Patients in Pain: The Value of Compounded Topical Creams Using a Permeation-Enhancing Base

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I remember my first experience with compounding, which interestingly turned out to be a topical pain preparation using a permeation-enhancing base. I was a pharmacist intern at a compounding pharmacy back in the summer of 1998, in a small town on the Mississippi Gulf Coast. We were using a combination of ibuprofen 20%, piroxicam 1% and cyclobenzaprine 1% in PLO (PCCA Formula #3444) for patients with inflammatory conditions. The pharmacy even had its own catchy name for it: "Flexi-cam."

I couldn't believe that it would be possible to drive these drugs through the skin to the site of inflammation. They didn't teach this in pharmacy school. It was such an influential experience that the light bulb went off in my head, and I knew I was going to have a future in compounding. Now here I am, working as a consultant at PCCA.

PATIENTS IN PAIN

An analysis of data from the 2012 National Health Interview Survey (NHIS) showed that nearly 40 million adults (17.6%) in the United States experience severe levels of pain, with 25.3 million adults (11.2%) having pain every day for the preceding three months.[1] Aside from the pain epidemic in general, this is especially important in today's current environment of drug addiction and opioid abuse. Every day approximately 1,000 people are treated for misuse of opioid medications, and drug overdoses have surpassed motor vehicle crashes as the major cause of unintentional death in the U.S., according to the CDC.[2]

The costs of prescription opioid abuse have been estimated to be over $55 billion in the U.S. alone, accounting for lost work productivity, health care costs and criminal justice costs.[2] Additionally, physicians are coming under scrutiny for prescribing opioid medications and are looking for better options for their patients. Furthermore, *The British Medical Journal* recently published a meta-analysis of data on 446,763 Canadian and European patients, which suggested that oral NSAID use for more than one week increases the risk of myocardial infarction, and that higher doses corresponded with greater risk.[3] This is where the compounding pharmacist comes in.

There is a need and a place for the delivery of drugs through the skin due to the side-effect profile of many oral medications, a tendency for abuse of and addiction to opioid medications, administration challenges, prescriber challenges, and lack of efficacy of traditional therapies.[4] Benefits of topical administration using a permeation-enhancing base may include convenience and ease of administration, improved patient compliance, and allowing for less-frequent dosing.[5]

As a result, the use of topical pain medications using a permeation-enhancing base may be considered a viable alternative to oral pain therapies in many patients. There are a multitude of studies to show the active pharmaceutical ingredients we use have merit and clinical relevance today.[6,7] [For clinical information on a specific API, click on "Clinical References" when viewing the API in the Members-Only Website catalog.]

EVOLUTION OF PAIN CREAMS

Human skin has many functions, and its most apparent one is that of a defense organ, both physical and biological.[8] Penetration of any compound from outside into the body is primarily prevented by the corneal layer of the epidermis. This outer layer is just a few micrometers thick, but effectively forms a barrier that preserves life.[8] The 500 Dalton rule states that when molecular weight increases to over 500 Daltons, absorption of molecules through normal skin rapidly declines.[8] This further highlights the importance of using a base that will transverse the skin.

First Generation

The first widely recognized compounded topical permeation-enhancing base was pluronic lecithin organogel (PLO). This is an oil-and-water emulsion introduced as a drug-delivery vehicle in the 1990s.[9] The technology was derived from studies on "organogels" created from incorporating lecithin into organic solvents.[10] One study involved using pluronic 20% with ketoprofen on carrageenan-induced paw edema in rats.[11] This base was quite revolutionary in the compounding world and led to many drugs being used topically with a permeation enhancing base that had never been used before. However, PLO is considered first-generation, and more advanced versions of permeation-enhancing topical bases have been introduced.

Current Generation

The Lipoderm® family is a collection of current-generation, proprietary penetration-enhancing bases that are improvements over PLO in consistency, stability and penetration.[12,13,14,15] In a comparison study, Lipoderm outperformed PLO when evaluating the percutaneous absorption of promethazine.[15] Lipoderm also has been shown to successfully deliver four pain medications, including ketamine hydrochloride, gabapentin, clonidine hydrochloride and baclofen,

PATIENTS IN PAIN: THE VALUE OF COMPOUNDED TOPICAL CREAMS USING A PERMEATION-ENHANCING BASE *(Continued)*

simultaneously into human skin.[12] A topical cream base does not have these characteristics and may stay on top of the epidermis, working topically. Physicians may be very interested in the differences and the importance of using true penetration-enhancing vehicles versus topical vehicles when considering positive patient outcomes. Topical pain management with the penetrating enhancing bases in the Lipoderm family can be used to address patients with conditions of inflammation, musculoskeletal pain and neuropathic pain, to name a few.

This is an incredible opportunity for compounding pharmacists. Patients in pain can be very challenging to treat, and their quality of life is often negatively affected by their painful conditions. Compounding pharmacists can be of great value to both prescribers and their patients who are suffering.

COMPOUNDING IDEAS AND FORMULATIONS

Commonly Requested for Patients With Inflammatory Pain

PCCA FORMULA #	FORMULA INGREDIENTS
9448	Ketoprofen 10% Topical Lipoderm (FormulaPlus™ BUD Study)
9447	Ibuprofen 20% Topical Lipoderm (FormulaPlus BUD Study)
11096	Ketoprofen 10%/Cyclobenzaprine HCl 2% Topical Lipoderm ActiveMax® (FormulaPlus BUD Study)
9450	Piroxicam 5% Topical Lipoderm (FormulaPlus BUD Study)
9517	Ibuprofen 20%/Piroxicam 1%/ Cyclobenzaprine 1% Topical Lipoderm

Commonly Requested for Patients With Inflammatory Pain (Alternative to NSAIDs)

PCCA FORMULA #	FORMULA INGREDIENTS
11968	Magnesium Chloride 10%/Naltrexone HCl 1% Topical Lipoderm ActiveMax

Commonly Requested for Patients With Musculoskeletal Pain

PCCA FORMULA #	FORMULA INGREDIENTS
11096	Ketoprofen 10%/Cyclobenzaprine HCl 2% Topical Lipoderm ActiveMax (FormulaPlus BUD Study)
10056	Guaifenesin 10%/Magnesium Sulfate Heptahydrate 10% Topical Lipoderm
12244	Guaifenesin 10%/Magnesium Chloride Hexahydrate 10%/Sodium Bicarbonate Topical Lipoderm

Commonly Requested for Patients With Neuropathic Pain (General)

PCCA FORMULA #	FORMULA INGREDIENTS
10287	Diclofenac Sodium 5%/Gabapentin 5%/ Amitriptyline HCl 2% Topical Lipoderm ActiveMax (FormulaPlus BUD Study)
12329	Amitriptyline HCl 2%/Clonidine HCl 0.01% Topical Lipoderm (FormulaPlus BUD Study)
10835	Gabapentin 10%/Ketamine HCl 5%/Baclofen 2%/ Clonidine HCl 0.2% Topical Lipoderm (FormulaPlus BUD Study)
9376	Ketoprofen 10%/Ketamine HCl 5%/Amitriptyline HCl 2%/Baclofen 2% Topical Lipoderm
11090	Flurbiprofen 10%/Baclofen 2%/Cyclobenzaprine HCl 2%/Tetracaine 2% Topical Lipoderm ActiveMax (FormulaPlus BUD Study)

Commonly Requested for Patients With Neuropathic Pain (Diabetic)

PCCA FORMULA #	FORMULA INGREDIENTS
8541	Ketamine HCl 10%/Gabapentin 6%/Nifedipine 2%/Clonidine HCl 0.2% Topical Lipoderm
11019	Ketamine HCl 10%/Gabapentin 6%/Nifedipine 2%/Tizanidine 0.2% Topical Lipoderm ActiveMax
9875	Pentoxifylline 5%/Nifedipine 2% Topical Lipoderm (FormulaPlus BUD Study)

If you have any questions, please contact the PCCA Clinical Services team at 800.331.2498.

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