CHAPTER **40**

THE ROLE OF TOPICAL AGENTS IN PODIATRIC MEDICINE

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INTRODUCTION

Topical agents have been used for thousands of years with the earliest records of medicinal agents from the 3rd century B.C. Pharmacists have compounded multiple medicinal agents in topically applied creams, ointments, gels, and solutions in this country since its inception. More recently, within the past 20 years, compounding pharmacies and compounding pharmacists have become a separate and distinct specialty of the practice of pharmacy. Compounding pharmacies have become proficient at providing safe and therapeutic topical agents. These pharmacies have given patients greater accessibility and reduced the cost of these products, often getting the compounded agents covered by third-party insurance.

Until recently, topical agents for pain and inflammation were not commercially available in the US. Within the past decade, diclofenac has become available in solution, gel, and a transdermal patch. Diclofenac sodium is available as a 1.5% solution that contains dimethyl sulfoxide (DMSO) as a penetration enhancer. Diclofenac sodium is also available as a 1% gel. Diclofenac epolamine is available as a 1.3% transdermal patch. Other topical nonsteroidal anti-inflammatory (NSAID) preparations are approved in Europe and include; ibuprofen creams and gels, ketoprofen gel, felbinac gel and foam, and piroxicam gel (1).

Topical agents can be used as an adjunct to oral, injectable, and other physical modalities. Transdermal routes provide viable therapeutic options to assist in treating conditions that cannot be managed by conventional medications or procedures alone. Often, the topical agents will first be used as an adjunct but then will become the primary treatment to manage certain chronic conditions.

LITERATURE

The majority of these agents are used for pain and inflammation. These topical agents can be a safe and practical alternative to oral agents aimed at treating the same diagnoses. Topical agents offer the benefit of delivering therapeutic agents locally at the site of pain and/or inflammation, while minimizing systemic concentrations. These topical medications can attain a much higher tissue level versus oral administration, yet produce much lower serum drug levels compared to oral medications, resulting in less risk for adverse effects (AEs) and end organ toxicity. Pharmocokinetic studies have shown that serum levels, for topically administered ketoprofen and diclofenac, are less than 1% of those levels achieved after oral dosing (2, 3).

Additional advantages include avoidance of the gastrointestional (GI) tract, reducing discomfort, irritation, and ulcer potential. Topical route medications avoid hepatic first-pass metabolism and reduce systemic side effects. In the 15 years that the diclofenac patch has been used, there have been no reported drug-related GI bleeds, ulcers, or cutaneous events characteristic of Steven-Johnson syndrome (3). A review of 14 clinical trials demonstrated that diclofenac epolamine topical patch was well tolerated, with a low incidence of GI adverse events (4). A randomized, double-blind, parallel-group, multicenter trail using diclofenac sodium 1% gel on symptomatic osteoarthritis of the knee, demonstrated significant reduction in WOMAC pain scores, no gastrointestinal AEs, and only application site dermatitis as an adverse event (5). These topically applied medications, whether in a cream, gel, suspension, or transdermal patch, are nonaddictive and provide localized pain relief.

Disadvantages of the topical route of administration include sensitivity and allergy to the topical agents and/or the vehicle at the site of administration. If ketoprofen is used topically, the treated skin area should not be exposed to direct sunlight during the treatment period and for 2 weeks after treatment, as topical photosensitization has been reported (2). Systemic reactions, although rare, can occur with topically applied agents. NSAIDs are widely used in the treatment of pain associated with a variety of conditions, but their usefulness is often limited by dose-dependent adverse events, such as GI disturbances, cardiovascular events, and renal toxicities (1). The same NSAID agents administered topically have the same contraindications as the oral counterparts, but are much less likely to occur with the topically administered agents. The commercially available topical diclofenac preparations have the same Food and Drug Administration-induced black box warning for cardiovascular risk as the oral diclofenac and all other oral NSAIDs. Diclofenac or ketoprofen used in compounded

formulas, while not required to have the black box cardiovascular warning, should be considered to have the same potential risk as the commercially available topicals.

Evidence supporting these advantages and disadvantages of topical applied medications are bountiful. One study showed that the plasma concentration of ketoprofen after oral administration is approximately 80 times greater than transdermal administered ketoprofen. The concentration within the skin after transdermal delivery of ketoprofen is 15 times greater than oral but the concentration within the knee joint is only 1.5 times less with the transdermal delivery versus the oral (6).

A study with the diclofenac sodium 1% gel shows that systemic exposure is 5-17 times lower than with oral diclofenac. Also topical diclofenac did not inhibit platelet aggregation and inhibited COX-1 and COX-2 less than oral diclofenac (7). Other studies have shown that ketoprofen decreases prostaglandin E-2 production in skin and joints (8).

These topical agents can be used for acute pain relief also. In a study of 274 patients with acute ankle sprains, topical diclofenac showed superior pain relief compared to placebo at the 3-hour point (3). The more interesting concept that this and other studies have demonstrated is the presence of a tissue reservoir. With a single diclofenac patch applied for 12 hours, the drug appears in the plasma at a mean of 4.5 hours (range 2-8 hours). Yet pain relief was noted at the 3-hour point at which no drug is found in the plasma. This demonstrates a local tissue accumulation of the drug. The normal half-life after oral administration of diclofenac is 1-2 hours while the plasma half-life after patch application of diclofenac is 9-12 hours, implying the presence of this tissue reservoir (3).

GENERAL PRINCIPLES

The majority of topical agents in podiatric medicine will be used for pain and inflammation. The multitude of inflammatory conditions seen on a daily basis in podiatric medicine are ideal for topically applied medications due to their localized nature and relatively superficial target tissues to be treated. The often times more difficult pain treated in podiatry is neuropathic pain. Topically applied agents are also ideal for this condition due to the lack of central nervous system side effects that are typically seen with orally administered agents for painful neuropathy. With the compounding pharmacies, the prescribing physician is able to design patient specific compounds using multiple medications for a synergistic effect.

Topical and transdermal applications are often used interchangeably. With both delivery systems, the drug or drugs must cross the skin in order to reach the target tissue. Transdermal medications are expected to reach systemic concentrations comparable to orally administered medications. These agents may be applied distal to the target tissues. Examples of these transdermal applications for systemic effect are patches for hypertension, hormonal replacement therapy, and narcotic administration. The diclofenac patch is not an example of this. This patch is designed to be applied at the target tissue and administer a local effect, acting as a topical medication. Topical medications then are intended to reach local tissue and achieve therapeutic local concentrations. These typically do not reach therapeutic systemic concentrations.

Pharmocokinetic absorption from topical formulations can vary markedly depending on the agent, the vehicle, the underlying disorder, and the site of application. These agents may be more difficult to use when applying to large areas, again not usually a concern when treating the foot and/or ankle. As the surface area increases and the thickness of the epidermis decreases, the rate of absorption of topically applied agents will increase. Variations in the stratum corneum layer will affect absorption. The stratum corneum, or horny layer of the skin, acts as a protective barrier to the underlying epidermal layers and the dermis. The stratum corneum can be compared to bricks and mortar. The 10 to 15 layers of flattened cornified cells constitute the bricks. The lipid-rich intercellular matrix constitutes the mortar. This brick and mortar design provides an effective barrier to transdermal water loss and external chemical access. If a drug is to pass through the skin and into the general circulation, it must first pass through this barrier.

The flow of compounds across the stratum corneum is directly proportional to the concentration gradient and therefore can be attributed to passive diffusion. But since the "mortar" of the stratum corneum is lipid-rich, lipophillic compounds absorb well across the horny layer. The underlying epidermis and dermis is an aqueous environment, so lipophillic compounds will absorb poorly when they reach these layers. Therefore, for a drug to be delivered to the general circulation, the drug/vehicle must maintain affinity for both aqueous and lipid environments to absorb effectively.

The vehicle used to deliver a drug or combination of drugs to the target tissues is equally as important as the active ingredients themselves. Two vehicles are commonly used. Pluronic lecithin organobase (PLO) is one such vehicle. The pluronic is the hydrophilic portion and the lecithin isopropyl palmitate is the lipophillic portion. This vehicle provides good penetration into the skin and works well with a variety of lipophillic and hydrophilic agents. Disadvantages of PLO are a "sticky or tacky" feeling to the

area of application and the two phases of the vehicle can separate under extreme cold or heat.

The newer vehicle and more widely used is lipoderm. This vehicle is creamier, less sticky, less smell, and generally better cosmetically accepted when compared to PLO. It is not as temperature sensitive as PLO and has less chance of a rash versus PLO. It has been studied to deliver single agents such as ketoprofen and tramadol into human skin, and is the only vehicle proven to deliver up to four ingredients into human skin.

Other factors that affect absorption is the frequency of application by the patient and the proper use of the product by the patient. These topical agents should be rubbed in for at least one to two minutes. The absorption of topical agents can be augmented by occlusive dressings, heat, epidermal hydration, phonophoresis, and iontophoresis.

There are unlimited possibilities of therapeutic options in the transdermal route of administration. Multiple medications can be used synergistically to attain favorable outcomes. The commercially available topical agents for pain and inflammation contain only one active ingredient. With compounded topical creams, not only can multiple agents be used, but also greater concentrations of the active ingredient, found in the commercially available products, can be achieved.

CLINICAL USE

There are many clinical conditions in podiatric medicine that can be treated effectively with compounded topical agents. Some of these conditions include: hyperhydrosis, verruca, wound healing, neuropathic pain, pain and inflammation, and gout. Hyperhydrosis can be treated with local anesthetics (lidocaine or prilocaine), and drying agents (formaldehyde or glutaraldehyde) combined with constrictive agents (scopolamine or atropine). Verruca can be treated with a combination of cantharidin, podophyllin, and salicylic acid. Verruca can also be treated with cimetidine 2% combined with 5-flurouracil 5%. Multiple agents can be combined to work together to promote wound healing. Phenytoin, an anticonvulsant, promotes soft tissue growth. Nifedipine, a calcium channel blocker, enhances blood flow, promotes epidermolysis and microvascular neogenesis. Misoprostol, a gastric ulcer drug, increases mucosal blood flow and the integrity of mucosa. Lidocaine can be added to block pain sensation if the patient is not neuropathic. Metronidazole, an anerobic antibiotic, is used to reduce odor and promote healing. Ketoprofen or diclofenac can be added to reduce the inflammatory reaction in chronic wounds.

The most common condition for which topical agents are prescribed in podiatric medicine is pain. Pain is the body's natural response to tissue injury. Acute pain is nocieceptive in nature and mediated by the stimulation of A-delta and C pain receptors. Chronic pain is neuropathic in nature and results when there has been damage or pathologic changes to the peripheral nervous system or the central nervous system. Acute pain is self-limiting and serves as a protective function to warn of on-going tissue damage. Minimal psychological symptoms are associated with acute pain. Neuropathic pain, on the other hand, serves no protective function. It is in fact a disease process in and of itself. Psychological symptoms such as anxiety, fear, depression, and sleeplessness, often are associated with chronic pain. Neuropathic pain is typically described as burning, electric type sensations, tingling, or a shooting pain.

Neuropathic pan is hallmarked by allodynia (pain from a stimulus that does not normally produce pain, i.e., light touch) and hyperalgesia (increased sensitivity to a normal painful stimuli). Neuropathic pain has traditionally responded poorly to NSAIDs and opioids. This condition highlights the ability to combine multiple agents working synergistically together in a topical formula that can be applied at the site of neuropathic pain without the concern of associated central nervous system adverse effects. These very specialized compounds are most commonly used for painful diabetic neuropathy (DPN), but can also be used to treat postsurgical nerve entrapments, traumatic neuropathies, non-diabetic peripheral neuropathy, and possibly tarsal tunnel or similar nerve entrapment syndromes.

The two common ingredients to neuropathic pain creams are gabapentin and a local anesthetic such as lidocaine or bupivicaine. Gabapentin has been used orally for many years for painful neuropathy. Its mechanism of action is not fully known but it decreases transmission of pain signals to the brain, presumably from interference with calcium channels along the peripheral nerves. Topical anesthetics work to block pain sensation by blocking sodium channels. The other mainstay ingredient in DPN topical treatment is ketamine. Ketamine is a controlled substance (C-III). It is a general anesthetic agent that blocks receptors preventing increase in calcium found in hyper excited neurons. Ketamine prevents the two hallmarks of neuropathic pain, both hyperalgesia and allodynia. There are no central nervous system side effects because there is no first pass metabolism by the liver. Ketamine has the highest affinity for NMDS receptors. In 2005, *Journal of Pain* reported a 3/5 or greater overall satisfaction in pain relief in 89% of patients treated with topical ketamine.

Tricyclic antidepressants are often added to prescriptions for topical neuropathic pain creams. Amitriptyline, imipramine, and doxepin work synergistically with ketamine.

They are also NMDA receptor antagonist but they do not possess the same affinity for these receptors as ketamine. Tricyclic antidepressants also inhibit norepinephrine (NE) and serotonin reuptake, as well as, block alpha-2 receptors and sodium channels.

Other ingredients added to topical preparations for DPN is clonidine, an alpha-2 agonist that blocks the release of NE, and works well for nerve pain with a sympathetic component. Nifedipine, a calcium channel blocker, acts as a vasodilator to increase tissue perfusion. Pentoxyifylline is a rheologic agent affecting red blood cells and possesses anti-inflammatory properties.

A typical prescription for DPN may include: gabapentin 6%, ketamine 10%, imipramine 3%, lidocaine 5%, and clonidine 0.2%. If there is an inflammatory component to the DPN or other nerve pain, then a typical prescription may include: diclofenac 5%, baclofen 2%, bupivicaine 1%, and gabapentin 6%. These can be individualized for the patient and for the physician's preference. Most compounding pharmacies have ready pre-set formulas for the most common conditions and offer a good starting point for the prescriber.

In podiatric medicine, many common conditions we treat daily of the foot, ankle, and leg are inflammatory in nature. Whether it is traumatic in origin, chronic conditions related to biomechanical faults, or systemic in origin, these conditions respond well to topical anti-inflammatory medications. The topical medications can be used as an adjunct to oral medications and other treatment modalities initially, and then the more chronic conditions can often be managed more safely and effectively with topical agents. Some of the pain and inflammation indications in podiatric medicine are Achilles tendonopathy, plantar fasciitis, osteoarthritis, other tendonitis of the foot and ankle, soft tissue injuries, and gout.

The two main ingredients used in compounding creams for pain and inflammation are ketoprofen and diclofenac. Less commonly indomethacin has been used. Again, while diclofenac is commercially available as a solo agent, compound pharmacies can increase the potency of this agent, and add other synergistic agents. Diclofenac showed low GI AEs, significant pain reduction in knee osteoarthritis (9), inhibits COX-1 and COX-2 less than orally administered diclofenac, shows no platelet aggregation, and demonstrated a tissue reservoir effect. Ketoprofen has been shown to have 100-times greater concentration in intra-articular tissues, joint capsule and synovial fluid than the plasma concentration (10). This is presumed to be as a result of a reservoir effect at the joint level (11). In Achilles tendonopathy, ketoprofen topically was found to have low plasma levels and high levels in the subcutaneous tissues, tendon, and tendon sheath. It was suggested in this study that the subcutaneous tissues act as a reservoir (12).

Other ingredients often combined with the primary NSAID are baclofen, which works on peripheral pain receptors to augment pain relief topically. Cyclobenzaprine is a skeletal muscle relaxant that can be combined in acute injury and for spasms. A typical prescription for pain and inflammation may include ketoprofen 20% or diclofenac 5%, baclofen 2%, and lidocaine 5% or bupivicaine 1%.

Miscellaneous ingredients that can be used alone for different conditions or combined include verapamil, nifidipine, and triamcinolone. Verapamil is a calcium channel blocker that has been shown to act as an antifibrinogenic agent. It is used in dermal and subcutaneous fibrosis, scarring, strictures, and adhesions. Verapamil may be combined with a local anesthetic and an NSAID for the treatment of plantar fibromatosis. Nifidipine is a vasodilator and may be of benefit in Reynaud's. Triamcinolone, a corticosteroid, may be added to inflammatory arthritic joints, especially those seen with gouty arthropathy.

CONCLUSION

Topical agents have been used for decades in podiatric medicine. With the advancements made in compounding pharmacy, especially in the vehicles used for better penetration of multiple medications, this treatment modality is too often underutilized. The pathologic condition must be matched to the correct formulation, but the possibilities are endless. Topical agents applied to the skin for pain and inflammation and for neuropathic pain provide the physician with an excellent treatment modality, alone or in combination with other treatments. The ability to deliver multiple drugs directly to the affected target tissue, with minimal systemic side effects and adverse events, give compounded topical agents a substantial advantage over the other means of treatment physicians provide to their patients.

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