

# Update on Transdermals for Animal Patients



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Approximately 2 years have passed since publication of the last series of articles in this journal on transdermal drug delivery in animal patients. That series of articles presented an overview of the benefits and risks of using transdermal drug therapy in animals, and reviewed the few scientific investigations that had been published at the time. Two years later, what we know of the medical risks and benefits remains relatively unchanged; however, the relative legal risks may have increased. Scientific activity has burgeoned during this period. While the scientific community still has not unraveled the complete mystery of (what this author now refers to as) “pulsed” transdermal drug therapy in animals (single immediate-release gels as opposed to continuous-release patches), some insight has been gained as to the relative bioavailability of some transdermally dosed medications; initial predictions of transdermal drug disposition have been far off the mark. This article is intended to update the compounding pharmacist regarding the past 2 years of activity in veterinary transdermal drug therapy since the last featured article in the March/April 2003 issue of *International Journal of Pharmaceutical Compounding (IJPC)*.

## Scientific Investigations

At the time of the last publication, there were no published studies examining safety and efficacy of transdermally administered drugs in animals. Since 2003, two safety and efficacy studies have been published.<sup>1,2</sup> The objective of the first study (Sartor et al) was to determine whether transdermal methimazole is as safe and effec-

tive as oral methimazole for the control of hyperthyroidism in cats. Forty-seven client-owned pet cats with newly diagnosed hyperthyroidism were randomized to receive 2.5 mg methimazole twice daily either as a transdermal preparation [5 mg/0.1 mL in Pluronic lecithin organogel (PLO)] or orally as tablets.

By the end of the study, 44 cats (17 that received oral drug and 27 that received transdermal drug) had followed the protocol and had been evaluated at weeks 0, 2, and 4 of the therapy with a physical examination, body weight determination, and completion of a questionnaire by the owners. More cats in the oral methimazole group had a  $T_4$  level within normal limits after 2 weeks, but by 4 weeks there was no statistical difference between the two groups in response to therapy. There also were no differences between the groups in terms of occurrences of neutropenia, hepatotoxicity, or facial excoriations; however, the oral-treatment group had a statistically higher incidence of adverse gastrointestinal effects. The study concluded that transdermal methimazole is a viable treatment option for feline hyperthyroidism and may pose a lower risk for methimazole-induced gastric disturbance.

The second safety and efficacy study (Chastain and Panciera) prospectively administered transdermal methimazole to 13 hyperthyroid cats in doses empirically ranging from 2.5 mg daily to 10 mg twice daily. All cats eventually showed improvement in clinical signs of hyperthyroidism; half of the cats had a  $T_4$  level within normal range at the first recheck, and all but one cat had a  $T_4$  level in the normal range at the second recheck. No adverse effects were noted in any of the cats, including two cats that had a history of vomiting while receiving oral methimazole. These researchers concluded that transdermal methimazole could be used successfully to treat feline hyperthyroidism.

Several other long-term dosing studies are underway, examining transdermal administration of amlodipine, diltiazem, buspirone,

amitriptyline, glipizide, and ondansetron. Results will, we hope, be available for publication in the very near future.

In 2003, only one single-dose pharmacokinetic study of a transdermally applied drug had been published.<sup>3</sup> Single doses of transdermal methimazole were applied to healthy cats. The results were equivocal and were perceived by the scientific community as negative data; however, the results of this study prompted the same investigators to conduct the long-term dosing study that concluded with very positive results. Since that time, many single-dose pharmacokinetic studies have been performed on transdermally delivered drugs. Metoclopramide was administered transdermally to client-owned dogs that were randomized to receive the drug in oral, subcutaneous, or transdermal dosage forms, but transdermal metoclopramide produced no detectable serum levels after administration.<sup>4</sup> Another single-dose plasma disposition study was performed on dermally applied liposomal lidocaine (ELA-Max).<sup>5</sup> This study was intended to prove that this formulation was not absorbed systemically when applied dermally to cats. Lidocaine is systemically toxic to cats, and systemic absorption of the topical anesthetic would preclude its safe use in cats. Therefore, the results of this study were positive in that drug distribution remained dermal and not systemic. Searches of medical search engines for “transdermal”

and “veterinary” frequently retrieve this study, whose results have been misinterpreted by many as negative.

The pharmacokinetics of transdermal dexamethasone were examined after a single dose of either oral or transdermal dexamethasone to healthy cats.<sup>6</sup> After 72 hours, none of the cats that received transdermal dexamethasone had a measurable blood level of the drug, whereas those that received the oral dose had a peak blood concentration within 15 minutes. Many of the cats that received the oral drug vomited during the study, however, and the researchers emphasized the need to pursue further study of transdermal formulations of corticosteroids for cats. One important point to note is that the dexamethasone in PLO was compounded in New York and shipped to Florida for use in the study. Stability studies were not performed on the dexamethasone prior to use, and we cannot know if the drug was fully potent at the time the study was initiated, particularly since the physical stability of PLO is known to be dependent on temperature.

The pharmacokinetics and relative bioavailability of fluoxetine were investigated after single doses were administered transdermally or orally to healthy cats.<sup>7</sup> The formulation studied was a 150-mg/mL fluoxetine in PLO transdermal gel, which was compared to oral fluoxetine capsules. Serum drug levels after fluoxetine administration

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indicated that the bioavailability of the transdermal drug was approximately 10% of that of the oral dose. The authors emphasized that these results were measured after single doses only. Fluoxetine is well known to accumulate in cats, and transdermally administered agents are known to take several hours to achieve steady state even when administered via continuous-release transdermal patches. (For example, fentanyl administered by transdermal patch requires 18 to 72 hours to achieve steady state in cats.<sup>8</sup>) With pulsed dosing of a transdermally administered gel, the drug is very likely to accumulate with time, and clinicians should be cautioned that the oral dose cannot simply be factored upwards by 10 to achieve blood levels equivalent to those produced by oral dosing, as the study conclusion may imply.

In a study of single dosing of intravenous or transdermal diltiazem in healthy cats, relative bioavailability of transdermal diltiazem was, again, about 10% in spite of a mg/kg dose for intravenous diltiazem and a fixed dose of 7.5 mg/cat for transdermal diltiazem.<sup>9</sup> This transdermal dose was selected on the basis of an assumption that diltiazem is a high first-pass drug and that, by bypassing oral administration, plasma levels would be equal to or higher than those achieved by oral dosing. Plasma levels for this transdermally administered dose never approached the recommended therapeutic serum level of 50 to 300 µg/mL in cats. This particular fact began to dispel the previously held belief that transdermal drugs could be more toxic than oral ones because of bypassing the hepatic portal system. Interestingly, in this study, the kinetic behavior of transdermally applied diltiazem appeared to be influenced by both weight and body condition. Obesity appeared to have an impact on the disposition of transdermal cutaneous boluses, causing a later peak and larger area under the curve in larger cats. Factoring transdermal doses upward by 10 times the oral dose could have disastrous consequences, particularly in obese cats, as nonlinear kinetics emerge with multiple dosing. The results of this initial study caused investigators to repeat the study (results pending), but, prior to the study, these investigators performed a stability study on diltiazem formulated in a proprietary transdermal percutaneous absorption-enhancing gel (Lipoderm; Professional Compounding Centers of America, Houston, Texas) at 100 mg/mL and 250 mg/mL concentrations. The stability of diltiazem in Lipoderm is apparently concentration-dependent; the 100 mg/mL formulation is stable for 60 days at room temperature.<sup>10</sup> These investigators are now preparing for a randomized, crossover, prospective safety and efficacy study comparing transdermal and oral diltiazem in cats with cardiomyopathy.

Mealey et al investigated systemic absorption of amitriptyline and buspirone after single-dose oral or transdermal administration to healthy cats.<sup>11</sup> Like the other studies, this study showed that bioavailability of a single dose of transdermally administered drug is approximately 10% of that after comparable oral dosing. The results of this study further emphasize that high first-pass-extracted transdermal drugs do not achieve comparable or higher plasma concentrations than their oral counterparts, necessitating higher transdermal doses than originally predicted. Because both of these

drugs are very likely to accumulate after long-term transdermal dosing, using 10 times the oral doses for transdermal buspirone and amitriptyline cannot be safely recommended. Further investigation of long-term dosing kinetics in diseased cats is warranted for both of these drugs.

Most recently, Bennett et al investigated the pharmacokinetics, as well the effect on serum glucose, of transdermally administered glipizide.<sup>12</sup> This study was well designed, utilizing 16 healthy cats randomized into three groups. Six cats were randomized to receive either an oral or a transdermal placebo, and 10 cats were assigned to receive either 5 mg of encapsulated glipizide powder orally or 5 mg (0.1 mL of 50 mg/mL) of glipizide in PLO. Blood was sampled for 24 hours. Serum glipizide level was measured in all cats. Glipizide concentrations were significantly higher in the cats receiving oral medication, and bioavailability of the transdermal formulation was 20% that of the oral form. As in all other single-dose studies, oral drug was detected sooner (5 hours) than transdermal drug (16 hours), indicating delayed absorption of transdermal drug; however, the elimination half-lives were not statistically different (16 hours oral versus 15 hours transdermal). Plasma glucose concentrations were lower in cats receiving either oral or transdermal glipizide than in cats receiving placebo. For the first 6 hours after dosing, cats that received oral glipizide had significantly lower blood glucose levels than the cats that received transdermal drug; after 6 hours, however, there were no differences in glucose concentration despite a significant difference in serum glipizide concentrations. These investigators concluded that, in spite of apparent delay in transdermal absorption, transdermal glipizide might provide an alternate route of administration to oral glipizide for diabetic cats. They recommended long-term dose studies in diabetic cats.

### Are Transdermals Safe and Effective?

Without a doubt, the answer to this question is yes. Many veterinary patients simply cannot be orally medicated by their owners. Veterinary clinicians are frequently faced with utilizing transdermals as an alternative to euthanasia for pets when all other medication options have been exhausted.

The previously cited studies all indicate that disposition of transdermal medications in cats is highly individualized and affected by body condition, disease state, and even the choice of penetration-enhancing transdermal vehicle. Obviously, more long-term dosing studies are needed for transdermal drug therapies used in cats, but it does seem apparent that a single transdermal dose of any therapeutic drug given at an equivalent oral or intravenous dose is unlikely to cause severe systemic harm. Paradoxically, it also is obvious that extrapolation of kinetic behavior from single-dose studies is likely to overestimate safe and effective doses of transdermal drugs. Long-term therapeutic dosing of transdermals should be approached in a fashion similar to that recommended in the earlier *IJPC* series on transdermals: with careful collaboration between veterinarian, pharmacist, and pet owner to objectively assess therapy before, during, and after initiation, carefully observing for signs of therapeutic efficacy, therapeutic failure, or systemic toxicity.

## Regulatory Environment

One of the darkest clouds hanging over veterinary transdermal drug therapy is the current regulatory environment regarding use of bulk chemicals to compound veterinary drugs. While various parties argue the right of the US Food and Drug Administration (FDA) to declare use of bulk chemicals “out of bounds,” few argue the necessity of using pure chemicals to formulate absorbable transdermal therapies. FDA has promised to revise Compliance Policy Guide 7125.40, “Compounding of Drugs For Use In Animals,” but the current regulatory environment exclusively prohibits use of bulk chemicals to compound for companion animals. Until a compromise is reached regarding use of bulk chemicals in animals, veterinarians and compounding pharmacists should not be afraid to utilize this valuable dosage form, but should practice due diligence in documenting clinical decision-making when choosing to use transdermal therapy and reporting both positive and negative outcomes experienced while using this dosage form.

## Current Obstacles

The current regulatory environment regarding compounding of transdermals and other bulk chemical compounds has certainly rippled into other unforeseen arenas. The FDA certainly did not intend to suppress the communication of scientific investigation when banning the use of bulk chemicals; however, this is exactly what has occurred. As a result of the revision of the Compliance Policy Guide, many veterinary peer-reviewed journals and specialty colleges have adopted editorial policies precluding publication of research or case studies involving products that are not commercially available. In fact, some of the most impressive research regarding safety and efficacy of transdermally administered drugs was rejected for publication by a peer-reviewed journal solely on the basis that a bulk chemical was used in the study. Fortunately, another scientific journal saw learning value in the study and decided to publish.

Another unforeseen consequence of recent FDA scrutiny on compounding has resulted in a re-evaluation of liability insurance coverage by both veterinary and pharmacy practitioners. As compounding from bulk chemicals for companion animals has been declared illegal by FDA, any veterinarian or pharmacist engaging in such practice has come under the Professional Liability Insurance Trust malpractice insurance microscope. Veterinarians or pharmacists who provide drug therapies from bulk chemicals may not be protected in the event of a lawsuit involving use of these compounded products.

## Frontiers for Transdermal Drug Applications

Is there a future for transdermal drug delivery in veterinary practice? Most definitely. The value of the transdermal drug delivery market was about \$8 billion in 2002 and is expected to top out at \$16.3 billion in 2007.<sup>13</sup> These figures apply to commercially available products, but the trend is obvious—healthcare professionals and consumers want noninvasive, systemic drug delivery, and transdermal technology is the answer.

Interestingly, the Grand Award in the *Popular Science* 2004 “Best of What’s New” Awards went to the SonoPrep (Sontra Medical Corporation, Franklin, Massachusetts), which is an ultrasonic skin permeation device.<sup>14</sup> SonoPrep applies ultrasonic energy to the skin surface, disorganizing the lipid layer of the stratum corneum and increasing skin permeability 100-fold for as long as 24 hours after treatment. The FDA recently cleared this device for use with topical lidocaine to achieve rapid skin anesthesia for invasive procedures as well as multiple needle sticks and intravenous catheterization. The SonoPrep is also to be evaluated for continuous noninvasive monitoring of blood glucose and for transdermal delivery of vaccines, analgesics, and large protein biopharmaceuticals. Paired with the SonoPrep and other such devices, transdermal gel drug delivery could become the standard for drug therapy.

## Summary

Much insight has been gained into the disposition of transdermally administered medications to animal patients over the last 2 years. Scientific investigations are beginning to unravel the mystery of percutaneous drug disposition of transdermally applied drugs. While exact disease-specific protocols for transdermal drug therapy are yet to be determined, pulsed transdermal drug delivery in feline patients still offers much hope for life saving, noninvasive



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therapeutic intervention. While the regulatory and scientific environments are still developing on the subject of pulsed transdermal therapy, this dosage form still represents one of the most promising therapeutic tools in the veterinarian's "black bag." By keeping pace with the results of scientific investigations in veterinary transdermal therapy and by practicing due diligence in chronicling transdermal therapeutic outcomes, the compounding pharmacist can maximally contribute to the veterinary care quadrad.

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