

## Palmitoylethanolamide Formulations in Chronic Pain, Which to Select?

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### Abstract

Palmitoylethanolamide (PEA) is increasingly popular as a compound with analgesic and anti-inflammatory properties. Anno 2018 nearly 700 PubMed indexed publications can be found, and since 2005 an increasing number of publications have discussed and presented clinical data. Two different companies, Epitech Srl. and Russell Science Ltd. introduced innovative formulations of PEA, containing fine and ultra-fine PEA particles (micro-PEA) some years ago. Since these formulations were developed, various me-too formulations of unknown quality have entered the market, containing mostly unprocessed PEA. Therefore there is confusion about which PEA formulation to choose from. As it currently stands, only the two first formulations introduced in the market, prepared via patented procedures, have given rise to sufficient plasma levels and have been clinically assessed by medical doctors, with its results published in peer reviewed Journals. Unprocessed PEA is highly unlikely to lead to measurable increases in plasma levels. It is therefore recommended to use PEA formulations containing micro-PEA formulations, such as ultra-micronized (PEA-um) and the optimized (PEA-opt) formulations.

**Keywords:** *Endocannabinoids; Neuropathic; Analgesia; Micronized; Optimized*

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### Introduction

#### PEA as analgesic and anti-inflammatory compound

PEA was discovered in the middle of the last century, by scientists of Merck. [1] During some decades the compound was known for its prophylactic properties in respiratory disorders, and was marketed under two different brand names in the period between 1980 to 2015, Palmidrol and Impulsion. These formulations are no longer available. Palmidrol was a drinkable suspension, and Impulsion was a tablet containing 500 mg PEA. The indication for both formulations was respiratory infection, and in the 70s and 80s a number of clinical studies supported the efficacy and safety of PEA in this field, especially in the prophylaxis and treatment of the flu. [2] However, due to the absence of insight in the exact mechanism of action, PEA did become a mainstream treatment. PEA belongs to the class of autacoids, local tissue-hormones, with broad clinical applications, from glaucoma to neuropathic pain. [3,4]

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In the early 90s it was the Nobel laureate Rita Levi-Montalcini who first discovered indicators for the mechanism of action, and it seemed that PEA as an autacoid regulated and inhibited the mast cell. [5-7] Various animal models supported PEA's analgesic effects. [6] Later, along the lines of her work, it was recognized that PEA could inhibit many immune-competent cells, such as the glia. The key characteristics of PEA appears therefore to target some new non-neuronal targets, the glia and other immune-competent cells such as the mast cells. [7] In the beginning of this century the first data were published on the clinical efficacy of a PEA formulation containing ultrafine PEA particles, produced via a patented procedure. [8] Some years later a new mechanism of action was presented, based on the high affinity of PEA for the 'master-anti-inflammatory nuclear switch', the nuclear receptor peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ). [9] The first pivotal and supportive studies however, evaluating such formulation, appeared in a Spanish Journal and was therefore not widely read. [10,11]

### PEA as an effective and safe analgesic

Since the early 2000s, the analgesic properties of PEA were realized over a wide range of chronic pain states. [12-17] Serious adverse events have never been documented to date. In 2012 the clinical analgesic effects of many hundreds of patients, suffering from chronic pain syndromes, who were treated with PEA in a special micro-PEA formulation was summarized in the first clinical review. [13] This paper was instrumental to introduce the PEA concept to a broader audience, as most studies and papers up to that date were published in the Italian and Spanish literature. Western physicians were at that time not aware of the clinical relevance of PEA in the treatment of chronic pain disorders in general, and more specific in neuropathic pain. Soon after the publication of the first review paper a case series was presented, where PEA was effective in treating pain in chronic idiopathic axonal neuropathy and related painful neuropathies. [14] Other studies and meta-analysis supporting PEA's role as an analgesic compound followed. [15]

In addition to its anti-inflammatory properties, these target sites may be a reason for its success in treating various types of neuropathic pain. In a number of clinical studies involving nerve compression syndromes, such as sciatic pain, a micro-PEA formulation proved to be safe and effective. [16] Some studies however, assessed a dose-range that was probably too low (600 mg/day). In one of the more recent studies for instance, in carpal tunnel syndrome, it was stipulated that dose might need to be around 1200 mg/day. [17] This is in line with our clinical impression, and as the safety margin of the compound proved to be excellent, we always recommend to use the initiating dose of 1200 mg/day, and in case of insufficient effect, to double the dose after some weeks. However, formal dose-finding studies in the higher dose-range are still absent.

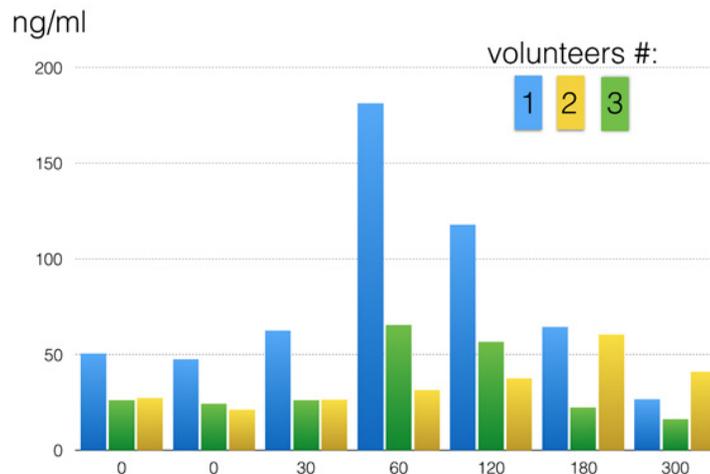
The dose-range selected for studies in humans is between 5 mg/ kg bodyweight (BW) to 100 mg/kg BW. In most studies 600 or 1200 mg daily has been administered. Since 2011, collaborations with the two patented PEA formulations have enabled us to provide more accurate dosing schedules that have achieved faster dose escalations. A minimal dose of 1200 mg/day is now recommended and in the case of insufficient effect, the dose can also be doubled after 6-8 weeks and reassessed for effectiveness during the next 2-3 months of its use. Recent studies support faster dose escalations and a higher dose-range. Low doses (below 600mg/day) are discouraged.

### Micro-PEA: measurable and therapeutic relevant plasma levels

Micro-PEA formulations are scarce in the world, and are characterized by a sufficient amount of fine and ultrafine particles. The clinical articles so far published have all been conducted with formulations containing micro-PEA, and the two main producers are the Italian company Epitech, and the Cypriote company Russell Science. Both these companies have prepared their formulations based on patented production procedures. These specialized patented procedures have resulted in formulations containing micro-PEA (Epitech) and in the case of Russell Science, excipient free formulations containing micro-PEA. [18] Such formulations have been developed based on pharmaceutical indications that lipid compounds might be compromised in the absorption by for instance magnesium stearate; furthermore, its genotoxic potential is still unexplored. [19,20]

There are clear indicators that formulations containing micro-PEA, such as ‘PEA-um’ (ultramicrosized) and ‘PEA-opt’ (optimized), lead to measurable and therapeutically relevant plasma levels. We will present some of these data. As animal data are published in more detail in various papers, we will review only one of the more recent studies, where naïve unprocessed PEA has been compared to a micro-PEA version. Subsequently we will present and discuss some new data from the University of Wageningen, the Netherlands, where plasma levels have been measured in 3 volunteers, using a micro-PEA formulation containing PEA-opt.

It was clear in a recent animal study, that micro-PEA, ‘PEA-um’, containing ultrafine particles and produced according to a patented procedure, lead to considerably higher levels of PEA in the blood than unprocessed PEA. [21] More specifically the administration of an ultrafine PEA formulation led to clear plasma level increases in a rat model, while unprocessed PEA did not lead to a rise in plasma levels. The micro PEA formulation was also more active in pain- and inflammation models, and was capable of down-regulating spinal inflammatory and oxidative pathways. These recent findings also suggest that spinal mechanisms are involved in the anti-hyperalgesic effect of PEA in inflammatory pain. However, these mechanisms of action were only achieved with the use of the patented formulations which contain sufficient ultrafine PEA. In light of a number of recent PEA formulations, mostly low priced, containing only coarsely grinded PEA, these data point out that to achieve the full beneficial effects of PEA, one should select the patent-protected micronization techniques.



**Figure 1:** plasma levels of 3 volunteers after intake of 800 mg PEA-opt (2 x 400 mg PEA-opt capsules): clearly this formulation leads to a clinical relevant rise in plasma levels of PEA, and the peak (C-max) is at least more than double of the base-line levels, which are around 25 ng/ml. There is an individual difference in time-to peak, for instance volunteer 1 reaches Cmax after 60 minutes, while volunteer 2 reaches Cmax after 180 minutes.

The pharmacokinetic properties of the micro-PEA formulation of the PEA-opt formulation were explored in a first pilot study by professor Renger Wit Kamp at the University of Wageningen, the Netherlands (personal communication, data on file). [22] The aim of this pilot study was to investigate if PEA-opt is taken up in the blood and to collect some first indications related to the kinetics of PEA-opt. PEA-opt is a specific micro PEA formulation free of any excipients which has been known to increase plasma PEA levels. In a pilot study three healthy volunteers (see diagram, volunteers #1,2 and 3) gave consent to take part in this pilot, evaluating the kinetics of PEA-opt capsules. It was decided that blood would be drawn at seven different time points, from baseline up to 10 hours after ingestion of the supplement. The subjects came in fasted and at T = 0 minutes, 800 mg of PEA (2x 400mg PEA Pure, JP Russell Science Ltd) was taken orally. The subjects remained fasted up to T=180 minutes. The blood was centrifuged and the plasma was isolated and frozen at -80-degree C until further analysis of the samples. At baseline (fasted): 10ml blood was drawn for measuring the level of PEA in the blood

without supplement. In one volunteer the baseline level was twice as high as in the other 2 (50 ng/ml versus 25 ng/ml). This volunteer clearly showed the highest rise in PEA blood levels, and after 60 minutes after intake the plasma level was around 180 ng/ml. The other 2 volunteers showed a slower absorption, but after 60-180 minutes the PEA levels were more than doubled.

### Conclusion

Studies so far have confirmed that oral micro-PEA formulations enters the blood and is capable of increasing plasma levels whilst coarsely processed PEA does not enter the blood stream and is not able to achieve clinically effective plasma levels. Animal studies have further demonstrated that micro-PEA formulations are superior when compared to unprocessed PEA, both from the pharmacokinetic as well as from the pharmacodynamics perspective. To date, considerable increases in PEA plasma levels have been documented only for patent protected micro-PEA formulations. The clinical data reviewed above further supports the clinical recommendation to start treating with 1200 mg/day, and in case of insufficient effect after one month to double the dose.

**Conflict of interest:** Authors report no conflict of interest

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