TRANSDERMAL DRUG DELIVERY IN PAIN MANAGEMENT

The compounding pharmacist should be, and should be perceived as, a problem-solver. When administration, compliance, and efficacy are problematic for a particular patient, prescribers and patients should rely on the pharmacist to assist them with both knowledge and innovation to achieve the goal of overcoming the problem. Transdermal administration of medication has, in many cases, become one such innovation. While numerous clinical reports support this innovation, scientific data remains sparse, and the decision to utilize transdermal delivery remains a matter of professional judgment – meaning extrapolation and application of documented scientific information. Providing a solution to the problem is always the goal, and as with all innovation, some daring is required. So, we work together with other professionals to discern whether or not this innovative delivery system is appropriate. In the U.S., formulations for and clinical reports of efficacy have appeared in the literature over the course of the last decade.[1-5] These are generally written for the use of PLO as the transdermal vehicle. Fagron U.S. has documented improved efficacy by using Pentravan® as the transdermal vehicle, thus moving forward to the next level of innovation provided by this cream version of the PLO which is more cosmetically elegant and has better penetrating properties than the original PLO vehicle.[6]

For more detailed information about the advantages of Pentravan® compared to PLO and other transdermal bases, please see the Pentravan® global asset kit and the article by Lehman and Raney, 2012.[6] The Pentravan® global asset kit can be downloaded from the Fagron digital asset library, accessible through https://fagron.fluxiom.com/user/login.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY

Transdermal delivery represents an attractive alternative to other routes of administration of drugs. Transdermal delivery systems are popular because they have the following advantages over conventional drug delivery:

- They can avoid gastro-intestinal drug absorption difficulties caused by gastrointestinal PH, enzymatic activity and drug interactions with food, drink, and other orally administered drugs.
- They can substitute for oral administration of medication when that route is unsuitable, as in case of vomiting and diarrhoea.
- They avoid the first-pass effect of the liver that can prematurely metabolize drugs.
- They increase elimination half-life and establish high joint tissue:plasma concentration ratios resulting in prolonged therapeutic effect; thus improving compliance because less frequent dose administration is required.
- Drug therapy may be terminated rapidly by removal of the transdermal drug delivery systems from the surface of the skin.
- They are non-invasive, avoiding the inconvenience of parenteral therapy and increasing the patient's acceptability.
- They can be self-administered, allowing the patient to have self-control over the therapy.
- They allow combination therapy with one dosage; a wide range of drugs with different chemical properties can be included in the transdermal drug delivery system.
- Transdermal creams are easy to prepare, transdermal creams can be compounded in a few simple steps.
- The systems are generally inexpensive.[7-10]

More information about the advantages of transdermal drug delivery can be found in the Pentravan® global asset kit and the article by Allen, 2011.[11]

Fagron Group BV - Kralingseweg 207-211, 3062 CE Rotterdam, The Netherlands
KvK 24183722 - VAT NL 8093.16.523.B.05 - ING Utrecht 67 80 83 533 - IBAN NL61INGB 0678 083533 - BIC INGBNL2A
Tel. +31 (0)88 33 11 211 - Fax +31 (0)88 33 11 210

MECHANISM OF TRANSDERMAL DRUG DELIVERY

The stratum corneum is the greatest barrier to transdermal transport and acts as a drug reservoir. Transdermal absorption of a drug generally results from direct penetration of the drug through the stratum corneum (SC), a 10 to 15 µm thick layer of flat, partially desiccated, nonliving tissue. After application on the skin, the drug molecules that are dispersed within the transdermal cream penetrate the SC through the intercellular channels. Once through the SC, drug molecules may pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the systemic circulation.[11] As a result of this absorption process, there is a gradual release of the drug, which avoids peaks in plasma concentration and so adverse events are minimized.[7,11,12] A number of studies have shown that compounding bases for transdermal drug delivery systems have the unique capacity to deliver drugs across the epidermal barrier and deliver particular medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetics to a specific site.[13]

TRANSDERMAL DRUG DELIVERY IN PAIN MANAGEMENT

The management of pain is perhaps the most obvious area where transdermal administration of commonly used medications can be clinically effective in avoiding suboptimal outcomes. The primary benefit of transdermal administration is most often the avoidance of unpleasant adverse events that either reduce the quality of life, or worse, are at the root of non-compliance. Although oral NSAIDs are effective in relieving pain and reducing inflammation, their use show a high incidence of adverse events, notably dose-dependent gastro-intestinal disturbances such as nausea, vomiting, or dyspepsia. Furthermore, continued use of NSAIDs in particular can be harmful to body systems, because of accumulation in non-target organs. Prolonged high systemic drug concentrations after oral NSAID therapy may result in potentially serious adverse events such as gastrointestinal ulceration or bleeding, hypertension, and cardiovascular events, acute renal impairment, and hepatotoxicity.[13,14] The risk of such effects could be reduced by the use of topical formulations, which can deliver effective analgesic concentrations at the site of inflammation while minimizing systemic concentrations. Lower systemic concentrations after topical administration would also be expected to result in a lower risk of drug–drug interactions resulting from NSAID-mediated displacement of drugs binding to plasma proteins or alterations in drug concentrations due to induction or inhibition of cytochrome P450 enzymes. We also observe that invasive delivery systems for opioids are often uncomfortable for patients and stressful for caregivers. Patient acceptance and adherence to therapy may be better with topical formulations than with oral and invasive treatment because of the combination of improved tolerability and convenient dosing regimens.[13,14] Development of transdermal formulations has been based on this approach to overcoming these significant obstacles to efficacy and compliance.

NSAIDs are mainly used in the treatment of acute, nociceptive pain. Neuropathic pain however, responds poorly to treatment with NSAIDs and is difficult to treat successfully. Neuropathic pain is primarily the result of a neuropathic injury or modulation within the central nervous system and generally is a chronic, long-term disease process. Various types of drug therapy are used to treat neuropathic pain. While none are specifically designed for this purpose, there is some rationale for their use. Examples include: anticonvulsants, NSAIDs, narcotic analgesics, tricyclic antidepressants, ketamine, and clonidine.[15,16]

Due to the chronic nature of neuropathic pain, and undesirable side effects associated with most of the oral medications available for it, manufacturers and compounding pharmacists have worked on medications to treat neuropathic pain topically. Today, many compounded topical medications are used to treat chronic neuropathic pain effectively. The recent use of multifaceted regimens of topically applied medications has been anecdotally reported as being successful.[1-5,10,16,17]

In many instances, pain and inflammation are localized to one part of the body. The bioavailability of topical NSAIDs has been reported to be generally less than 5% to 15%, while drug concentration at the site of administration can be 30-fold higher than with oral dose.[17] A plausible explanation might be

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Tel. +31 (0)88 33 11 211 - Fax +31 (0)88 33 11 210

that topical applied NSAIDs exert their pharmacological effects through localized accumulation at the application site rather than from systemic absorption.

TRIAD OF CARE: PATIENT, PRESCRIBER, PHARMACIST

Traditional dosage forms are prescribed by a doctor, physician's assistant or nurse practitioner and provided to the patient by the pharmacist. To successfully employ the innovation of transdermal drug delivery, the "triad of care" concept is imperative and it is best carried out through a partnership between prescriber and pharmacist. The experienced compounding pharmacist is essential to the physician, and the working partnership between these health-care professionals builds the practices of both groups while providing the best possible care for the patient. The triad works as follows.

Beginning with the patient, the prescriber identifies and assesses the need of the patient. A medication is chosen by the prescriber based on diagnosis, prognosis, their experience with traditional delivery systems and knowledge of the patient. What is the expected duration of treatment? For example, is pain medication required short-term post-injury or surgery, or will the patient require the medicine for many years? Has the patient shown a tendency for non-compliance? For example, is pain persisting due to non-adherence to the prescription protocol due to significant gastrointestinal distress that the patient associates with taking the medication? Is the pain transient or focused? Is it possible that an alternative dosage form would be more effective than traditional routes of administration? All these considerations constitute definition of the problem to be solved to improve outcomes.

Physicians and other prescribers need guidance from the pharmacist to meet the challenges presented in patients experiencing uncontrolled pain. The preponderance of clinical evidence regarding transdermal application of the medication should be seen as useful. This chapter includes references to scientific literature, but the combination of "proof" and "evidence" is the basis for professional judgment. The prescriber and pharmacist working together should determine a course of therapy including agreement on regular evaluation of the patient which may be used to adjust, or discontinue the chosen transdermal drug therapy. In truth, transdermal administration is most often supported by prescribers based on clinical response. A strong partnership between the professional prescribers and pharmacists builds confidence, innovation, and positive outcomes for patients. Formation of these bonds with prescribers results in repeat prescriptions for the pharmacy practice. Expansion of successful treatment regimens within the prescribers practice results in additional prescriptions. But the most important result is that more patients receive better relief from pain.

Finally, we return to the patient. What explanation is required to make them comfortable with the reason the transdermal route has been chosen and what instruction is required to ensure proper use of this unique dosage form? The first question may be answered most easily by explaining that the prescriber has chosen this medication to eliminate the unpleasant adverse events they have reported. Some patients can grasp the concept that by applying medication to the skin, their gut is avoided. Some patients cannot. Again, the pharmacist's role is imperative for compliance and time should be taken to explain as much as the patient can understand. Detailed instructions for use can often replace theoretical explanations.

An effective consult would include definition of the medication, instruction regarding use of the delivery device, and specific details of the method of application. For example: "Every gram of this cream contains one dose of your medication and you will be applying it to the site of your pain each 4 to 6 hours as needed. Your medication is packaged in a pump dispenser that releases one half of one gram each time you depress the top, so you will need to press the top twice to release one dose. Rub the cream into the skin until it disappears completely. Massaging the area for a full minute is recommended to ensure that all the cream containing medication vanishes into your skin. Wash hands after application so that any residue of the medication does not transfer to other persons through skin-to-skin contact or to eyes or mouth." If a caregiver will be administering the medication these same instructions must be delivered to that individual.

Prescribing, compounding, and delivering transdermal medications represent the epitome of individualized patient care. It employs the knowledge and experience of health-care professionals to provide the best results for an individual patient. Clinical successes, and documentation of these successes, extend this possible benefit to more and more patients suffering from pain, which drives increased opportunities in the niche practice of compounding.

INNOVATIVE COMPOUNDING FOR PAIN MANAGEMENT

In the U.S., transdermal administration of medications grew primarily out of the need for innovation in pain management. Prescribers and pharmacists working together developed the transdermal drug system to address several issues such as non-compliance resulting from gastrointestinal adverse events and concerns about accumulation of drug in the liver and kidneys. In the 1990s, PLO became a frequently used base in which drugs can be incorporated for transdermal delivery. Collaborations between physicians and pharmacists led to the incorporation of a number of drugs into PLO and anecdotal evidence of its efficacy as a transdermal drug delivery vehicle.[18] In 2008, Pentravan®, a next-generation transdermal vehicle in this innovative delivery system was introduced. Prescribers and pharmacists requiring alternate dosage forms which avoid the issues inherent in pain management are using Pentravan® with extraordinary success.

Each of the formulations included in this chapter was originally written for use with PLO as the transdermal delivery vehicle. In a recent comparative study a greater rate and extent of absorption of two drugs was found from the Pentravan® formulation than from the PLO formulation.[6] Based on these results, the mentioned formulations have been adapted to utilize Pentravan® instead of PLO. It is important that pharmacists introducing transdermal drug delivery make themselves familiar with the information in this study. Please find this study listed in the references.

Download the Pentravan® global asset kit for more information about Pentravan®, its characteristics, advantages, technical information, compounding information and suggested formulations for various therapeutic indications. The Pentravan® global asset kit can be found on the Fagron digital library, accessible through https://fagron.fluxiom.com/user/login.

KETOPROFEN

Ketoprofen was among the first drugs for which transdermal drug formulations were developed, and it remains the "strong-man" of most formulations used in managing pain. An NSAID like ketoprofen is usually given orally. Patients are evaluated for hypertension and cardiovascular health before receiving this drug and are also assessed for their individual potential for hepatotoxicity and renal impairment. In addition, gastrointestinal disturbances like nausea, vomiting, or dyspepsia as well as more potentially serious ulcerations or bleeding are concerns and are monitored during treatment with oral administration of ketoprofen. Transdermal administration of ketoprofen is expected to result in lower systemic absorption than in oral delivery, thus reducing these concerns. In transdermal delivery, ketoprofen is expected to act locally to relieve muscle pain. It has been found to be superior to diclofenac and piroxicam when applied three to four times daily to the site of pain[14] and formulations for 10%, 15%, and 20% are used widely in sports medicine.[19] A double-blind trial of transdermal ketoprofen returned reports that ketoprofen was comparable with oral celecoxib in relief of acute arthritic pain.[14] Case reports have shown benefits for patients suffering from neuropathic pain, post polio syndrome, fibromyalgia, and degenerative disc disease.[1-4]

Generally, ketoprofen is included in Pentravan® as a percentage of the volume dispensed. The most common formulations for treating muscle pain are written for 10% or 20% ketoprofen. When used to treat neuropathic pain, ketoprofen is often augmented with drugs more commonly associated with use in treating neuropathy. The pharmacist should keep this in mind when advising the prescriber, as the addition of another drug or drugs may contribute to further pain relief.

Tips and tricks

It is important to use ethoxy diglycol as solvent for ketoprofen in transdermal preparations. In order to dispense an elegant preparation, and to achieve best results, the active pharmaceutical ingredient should be in solution. Solubility of ketoprofen is approximately 1 to 1 in ethanol. In the following formulation written to make 100 grams of 10% ketoprofen in Pentravan®, this would require 10 mLs of ethanol. Adding that amount of liquid to Pentravan® will significantly thin the preparation and obviously ketoprofen 20% in 100 gram quantity even more so. Although references do not list ethoxy diglycol specifically as a solvent for ketoprofen, in fact, approximately 2 mLs of ethoxy diglycol will completely solubilise 10 grams of ketoprofen, thus keeping the Pentravan® in its original viscosity.

KETOPROFEN 10% in Pentravan®

Calculated to make 100 g

INGREDIENTS

ketoprofen	10.00 g
ethoxy diglycol	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the ketoprofen, if necessary with the use of a mortar and pestle.
- Levigate the ketoprofen with an appropriate amount of ethoxy diglycol to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Ketoprofen is practically insoluble in water but freely soluble in ethanol and ether. Although it is not listed in references, ethoxy diglycol has be found to be a more suitable solvent for this formulation because the amount needed to put ketoprofen into solution is far less than the listed solvents.

GABAPENTIN

Anticonvulsants are traditionally given orally for treatment of seizures and can be an adjunct to treatment of neuropathic pain when other therapy does not adequately control the pain. It is thought that the mechanism of action for these agents is due to the stabilization of membranes. Success has been reported with some drugs in this class; however, gabapentin, an amino acid structurally related to the inhibitory neurotransmitter gamma-amino butyric acid (GABA), may be the best choice because blood counts are not necessary as with other anticonvulsant agents.[10,16,20] In addition, a review article from 2006 showed that gabapentin is effective in reducing postoperative pain, and that addition of the drug to an opioids regimen allows reduction of opioids use. The precise mechanism of analgesic action is unknown.[10]

While some systemic absorption of the drug is to be expected, transdermal administration of gabapentin results in lower systemic absorption than oral administration.[12] Transdermal administration of gabapentin should not be considered when treating seizures as blood level maintenance may not be reliable. However, in the treatment of neuropathy, especially diabetic neuropathy of the feet, clinical evidence supports transdermal administration of gabapentin.[17] In addition, because administration of gabapentin is usually long-term, transdermal administration solves the problem of dangerous accumulation of the drug. In addition, gastrointestinal distress, perhaps the most common and severe adverse events of continued oral administration, is avoided.[21]

Generally, gabapentin is included in Pentravan® as a percentage of the volume dispensed. Clinical reports are based on formulations containing 2%, 6% or 10% gabapentin applied directly to the site of pain. Gabapentin is often combined with ketoprofen, another NSAID, or a drug commonly used to treat neuropathy, muscle or nerve pain by oral administration, e.g. amitriptyline. Various formulations and case reports describing the effectiveness of transdermal systems with gabapentin have been published.[1-4,10,15,17,21] The pharmacist should keep this in mind when advising the prescriber since the addition of another drug or drugs to the gabapentin may contribute to improved pain relief.

Tips and tricks

The Zwitter-ionic nature of gabapentin may overwhelm the Pentravan® emulsion and thin the preparation. The compounding pharmacist should be prepared to thicken the preparation back to its original viscosity. This may easily be accomplished by the addition of up to 5% Versigel® a sodium polyacrylate thickener which forms a gel matrix within the gel or emulsion. If needed, Versigel® should be added before final concentration is reached to avoid changing the concentration of the gabapentin. Note that, although the Pentravan® may be thinned as a result of the addition of the gabapentin, the medication does not loose its liposomal penetration characteristics.

Versigel® (Fagron US) is a thickening, dispersed into a vegetable oil, ready-to-use liquid polymer that may be used over a wide pH range and immediately forms a gel on contact with water. Versigel® can be ordered at Fagron US and is available in volumes of 100 g and 500 g at a transfer price of USD 7.75 (ex works Fagron US; sales price USD 16.48) and USD 26.25 (ex works Fagron US; sales price USD 66.95), respectively. When there is sufficient interest for this product in Europe, distribution may be transferred to Europe. For orders and questions about Versigel® please contact Fagron US.

GABAPENTIN 6% in Pentravan®

Calculated to make 100 g

INGREDIENTS

gabapentin	6.00 g
water	q.s.
Versigel®	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the gabapentin, if necessary with the use of a mortar and pestle.
- Levigate the gabapentin with an appropriate amount of purified water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to reach approximately 90% of final volume, stirring well after each addition of Pentravan®.
- Evaluate viscosity of the preparation and add Versigel® as needed with mixing to obtain desired thickness.
- Add sufficient Pentravan® to bring to final weight.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

The Zwitter-ionic nature of gapabentin may overwhelm the Pentravan® emulsion and thin the preparation. In this preparation, Versigel® - a sodium polyacrylate thickener - seeks out the water in the vanishing cream and forms a gel matrix within the cream, thus thickening it. Versigel® may be added drop-wise to thicken the preparation to its original viscosity. Versigel® should be added before final weight is reached so that the concentration of active ingredient is not reduced.

AMITRIPTYLINE

Tricyclic antidepressants are most widely utilized for treatment of depression. Their role in neuropathy has recently emerged. Tricyclic antidepressants such as amitriptyline have been shown to be effective in a variety of pain syndromes such as diabetic neuropathy, sciatic nerve pain, and migraine. Amitriptyline is commercially available only in tablet form, and thus a topical form must be compounded. A case study published in 1999 revealed that transdermal amitriptyline reaches therapeutic systemic levels. The mechanism of action of amitriptyline in pain relief is not known, but it is thought to inhibit the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons.[10] Various formulations and case reports describing the effectiveness of transdermal systems with amitriptyline and have been published.[10,15,18]

Amitriptyline has been shown to be superior to placebo in neuropathic pain management and has a quicker onset of action when employed for analgesia than it has antidepressant activity. An additional benefit of transdermal administration of amitriptyline in neuropathic pain management is that the dose required for analgesia is one half to one third of the antidepressant dose, resulting in lower adverse events profile; but adverse events still exist, including dry mouth, constipation, and cardiac adverse events.[20]

Transdermal absorption relies upon lipid solubility of the medication; the greater the lipid solubility, the greater the transdermal absorption. Amitriptyline is a very suitable candidate for transdermal delivery given its highly lipid-soluble nature. This characteristic results in absorption in a lipid environment, as well as excellent binding to tissues and plasma proteins.[18,22]

In a case report of a patient receiving oral amitriptyline to treat both chronic pain and depression, there was no change in the relief of chronic pain when the route was changed from oral to transdermal. However, while the transdermal route achieved the same response as the oral route, the patient experienced fewer adverse events. The prescribing physician noted no improvement in depression; however, the patient reported an elevation in mood as well as a decrease in pain level. Although efficacy between oral and transdermal administration of amitriptyline seems to be equivalent, the improvement in compliance achieved by transdermal administration is strongly associated with lessened adverse events, making it a good solution the problems attributed to oral administration of amitriptyline.[22]

Tips and tricks

The Zwitter-ionic nature of amitriptyline HCl may overwhelm the Pentravan® emulsion and thin the preparation. The compounding pharmacist should be prepared to thicken the preparation back to its original viscosity. This may easily be accomplished by the addition of up to 5% Versigel®, a sodium polyacrylate thickener which forms a gel matrix within the gel or emulsion. If needed, Versigel® should be added before final concentration is reached to avoid changing the concentration of the amitriptyline HCl. Note that, although the Pentravan® may be thinned as a result of the addition of the amitriptyline HCl, the medication does not loose its liposomal penetration characteristics.

Versigel® (Fagron US) is a thickening, dispersed into a vegetable oil, ready-to-use liquid polymer that may be used over a wide pH range and immediately forms a gel on contact with water. Versigel® can be ordered at Fagron US and is available in volumes of 100 g and 500 g at a transfer price of USD 7.75 (ex works Fagron US; sales price USD 16.48) and USD 26.25 (ex works Fagron US; sales price USD 66.95), respectively. When there is sufficient interest for this product in Europe, distribution may be transferred to Europe. For orders and questions about Versigel® please contact Fagron US at.

AMITRIPTYLINE 2% in Pentravan®

Calculated to make 100 g

INGREDIENTS

amitriptyline HCl	2.00 g
water	q.s.
Versigel®	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the amitriptyline HCl, if necessary with the use of a mortar and pestle.
- Levigate the amitriptyline HCl with an appropriate amount of purified water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to reach approximately 90% of final volume, stirring well after each addition of Pentravan®.
- Evaluate viscosity of the preparation and add Versigel® as needed with mixing to obtain desired thickness.
- Add sufficient Pentravan® to bring to final weight.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

The Zwitter-ionic nature of amitriptyline HCl may overwhelm the Pentravan® emulsion and thin the preparation. In this preparation, Versigel® - a sodium polyacrylate thickener - seeks out the water in the vanishing cream and forms a gel matrix within the cream, thus thickening it. Versigel® may be added drop-wise to thicken the preparation to its original viscosity. Versigel® should be added before final weight is reached so that the concentration of active ingredient is not reduced.

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Tel. +31 (0)88 33 11 211 - Fax +31 (0)88 33 11 210

MORPHINE

Morphine has been widely utilized in pain management and provided in numerous delivery systems. Typically used in end-of-life cases, morphine can be delivered by intravenous, subcutaneous, and oral routes. However, these routes may pose problems for caregivers and patients. Injectable delivery of morphine sulfate can be uncomfortable for the patient and increase risk of complications such as infection and phlebitis. Oral administration may not be feasible as patients may have difficulty swallowing. Application to the skin for transdermal drug absorption is much more convenient for caregivers and assumes less risk for patients. The choice to use transdermal administration of morphine sulfate is usually based on demonstrated improvement of quality-of-life rather than on concerns of efficacy.

Topical morphine administration has been reported to provide rapid relief of cutaneous and other localized pain in a series of six patients receiving palliative care. Relief of diffuse chronic arthritic pain in several case studies has been reported too.[23]

The benefit of transdermal administration of morphine has been studied in two different types of pain: cancer-related pain and pain from decubitus ulcers. Due to varied bioavailability through the skin, transdermal administration of morphine does not usually replace traditional, invasive delivery methods for ongoing cancer-related pain.[23] However if tolerability and convenience issues arise, many end-of-life pain patients utilize frequent applications of transdermal morphine to manage pain. Topically administered morphine has been efficacious in instances of open wounds such as decubitus ulcers in bedbound patients.[4]

Although the systemic benefits of transdermal morphine have not been well established, use of transdermal morphine may provide relief for some patients, especially in end-of-life care, where quality-of-life is the most important concern for the patient.[23]

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Tel. +31 (0)88 33 11 211 - Fax +31 (0)88 33 11 210

MORPHINE SULFATE 5% in Pentravan®

Calculated to make 100 g

INGREDIENTS

morphine sulfate	5.00 g
water	q.s.
Pentravan®	q.s. ad 100.00 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the morphine sulfate, if necessary with the use of a mortar and pestle.
- Levigate the morphine sulfate with an appropriate amount of water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied, as needed. Areas for application are the area of pain, or non-hairy, thin-skinned area. The inner wrist or ankle are good sites as the capillary bed is just below the skin in these areas. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Morphine sulfate preparations should be protected from exposure to light and air.

FENTANYL CITRATE

Fentanyl citrate has been widely utilized in pain management and is available commercially as an injection, a transdermal patch, and as a buccal dosage form (sucker, in the US). Transdermal application certainly provides efficacy and avoids the invasive procedure of injection. In the U.S., duplication of a commercially available dosage form is forbidden, however compounding pharmacist may provide fentanyl citrate in Pentravan® when a patient exhibits contact dermatitis due to the adhesive on the commercially manufactured patch.

Tips and tricks

If compounded transdermal fentanyl citrate is prescribed, use of the Accutenth® syringe dispenser becomes an added benefit. This device delivers 0.1 gram per actuation of the device. This allows the pharmacist to include the smallest usual dose of fentanyl citrate to be contained in 0.1 gram of Pentravan®. Should a greater increment of that dose be needed, multiple actuations may be applied. In a compounded preparation, there is no slow or sustained release of the drug. Instead, multiple doses are delivered throughout the day.

FENTANYL 12.5 µg/0.1 g in Pentravan®

Calculated to make 10 g

INGREDIENTS

fentanyl *citrate*	1.963 mg
water	q.s.
Pentravan®	q.s. ad 10.00 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the fentanyl citrate, if necessary with the use of a mortar and pestle.
- Levigate the fentanyl citrate with an appropriate amount of water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS

Accutenth® syringe.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general the cream should be applied as needed. Areas for application are the area of pain, or non-hairy, thin-skinned area. The inner wrist or ankle are good sites as the capillary bed is just below the skin in these areas. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

100 µg fentanyl is equivalent to 157 µg fentanyl citrate. Fentanyl citrate preparations should be protected from exposure to light and air.

REFERENCES

1. Erickson B, Brown S. Pain from arthritis and postpolio syndrome. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 183-186.
2. Bryant-Snure SJ, Muller G. Pain from degenerative disc disease. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 187-190.
3. Mestayer III RF. Pain after spinal infusion. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 191-192.
4. McNulty JP. Update on managing neuropathic pain. *International journal of pharmaceutical compounding*. 2009; 13(3): p. 182-190.
5. Various formulations for analgesic transdermal drug delivery systems. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 185-194.
6. Lehman PA, Raney SG. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International journal of pharmaceutical compounding*. 2012; 16(43): p. 248-252.
7. Sharma N, Agarwal G, Rana AC et al. A review: transdermal drug delivery system: a tool for novel drug delivery system. *International journal of drug development & research*. 2011; 3(3): p. 70-84.
8. Prausnitz MR, Langer R. Transdermal drug deliver. *Nature biotechnology*. 2008; 26(11): p. 1261-1268.
9. Williams KD. Managing pain with transdermal ketoprofen. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 204.
10. Alexander K, Wynn T. Transdermal gel in the treatment of postoperative pain. *International journal of pharmaceutical compounding*. 2007; 11(3): p. 181-184.
11. Allen LV Jr. Transdermals: the skin as part of a drug delivery system. *International Journal of pharmaceutical compounding*. 2011; 15(4): p. 308-315.
12. Margetts L, Sawyer R. Transdermal drug delivery: principles and opioid therapy. *Continuing education in anaesthesia, critical care and pain*. 2007; 7(5):171-176
13. Franckum J, Ramsay D, Das NG et al. Pluronic lecithin organogel for local delivery of anti-inflammatory drugs. *International journal of pharmaceutical compounding*. 2004; 8(2): p.101-105
14. Barkin R. Topical nonsteroidal anti-inflammatory drugs: the importance of drug, delivery, and therapeutic outcome. *American journal of therapeutics*. 2012. Epub ahead of print.
15. Jones M. Clinical nuggets and pearls: chronic neuropathic pain and opioid tolerance. *International journal of pharmaceutical compounding*. 2002; 6(1): p. 4-6.
16. Cabaleiro J. Assessing and treating neuropathic pain. *Home healthcare nurse: the journal for the home care and hospice professional*. 2002; 20(11): p. 718-723.
17. Vadaurri V. Topical treatment of neuropathic pain. *International journal of pharmaceutical compounding*. 2008; 12(3): p. 182-190.
18. Vail J. Compounding for sports medicine. *International journal of pharmaceutical compounding*. 2004; 8(6): p. 443-447.
19. Murdan S. A review of pluronic lecithin organogel as a topical and transdermal drug delivery system. *Hospital pharmacist*. 2005; 12: p. 267-270.
20. Hodges CJ, Jones TH, Willoughby DL. Transdermal gels in the treatment of diabetic neuropathy. *International journal of pharmaceutical compounding*. 2000; 4(2): p. 91-93.
21. Jones M. Chronic neuropathic pain: pharmacological interventions in the new millennium a theory of efficacy. *International journal of pharmaceutical compounding*. 2000; 4(1): p. 6-15.
22. Scott M, Letrent K, Hager K et al. Use of transdermal amitriptyline gel in a patient with chronic pain and depression. *Pharmacotherapy*. 1999; 19(2): p. 236-239.
23. Paice JA, Von Roenn JH, Hudgins JC et al. Morphine bioavailability from a topical gel formulation in volunteers. *Journal of pain and symptom management*. 2008; 35(3): p. 314-320.

SUGGESTED READING

- **Fagron - Pentravan® global asset kit** (2012). The latest version can be downloaded from the Fagron digital asset library, accessible through https://fagron.fluxiom.com/user/login.
- Argemi A, Concepcion D, Sampaio de Sousa A et al. Characterization of new topical ketoprofen formulations prepared by drug entrapment in solid lipid matrices. *Journal of pharmaceutical sciences.* 2011; 100(11): p. 4783-4789.
- Dowling TC, Arjomand M, Lin ET et al. Relative bioavailability of ketoprofen 20% in a poloxamer-lecithin organogel. *American journal of health-system pharmacists.* 2004; 61(23): p. 2541-2544.
- Fedele D, Giugliano D. Peripheral diabetic neuropathy: current recommendations and future prospects for its prevention and management. *Drugs.* 1997; 54(3): p. 414-421.
- Godwin D, Fuhrman LC. Enhancement of skin penetration of nonsteroidal anti-inflammatory drugs from extemporaneously compounded topical-gel formulations. *International journal of pharmaceutical compounding.* 1999; 3(6): p. 496-499.
- Jones M. Hospice from a compounding pharmacist's perspective. *International journal of pharmaceutical compounding.* 2006; 10(2), p. 89-93.
- Oberlander K. Fibromyalgia. *International journal of pharmaceutical compounding.* 2000; 4(1): p. 21-23.
- Okyar A, Özsoy Y, Güngör S. Novel formulation approaches for dermal and transdermal delivery of non-steroidal anti-inflammatory drugs. Istanbul university faculty of pharmacy department of pharmacology, Beyazit, Istanbul.
- Pain management. *International journal of pharmaceutical compounding.* 2010; 14(3): p. 183-186.
- Peralta A. Principles of pediatric palliative care and pain control. *International journal of pharmaceutical compounding.* 2007; 11(1): p. 10-15.
- Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. *Yale journal of biology and medicine.* 2010; 83: p. 11-25.
- Vidrine E. Compounding for pain management. *International journal of pharmaceutical compounding.* 1998; 2(2): p. 104-105.
- White P. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesthesia and analgesia.* 2005; 101(55): p. S5-S22.
- Zugerman J, Reed T. Topical pain relief: assessment of patient satisfaction with a novel compound containing at least ketoprofen. *International journal of pharmaceutical compounding.* 2007; 11(6): p. 514-519.