A Proposed Mechanism for Pain Relief Following MIRE Therapy

Monochromatic infrared energy has become a frequent topic at CME meetings and is quite controversial.

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The most common neuropathy associated with diabetes mellitus is diabetic peripheral sensory neuropathy (DPSN).[1] The true prevalence is not known but has been estimated as high as 90%.[2] The treatment of DSPN with monochromatic infrared energy (MIRE) has become a frequent topic at continuing education meetings and remains shrouded in some controversy and mystery.

MIRE devices were Food and Drug Administration approved in 1994 to increase circulation and relieve pain.[3,4] The devices are commonly available in hospitals, extended care centers and private clinics/offices.[5] Patients may also purchase the units and use them at home.

Claims of improved sensation and pain relief are found in the literature.[6-,8] The mechanism of action is generally thought to involve the ability of photo energy to cause a release of nitric oxide (NO) from hemoglobin allowing it to be available to cause vascular and neurologic effects.[9] A recent double-blind, placebo-controlled study failed to demonstrate any improvement in plantar foot sensation in patients undergoing a 12-week course of MIRE therapy.[6] However, a similar study did demonstrate significant pain decrease with the therapy in patients who's DSPN had not evolved to profound sensory loss.[7] A proposed mechanism of action is put forth to explain these clinical findings. Background is based on literature review.

NITRIC OXIDE IS SYNTHESIZED IN CELLS

NO is synthesized within cells by an enzyme NO synthase (NOS). The human genome contains three distinct genes that encode these NO synthases: nNOS is found in neurons, iNOS is found in macrophages, and eNOS is found in vascular endothelium.[10,11] NO diffuses freely across cell membranes affecting cells only near its point of synthesis as NO is a free radical and is therefore highly reactive. It has a half-life of only a few seconds.[12]

The physiologic effects of NO have become more clearly elucidated over the past decade. The functions influenced include peristalsis in the gastrointestinal tract, contractility inhibition in birth, hormone release from the hypothalamus, pancreas and adrenal medulla, engulfed pathogen lysis within the lysosomes of macrophages, penile erection, the inflammatory response, fertilization, and of particular interest for this review are the affects on blood flow and neurologic activity.[10,11]

NITRIC OXIDE RELAXES SMOOTH MUSCLE

NO relaxes the smooth muscle found in the walls of arterioles allowing blood to pass through easily; this happens at each systole. It also inhibits the aggregation of platelets, keeping inappropriate clotting from impairing normal blood flow. These same vascular effects increase the rate of filtration in the kidneys. Nerves containing iNOS are common throughout the brain[11] and are associated in laboratory animals with long-term potentiation, a type of memory and learning. In the medulla oblongata, NO-sensitive cells respond to severe oxygen deprivation by increasing the rate and depth of breathing. NO has been demonstrated to act as a neurotransmitter in some motor neurons of the parasympathetic branch of the autonomic nervous system.[10] Simply stated, the influence of NO in human physiology is far reaching.

Pain in peripheral neuropathy is an equally daunting

subject. The culprits range from irritable nociceptors to impaired central nervous system inhibition to phenotypic changes in the dorsal root ganglion. The purpose of this article does not include an investigation into the mechanisms of neuropathic pain. We do know, however, that axonal loss may develop in DSPN and attempted axonal regeneration follows.[13] In DSPN, the regeneration of these axons decreases so that it can no longer compensate for the massive loss of fibers in the latter stages of the disease.[14-16] Nerve regeneration is associated with painful peripheral paraesthesiae.[17]

The regenerative cascade following nerve injury has been published often, dating back at least to 1928.[18.] Myelin degradation quickly follows axonal loss. NO released from Schwann cells and macrophages participates in axon and myelin dissolution. NO and superoxide combine to form a highly potent nitrating species called peroxynitrite, which plays a role in myelin peroxidation.[19,20] A potential mechanism of impaired axon regeneration in diabetes is excessive oxidative stress.[21] Oxidative stress elicits apoptosis, a mechanism of cell death characterized by cytoplasmic shrinkage, DNA fragmentation and membrane changes.[22]

Oxidative stress is closely linked to nitrergic stress, an excessive elaboration of NO or its toxic byproducts. When NO is elaborated it can combine with superoxide to form peroxynitrite. This impairs cellular functioning by nitrating thiol proteins.[23] NO donors also collapse neuronal growth cones rapidly and reversibly in vitro. Exposure of the regenerating nerve to NO produces a relatively long lasting inhibition of growth.[23,24] Interestingly, broad-spectrum NOS inhibitors improves peripheral nerve regeneration in laboratory animals.[25-27]

MIRE PREMISE

In summary, the premise of MIRE therapy is that it makes NO available for "vasodilation, analgesia, angiogenesis, and other physiologic effects known to be produced by NO."[8] In theory, this may have a beneficial effect on microangiopathy and endoneurial hypoxia.[23] However, the injured nerve in DSPN attempts to regenerate.[13,23] Active nerve regeneration is associated with peripherally generated pain.[17] NO has been demonstrated to produce neuronal growth cone collapse and impaired cellular functioning in the regenerating sensory nerve.[23,24]

We propose that the unregulated administration of an exogenous nitric oxide stimulus likely leads to inhibition of axonal regeneration. This may explain the clinical findings of transient pain relief after MIRE therapy with failed sensory restoration. Assuming MIRE frees NO, then the NO halts the painful attempted nerve regeneration. This effect is predictably transient. Also predictably, the now quiescent nerve does not result in sensory improvement. If MIRE therapy is beneficial in DSPN, dosing may be necessary. ■

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