TRANSDERMAL DRUGS: WHAT DO WE KNOW?
Lauren A. Trepanier, DVM, PhD, DACVIM, DACVCP

Although nitroglycerin ointment has been in use for veterinary patients for decades, only recently have veterinary transdermal formulations been available for a wide variety of drugs through custom compounding pharmacies. For the vast majority of these formulations, however, absorption and efficacy data is absent, and the clinician should keep a clear view of the pros and cons of transdermal delivery when considering this route of administration.

Transdermal: goal is therapeutic drug concentrations in the systemic circulation
Topical: goal is local therapeutic drug concentrations in surface organs (skin, eye, ear canal)

<table>
<thead>
<tr>
<th>Potential advantages and disadvantages of the transdermal route</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature of transdermals</td>
<td>Potential advantage</td>
<td>Potential disadvantage</td>
</tr>
<tr>
<td>Do not require “pilling” or injections</td>
<td>May be better accepted by many cats</td>
<td>Some cats resent sensation of gel or patch</td>
</tr>
<tr>
<td>No direct gastric or intestinal contact</td>
<td>Decreased direct GI irritation</td>
<td>Inappropriate route for drugs acting locally in the GI tract</td>
</tr>
<tr>
<td>Avoid first pass oral biotransformation</td>
<td>May avoid variable absorption seen with the oral route</td>
<td>May be inappropriate for pro-drugs dependent on biotransformation</td>
</tr>
<tr>
<td>Absorbed slowly from depot formed in skin</td>
<td>May provide longer duration of action</td>
<td>May never reach therapeutic plasma concentrations</td>
</tr>
<tr>
<td>Avoid high peak plasma concentrations</td>
<td>May decrease acute dose-dependent side effects</td>
<td>Lack of immediate effect for most drugs needed in an emergency setting</td>
</tr>
<tr>
<td>Require custom formulation</td>
<td>Concentration can be tailored to patient’s size</td>
<td>Often more expensive; stability data often unavailable</td>
</tr>
</tbody>
</table>

I. Transdermal formulations
   A. Mechanisms of permeation enhancers
      1. Change in lipid fluidity in the stratum corneum
      2. Solubilization of lipids between corneocytes
      3. Generation of pores on the surface of corneocytes
      4. Actual exfoliation of the stratum corneum
   B. Commonly used permeation enhancers
      1. PLO (Pluronic lecithin organogel)
         a) Pluronic F127: Polymeric surfactant that enhances drug micelle formation shown to enhance the skin permeation of many drugs
         b) Lecithin: Increases fluidity of stratum corneum; leads to exfoliation of stratum corneum and low grade inflammation with chronic use
         c) PLO separates at cold temperatures
            (1) Do not refrigerate or send through mail during cold months
      2. Lipoderm
         a) Proprietary formula (PCCA) containing lecithin
         b) Less greasy than PLO; can be refrigerated
      3. VanPen
         a) Proprietary formula (PCCA) used for more lipophilic drugs
   C. Other permeation enhancers
      1. Oleic acid, propylene glycol, ethanol, and glycol ethers
         a) Many good permeation enhancers are also irritating
         b) Lower-dose combinations of enhancers have been used to decrease irritation
      2. Glycol ether/isopropanol
         a) Used in Revolution® for transdermal absorption of selamectin
      3. DMSO not recommended
         a) Local irritation, odor
         b) Inadvertent absorption of skin contaminants
   D. Patches
      1. Matrix-type patches
         a) Contain high concentrations of drug in a matrix or solvent, with one or more permeation enhancers
         b) Rely on skin permeability to regulate drug delivery
      2. Reservoir-type patches
         a) e.g. Duragesic® fentanyl patch
         b) Additional semi-permeable membrane that controls the rate of drug delivery

II. What formulations work for humans?
A. Commercially available human transdermals:
1. Fentanyl patch
2. Contraceptives
3. Hormone replacement therapy
4. Nicotine
5. Oxybutynin, clonidine, and testosterone.

B. What do these formulations have in common?
1. Small compounds (i.e. molecular weight less than 500 g/mole)
2. High lipid solubility
3. Total daily dosages less than 50 mg per day (for 70 kg. person)
   a) Existing patches limited in size to 50 cm$^2$ (less than 3 inches square)
   b) Stratum corneum barrier limits transdermal delivery to about 1 mg per cm$^2$ of skin surface area

III. Absorption and efficacy of transdermal veterinary drugs
A. Nitroglycerin ointment
1. Effective venodilator to reduce preload in acute heart failure
2. Absorbed transdermally
   a) Small molecule
   b) Local venodilation, increases blood flow

B. Fentanyl patch
1. Well established method of post-operative pain relief in dogs and cats
   a) Spay, declawing, orthopedic procedures
   b) Less sedation or hypothermia compared to injectable narcotics
2. 12.5, 25, 50, 75, 100 ug/hr sized patches
3. Applied to shaved skin that is cleaned with warm water and alcohol, and dried thoroughly before application
4. Dose: 3-5 ug/kg/hr
   a) Variable absorption
   b) Must be applied prior to need for analgesia
      (1) Cats
          a) In cats, apply 12 hours prior to surgery
          b) Analgesic concentrations sustained for 3-5 days
      (2) Dogs
          a) Apply 18-24 hours prior to surgery
          b) Analgesic concentrations sustained for 1-3 days
   c) Hypothermia decreases absorbed fentanyl concentrations (e.g. under anesthesia)
   d) Heating pad in contact with patch can lead to exaggerated fentanyl absorption

C. Single dose pharmacokinetic studies
1. Fluoxetine
   a) Fluoxetine (15% in PLO, = 150 mg/ml) is only 10% bioavailable relative to oral fluoxetine (Ciribasssi, 2003)
   b) Roughly comparable bioavailability can be obtained by dosing transdermal fluoxetine at 10 mg/kg (compared to the 1 mg/kg oral dose)
   c) Slower absorption and lower peak serum concentrations with transdermal route
   d) Skin irritation with repeated doses
2. Fentanyl and morphine in PLO
   a) Essentially undetectable (below limit of quantitation) serum levels after single transdermal doses of 0.88 mg/kg of transdermal fentanyl (almost 90 times the IV dose) and 2 mg/kg of transdermal morphine (almost 7 times the IV dose) (Krotscheck, 2004)
3. Dexamethasone
   a) No significant absorption after single transdermal dose in PLO (0.05 mg/kg) (Willis-Goulet, 2003)
   b) Multiple dose studies needed
4. Buspirone, amitriptyline in cats
   a) Poor transdermal absorption after single transdermal doses (Mealey, 2004)
   b) Multiple dose studies needed
5. Diltiazem
   a) Poor transdermal absorption after a single dose of 7.5 mg per cat (DeFrancesco, ACVIM, 2003)
   b) Bioavailability 10% that of IV diltiazem
   c) Diltiazem is stable in Lipoderm for 60 days at 100 mg/ml (Burr 2005)

D. Multiple dose studies
1. Methimazole
   a) Poor absorption after a single dose, but…. 
   b) Effective in lowering serum T4 with chronic administration in hyperthyroid cats
(1) Methimazole in PLO, no DMSO; 50 mg/ml (5 mg per 0.1 cc)
(2) 2.5 mg q. 12 h. to inner pinna
(3) Owners wear exam gloves or finger cots
(4) Alternate ears with each dose
(5) Remove crusted material before next dose

c) Fewer GI side effects (4% of cats) compared to oral (24%) methimazole (Sartor, 2004)
d) No difference in incidence of facial excoriation, neutropenia, thrombocytopenia, or hepatotoxicity
e) Somewhat lower efficacy (67% euthyroid by 4 weeks) compared to oral methimazole (82% euthyroid by 4 weeks)

2. Atenolol
a) 6.25 mg transdermally BID for one week in propylene glycol/glycerin/Tween
b) Lead to therapeutic concentrations in 2 out of 7 cats (MacGregor 2008)
c) Heart rate did decreased overall in cats treated transdermally
d) Transdermal dose needs to be optimized, but drug was absorbed

3. Amlodipine
a) Amlodipine 0.625 mg per cat once daily on Lipoderm
b) Given to hypertensive cats for one week after control with oral amlodipine for one week
c) Plasma concentrations were about ¼ of those seen after oral administration
d) Blood pressure control was not controlled as well, but did not return to hypertensive baseline

4. Glipizide
a) 20% transdermal bioavailability after single dose
b) Can lower blood glucose

E. EMLA (Topical analgesia)
1. EMLA cream (Eutectic mixture of local anesthetics)
a) Lidocaine and prilocaine
b) Effective in our hands for topical/local analgesia in cats
c) Essentially no transdermal (systemic) absorption of lidocaine or prilocaine (and no side effects) in healthy or sick cats when dosed at 1 gram of cream over 10 cm² area, with one hour of occlusion (Gibbon, 2003; Wagner, 2005)

IV. Dosing of transdermal drugs without absorption or efficacy data
A. There is no single useful rule to extrapolate an oral dose to a transdermal dose
   1. Transdermal dose needed may be much higher (if skin penetration is poor)
   2. Transdermal dose may be the same (if transdermal and oral absorption are comparable)
   3. Transdermal dose may be much lower (if oral drug is subject to first pass metabolism)

Checklist for the use of transdermal medications without absorption or efficacy data
- Choose only drugs with a quantitative endpoint
  - T4
  - Heart rate
  - Blood pressure
  - Blood glucose
  - Plasma drug levels
- Do not use transdermal antimicrobials without absorption or efficacy data
- Choose potent drugs (total dosages < 50 mg)
- Choose small (< 500 g/mole) and lipophilic drugs (talk to your pharmacist)
- Choose only drugs with a wide safety margin

Ask yourself….
- Are proven routes (oral or parenteral) not possible in this patient?
- Can you wait for a therapeutic response?
  - Not appropriate for conditions that require immediate efficacy
- Have you informed the client that the appropriate dosage is not established for this route, and that other, better established routes are available?
- Will your pharmacy tell you what is in the formulation?
- Can your pharmacy provide you with a shelf life for the formulation?
- Do you have a rationale for your dose?
  - For example, starting with the oral dose and titrating to quantitative endpoint (only acceptable for drugs with large margins of safety)

V. Other approaches: besides permeation enhancers
A. Physical disruption of the stratum corneum
   1. For presently available patches and solvent systems in humans, all drugs that can be delivered are small (<500 g/mole), relatively lipophilic, and effective at low total daily doses.
   2. For delivery of larger or more polar molecules, physical disruption of the highly ordered lipid bilayers of the stratum corneum is necessary

B. Sonophoresis
   1. Brief (10 second) pre-treatment of the skin with low frequency ultrasound waves
   2. Has been shown to speed the onset of action of EMLA cream (lidocaine/prilocaine) in humans, reducing the time needed for local analgesia from 60 minutes to only 5 minutes.

C. Microneedles
   1. Tiny arrays of microneedles to either directly allow drug diffusion from a drug-impregnated patch (“poke with patch”) or to act as drug carriers through needles surface-coated with drug (“coat and poke”)
   2. Reported to be painless by human subjects.
   3. Has been studied for transdermal delivery of insulin and desmopressin.

D. Iontophoresis and electroporation
   1. Use an electric field to enhance the skin penetration of polar drug molecules
   2. Has been studies for transdermal delivery of:
      a) Peptides such as insulin, calcitonin, vasopressin, PTH, and octreotide
      b) Non-peptide drugs such as opioids, non-steroidal anti-inflammatory agents, and anti-emetics.
      c) Chemotherapeutic drugs
         (1) Local delivery to surface tumor
   3. Compact, battery-operated, and well tolerated by human patients (e.g. Iontopatch™ 80, Sammons Preston Rolyan, Bolingbrook, IL).

E. Needleless jet injectors
   1. Narrow gauge, high stream pressure
   2. Medi-jector, Dermo-jet