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Evaluation of the Percutaneous Absorption of Ketamine HCl, Gabapentin, Clonidine HCl, and Baclofen, in Compounded Transdermal Pain Formulations, Using the Franz Finite Dose Model

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Abstract

Objective. This study evaluates the ability of four commonly used analgesics (ketamine HCl, gabapentin, clonidine HCl, and baclofen), when incorporated into two transdermal compounding bases, Lipoderm and Lipoderm ActiveMax, to penetrate human cadaver trunk skin *in vitro*, using the Franz finite dose model.

Design. *In vitro* experimental study.

Methods. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into two transdermal bases, Lipoderm and Lipoderm ActiveMax. Each compounded drug formulation was tested on skin from three different donors and three replicate skin sections per donor. The Franz finite dose model was used in this study to evaluate the percutaneous absorption and distribution of drugs within each formulation.

Results. Rapid penetration to peak flux was detected for gabapentin and baclofen at approximately 1 hour after application. Clonidine HCl also had a rapid penetration to peak flux occurring approximately 1 hour after application and had a secondary peak at approximately 40 hours. Ketamine HCl exhibited higher overall absorption rates than the other drugs, and peaked at 6–10 hours. Similar patterns of drug distribution within the skin were also observed using both transdermal bases.

Conclusions. This study suggests that the combination of these 4 analgesic drugs can be successfully delivered transdermally, using either Lipoderm or Lipoderm ActiveMax. Compounded transdermal drug preparations may then provide physicians with an alternative to traditional oral pain management regimens that can be personalized to the specific patient with the potential for enhanced pain control.

Key Words. Baclofen; Clonidine; Gabapentin; Ketamine; Neuropathic Pain Management

Introduction

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Pain can be classified by several characteristics including type, intensity, and duration. Acute pain results from disease or injury that begins suddenly and can last from a few seconds to weeks or months, and may eventually become chronic [2]. Chronic pain affects at least 100 million people in the United States (US) and millions more worldwide [2], and is the most common cause for long-term work disability [3], which leads to a substantial economic burden in medical treatment and lost productivity [2]. In general, pain has a complex pathophysiology that involves both peripheral and central factors that characterize the type of pain [4]. For instance, pain is classified as neuropathic in nature when the sensation of pain is a result of nerve injury [5].

Pain treatment is highly individualized and depends on the type of pain experienced by patients [2].

Medications used for chronic neuropathic pain typically include N-methyl-D-aspartate (NMDA) receptor antagonists, glutamate antagonists, α-2 agonists, and γ-aminobutyric acid$_{\beta}$ (GABA$_{\beta}$) agonists such as ketamine HCL, gabapentin, clonidine, and baclofen [5]. These drugs act through different mechanisms to provide pain relief. Though Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and opioids are routinely prescribed for acute and chronic pain management, chronic use of NSAIDs typically result in gastrointestinal complications [6], while opioids often do not provide relief for patients with chronic neuropathic pain [7].

According to the guidelines established by the IASP Neuropathic Pain Special Interest Group, combination of medications could potentially be more efficacious than monotherapy regimens in the treatment of chronic neuropathic pain [8]. The combination of analgesics can lead to synergistic effects and potentially enhance analgesia [9]. However, combinations of analgesics that target multiple pain pathways may also necessitate the administration of several drugs with different dosing regimens, leading to poor patient compliance. In fact, the World Health Organization cites "complexity of regimen" as a major factor leading to patient noncompliance to treatment regimens [10]. Therefore, the combination of multiple drugs into a single formulation may enhance treatment compliance by decreasing the number of drugs a patient has to take [9].

When evaluating available pharmacologic options for analgesia, prescribers must choose not only the correct drug or drug combination, but also the most appropriate route of administration. Oral drugs are commonly used for pain management as they are the least invasive route of administration [11]. However, oral drugs have disadvantages that may limit their utility in certain patient populations. For instance, terminally ill patients, such as those with cancer or those in hospice care, are often unable to tolerate orally administered drugs secondary to nausea and vomiting [12]. These challenges may be amplified in patients who require multiple drugs for adequate pain relief.

Disadvantages of orally administered analgesics can be overcome using transdermal drug formulations that provide a convenient and painless method of administration [13]. The skin is an important target for treatments aimed at pain management as several studies have demonstrated the presence of receptors and ligands on peripheral nociceptors and non-neural cells, as well as signaling between neural and non-neural skin cells (reviewed in [14]). Several studies have demonstrated that the use of compounded transdermal analgesics leads to high drug concentrations at the target site while maintaining low systemic drug levels, leading to decreased systemic side effects (reviewed in [15]).

Pharmaceutical compounding provides for the preparation of customized drugs to meet the needs of individual patients and allows the patient the benefit of a personalized therapy. Compounded drugs can be formulated to include special combinations of drugs at particular concentrations that may not be commercially available [16].

Compounded transdermal preparations that include multiple analgesics may offer numerous therapeutic benefits, but there are limited data on such formulations and a host of challenges accompany their development. Furthermore, not all drugs and formulations are suitable candidates for transdermal delivery as the skin is a natural barrier to drug absorption. The skin is composed of three layers: epidermis, dermis, and hypodermis. Within the epidermis, the stratum corneum is the outermost layer of the skin that serves as the main barrier to drug entry [17]. Formulation of a medicine that is adequately absorbed through the skin depends on the careful determination of optimal drug combinations, effective concentrations of each drug, and suitable vehicles for delivery [18]. Consequently, solubility characteristics, skin barrier modifications, and stability are among the key determinants of effective compounding bases [19]. The success of the compounding base in delivering drug is ultimately a function of its interaction with both the skin and the drug molecule [13,19]. Penetration of a drug or combination of drugs can be optimized when it is incorporated into a base with the appropriate physiochemical properties.

The goal of the present study was to evaluate the percutaneous absorption and mass distribution pharmacokinetics of four drugs commonly used in the management of neuropathic pain [5,20]: ketamine HCl, gabapentin, clonidine HCl, and baclofen. The four drugs were compounded in two creams, Lipoderm and Lipoderm ActiveMax, which are transdermal compounding bases with proprietary liposomal components that are likely to increase the permeation of drugs.

Methods

Materials

Ketamine HCl (Lot C140396), gabapentin (Lot C139010), clonidine HCl (Lot C139957), baclofen (Lot C140868), Lipoderm, and Lipoderm ActiveMax were provided by Professional Compounding Centers of America (PCCA).

Two transdermal creams were compounded by a licensed pharmacist at PCCA. Both preparations contained ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w. One cream was compounded using Lipoderm and the second was compounded using Lipoderm ActiveMax.

Skin Samples and Preparation

Human cadaver trunk skin without obvious signs of skin disease was harvested between 24 and 48 hours after death for use in this study. The skin was dermatomed,

cryopreserved, sealed in a water impermeable bag, and stored at −70°C until the day of the experiment. Prior to use, donor skin was thawed in a 37°C water bath and rinsed with water to remove any adherent blood and other materials from the surface. Donor skin was then cut into multiple sections large enough to fit onto 1 cm^2 static Franz diffusion cells.

Donor Demographics and Skin Integrity

All skin donors were male and all skin samples were taken from the posterior torso. To ensure the integrity of each skin section, its permeability to tritiated water (^3H_2O) was determined in a Franz diffusion cell before application of the test products. Following a 30 minutes to 1 hour equilibrium period, ^3H_2O (PerkinElmer, Boston, MA, USA) was layered across the top of the skin so that the entire exposure surface was covered (approximately 200–300 μL/cm^2). Five minutes after application, the ^3H_2O aqueous layer was removed. At 30 minutes, the receptor solution was collected and analyzed for radioactive content by liquid scintillation counting. Donor skin specimens in which absorption of ^{3}H2O was less than 1.56 μL-equ/cm^2 were considered acceptable.

Dosing and Sample Collection

Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into two transdermal bases, Lipoderm and Lipoderm ActiveMax, by a PCCA pharmacist. Each compounded drug formulation was tested on skin from three different donors and three replicate skin sections per donor. One nondosed control diffusion cell was included per donor as a negative control.

The Franz finite dose model was used in this study to evaluate the percutaneous absorption and distribution of compounded pain medication, as described previously [21]. Briefly, a section of skin from a single donor was placed into a Franz diffusion cell so that the underside of the skin was exposed to a receptor solution containing PBS with 0.1% Oleth-20 and 0.008% Gentamicin. The receptor solution was stirred magnetically at 600 rpm and maintained at 32.0 ± 1.0°C. The outer surface of the skin was accessible via a chamber chimney that could be exposed to the environment. Prior to administration of transdermal test formulations to skin sections, a predose receptor solution sample was collected and the entire receptor compartment was refilled with PBS with 0.1% Oleth-20 and 0.008% Gentamicin. Transdermal solutions of 5 mg/cm^2/skin section were then dispensed by weight onto the outer surface of three replicate skin sections for each donor using a glass rod. Approximately 5–10 minutes after dose application, the donor compartment of the diffusion cell was replaced. The receptor solution was removed in its entirety at 2, 4, 8, 12, 24, 32, and 48 hours after dose application, and was replaced with fresh receptor solution. After sample collection at 48 hours, the surface of the skin was cleansed twice with 0.5 mL of 80:20 MeOH:H_2O to collect any unabsorbed formulation from the skin surface.

Following the surface cleanse, the donor compartment was removed and the skin was tape-stripped to remove the stratum corneum. Tape strips were collected using 3M Transpore® tape and were extracted overnight at room temperature in acetonitrile. The skin was removed from the diffusion cell and separated into the epidermis and dermis. The epidermal and dermal skin samples were extracted overnight at room temperature in 80:20 MeOH:H_2O. All samples were stored at −20°C pending analysis.

Quantification of Drug Levels by LC/MS

Quantification of ketamine HCl, gabapentin, clonidine HCl, and baclofen was performed using high performance liquid chromatography/mass spectrometry (HPLC/MS). A gradient solvent system consisting of 0.04% ammonium acetate in ddH_2O, pH = 5.5, and methanol was run through a Phenomenex Gemini C18 (50 × 3.0 mm, 3 μm) column at a flow rate of 0.4 mL/min. Eluting peaks were measured with MS monitoring mass units at 238.1 (ketamine HCl), 172.2 (gabapentin), 230.0 (clonidine HCl), 214.1 (baclofen), or measured with a diode array detector (UV) monitoring 202 and 220 nm referenced to 500 nm.

Statistical Analysis

The rate of percutaneous absorption is presented as the flux of ketamine HCl, gabapentin, clonidine HCl, and baclofen that appeared in the receptor solution under the skin. Individual diffusion cell values were calculated and averaged across replicates for a donor. The mean from each donor was averaged and results are expressed as mean ± standard error (SE). Differences in percutaneous absorption between the two drug formulations were evaluated using a 2-way analysis of variance (ANOVA) (significance level of $P < 0.05$) with a Bonferroni post-test to compare each time point. As flux (rate of absorption) is not a discrete, directly measurable value, but rather is a time-averaged value determined across a sampling period, by convention it was reported at the midpoint of sample collection for that sample period.

The cutaneous distribution of ketamine HCl, gabapentin, clonidine HCl, and baclofen is presented as percent of applied dose. Percent recovery was based on the gravimetric application of the dose. Individual diffusion cell values were calculated and averaged across replicates for a donor. The mean from each donor was averaged and results are expressed as mean ± SE. Differences in cutaneous distribution between the two formulations were evaluated using a student's *t*-test with a significance level set at $P < 0.05$.

Table 1 Demographics of skin donors

Donor Identification	Age	Race	Sex	Anatomical Location	Integrity Result (μL-equ$^3H_20$)
HR032809	72	Black	Male	Posterior Torso	0.44 ± 0.20
MC111306	58	Caucasian	Male	Posterior Torso	0.22 ± 0.12
MD110308	68	Caucasian	Male	Posterior Torso	0.33 ± 0.25

Limitations of the Study

While this study offers insight into the transdermal delivery of multiple analgesics using Lipoderm and Lipoderm ActiveMax, it was not without limitations. Some amount of drug was inevitably lost during application and may have affected dose recovery assessments. However, this may reflect actual conditions, as some of the prescribed dose would likely be lost at the time of application [22]. In addition, sampling did not account for any established regional differences in skin permeability. All donor skin was taken from the trunk due to the need for large sections and replicates. Absorption and distribution characteristics have been shown to differ in skin from other areas of the body where transdermal agents could be applied in practice [23,24]. As the skin of the trunk is known to be thicker and harder to penetrate than skin in other areas that are traditionally targeted for transdermal therapy [25], it is anticipated that application of transdermal preparations to this area may underestimate the delivery of drug if it were to be applied to other sites on the body. Therefore, the generalizability of precise measures of absorption and distribution to different application sites is somewhat limited. Finally, a delivery vehicle without the ability to facilitate the penetration of drugs through human skin was not used as a negative control which limits the applicability of the results.

Results

Predose Skin Evaluation

The demographic characteristics of skin donors and skin integrity results of the specimen are displayed in Table 1. Integrity results met the acceptance criterion of less than 1.56 μL-equ/cm^2, indicating that drug absorption was not confounded by abnormal barrier function of the skin.

Ketamine HCl Penetrates Donor Skin Rapidly and Efficiently

As shown in Figure 1, after transdermal application of ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w compounded with Lipoderm or Lipoderm ActiveMax, ketamine HCl penetrated into and through human trunk skin. No significant differences in flux were observed between test

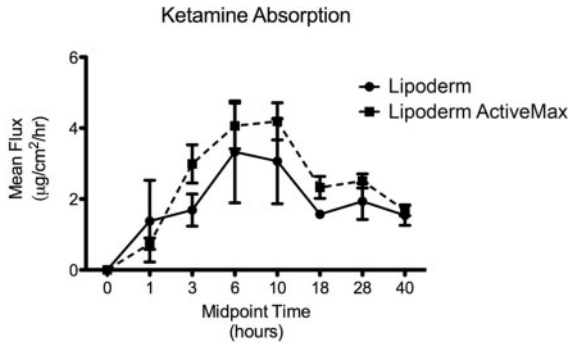

Figure 1 Percutaneous absorption of ketamine over time. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax. The formulation was tested on skin from 3 different donors with each formulation and 3 replicate skin sections per donor. Samples of receptor solution were taken over time and analyzed for ketamine content using HPLC/MS. The means from each donor were averaged and results are expressed as mean ± SE.

drug formulations. The absorption profile of ketamine HCl was characterized by a rise to peak flux between 6 and 10 hours after initial skin application, followed by a slow decline thereafter. Total absorption of ketamine HCl, defined as the mass of drug in receptor solution over 48 hours, was similar between the 2 drug formulations. A mean ± SE of 90.6 4 ± 22.95 μg ketamine HCl was absorbed when Lipoderm was the compounding base and 115.3 4 ± 6.07 μg was absorbed when Lipoderm ActiveMax was the compounding base. The distribution of ketamine HCl throughout all layers of the skin, receptor solution, and surface wash was similar between the two compounding bases, as displayed in Figure 2.

Gabapentin Absorption Peaks Quickly Before Stabilizing

As shown in Figure 3, gabapentin was able to penetrate into and through *ex vivo* human trunk skin. Its absorption profile was similar across the two compounded drug formulations. Peak flux occurred approximately 1 hour after dose application, absorption quickly declined

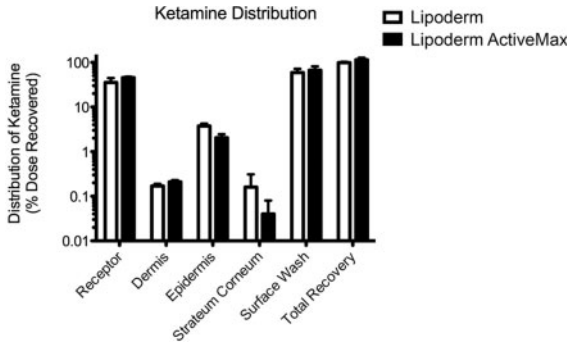

Figure 2 Distribution of ketamine in the skin 48 hours after transdermal application. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax and tested on skin from three donors with three replicate sections per donor. Forty-eight hours after application, the skin was tape-stripped and the amount of ketamine in each skin layer was determined using HPLC/MS. The results are expressed as mean ± SE.

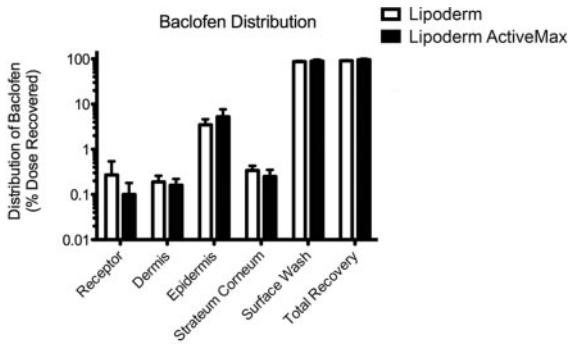

Figure 3 Percutaneous absorption of gabapentin over time. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax. The formulation was tested on skin from three different donors with three replicate skin sections per donor. Samples of receptor solution were taken over time and analyzed for gabapentin content using HPLC/MS. The means from each donor were averaged and results are expressed as mean ± SE.

thereafter, and a steady-state like flux was maintained over the remaining period. Mean total absorption for gabapentin after 48 hours was 2.0 8 7 ± 1.718 μg in Lipoderm and 0.9 5 3 ± 0.399 μg in Lipoderm ActiveMax. Although no statistical differences in absorption were observed between the 2 drug formulations, there was a statistically significant difference in the distribution of gabapentin between the two drug formulations in the epidermis (Figure 4, $P = 0.0272$). A similar

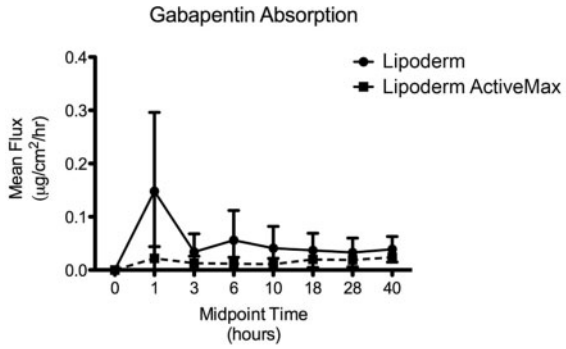

Figure 4 Skin distribution of gabapentin 48 hours after transdermal application. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax and tested on skin from three donors with three replicate sections per donor. Forty-eight hours after application, the skin was tape-stripped and the amount of gabapentin in each skin layer was determined using HPLC/MS. The results are expressed as mean ± SE.

trend was noted in the stratum corneum, although this was not statistically significant.

Percutaneous Absorption of Clonidine HCl Continuously Increases over Time

For both drug formulations, the penetration of clonidine HCl into and through human trunk skin was characterized by an early burst of absorption at approximately 1–3 hours after application, followed by a continuous slow increase in flux out to 40 hours after application (Figure 5). The total amount of clonidine HCl absorbed using Lipoderm was 0.4 0 7 ± 0.267 μg and, using Lipoderm ActiveMax, was 0.4 4 4 ± 0.095 μg. No statistically significant differences were observed across drug formulations in total dose recovered from the receptor solution, dermis, epidermis, or stratum corneum. However, a significantly greater amount of clonidine HCl was recovered from the surface wash in the Lipoderm ActiveMax formulation (Figure 6, $P = 0.0258$).

Baclofen Absorption Is Similar to That of Gabapentin

As shown in Figure 7, baclofen penetrated into and through human trunk skin quickly, with a rapid rise achieving a peak flux at approximately 1 hour after application for both drug formulations. Similar to the profile for gabapentin, the flux of baclofen quickly declined to a low steady-state like rate of absorption over the remaining period. A mean total of 0.2 8 0 ± 0.280 μg of baclofen was absorbed when Lipoderm was used as the compounding base whereas 0.1 0 3 ± 0.077 μg of baclofen was absorbed when Lipoderm ActiveMax was used as the compounding base. No statistically significant differences in distribution were observed between

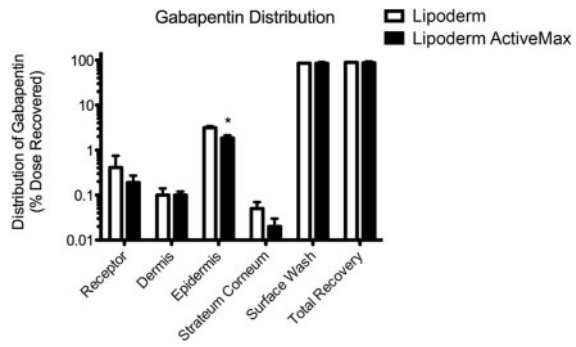

Figure 5 Percutaneous absorption of clonidine over time. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax. Each formulation was tested on skin from three different donors and three replicate skin sections per donor. Samples of receptor solution were taken over time and analyzed for clonidine content using HPLC/MS. The means from each donor were averaged and results are expressed as mean ± SE.

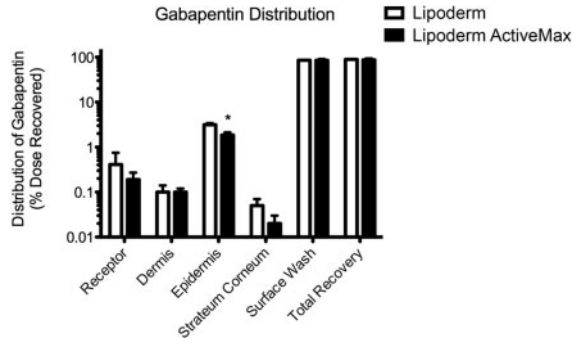

Figure 6 Skin distribution of clonidine 48 hours after transdermal application. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax and tested on skin from three donors with three replicate sections per donor. Forty-eight hours after application, the skin was tape-stripped and the level of clonidine in each skin layer was determined using HPLC/MS. The results are expressed as mean ± SE.

formulations for total receptor, dermal, stratum corneum, or epidermal content (Figure 8).

Discussion

The prescribing of compounded transdermal drugs for pain relief has increased considerably in recent years. A recent survey of physicians observed that 63% have prescribed a transdermal medication for neuropathic

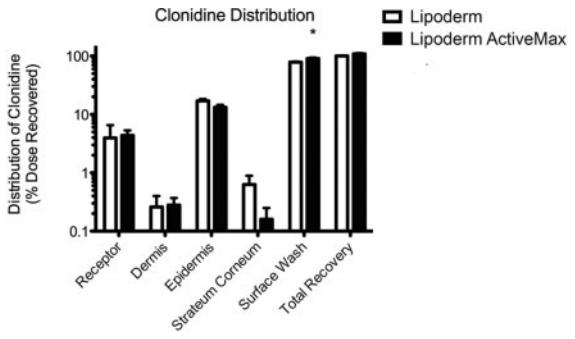

Figure 7 Percutaneous absorption of baclofen over time. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax. Each formulation was tested on skin from three different donors and three replicate skin sections per donor. Samples of receptor solution were taken over time and analyzed for baclofen content using HPLC/MS. The means from each donor were averaged and results are expressed as mean ± SE.

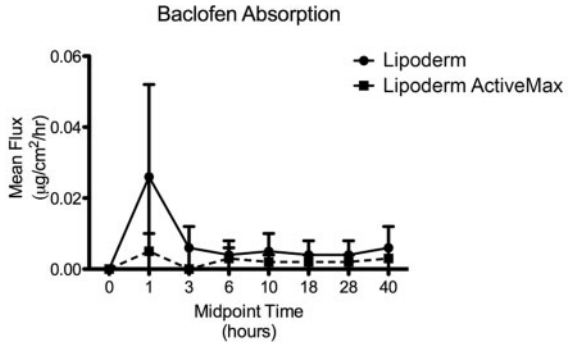

Figure 8 Skin distribution of baclofen 48 hours after transdermal application. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax and tested on skin from three donors with three replicate sections per donor. Forty-eight hours after application, the skin was tape-stripped and the level of baclofen in each skin layer was determined using HPLC/MS. The results are expressed as mean ± SE.

pain [26]. Compounded transdermal drug formulations are useful in situations when other routes of administration are not viable for clinical or functional reasons. As pain management often requires an individualized approach [27], an alternative route of administration also broadens the ability of providers to customize regimens for each patient [26]. Moreover, percutaneous delivery of multiple analgesics in a single compounded drug formulation provides a simpler option with the potential for greater potency from synergistic effects.

This study demonstrates the effective delivery of a combination of ketamine HCl, gabapentin, clonidine HCl, and baclofen simultaneously through human skin using two transdermal compounding bases, Lipoderm and Lipoderm ActiveMax. Combinations of these drugs are often beneficial as multiple receptors and pain pathways can be targeted simultaneously [5,9]. The analgesics chosen for this study are frequently used in the management of neuropathic pain. Ketamine HCl is a rapid-acting NMDA receptor antagonist that inhibits neuron excitability and may also reduce pain through actions at other sites [28]. Currently, only parenteral drug formulations of ketamine HCl are commercially available in the US, but compounded transdermal drug formulations of ketamine HCl with additional drugs have been successful in treating pain associated with a variety of disorders, including chemotherapy-induced neuropathy, arthritis, and general neuropathic pain [29–31]. Baclofen, a derivative of GABA, is frequently used as a muscle relaxant and pain reliever in transdermal preparations and was shown to be effective in treating chemotherapy-induced neuropathy when compounded with ketamine HCl and amitriptyline HCl [29]. Gabapentin, another derivative of GABA, is an anticonvulsant with analgesic effects in several models of neuropathic pain and can also enhance opioid-mediated analgesia [32]. The α2-adrenergic agonist clonidine is a centrally acting antinociceptive agent with the added benefit of prolonging the analgesic effect of other drugs [28,33]. Topical clonidine HCl has also been shown to be effective in the treatment of painful diabetic neuropathy [34] and inflammatory nerve injury (reviewed in [18]).

Although some published studies discussed the lack of efficacy associated with drugs such as ketamine HCL [35] or clonidine HCL [36] in the treatment of pain, the methodology for the studies may limit applicability of the findings. In Lynch et al., authors disclosed that the reasons behind lack of efficacy in the treatment of chronic neuropathic pain observed with topical ketamine could be due to short treatment duration and initial pain levels being lower than the limit for detection [35]. In *Bollag* et al., though results show that the administration of clonidine HCL did not reduce pain scores in women, postcesarean delivery, authors mentioned that the dose for clonidine used in the study may not have been adequate [36].

A drug's percutaneous rate of absorption depends on its molecular properties coupled with its solubility in the transdermal base [22,24], as well as the properties of the skin to which it is applied. To penetrate both the outermost layer of the skin, the stratum corneum, and the epidermis, the compounded drug should have both hydrophobic and hydrophilic properties (reviewed in [14]). Because the drug's potential therapeutic effect hinges, in part, on its ability to be absorbed, flux serves as an indicator of a compounded product's quality. In this study, the absorption profiles indicate a rapid penetration to peak flux for gabapentin and baclofen at approximately 1 hour after application. Clonidine HCl also had a rapid penetration to peak flux occurring approximately 1 hour after application and had a secondary peak at approximately 40 hours whereas ketamine HCl exhibited higher overall absorption rates than the other drugs, and peaked at 6 to 10 hours in both formulations.

The drugs' penetration was further assessed by measuring the amounts of drug distributed throughout the skin layers and in the receptor solution. Several studies have demonstrated variations in percutaneous drug absorption based on several biological characteristics of the skin, including age, gender, and ethnicity [37]. Additionally, the location of the skin to which transdermal drugs are applied affects the absorption rate and distribution of drug. The amount of drug in the dermis, a skin layer that is vascularized *in vivo*, represents drug distributed that could potentially reach the bloodstream [22]. By similar reasoning, drug retained in the epidermis is also expected to permeate because it has crossed the stratum corneum, which serves as the primary external barrier. In this study, each drug penetrated all skin layers during the 48 hours collection period. Ketamine HCl was predominantly found in the receptor solution, whereas the epidermal layer retained the greatest amount of gabapentin, clonidine HCl, and baclofen. This illustrates the continued absorptive process that may likely occur *in vivo*, secondary to the effective transfer of drug through the skin layers via the compounded base.

Conclusions

The potential for transdermal delivery of a combination of analgesics is an important option in the treatment of pain, particularly in patients whose condition does not allow for the administration of oral analgesia [12]. This study demonstrates the ability of the four drugs (ketamine HCl, gabapentin, clonidine HCl, and baclofen) to penetrate into and through human cadaver trunk skin *in vitro*, when incorporated into the two transdermal compounding bases, Lipoderm and Lipoderm ActiveMax. Results reveal that all four drugs may be suitable for transdermal delivery. Knowledge of this study could potentially be useful for practitioners considering the skin as an alternative route for the percutaneous delivery of any of the four drugs in neuropathic pain management. The findings may also be helpful when justifying the viability of using either compounded base as a vehicle for the transdermal delivery of ketamine HCl, gabapentin, clonidine HCl, and baclofen.

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