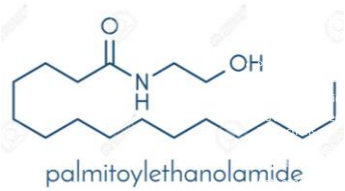


Patient History

- Pleasant 60-year-old female was evaluated by the palliative medicine inpatient service for management of uncontrolled pain in November 2018
- Mrs. K has past medical history significant for morbid obesity, s/p gastric bypass surgery in October 2016 where an incidental GIST of the stomach was discovered, 4 mm size, grade I, low risk, T2 DM, depressive and anxiety disorder, migraine headaches without aura, TIA in 2000 that led to a diagnosis of Factor V Leiden mutation, she has been taking dabigatran long term for this medical problem.

Patient History

- In April of 2001 she was diagnosed with stage IV non-Hodgkin lymphoma and treated with 6 cycles of CHOP plus rituximab, followed by three cycles of rituximab
- January of 2018, she developed neutropenia and thrombocytopenia which had developed gradually, and led to a bone marrow biopsy suggestive of early myelodysplastic syndrome
- In April of 2013 she was diagnosed with stage I-B shoulder melanoma, sentinel node biopsy negative for involvement. A palpable anterior chest wall mass led to PET-CT scan in May 2018 which revealed hypermetabolic liver and anterior chest wall masses. Liver biopsy determined the presence of metastatic malignant melanoma

Patient History

- She was started on a combination regimen of nivolumab and ipilimumab and completed day 16 of cycle 2. This combination regimen had to be discontinued due to grade 2 persistent arthralgias, worse over upper extremities.
- . The symptoms started as generalized aches, the day after combination therapy was initiated in May of 2018. At times she would describe deep muscle aches, more prominent over lower extremities, but fairly generalized in June of 2018. The pain escalated and in July of 2018 she experienced edema associated with erythematous rash to both upper extremities.

Patient History

- In October of 2018 she noticed worsening weakness in association with her painful numbness. Episodic exacerbation became worse in November of 2018, now primarily involving hands with achy joint, worse with movement, persistent, 7 to 10/10 and requiring repeated doses of oxycodone-APAP. She was started on morphine ER 30 mg via oral route twice daily in November of 2018.
- She required an admission for febrile neutropenia on November 25, 2018, found to have blood cultures positive for Corynebacterium spp., and Gram-negative rods. During this admission we started helping manage her pain, and she was continued on morphine ER 30 mg via oral route every 12 hours and morphine IR 15 mg every 4 hours as needed

Patient History

- Gabapentin was started with 300 mg at bedtime in December 2018, along with assistance in managing her chronic pain and generalized anxiety disorder by cognitive behavioral therapy interventions, along with diazepam 5 mg three times daily and venlafaxine XR 150 mg daily which she had been taking since July 2018.
- She described nausea, headaches worsened by the use of gabapentin and she did not wish to adjust her dosing scheme.
- On February 19 we decided to start the use of PEA 400 mg via oral route twice daily.

Patient History

- She noticed an improvement within the first two weeks, and upon further titration of her dose to three times daily reported essentially resolution of her dysesthesia, paresthesia over both hands, as well as residual arthralgia, allowing her to stop the use of opioids entirely.
- Further addition of duloxetine, starting at 30 mg and subsequently increasing to 60 mg at bedtime allowed great improvement in her anxiety.

Summary

- Cannabimimetic nutraceutical
- Reduces neuropathic pain, pain from endometriosis, entrapment neuropathies, thalidomide neuropathy, diabetes
- Palliative strokes, brain trauma, Alzheimer's disease, MS, autism
- Potentiates antidepressants
- No adverse effects or drug-drug interactions
- Improves analgesia of standard opioids and adjuvants
- Anti-cancer and anti-seizure activity

Historical

- Coburn described the clinical benefits to feeding poor children dried egg yolks to prevent rheumatic fever despite streptococcal exposure
- Pea was isolated from guinea pig and rat brain in 1957
- The nutraceutical was promoted as a treatment for influenza and the common cold
- In the 1960's SPOFA United Pharmaceuticals brought PEA to market as 300mg Impulsin ™
- This benefit has largely been ignored in the recent literature which now is largely concentrated on PEA benefits as an analgesic and modulator of neurological disorders

Classification

- Related endogenous cannabinoids are N-arachidonoyl ethanolamine (AEA) also known as anandamide, 2-arachidonoyl glycerol (2-AG) and oleoyl ethanolamine (OEA)
- PEA does not bind to classical cannabinoid receptors (CB1, CB2) to any significant degree and only indirectly activates classical receptors through an entourage effect.

Pharmacodynamics

- The main targets of PEA have been clinically associated with analgesia, antidepressant and antineuroinflammatory activity and are peroxisome proliferator-activated receptor alpha (PPAR), the vanilloid receptor TPRV1, the orphan receptor GPR-55 and indirectly through alterations in monoamine neurotransmission and classical cannabinoid receptors
- Actions are similar to cannabidiol

Observational Studies

- PEA accumulates in painful tissues
- This was seen in trapezius muscle of women with chronic neck pain
- PEA plasma levels are increased in pain processing disorders such as fibromyalgia and patients with wide spread non-localized pain

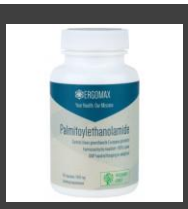
Clinical Studies

- We found 19 studies and 5 randomized controlled trials (RCT).
- PEA reduced painful diabetic neuropathy, neuropathy from chemotherapy, pain from idiopathic axonal neuropathy, non-specific neuropathy, and pain from sciatic and lumbosacral spine disease
- PEA failed to improve pain from spinal cord injury in one RCT
- PEA improved pregabalin, oxycodone and codeine analgesia
- Multiple studies of PEA in carpal tunnel syndrome demonstrated improvement in symptoms and objective improvement in nerve function

Clinical Studies

- In two meta-analyses, PEA has had significant analgesia either as a single agent or as an add-on analgesic

Study	Design/Number	PEA/Timeframe	Comparator	Outcomes	Results	Adverse Effects
Paladini, A, 2016	Meta-analysis, N=12 studies, 3RCT, N=1485 patients, multiple phenotypes, 2010-2014	m or umPEA 300-1200mg/d for 60 days, add-on to analgesics	In RCT placebo or active comparator	VAS pain severity	Pain severity reduced at 2 weeks with placebo decreased by 0.2 with PEA 1.04 (P<0.001)VAS pain severity at 60 days, Placebo 6.6 to 6.6, VAS pain with PEA 6.6 to 2.9, VAS </= 3/10 Placebo 41%, PEA 82%	
Artukoglu, B, 2017	Meta-analysis, N=10 RCT, N=1289 patients, multiple pain phenotypes	PEA 300-1200mg/d, 14 to 180 days	Active and inactive controls	VAS pain severity	PEA>Placebo with WMD 2.03 (P<0.001), no difference if blinded or open label study. Active controls PEA> control WMD 1.31 (P<0.005), no association of benefits to duration of therapy	Attrition PEA 1.1%, comparator 4.3%



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