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Palmitoylethanolamide (PEA)

INTRODUCTION

Palmitoylethanolamide (PEA) is a type of lipid (fatty acid ethanolamine) found in foods such as egg yolks, safflower lecithin, soybeans, and peanuts, but also endogenously produced in microglia and mast cells. Its primary benefits, including analgesic, neuroprotective, and anti-neuroinflammatory properties, appear to be mediated chiefly through activation of the PPAR-α nuclear receptor. It is also thought to prevent mast cell degranulation, activate the GPR55 receptor, and indirectly activate the CB1 and CB2 receptors, and the TRPV1 channel (aka the capsaicin receptor) (Rinne et al., 2018; Petrosino & Di Marzo, 2017; Skaper et al., 2015; Artukoglu et al., 2017; Paladini et al., 2016; Skaper & Facci, 2012). This latter indirect activation has explained PEA's so-called entourage effect; for example it indirectly induces analgesia by increasing levels of anandamide, which has direct analgesic effects mediated via the CB1 and CB2 receptors.

Many conditions associated with chronic pain appear to be responsive to therapy with PEA. There is now good clinical evidence of its benefits for nerve compression syndromes, including carpal tunnel syndrome and sciatica; in a double-blind placebo-controlled trial with over 600 participants with radicular compression of the sciatic nerve, PEA was given at dosages of 300 or 600 mg per day, and compared to placebo. A robust clinical response was seen, with a mean reduction on the visual analogue scale (VAS) from 7.1 to 2.1, a more than 50% pain reduction with the highest dose. Additionally, the NNT (number needed to treat) to reach a 50% reduction in pain was 6.5 for the 300 mg group, and only 1.5 for the 600 mg group after three weeks of treatment (Keppel Hesselink & Kopsky, 2015). Similarly, in a small group of patients with carpal tunnel syndrome, significant improvements in distal motor latency after PEA treatment were seen, with a dose-dependent effect (1200 mg per day was more effective than 600 mg per day) (Conigliaro et al., 2011).

In an observational trial with 610 participants with pain of more than 6 months duration, PEA was given at a dose of 600 mg twice daily for three weeks, followed by a dose of once daily for four weeks. PEA was given in addition to standard analgesic therapies (including opioids, anticonvulsants, and other rescue medications), or as a single therapy if participants discontinued their other analgesics for any reason. The etiology for the majority of these participants was radiculopathy (54%), but also included pain due to osteoarthrosis (8.9%), herpes zoster infection (7.2%), diabetic neuropathy (5.3%), failed back surgery syndrome (12.4%), oncologic disease (3.6%), and other (8.3%). PEA reduced the mean numeric rating scale (NRS) of pain intensity in all patients who completed the study, from a baseline mean of 6.4 to 2.5 by the end of the study. Importantly, PEA reduced pain regardless of etiology, and when used as a stand-alone treatment or in combination with other medications, with no adverse effects (Gatti et al., 2012).

PEA has also shown benefit for the temporomandibular joint (TMJ); in a triple-blind trial comparing PEA to ibuprofen among participants with TMJ osteoarthritis or arthralgia, PEA was given at a dose of 300 mg in the morning and 600 mg in the evening for 1 week, followed by 300 mg twice per day for one additional week. Both maximum mouth opening (P = 0.022) and pain (P = 0.0001, measured by VAS) were significantly improved compared to ibuprofen, again with no adverse effects (Marini et al., 2012).

PEA has been reported to improve depressive symptoms among participants with major depressive order, when used in conjunction with citalopram. By the second week of receiving 600 mg PEA twice daily, a significantly greater reduction in Hamilton Depression Rating Scale (HAM-D) scores compared to the placebo group was observed (8.30 ± 2.41 vs. 5.81 ± 3.57, P = .004). Additionally a 100% response rate (defined by a 50% or greater reduction in HAM-D scores) was observed in the PEA group compared to 74% in the placebo group (note that both groups received citalopram) (Ghazizadeh-Hashemi et al., 2018). PEA has also been shown to improve endothelial function and reduce intraocular pressure among patients with ocular hypertension (Strobbe et al., 2013, Gagliano et al., 2011).

ASSESSMENT

A number of scales for pain are in clinical use. Most of the published trials with PEA have employed the visual analogue scale or numeric rating scale to determine pain intensity and monitor progress (Haefeli et al., 2006). A standard physical examination and history should always be performed, as well as any indicated imaging or other diagnostic tests needed for an accurate diagnosis. For example, distal motor latency and/or nerve conduction velocity determination provides a benchmark when treating carpal tunnel syndrome. Also, given the possible improvements in anxiety and depression, tracking of symptoms (e.g., the Depression Anxiety Stress Scale) among patients with these conditions may document improvements secondary to the main treatment goals.

GENERAL RECOMMENDATIONS AND DOSING

Currently, no drug interactions are known for PEA, and it has been used successfully among patients taking a variety of other medications, including anticonvulsants, antidepressants, and opioids, and its efficacy for reducing pain does not seem to depend on medications given concomitantly.

Most clinical trials have found greater benefit with higher doses (1200 mg per day, in divided doses), though lower doses have also been found effective. An initially higher dose followed by a lower maintenance dose has also been used in clinical trials.

PEA has an excellent safety profile, with a lower study dropout rate among participants receiving PEA than control. Safety has not been established during pregnancy or lactation (Artukoglu et al., 2017; Nestmann, 2016).

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SUMMARY

- Palmitoylethanolamide (PEA) is an endogenously produced fatty acid ethanolamine
- PEA has analgesic, neuroprotective, and anti-neuroinflammatory properties
- PEA is used for chronic pain management and has been studied for nerve compression syndromes, radiculopathy pain, TMJ, and depressive symptoms
- Clinical trial dosages typically range from 400–1200 mg daily in divided doses
- No known contraindications exist, though safety during pregnancy and lactation has not been established

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