

## The Role of Palmitoylethanolamide, an Autacoid, in the Symptomatic Treatment of Muscle Cramps: Three Case Reports and Review of Literature

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### Abstract

Physicians frequently see patients suffering from muscular cramps. Diagnosis of muscular cramps in general is not complex and can mostly be based on history and physical examination only. However, there is no clear evidence for the efficacy of pharmacological or other treatments for muscular cramps, apart from magnesium salts in pregnancy-associated cramps. New therapies are therefore urgently needed. We present three patients with treatment-refractory muscular cramps who responded favorably to treatment with the supplement and endogenous lipid messenger, the autacoid palmitoylethanolamide (PEA).

**Keywords:** Muscular cramps; Palmitoylethanolamide; Idiopathic; Leg cramps; Diabetes; Autacoid; Treatment

### Introduction

Secondary and primary idiopathic leg cramps are common. More than half of all adults reports nocturnal leg cramps [1]. Cramps can disrupt sleep and have a substantial negative impact on quality of life. Muscle cramps may be a symptom of peripheral vascular disease, radiculopathies and lumbar canal stenosis, diabetes mellitus, liver disorders and cirrhosis, metabolic myopathies and neuropathies. Muscle cramps can also be a side effect of diuretics [2]. The medical history and physical examination are generally seen as sufficient to diagnose idiopathic nocturnal leg cramps and differentiate from other conditions, such as restless legs syndrome, claudication, myositis, and peripheral neuropathy [1]. Regarding treatments, quinine cannot be recommended due to severe or fatal thrombocytopenia as a side effect [3]. In 2010 the U.S. Food and Drug Administration issued a warning about troublesome drug interactions with quinine, and recommended that the potential for serious adverse effects outweigh the modest benefit of the drug. Evidence for the efficacy of magnesium is lacking except for pregnancy-associated cramps [4]. Evidence for calcium channel blockers, carisoprodol, or vitamin B12 is limited or absent [5]. Other non-drug treatments for lower limb muscle cramps have limited value only [6]. Forced gastrocnemius stretching has long been recommended to prevent leg cramps, but also here the evidence is only experience based [7]. Since some years we are treating patients suffering from nocturnal muscle cramps with the supplement palmitoylethanolamide (PEA) as in PeaPure 400 mg capsules (J.P. Russell Science Ltd.), an endogenous lipid messenger molecule and autacoid. We will discuss three patients suffering from nocturnal cramps, who all responded favorably after being treated with PEA.

### Case Report

The first patient was an 84-year-old male, still very vital and able to walk many kilometers, with complaints of muscular cramps, mainly nocturnal, since 2005. The cause of these cramps was diabetes type 2 diagnosed in 2000. His treatment consisted of rosuvastatin calcium 2.5 mg daily, diltiazem 200 mg daily, hydrochlorothiazide 12.5 mg daily, losartan 50 mg daily, aspirin 100 mg daily and metformin 1000 mg twice daily. He started suffering from neuropathic pain in both feet since 2005, and increasingly frequent painful nocturnal cramps; mean score of these cramps during one week on the 11-point numeric rating scale (NRS) was 5. Patient visited our Institute and because he did not want to try drugs, such as pregabalin and amitriptyline, we started treatment with PEA, 400 mg twice daily. Within one week his cramps were noticeably reduced, and after 2 weeks the pain cramp

score was down to 1 on the NRS. Actually he stated that the last month of treatment no cramps occurred anymore. The second patient was a 73-year-old lady suffering from a chronic intoxication probably due to long exposure to high doses of vitamin B6. She was using a supplement containing more than 2000% of the daily-recommended dose. She suffered from neuropathic sensibility disturbances and slight extensor weaknesses in both feet, and a positive Romberg sign during neurological examinations was documented in 2011 and 2014. In 2011 vitamin B6 level was above 800 nmol/L (norm 30 - 144 nmol/L), the EMG at that time showed clear signs of an axonal neuropathy. In 2011 she stopped vitamin B6 intake, however in 2014 there were still marginally increased B6 levels (180 nmol/L). Since 2011 her main complaint was four to six muscle cramp attacks each night and she had stretch extensively each night to counteract the cramps. She slept only 3-4 hours each night due to these nocturnal cramps. Magnesium salts and temazepam 10 mg daily did not result in any improvement. In 2014 we treated her recurrent nocturnal cramps with PEA 3 times 400 mg daily. Within 12 days the cramps vanished totally and she 'slept again as a newborn baby'. The nocturnal cramps reoccurred 2 days after forgetting to take PEA capsules, due to such positive effects. Within a day after starting PEA again, she could notice the anti-cramp effects. This unintended challenge-rechallenge effect occurred two times in several weeks. Also the second time cramps re-appeared within 24 hours after stopping taking PEA.

The third patient was an 81-year-old lady suffering from chronic axonal polyneuropathy, and frequent nocturnal cramps (2-3 painful cramps each night, during some minutes). Diagnoses were based on clear clinical signs for polyneuropathy and physical examination: pins-and-needles, hypesthesia and absent ankle jerk reflexes at both feet. Laboratory values were normal except for a clear vitamin D3 deficiency (39 nmol/L). After supplementation of vitamin D3 the level increased to 87 nmol/L, however without leading to diminishment of her complaints. Treatment with a cramp-blockade-or these did not solve the problem.

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Received February 06, 2016; Accepted March 20, 2016; Published March 25, 2016

**Citation:** Hesselink JMK, Kopsky DJ (2016) The Role of Palmitoylethanolamide, an Autacoid, in the Symptomatic Treatment of Muscle Cramps: Three Case Reports and Review of Literature. J Clin Case Rep 6: 744. doi:10.4172/2165-7920.1000744

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We started with PEA 3 times 400 mg daily. Within 14 days the cramps diminished in intensity and frequency and after 4 weeks all cramps vanished.

## Discussion

The underlying physiological mechanism of muscle cramping is still unknown, and there are many speculations. In the absence of a rational explanation and as no current treatments for leg cramps have been proven both safe and effective, its therapy is still based on the experience of the treating physician. PEA is a nutraceutical available under different brand names: PeaPure (supplement), Normast and PeaVera (diet food for medical purposes in Italy). These formulations are all standardized produced according to formulation patents, and all contain fine and ultra-fine particles (smaller than 10 micron). PEA belongs to a class of lipid autacoids, the N-acylethanolamides, together with other endogenous lipids such as the resolvins, the lipoxins and the protectins. The term 'autacoid' is derived from the Greek "Autos" (self) and "Acos" (relief, treatment). Autacoids can be defined as locally produced modulating factors, influencing locally the function of cells and/or tissues, which are produced on demand and which subsequently are metabolized in the same cells and/or tissues [8]. PEA is such an autacoid, with high affinity for the nuclear factor peroxisome proliferator-activated receptor (PPAR). In addition to its affinity for the PPAR, PEA has high affinity for the GPR55 receptor and a number of other targets, among which the TRPV1 channel [9]. This might be of importance, since certain TRPV1 channel activators have been recently patented for the treatment of muscular cramps [10]. PEA has been evaluated in a number of placebo controlled randomized clinical trials and has been found to be effective in various neuropathic pain states and inflammation [11-14]. PEA is produced in the body on demand, as all lipid autacoids, and accumulates locally during inflammatory and pain disorders. PEA can be synthesized in muscle tissue; such synthesis seems to be disturbed in fibromyalgia [15]. Although the pathophysiology of muscular cramps remains poorly understood, the pleiotropic lipid autacoid PEA might play a role in stabilizing overactive muscles giving rise to cramping during the night [16]. One of the mechanisms of action for PEA's anti-cramp activity might be its agonistic action at the TRPV1 receptor [17]. This however remains speculative. Another explanation could be that lipid autacoids such as PEA, based on their clear inflammation-resolving and anti-inflammatory capacity, could reduce the systematic low grade inflammation in diabetes and obesity-related indications, and so stabilize the muscles against overstimulation by pro-inflammatory cytokines.

PEA's side effect profile is very benign, its tolerability is good, and dose-limiting side effects up to several grams daily have not been reported [18]. Drug-drug interactions have also not been reported so far. Meanwhile in our clinic we have patients who used PEA for many years, without problems, and longtime use thus seems possible. Moreover, if patients suffering from chronic disorders such as diabetes stop PEA treatment, pains and cramps tend to re-occur within 1-2 weeks. There are no known contra-indications for PEA, and patients with reduced renal and hepatic clearance can be treated with PEA, as its metabolism based on being an autacoid, is localized and cellular

and independent of kidney and liver functions. Due to the positive balance between efficacy and safety, PEA is a new compound in the armamentarium for the treatment of neuropathic pain, and perhaps nocturnal painful muscular cramps.

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