CHAPTER **44**

PAIN MANAGEMENT WITH TRANSDERMAL THERAPY

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The compounding cream market has exploded across the country in the past few years. There are numerous pharmacies promoting these products, many different combinations of topical medications available, and the cost of these formulations is quite high. This can be quite intimidating to a physician, especially when there is inadequate time available for them to thoroughly evaluate these products and pharmacies for efficacy and patient safety. The author had doubts about these compounding formulas when they first appeared on the market and wanted to determine if these products were really effective and if there was a place for them in today's medical management of pain. Were we really getting a bang for our buck with these topical combinations?

After significant research and personal clinical applications, the author feels there is a definite place for these compounding products, especially in pain management, but again like many new medical advances, they are being over-utilized and often times rendered ineffective due to improper usage. These compounding creams can be very beneficial for treating pain when prescribed appropriately. The author has had success with many topical formulations, and has seen them make a big difference to many patients in the pain management protocol.

There are many advantages to topical therapy versus oral pain management and the author feels that transdermal therapy can be a very positive adjunct to treatment protocols. This article will review some of the difficulties we face as physicians in managing pain and the societal and economic consequences of pain. Common medications being utilized in compounding creams will also be reviewed so you can familiarize yourself with their indications and use them effectively. Finally, some literature evaluating the success and effectiveness of topical medications will be evaluated.

OVERVIEW OF PAIN

According to the International Association for the Study of Pain, pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." There are two main components of pain, nociceptive pain and neuropathic pain. Nociceptive pain arises from actual or threatened damage to non-neural tissue. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. It is understandable that most pain is mixed and components of continued nociceptive pain such as chronic inflammation may coexist with components of neuropathic pain such as nerve irritation, impingement, or damage.

Pain is our body's natural protective mechanism. Acute pain triggers a biological response that provides a warning that illness or injury has occurred. It stimulates the sympathetic nervous system resulting in a fight or flight response. This is beneficial and it is our body's way to prevent further injury and promote healing. Fortunately, acute pain is usually localized to the affected area and has a time limitation. Chronic pain however, is prolonged pain that persists beyond the expected normal healing time and is pathologic. The body unfortunately adapts to these persistent pain impulses and no longer responds with acute symptoms.

Chronic pain continues to challenge physicians despite advances in medical technology and health-care providers are very familiar with the negative impact chronic pain can have on an individual's quality of life. Part of the challenge in treating pain is due to the fact that pain sensations vary between patients because each individual's brain processes pain responses uniquely. Also, different pain receptors are involved which can alter the pain response.

Chronic pain not only causes physiologic changes but there is an emotional impact as well. It can affect normal daily activities, work productivity, and can lead to anxiety and depression. The depression and anxiety can cause a patient to feel that they are beyond help and that they will never get relief. Their life revolves around their pain and demands their constant focus. Chronic pain is in fact, a disease state and should be treated like other chronic diseases (1). The somatic awareness of their pain can sometimes be positive for a patient because they are usually very aware of what does and does not work for their pain. From the negative perspective however, they can exhibit hypochondriac type behavior and physicians often dismiss or ignore the severity of their pain (2).

SOCIETAL AND ECONOMIC IMPACT OF PAIN

Fifty percent of all patient visits to physicians are related to pain. It is also estimated that persistent pain impacts nearly 100 million adults. According to the *Journal of Pain,* annual total costs for pain in the US range from 560 to 635

billion dollars. This exceeds costs to treat cardiovascular disease ($309 billion), cancer ($243 billion), and diabetes mellitus ($127 billion) (3). It should be noted that these estimates are conservative because they do not include costs associated with pain for nursing home residents, children, military personnel, persons who were incarcerated, and the costs of pain to caregivers. A person with moderate pain had health care expenditures that were $4,516 higher than those of someone without pain. Compared with other major disease conditions, the per-person cost of pain is lower but the overall total cost is higher (4).

There are also indirect costs of treating pain including work days missed, number of annual hours worked, and hourly wages. When taking these components of productivity into consideration, the indirect costs of pain are another 299-335 billion dollars (3).

CHALLENGES OF PAIN MANAGEMENT

Physicians face many challenges when trying to manage a patient's pain. Therapeutic success is often limited by the efficacy of available analgesics, systemic effects of oral medications, and cognitive impairment of drugs due to central effects. Opioid analgesics can be very effective for pain management and are very commonly prescribed. Sales of opioids have increased four-fold from 1999-2010 (5). Unfortunately, although they can be beneficial in treating pain, they are becoming associated with increasing public health problems and many states are implementing prescription drug monitoring programs to track the prescribing and dispensing of these controlled substances.

Some of the increased abuse of opioid analgesics is due to the misguided belief that since these medications are prescribed by physicians, they are safer than illicit drugs. Unfortunately, nearly three out of four prescription drug overdoses are caused by prescription pain relievers, and opioid overdoses are the second leading cause of accidental death in the US, second only to motor vehicle accidents. In 2008, there were over 14,000 deaths due to opioid overdose, more than cocaine and heroin combined (5).

In addition to the public health concerns of opioids, there are many possible adverse effects including constipation, nausea, pruritus, sedation, cognitive changes, and addictive potential. Also, in a patient with decreased renal function, opioid accumulation can increase (6).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are another commonly prescribed analgesic. Some physicians prefer them over the opioids because they do not have the addictive potential and the social concerns of the opioids, but others are concerned with the health risks of the NSAIDs and believe that the opioids are a safer choice in many patients. Gastrointestinal (GI) disturbances including nausea, vomiting, and dyspepsia are some of the more common potential complications of oral NSAID use. Unfortunately, NSAIDs also have a potential for more serious events including gastrointestinal ulceration or bleeding, hypertension, cardiovascular events, acute renal impairment, and hepatotoxicity (7). In addition to these potential side effects, NSAIDs also have many potential drug interactions including the anti-coagulants and are therefore, contraindicated in those patients.

A study in the *American Journal of Medicine* reported the actual expenditure of treating arthritis as well as the medical costs associated with NSAID-induced GI side effects (8). Approximately 25% of the population in this study experienced GI side effects requiring further medical care. They concluded that direct medical costs of arthritis treatment in the US was 8.6 billion dollars and another 3.9 billion dollars was spent on treating GI side effects of NSAIDs for a total annual cost of 12.5 billion dollars. It can be concluded then that when using oral NSAIDs, 30% of medical costs can be attributed to GI side effects. This includes pharmaceutical claims, hospital claims, and physician charges (8).

There are various other medications utilized to try to treat pain but again there are limitations to their efficacy and many of them have serious side effects as well. Glucosamine and chondroitin appear safe as far as medication and disease interaction, but the data regarding their effectiveness in pain relief is inconsistent. Capsaicin is a common topical analgesic but has been reported to produce burning, stinging, and/or erythema as common side effects. Gabapentin, Pregabalin, and the tricyclic anti-depressants are also commonly prescribed analgesics, particularly for neuropathic type pain, but again have common side effects such as somnolence, dizziness, confusion, and fatigue. In addition, Pregabalin has been associated with peripheral edema and the tricyclic anti-depressants have been associated with cardiovascular events, dry mouth, urinary retention, constipation, and many drug interactions.

ADVANTAGES OF TOPICAL PAIN MANAGEMENT

After reviewing the impact pain management has on public health and all of the treatment obstacles physicians face including the potential side effects of the analgesics, it is easy to understand why healthcare providers are looking for alternatives in the treatment of pain management. Topical pain preparations can be used as either primary or adjunct therapy and offer several advantages.

Fortunately, many of the pain receptors known to exist centrally are also present in the periphery. Topical pain preparations contain multiple ingredients; therefore, there is inhibition of multiple pain receptors at the site of application and we get a therapeutic response when the

analgesic is applied topically. Since the topical medications are applied at the site of the pain, there is a higher level of the medications locally and lower levels systemically. Therefore, there is decreased toxicity, drug interactions, and side effects when using topical therapy compared to oral analgesics. A study by Rolf et al confirms that maximum concentrations of topical ketoprofen were found in the cartilage and meniscus and minimized in synovial fluid and plasma; whereas, oral ketoprofen was maximized systemically and minimized in the cartilage and meniscus (9).

Supporting Evidence

The effectiveness of topical analgesics has been questioned by many physicians. The author has not only had personal, clinical proof of success of many of these preparations but there is some supporting evidence as well. A double-blind placebo-controlled trial was done in 2009 to evaluate the effectiveness of topical ketamine 10% cream in the treatment of allodynia in patients with complex regional pain syndrome (CRPS). In this study, ketamine was applied to the symptomatic limb and was found to successfully inhibit allodynia to light brushing and hyperalgesia to punctate stimulation and pressure. They concluded that these effects were in fact due to the topical application of the ketamine and not due to systemic effects of the drug since the plasma levels for both ketamine and its metabolite, norketamine, were below detectable limits (10).

In 2012, another study evaluated the use of 0.1% clonidine gel in patients with painful diabetic neuropathy (11). It was a randomized double-blind placebo-controlled trial and included 179 patients. Nociceptor function was first confirmed by determining the painfulness of 0.1% topical capsaicin. Patients were then randomized to topical clonidine or placebo applied 3 times a day to their feet for 12 weeks. The study concluded that pain reduction was greater in the clonidine group versus placebo group. In subjects who felt any level of pain to capsaicin, clonidine was superior to placebo. The difference between the groups was more pronounced with increasing capsaicin pain ratings. This study also measured clonidine plasma levels, which were below detection in all but 2 patients. Neither of these patients however, had any side effects or blood pressure changes. Skin site reactions were mild and observed only in the placebo group.

A meta-analysis was done evaluating the effectiveness of topical NSAIDs (12). This was a review of 36 randomized double-blinded trials comparing topical NSAIDs with either placebo or active treatment for acute pain. Patients in these trails mainly had sports injuries or sprains and strains. Inclusion criteria included at least daily application of the topical NSAID, at least 10 patients had to be randomized to a treatment group, and success was defined as a 50% reduction in pain. In the placebo-controlled trials, the analysis concluded that the topical NSAID utilized was significantly better than placebo in 19 of 26 trials. The mean response rate of placebo was 39% compared to the topical NSAID, which was 65%. There was no difference in adverse effects between the topical NSAID and placebo groups. In the active-controlled trials there was no statistically significant difference between the oral NSAID and topical NSAID in any of the studies evaluated. The mean response rate of the oral NSAIDs was 62% and 57% for the topical NSAIDs.

Clinical Applications

Topical analgesics have many possible applications for foot and ankle surgeons including but not limited to plantar fasciitis, tendonitis, tendinosis, myofascial pain, acute injury, osteoarthritis, rheumatoid arthritis, gout, joint pain, acute post-surgical therapy, plantar fibromatosis, diabetic peripheral neuropathy, chronic neuropathic pain, tarsal tunnel syndrome, CRPS/RSD, and fibromyalgia.

Although these compounding preparations can be used as primary treatment, the author utilizes topical analgesics mostly as an adjunct to therapy. The author feels that although topical therapy has several advantages, treatment protocols should not be changed, especially for our more common disorders such as plantar fasciitis and tendonitis. Topical therapy can be very effective but should be utilized as an adjunct when our patients are not responding to our standard protocols or when other therapies and/or oral medications are contraindicated or places our patients at risk for complications and side effects.

Some of the more common areas the author will use topical pain preparations as a primary course of treatment include patients with a history of gastrointestinal problems and patients on anti-coagulation therapy where NSAID use is considered a high risk or is contra-indicated. The author also utilizes topical medications as a primary therapy in patients with peripheral vascular disease, where delivery of oral medications to the site of pain, are many times unsuccessful.

COMMON TOPICAL AGENTS

One of the major advantages to topical compounding therapy is that multiple agents can be combined and utilized as one product to treat the patient's symptoms. Following are some common medications and the symptoms they most effectively treat. Topical NSAIDs are very common and are effective in treating musculoskeletal pain involved with many conditions we encounter on a routine basis as foot and ankle physicians. The author has found that these topical agents are also very useful for postoperative and postinjury pain management. There are various topical NSAIDs to choose from including ibuprofen, ketoprofen,

flurbiprofen, diclofenac, indomethacin, and meloxicam to name a few. Just as with oral therapy, topical NSAIDs are effective for inflammatory pain reduction, but the topical NSAIDs do vary in their "elegance" and feel on the patient's skin. Although diclofenac and ketoprofen are common agents and effective for musculoskeletal pain, the author often prefers the use of flurbiprofen because of the elegance in application. Meloxicam is also a favorite agent of the author because it is both elegant and potent.

Topical anesthetics such as lidocaine and bupivacaine are added to many compounding formulas and effectively assist in treating inflammatory and neuropathic pain. Topical ketamine is a popular agent and effective in treating neuropathic pain, chronic pain, and postoperative pain. Similar to the oral effectiveness, topical gabapentin and the tricyclic anti-depressants have been found to be a great benefit in treating neuropathic pain. Clonidine is commonly used for chronic pain and neuropathic pain and has been proven to be advantageous topically for treatment of RSD/CRP. Baclofen is an effective muscle relaxer and is commonly utilized topically to aid in the treatment of muscle cramps and spasms and fibromyalgia. Colchicine has also been effective topically when added to compounding formulas for the treatment of gout.

There are also topical agents that can assist the physician with pain management in the presence of vascular disease. Nifedipine can be added to a formula if vascular impairment is present, as it improves perfusion to the area. Pentoxifylline also improves blood flow through peripheral blood vessels and is often times used as a driving agent in many compounding formulas. Verapamil is another agent that can be utilized to improve perfusion to an area but in addition to its vascular benefits, it also aids in scar reduction. Verapamil decreases production of collagen and fibronectin from fibroblasts and increases the activity of collagenase; therefore, it can be used for treating postoperative fibrosis and scarring and plantar fibromatosis.

As previously discussed, topical medications have been shown to penetrate through the skin to the deeper structures. The success of these products however, depends on the carrier or vehicle by which these compounds are able to be delivered and penetrate through these tissues. Lipoderm is a common carrier for many of the newer compounding formulas currently being utilized. PLO is a medium that is commonly utilized in some of the popular gel type of formulas including diclofenac gel. Lipoderm has been shown to demonstrate superior ability to deliver ketoprofen transdermally versus PLO (13). This is important because many patients may have already tried topical therapy, such as diclofenac gel, and found that it was not effective for their pain reduction. They may not understand the unique differences between topical formulas. It is important then for the physician to inquire about the topical agent(s) the patient has utilized previously before determining whether or not further or alternative topical therapy could be beneficial. Often, changing the ingredients or the medium of a topical formula can render it more effective. Also, a physician may consider changing the percentages of the active ingredients in a formula. The higher the percentage of a medication utilized, the higher its potency. Typically however, the higher the potency of the ingredients, the lower the elegancy of the final product. Therefore, since the total percentage of the formula affects its elegancy, the physician should try use the lowest percentage possible to get the maximum desired relief.

COMMON COMPOUNDING FORMULAS

The uniqueness and major advantage to compounding therapy is the ability of the physician to construct his/her own formulations for clinical application. The author has utilized the following combinations effectively for some common conditions routinely encountered.

Tendonitis/Joint Pain: Flurbiprofen, Baclofen, Lidocaine.
Musculoskeletal pain: Diclofenac, Baclofen, Bupivacaine, Ibuprofen.
Plantar fasciitis/neuroma: Diclofenac, Baclofen, Bupivacaine, Cyclobenzaprine, Gabapentin.
Neuropathic pain: Gabapentin, Clonidine, Amitriptyline, Baclofen, Bupivacaine.
Acute postoperative pain: Ketamine, Baclofen, Gabapentin, Verapamil.

SUMMARY

Pain management can be quite challenging for physicians. It has been estimated that up to 50% of all physician visits are related to pain. It is advantageous then for physicians to have an armamentarium of treatment options available for individualized patient care. The societal and economic toll of pain management is staggering and the use of opioids and other oral medications are limited due to side effects and concomitant patient disease states. Topical pain therapy offers several advantages in the treatment of pain and is a useful alternative or adjunct to commonly used medications.

There are many compounding pharmacies out in the marketplace today. Unfortunately, not all compounding pharmacies are created equally nor should they be treated as such. The author recommends the physician thoroughly evaluate the potential compounding pharmacy to be utilized. Although compounding products themselves do not undergo the Food and Drug Administration (FDA) approval process, the ingredients chosen for these formulas should come from FDA approved and/or licensed sources. The Pharmacy Compound Accreditation Board and the

Continuous Quality Improvement program are entities that compounding pharmacies can voluntarily participate. Inclusion in these assists the physician in recognizing that a compounding pharmacy is meeting nationally accepted quality and safety standards.

Disclaimer: The author has given sponsored lectures previously for Bellevue Pharmacy.

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