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Mini Review

Chronic Pain and the Use of Palmitoylethanolamide

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Abstract

In this short review, we will discuss some practical points to consider when using palmitoylethanolamide (PEA) as an analgesic and anti-inflammatory compound. Since the emergence of PEA in a number of food supplements, it is important to be aware of practical issues related to what dose to use, how long to use it and what formulation to choose. As PEA resets a nuclear receptor, and down regulates over-active inflammatory pathways by doing so, it is recommended to use PEA for at least 2 months before deciding how to proceed. The standard daily recommended dose is 1200 mg and the author most often prescribes a fixed combination between PEA and low dosed vitamins B in order to achieve synergistic effects.

Introduction

PEA is a natural occurring lipid belonging to the class of autacoids, we could characterize these molecules as tissue hormones. [1]. Autacoids such as PEA may become a new cornerstone in the treatment of chronic pain and inflammation [2]. PEA is not a registered drug, but it is widely available as supplement. I use PEA in my patients suffering from neuropathic pain since 2010, and have done quite some research on it. In the many hundreds of patients I treated, dose-limiting and serious adverse events did not occur. This probably is related to the fact that PEA is an endogenous lipid, produced on demand in the membranes of our cells, and easily metabolized in the cell into metabolites which are than recycled in those membranes. It also implies that dose-reduction in case of liver- or kidney-insufficiency is not required. As more and more patients and doctors become aware of this natural compound, a short introduction might serve both groups.

PEA as a Painkiller

The use of PEA as a painkiller in the first decade of this century was limited to Italy and Spain only, because clinical papers in the English language were missing. In Italy, the compound was used widely by neurologists and pain specialists, due to the work of the Italian Nobel laureate professor Rita Levi-Montalcini, who first clarified its mechanism of action as an Anti-Inflammatory Agent [3].

The author first learned about PEA at the 3rd International Congress on Neuropathic Pain (NeuPSIG) that took place in Athens, Greece in 2010. In the basement of the congress building a young PhD student from the group of Professor Giorgio Cruccu of the Sapienza University of Rome, presented first clinical data supporting the analgesic effect of PEA in painful neuropathy [4]. Soon, in 2001, the first PubMed publication from the same group appeared, presenting results from an open study in patients suffering from multiple myeloma and treated with thalidomide and bortezomib [5]. Both neuropathic pain as well as the neurophysiological indicators measured for the function of the Aα, Aβ, and Aδ fibers significantly improved compared to baseline. First indications for its use in osteoarthritic pain was based on a controlled clinical study which supported its safety and efficacy [6].

In 2012 we presented a review on 22 clinical studies published up to that year, including studies published in Spanish or Italian papers. [7].

Some years ago, we published the first qualitative meta-analysis on all studies conducted in nerve compression syndromes. Both for carpal tunnel syndrome, as well as for sciatic pain, PEA could significantly and clinically relevant reduce pain [8]. Meanwhile, anno 2018, there are more than 200 entries in PubMed if one conducts a search using the keywords 'palmitoyl ethanol amide' and 'pain'.

PEA has an interesting mode of action, it actives a nuclear receptor, the Peroxisome Proliferator-Activated Receptor alpha (PPAR-alpha), which is a master-switch for a great number of genes activating inflammatory cascades [3]. This most probably is one of the main reasons for its analgesic and anti-inflammatory activity (Figure 1).

PEA resets over-active genes, which code for inflammation, and in order to reset these *via* the PPAR receptor, PEA needs some time. This is the reason for recommending to use PEA for at least 2 months. It is not a quick fix; it works *via* adapting the cellular metabolism.

Practical aspects: how to use PEA and what formulation?

The use in the clinic is easy. The recommended daily dose is 1200mg/day. In case of insufficient effect, we always recommend to double the dose after some weeks. One should at least use PEA for 2months, in order to let it unfold its action. It has to reset a number of targets in patients suffering from chronic pain, and in order to do so properly, it needs some weeks.

PEA has been proven to be safe in adults in a dose-range up to 50-100mg/kg bodyweight [9]. In our clinic we prefer the combination between PEA and low-dosed vitamins B, a special combination which is based on synergistic actions between PEA and these vitamins.

To date no drug-drug interactions have been documented. Since the increasing world-wide criticism on the abundant use of opioids, a new and safe compound, which can be given without any hesitation to elderly patients and also in case of polypharmacy, is very much welcomed. PEA not only can exert its analgesic effects as a stand-alone therapy, but also seems to be able to boost the analgesic effects

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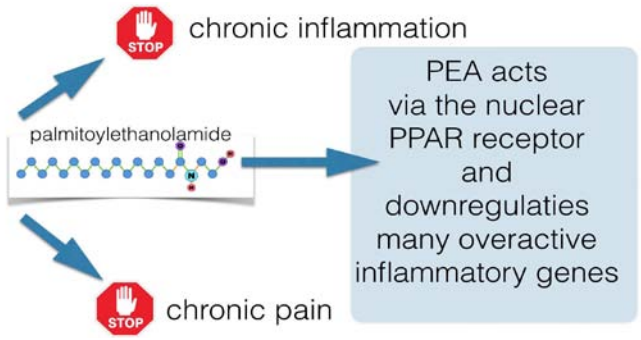

Figure 1: PEA acts as an analgesic and anti-inflammatory compound; its mechanism of action is via the nuclear PPAR receptor, a master-switch for many inflammatory genes.

of classical analgesics such as pregabalin and opioids [10]. In such situations we start PEA (dose: 1200mg/day), and subsequently after some weeks tapering down opioids or other analgesics, such as pregabalin, in general without losing efficacy, resulting in reduced adverse events and better compliance and tolerability. Some patients can stop all other analgesics.

Sadly enough, since 2012 a number of clinically untested PEA formulations flooded the market, as me-too formulations, mostly with unspecified characteristics. It is therefore important to point out that only PEA formulations containing sufficiently ultrafine particles have been tested sufficiently. Only such formulations are proven to lead to increased plasma levels of PEA after intake so far. Such micro PEA formulations are known under the names micronized PEA (PEA-m), ultra micronized PEA (PEA-um) and optimized PEA (PEA-opt). All clinical data so far, published in peer-reviewed Journals, are based on these formulations only.

Of course, there will always be non-responders to this analgesic endogenous compound, but its safety profile is so benign, that in light of the clinical data one could suggest to always start treatment of pain in chronic pain patients with PEA, given one uses a sufficient dose and the appropriate formulation.

Conclusion

After being used in the clinic since a decade for the treatment of chronic pain, PEA has become more visible as an adjunct treatment for the treatment of chronic pain, and as a stand-alone therapy. For neuropathic pains, as in nerve compression syndromes, PEA has been proven to be effective and safe in many randomized clinical trials. Its use as an anti-inflammatory agent started already in the 70s of last century, but it did not yet penetrate mainstream medicine. This is sad, as the compound is extremely safe and easy to use, and has been found to benefit many patients. One should always select a formulation containing micro-PEA, such as formulations containing micronized (PEA-m), ultra micronized (PEA-um) or optimized PEA (PEA-opt). Only these PEA formulations are based on standardized and patented production processes.

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