbosciatalgia diagnosed via an exhaustive clinical exam (and, as needed, additional diagnostic tests), and met the trial inclusion and exclusion criteria.

Inclusion criteria

Age 18-75 with total pain score (measured by visual analog scale, VAS) ≥5.

Exclusion criteria

Patients whose lumbosciatalgia diagnosis was not confirmed at baseline clinical exam; confirmed or suspected pregnancy; concomitant use of medications that can cause drug-induced peripheral neuropathies; and comorbidities that could interfere with the assessment of efficacy of the investigational drug (vertebral osteoporosis, pancreatitis, peptic ulcers, ulcerative colitis, diverticulitis, abdominal aortic aneurysm, severe dysmenorrhea, endometriosis, uterine prolapse, retroverted uterus, prostatitis; diabetic, uremic, alcoholic, or toxic neuropathy; psychiatric disorders; and severe hepatic or renal impairment).

Additionally, patients who had participated in a clinical study in the preceding 4 weeks or whom the investigators considered unlikely to comply with clinical trial protocols, were excluded.

In accordance with the Declaration of Helsinki and good clinical practice guidelines, study objectives were explained to all patients and written informed consent obtained.

Study design

In this double-blind, randomized, placebo-controlled trial, eligible patients were randomly assigned to receive Normast (one of two dose levels) or placebo; randomization was performed using a centralized computer-generated schedule. All patients were allowed to continue treatment for comorbidities not identified in the exclusion criteria.

Study interventions and dosage

Normast and placebo were administered orally for 21 days. The first group received two placebo capsules daily for 21 days; the second group received one 300mg Normast capsule plus one placebo capsule daily for 21 days (300mg/day Normast); and the final group received two 300mg Normast capsules daily for 21 days (600mg/day Normast). Capsules were administered every 12 hours.

Capsules and external packaging for both Normast and placebo were identical, and investigators remained blinded until statistical analyses were completed at the end of the study.

Study measurements

Table 1 summarizes the measurements performed throughout the trial. At the baseline (T0) visit, all patients underwent an extensive clinical exam that also included detailed medical history and hematology, clinical chemistry, and urinalysis; if necessary, additional diagnostic tests were performed to confirm the clinical diagnosis of lumbosciatalgia. Additionally, pain intensity (via visual

Table 1: Study measurements performed at enrollment (baseline) and subsequent clinical site visits

Days of clinical site visit	Clinical/ physical exam	Labs	EVA	RDQ	Subjective evaluation of efficacy	Adherence	Tolerability & safety
T0 (baseline)	X	X	X	X			
T7			X	X		X	X
T14			X	X		X	X
T21 (end of treatment)	X	X	X	X	X	X	X

VAS: visual analog scale; RDQ: Roland-Morris disability questionnaire

analog scale, VAS30} and quality of life (via Roland-Morris Disability Questionnaire, RDQ30) were evaluated at the baseline visit, prior to initiation of treatment. In subsequent clinical visits at days 7 and 14 (T7 and T14), patient adherence, tolerability, and safety of study drug were evaluated in addition to pain (VAS) and quality of life (RDQ). At the end-of-treatment visit on day 21 (T21), both patients and physicians were additionally asked to provide a subjective assessment of efficacy.

Both the VAS and RDQ were administered to each patient by the same investigator at every study visit. The subjective assessment of efficacy at the end of the study was obtained separately for patients and investigators.

EFFICACY AND SAFETY MEASURES/SCALES

Visual analog scale (VAS)

Pain level was evaluated using a VAS, a simple but useful instrument to monitor pain intensity over time. The VAS is a 10cm-long line where one end (0cm) represents the absence of pain and the other end (10cm) represents the worst pain imaginable. Patients mark the point on the line that represents the level of pain they are experiencing; the distance from the no-pain end (0cm) and the mark, measured in millimeters, quantifies the level of pain.

Roland-Morris Disability Questionnaire (RDQ)

The RDQ is designed to measure, quantitatively and objectively, the extent to which the pain and motor dysfunction resulting from a patient's compressive-type lumbosciatalgia affects daily quality of life.

Subjective evaluation of efficacy

Non-parametric scale ranging from 1-4, where 4 corresponds to excellent efficacy, 3 to good efficacy, 2 to modest efficacy, and 1 to no efficacy.

Safety and tolerability

Safety was evaluated as a function of treatment-emergent adverse events (TEAEs); tolerability was assessed based on the outcomes of the comprehensive physical exam, hematology, clinical chemistry, and urinalysis performed at both the baseline and end of treatment visits.

Statistical analyses

Differences in VAS and RDQ values were analyzed using ANOVA, using last observation carried forward to handle missing data. Multiple comparisons (of the mean) between groups were conducted using the Schef-

Table 2: Baseline characteristics of enrolled patients

	Total	Treatment		
		Placebo	Normast®	
			300 mg/day	600 mg/day
Number of patients	636	209	212	215
Mean age ± SD	42,8 (11,2)	43,6 (11,5)	42 (10,7)	43 (11,4)
Men	336 (52,8)	106 (50,7)	114 (53,8)	116 (54,0)
Women	300 (47,2)	103 (49,3)	98 (46,2)	99 (46,0)
Mean weight in kg ± SD obese patients	69,7 (12,4)	69,9 (11,8)	69,2 (12,0)	70 (13,4)
Obese patients	89 (14,6)	33 (16,4)	25 (12,3)	31 (15,0)
Mean height in cm ± SD)	168,7 (8,7)	167,7 (8,7)	168,8 (8,7)	169,5 (8,6)
Specific diagnosis	**# of patients**	**# of patients**	**# of patients**	**# of patients**
Unilateral sciatica with lumbago	210	71	72	67
Herniated disc	202	65	69	68
Lumbago, sciatica, thigh pain	55	20	18	17
Lumbar discopathy	48	14	18	16
Lumbar radiculopathy	12	3	2	7
Bilateral sciatica with lumbago	21	8	8	5
Sciatica (unilateral or bilateral)	37	14	18	16
Rachialgia	41	11	15	15
Spondylolisthesis	10	3	0	7

fé test. The χ^2 test was used to analyze the results of the subjective evaluation of efficacy (for both the patient and the investigator). We used $p < 0.05$ as the level of statistical significance.

RESULTS

636 patients with confirmed lumbosciatalgia caused by radicular compression or discopathy participated in this multicenter trial; 336 (52.8%) men and 300 (47.2%) women, with ages between 19-72 (mean 42.8 ± 11.2 years). Demographic characteristics of the 636 patients are listed in Table 2. Demographic characteristics were similar across all groups.

Patient disposition is outlined in Table 3. There were 17 discontinuations throughout the study, 12 in the placebo group, 4 in the 300mg/day Normast group, and 1 in the 600mg/day Normast group. Two patients (one in the placebo group and one in the 300mg/day Normast group) dropped out of the study after the baseline visit to undergo surgical intervention for lumbosciatalgia. One patient in the 300mg/day Normast group did not show up for the day 7 (T7) visit, and 14 patients (11 in the placebo group, 2 in the 300mg/day Normast group, and 1 in the 600mg/day Normast group) withdrew from the study between days 7-21. Lack of efficacy was the most common reason for discontinuation.

Table 3: Patients that completed the study and that withdrew at various clinical visits

	Placebo		Normast® 300 mg/day		Normast® 600 mg/day	
Control	**N**	**W**	**N**	**W**	**N**	**W**
T0 (baseline)	209	1	212	1	215	
T7	208		210	1	215	
T14	203	5	209	1		
T21	197	6	208	1	214	1
Total	197	12	208	1	214	1

A: abandonos

Efficacy

Table 4 lists the results for the VAS and RDQ instruments. Baseline values were similar across the three groups, both in terms of reported pain (mean VAS for each group >6) and quality of life impairment (mean RDQ for each group ~12). At the end of treatment, there was a statistically significant difference in VAS score between the three groups (ANOVA: $p < 0.001$). Between-group comparisons indicate that the 600mg/day dose is statistically significantly more efficacious than the 300mg/day dose (Scheffé test: $p < 0.05$), and that both Normast doses are statistically significantly more efficacious than placebo (Scheffé test: $p < 0.05$).

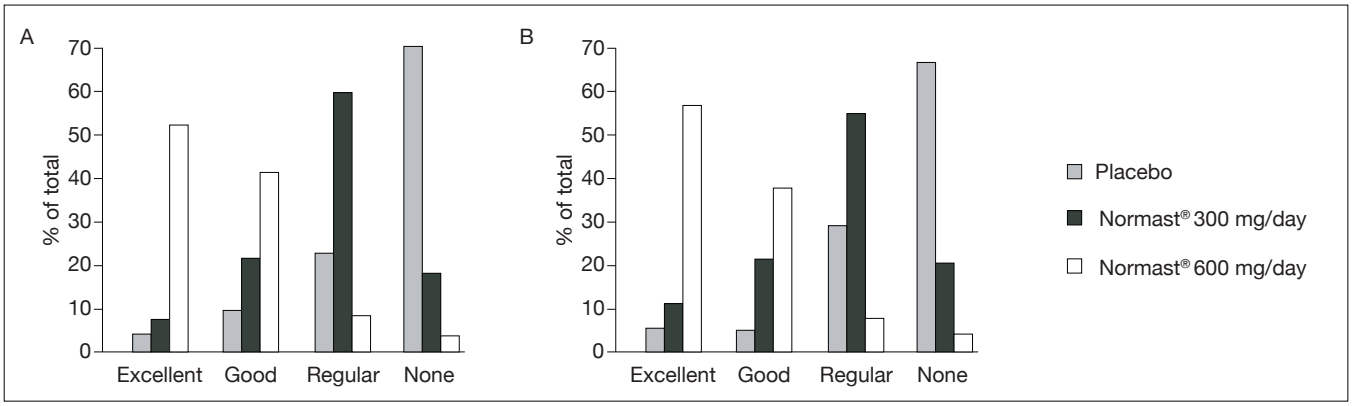
Quality of life (measured by RDQ) also improved relative to baseline at the end of treatment visit, with a statistically significant difference between the three groups (ANOVA: $p < 0.001$). Between-group comparisons indicate that both the 300mg/day and 600mg/day Normast doses result in statistically significantly larger improvements than placebo (Scheffé test: $p < 0.05$) with the 600mg/day dose resulting in the greatest improvement.

In the patient-reported subjective evaluation of efficacy at the end-of-treatment visit, 51% of patients taking 600mg/day Normast reported 'excellent' efficacy. 58% of patients taking 300mg/day Normast reported 'modest' efficacy, whereas 70% of patients taking placebo reported 'no' efficacy (Figure 1A). The investigator-reported subjective evaluation of efficacy at the end-of-treatment visit revealed similar results (Figure 1B). There was a statistically significant positive rela-

Table 4: Mean ± standard deviation for VAS and RDQ scores at T0 (baseline) and T21 (end of treatment)

	Placebo	Normast®		Anova p	Scheffé
		300 mg/day	600 mg/day		
Patients	208	210	215		
VAS					
T0	6,6 (1,7)	6,5 (1,9)	7,1 (1,8)		
T21	4,6 (1,7)	3,6 (1,8)	2,1 (1,7)		
Delta	2,0 (1,9)	2,9 (2,3)	5,0 (2,5)	< 0,001	< 0,05†
RDQ					
Day 0	11,9 (3,8)	11,7 (4,0)	12,7 (4,1)		
Day 21	8,9 (3,2)	6,7 (3,5)	3,5 (2,7)		
Delta	3,0 (3,4)	5,0 (3,3)	9,2 (4,2)	< 0,001	< 0,05†

* The total number of patients that completed the study were 197 (placebo), 208 (300mg/day Normast), and 214 (600mg/day Normast); † between-group comparison



tionship between dose (0, 300, or 600mg/day) and perceived efficacy for both patients and investigators ($p<0.001$, χ^2 test).

CONCLUSIONS

Daily administration of Normast for 21 days resulted in improvements in symptoms and daily activity of adult patients with lumbosciatalgia resulting from radicular compression and/or discopathy. The effects of Normast on pain reduction and quality of life improvement are dose dependent. Both the 300mg/day and 600mg/day doses of Normast were well tolerated, with no reported adverse events or clinically-relevant changes in clinical or laboratory observations.

The results of this clinical trial confirm the low pain reduction observed with standard of care (SOC) medications for chronic neuropathic pain. This is evidenced by the fact that patients in the placebo arm--who were receiving SOC medications-- had mean VAS and RDQ scores of 4.6 and 8.9, respectively, at the end-of-treatment visit, indicative of persistent pain and poor QoL. Treatment with 600mg/day Normast meaningfully reduced mean VAS and RDQ scores at end of treatment to 2.1 and 3.5, respectively, suggestive of clear improvements in clinical symptoms and QoL.

Despite the availability of several approved agents--and others in development-- for pain management, treatment of chronic pain remains problematic since molecules with analgesic effects often result in undesired off-target effects in addition to poor resolution of clinical symptoms. In contrast, consumption of Normast--both in this and other trials[31,32]-- does not result in AEs. Additionally, PEA is an endogenous substance and, in contrast to other N-acylethanolamines like endocannabinoids, does not directly activate the CB1 receptor that mediates most of the psychotropic effects of cannabinoids9.

The data from this clinical trial confirm the results of numerous experiments that demonstrated the ability of PEA to downregulate chronic inflammation; this activity of PEA is attributed to its ability to modulate mast cell hyperactivation--responsible for the initiation, amplification, and maintenance of inflammatory processes and pain-- without interfering with normal, physiological mast cell degranulation. The results from this trial suggest that PEA can also act at the level of the spinal cord: traumatic and/or compressive damage to the peripheral nerve are often accompanied by alterations in the spinal cord. In particular, sciatic nerve damage in rat models results in activation of glial cells[33], cells implicated in regulating the repair of neurons following injury and that, like mast cells in the peripheral nervous system,

produce PEA. Recent work[11] demonstrated that the effects of PEA on reducing neuropathy-induced allodynia and hyperalgesia stem from normalization of various neurotrophins (including NGF) not only in the damaged nerve but also in the spinal cord. Given that the NGF found in the spinal cord did not originate in the peripheral nervous system, these observations suggest that PEA exerted its effects directly on the central nervous system (CNS). Additionally, neuroprotectivve effects of PEA (to prevent neuroinflammation) have been observed in experimental models of spinal cord injury[23], multiple sclerosis[26], and ictus[27].

In conclusion, the results of this study demonstrate the PEA, de active ingredient in Normast, is efficacious in the treatment of chronic neuropathic pain and in the functional alterations of peripheral nerve fibers resulting from discopathy and radicular and/or truncal compression of the sciatic nerve. Additionally, ingestion of PEA is not associated with undesired side effects.

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