Phenylalanine for Musculoskeletal Pain Relief: An Often Forgotten and Neglected Complementary Orthomolecular Treatment

In an article about opioids, Dr. David Juurlink highlights the many problems associated with using opioids for chronic pain, and how no studies published in the last twenty years have shown them to be safe and effective for the long-term treatment of chronic pain.[1] Many Canadians have unfortunately died from opioids, according to Juurlink, being responsible for some ten to twenty thousand deaths since 1995. He urges physicians to resist increasing the opioid dose because of the rapid development of tolerance and physical dependence. Of note, is the opioid-induced hyperalgesia syndrome that physicians are often unaware of, and which can be responsible for a worsening of chronic pain over extended periods of time.

As all of us clinicians know from experience chronic pain is the primary complaint among individuals with chronic musculoskeletal (MSK) disorders.[2] Among individuals that present with MSK pain, it is usually non-specific and cannot be related to a single specific cause, even when the pain is restricted to one location (e.g., the lower back).[3] While MSK pain affects between 13.5% and 47% of the general population, it is often associated with chronic widespread pain (i.e., pain of longer than three months duration with a widespread distribution affecting both sides of the body including the axial skeleton) that has a prevalence of 11.4% and 24% of the general population.[4] Chronic widespread pain increases with age and its symptoms include multifocal pain, fatigue, insomnia, memory problems, and a high rate of comorbid mood disorders.[5] The pathophysiology of chronic widespread pain (e.g., fibromyalgia syndrome) is complex, but probably involves alterations of central pain sensitization pathways, hyporeactivity of the hypothalamic-pituitary-adrenal axis, increased systemic pro-inflammatory and reduced anti-inflammatory cytokine profiles and disturbances in the dopaminergic and serotonergic systems.[6]

Clearly measures are needed to not only reduce the morbidity of chronic pain, but to lessen the growing reliance on the long-term use of opioids. Research dating back to the 1980s has shown D-phenylalanine (DPA), i.e., an enkephalinase inhibitor, to be an effective treatment for chronic intractable pain and a variety of chronic pain conditions.[7,8] DPA has been shown to potentiate the analgesic effects of acupuncture.[7,8] An animal study demonstrated that DPA inhibited the degradation of met-enkephalin by mouse brain enzymes.[8] Other research suggests that DPA blocks the activity of carboxypeptidase, an enzyme that degrades enkephalins.[9] When DPA was given 30-minutes prior to acupuncture treatment, it was able to increase the pain threshold, which suggests that DPA enhances the analgesic effect of acupuncture by an endorphin-mediated mechanism.[9] From that same research paper, when 4,000 mg of DPA was given 30-minutes prior to acupuncture, there was prolonged acupuncture anesthesia among patients with low back pain. Similarly, patients undergoing tooth extraction had improvements in analgesia when 4,000 mg of DPA was given 30-minutes prior to acupuncture treatment. The acupuncture analgesic effects were potentiated by 35% when subjects were pre-treated with DPA. In other research from the same paper, different doses of DPA were used to determine the most effective analgesia-producing dose. Previous day DPA administration (500 mg three times daily) was superior to that of DPA administered 30-minutes prior to acupuncture treatment. In clinical research discussing the use of D,L-phenylalanine (i.e., includes equal amounts of the D and L forms of the amino acid; DLPA), data was presented demonstrating that the amino acid can amplify the effects of opioid medication, thus minimizing adverse effects by allowing for opioid dose reductions.[10]

Depression associated with chronic pain is no doubt a unique form of depression that merits treatment. One double-blind trial demonstrated that DPA (150-200 mg/

day) was equally as effective when compared to imipramine (150-200 mg/day) among patients treated for endogenous depression.[11] A single-blinded study failed to show benefit from DPA (median dose, 350 mg/day) for endogenous depression.[12] Since these studies did not evaluate depression associated with chronic pain, it is conceivable that much higher daily doses of DPA would be necessary when trying to lessen this specific variant of depression.

To assist patients with chronic pain, the cited evidence suggests 4,000 mg of DPA administered 30-minutes prior to acupuncture, or 500 mg three times daily (away from food) the day before acupuncture treatment. DPA is difficult to obtain by itself, but DLPA is readily available in many health stores. Other cited evidence recommended 500-1,000 mg of DLPA three times daily (away from food) as a reliable treatment for depression associated with chronic non-malignant pain, and for improving pain control by occasionally enabling lower doses of opioid medication. Thus, the recommended dose would need to consider the potential impacts of providing patients with both forms of the amino acid.

I have recently been experimenting with DLPA and have been delighted by some of the preliminary successes attributed to this low-cost orthomolecular intervention. I have not exceeded 4,000 mg of DLPA, and thus my clinical experience has been limited to a single dose of 2,000 mg of DPA to potentiate the therapeutic effects of acupuncture-analgesia. In a current patient with significant MSK pain that I am co-treating with a clinical intern, no adverse effects have resulted from 4,000 mg of DLPA given 30-60 minutes prior to acupuncture treatment. The patient has noted longer periods of analgesia following acupuncture treatment (i.e., lasting several days or more). The patient has fibromyalgia syndrome along with hip and/or spinal-related degenerative changes. When we first evaluated the patient, we suspected opioid-induced hyperalgesia given the chronicity of her pain, and how the chronic pain apparently worsened with the daily use of tramadol (i.e., an opioid medication). As a result of DLPA, she has discontinued tramadol and is now unburdened from chronic physical dependency and opioid-induced hyperalgesia that developed following many years of use.

It should be noted that the use of phenylalanine (form not specified) might cause anxiety, headache and hypertension, and should not be given to phenylketonurics or women that are pregnant or breast-feeding.[13] Concomitant use of DLPA with non-selective monoamine oxidase inhibitor medications might increase the risk of hypertensive crisis, even though this data was derived from an animal study that evaluated the effects of L-phenylalanine only.[14] In a study done on humans, a loading dose of L-phenylalanine was evaluated in patients with neuroleptic-treated unipolar depression, and the combination contributed to the development and severity of tardive dyskinesia.[15] Even though DPA was not used in this human study, the same contraindication would apply, and so the amino acid should not be combined with neuroleptic medication. DLPA should not be given to patients with Parkinson's disease as it has been shown to exacerbate tremor, rigidity, and "on-off" episodes.[16,17]

Conclusion

There appears to be an overabundance of people taking opioids for chronic pain unrelated to surgery and/or cancer, and which is responsible for unnecessary tolerance, physical dependence, hyperalgesia, and possibly death. While the use of DPA and DLPA requires more rigorous evaluation from randomized controlled trials, clinicians might wish to experiment with this amino acid to lessen opioid requirements among patients, and/or lessen depression that often accompanies chronic pain.

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Acknowledgements

Some of the contents of this editorial were adapted from the 'Chronic Musculoskeletal Pain' chapter from the *Textbook of Integrative Clinical Nutrition,* published by CCNM Press Inc, 2012.

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