

Assisi™ Animal Health

Non-pharmacologic, non-invasive pain control: Emerging alternatives to non-steroidal anti-inflammatories for treating chronic pain in animals

Abstract: The use of Non-Steroidal Anti-Inflammatories (NSAIDs) in animals and humans is coming under increasing scrutiny. In animals, veterinary NSAIDs may be associated with gastrointestinal ulcers/perforations, liver, and kidney toxicity. In humans, use of NSAIDs is contraindicated under current AHA guidelines for those with certain conditions, including cardiovascular risk factors and kidney abnormalities. For humans with these identified conditions, NSAID use should be avoided until all non-pharmacological interventions have been attempted and failed. In response to these and other drug-related problems, non-invasive, non-pharmacological interventions are being cleared by FDA and other regulatory bodies for the treatment of pain and edema in humans. While these technologies have been in use in clinics for many years, until recently they were not available in a simple, lightweight device that can provide benefits at home. Published clinical research conducted by 1 company over the past 5 years explicitly demonstrates the effectiveness of targeted pulsed electromagnetic field therapy (PEMF) to treat pain and other conditions by accelerating the endogenous anti-inflammatory cascade. That same non-invasive, non-pharmacological treatment is now available for animals, in both clinics and at home.

Problem

Pharmacological intervention for the treatment of pain is the principal standard of care in both veterinary medicine and human clinical practice. A long history of clinical experience has exposed a variety of potential contraindications with these pharmacological agents, especially with prolonged use, as is the case in many chronic pain conditions, such as arthritis.

Veterinary Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are used to control the pain and inflammation associated with osteoarthritis, and from post-operative or accidental trauma. Inflammation - the body's response to irritation or injury - is characterized by redness, warmth, swelling, and pain. NSAIDs work by blocking the production of prostaglandins, the hormone-like substance that causes inflammation.

In veterinary medicine, approved veterinary NSAIDs are used to control the pain of canine osteoarthritis and to control postoperative pain in canines. However, there are risks and benefits with all commonly prescribed veterinary drugs, including NSAIDs.

Veterinarians and pet owners should be aware of the following facts:

- Oral NSAIDs are approved for use in dogs

- All dogs should undergo a thorough history and physical examination before beginning NSAID therapy.
- Appropriate blood/urine tests should be performed to establish baseline data prior to, and periodically during, administration of any NSAID.
- Veterinary NSAIDs may be associated with gastrointestinal ulcers/perforations, liver, and kidney toxicity.
- Use with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided.
- Patients at greatest risk for kidney problems are those that are dehydrated, are on diuretic treatment, or have pre-existing kidney, heart, and/or liver problems.
- Veterinary NSAIDs can cause stomach or intestinal bleeding.

Veterinary risks associated with NSAIDs are detailed on the package inserts and Client Information Sheets. (<http://www.fda.gov/cvm/nsaids.htm>, last accessed 7.14.09)

Potential toxicity or side effects of NSAIDs in humans are described in new warnings from the FDA and in evolving clinical guidelines. The American Heart Association (2007) has developed guidelines expressly advising that all non-pharmacological alternatives to NSAIDs be attempted in human patients with chronic pain prior to starting therapy with NSAIDs, in any patients with risk factors for cardiovascular disease. These guidelines were developed to improve the non-pharmacological management of chronic pain patients, such as those who had historically been prescribed Cox-2 inhibitors, now known to increase risk of adverse cardiovascular

events, as well as gastrointestinal bleeding (Circulation 115: 1634-1642). Physical modalities, such as exercise, heat, electrical stimulation, and pulsed electromagnetic field therapy (PEMF) all fall into that category.

Over time, we have seen the risk profiles of agents previously thought to be “benign” analgesics, such as aspirin and acetaminophen, increase, relative to their benefits, especially with longer-term use. As described in the AHA guidelines and in the popular press, more sophisticated pharmaceuticals, like Cox-2 inhibitors, have also been seen, with time, to entail significant risks.

For pets, the availability of suitable analgesics has grown, but is still limited and in terms of actual labeled indications, there are none available for cats or exotic pets, as most development has focused on dogs and horses. Neither veterinarians nor owners can readily create alternatives, so, in general, as with human patients, our pets living with chronic pain are caught between the consequences of pain and the consequences of the drugs we give them to treat their pain. However, alternatives are emerging, and are making some inroads in veterinary medicine. These include electrical stimulation, low-level laser light, ultrasound, vibration and heat, to name but a few. These technologies have positive effects, but are not readily accessible other than through professionals, and, in general, are not useful for owners to use at home. As with human chronic pain

patients, non-pharmacological methods for pain control are poorly adopted, even when there is evidence supporting their efficacy.

Recently (December, 2008), a new class of these technologies has been cleared by FDA and is now commercially available. One version of that technology is now available in the veterinary market. This technology is lightweight (less than 2 ounces), battery-powered and disposable, with virtually no electromagnetic interference. The emergence of this advanced therapy comes out of a large body of research focusing on the mechanism of action in older PEMF technologies. That successful investigation, elucidating the mechanism of action, allowed for the production of therapeutics that used targeted pulsed electromagnetic fields (tPEMF) to provide only the energy necessary to improve that pathway and eliminate all the extraneous energy, hence low-power and lightweight portability.

Now

It is agreed that all living things depend on a myriad of complex biochemical activities, most of which happen automatically, in order to sustain life. The efficiency and regularity of those processes ultimately determines our pet's health and vigor. As our pets age, these processes slow, become less efficient or become uncoordinated. The modern response has been to add more complex biochemicals (drugs) into that beleaguered biochemical process, hoping to overcome the inefficiencies by sheer volume of added drugs.

In certain areas of clinical practice, such as orthopedics, there are technologies that use a pulsing electromagnetic field (PEMF) to transmit electrical impulses into tissue. This “inductive” method of creating electrical current is commonplace (used in rechargeable tooth brushes, etc.), but until recently had only been employed therapeutically to treat non-healing fractures (bone growth stimulators), or via large devices that are high-powered, requiring visits to a clinic or access to an AC electrical supply. Several technologies are cleared by FDA and reimbursed by Medicare to treat fractures; others are cleared to treat pain and edema. This latter class of therapies has been restricted, historically, to those high-powered technologies that produced significant electromagnetic interference and were not easily used due to size and power requirements.

The underlying principals of targeted PEMF are straightforward. As discussed above, pharmacological approaches to chronic pain add chemicals to a biochemical environment. Targeted PEMF, or tPEMF, is designed to improve the efficiency of the existing biochemical activity, by simply accelerating the endogenous anti-inflammatory cascade. Until the beginning of the 21st century, the mechanism of action of PEMF therapies was largely unknown. Since that time, efforts to elucidate the mechanism have demonstrated that PEMF signals targeted to a well-characterized electrochemical binding process have greater efficiencies and effectiveness than untargeted signals. The binding of calcium (Ca^{2++}) to calmodulin (CaM) is the first step in producing the overall anti-inflammatory, regenerative cascade. This pathway is well-understood and

is up-regulated by tissue damage. That binding is an electrochemical process and can be accelerated by adding microcurrents into the damaged tissue.

The immediate downstream effects of targeted PEMF accelerated Ca/CaM binding include the increased expression of the constitutive nitric oxide synthases, releasing nitric oxide (NO), the immediate anti-inflammatory response that reduces pain, improves blood flow, and reduces edema. This occurs within minutes. Production of NO leads to increased cGMP production, the “energy” molecule responsible for the production of pro-angiogenic and tissue regenerative growth factors. This chain is the natural response to inflammation and injury. Targeted PEMF simply accelerates the endogenous response.

A significant body of basic research supports the pathway. The Strauch Laboratory at the Albert Einstein College of Medicine and Montefiore Hospital, has produced a series of papers elucidating accelerations in wound healing (2007), tendon repair (2006), cardiovascular angiogenesis post-infarct (2006), flap survival (2004), and peripheral angiogenesis (2000). The Johnson lab (ISU) has demonstrated significant improvements in pain and edema in standard models, superior to those seen with NSAIDs and similar to those of NSAIDs with NO donors (2008). The Casper lab (Albert Einstein) has demonstrated accelerations in the expression of components of the pathway described (2008, 2009) as well as the ability to selectively inhibit the effects of targeted PEMF by selectively inhibiting steps in the pathway. In addition to this significant data in well-recognized animal models, tPEMF has been demonstrated to

produce significant pain relief in post-surgical models (Heden and Pilla 2008), as well as in ischemic pain (angina) Shen (2009).

These and additional references are available upon request by emailing info@assisivetrx.com.

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