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Chronic Pain and the Use of Palmitoylethanolamide: An Update

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Commentary

Palmitoylethanolamide (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.

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 fibres 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 'palmitoylethanolamide' 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. The use in the clinic is easy. The recommended daily dose is 1200 mg/day. In case of insufficient effect, we always recommend to double the dose. PEA has been proven to be safe in adults in a dose-range up to 50-100 mg/kg bodyweight [9]. 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 of classical analgesics such as pregabalin and opioids [10]. In such situations we start PEA (dose: 1200 mg/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. 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.

References

1. Keppel Hesselink JM (2015) The terms 'autacoid', 'hormone' and 'chalone' and how they have shifted with time. Auton Autacoid Pharmacol 35: 51-58.
2. Keppel Hesselink JM (2016) Autacoids: A New Fundament for Pain Medicine of the 21th Century. Anaesthesia, Critical Care and Pain Management 1: 3-6.
3. Keppel Hesselink JM (2013) Evolution in pharmacologic thinking around the natural analgesic palmitoylethanolamide: from nonspecific resistance to PPAR-α agonist and effective nutraceutical. J Pain Res 6: 625-634.
4. Biasiotta AS, La Cesa C, Leone G, Di Stefano A, Truini G, et al. (2010) Efficacy of palmitoylethanolamide in patients with painful neuropathy. A clinical and neurophysiological open study. Preliminary effects. European Journal of Pain Supplements 4: 1-77.
5. Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, et al. (2011) Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets 10: 916-920.
6. Marini I, Bartolucci ML, Bortolotti F, Gatto MR, Bonetti GA, et al. (2012) Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain 26: 99-104.

7. Keppel Hesselink JM (2012) New Targets in Pain, Non-Neuronal Cells, and the Role of Palmitoylethanolamide. The Open Pain Journal 5: 12-23.
8. Keppel Hesselink JM, Kopsky DJ (2015) Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res 8: 729-734.
9. Esposito E, Cuzzocrea S (2013) Palmitoylethanolamide is a new possible pharmacological treatment for the inflammation associated with trauma. Mini Rev Med Chem 13: 237-255.
10. Keppel Hesselink JM, Hekker TA (2012) Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res 5: 437-442.