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Where Are We With Transdermal Drug Administration?

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INTRODUCTION

Novel techniques for drug delivery have been investigated in human medicine in recent years. Among the new drug delivery systems is the use of transdermal applications. In addition to being user friendly, these therapeutics are safe, efficacious and may improve patient treatment compliance. Pharmacologic considerations including avoiding first pass effect and biotransformation may also be important advantages of transdermal administration. These advantages may easily be applied to the veterinary patient. Although limited studies have been conducted using this route of administration in veterinary patients many agents are currently being used empirically.

MECHANISMS OF ABSORPTION

The skin has been referred to as the largest organ system accounting for a large proportion of the body's total surface area. Due to easy access and the ability to maintain applied formulations for prolonged periods of time, transdermal drug administration has become a dynamic area of investigation.

In order for the veterinary clinician to utilize transdermal therapeutics one must understand the physical structure of the skin and the physicochemical structure of the agents being utilized. The skin provides a barrier to the outside environment while limiting water, electrolyte and other body constituent losses. Additional functions of the skin include thermoregulation, endocrinology, immunology, glandular secretion, mechanical support, and neurosensory reception.

Basically, the skin is composed of three layers consisting of the epidermis, dermis and subdermal tissue. The epidermis in haired skin of the dog and cat is composed of four layers including the stratum corneum, stratum granulosum, stratum spinosum and the stratum basale. The cornified layer of the stratum corneum appears to provide the rate-limiting step to transdermal drug absorption. Once thought to be a fairly inert layer, it is now known that this layer actively opposes absorption from outside and loss from within. Penetration of the skin depends on diffusion therefore the hydration of the skin will affect permeability.

Absorption via the transdermal route primarily occurs by passive diffusion through the stratum corneum. The rate of diffusion is dependent on the permeability coefficient of the drug, the applied concentration of the drug, the surface area of the skin exposed to the drug and the thickness of the epidermis (Fick's law of diffusion).

FACTORS AFFECTING ABSORPTION

There are many factors affecting absorption of therapeutics administered by the transdermal route. In addition to species variations in skin structure, sites of application may impact the absorption of the drug. The effects of hair or shaving the site of application may also alter the absorption from this site. Hair may be a detriment to absorption when using a patch delivery device but presence of hair follicles and sweat glands may facilitate absorption. Removal of the hair by shaving may help adherence of delivery device and shaving may lead to damage of the stratum corneum allowing better absorption. The effects of age, blood supply, body temperature and body composition also must be considered. For example, elevated body temperature or heating pads enhance transdermal absorption, hyperthyroidism leads to increased blood flow to the skin, inflammation enhances transdermal penetration, and absorption across mucous membranes is markedly enhanced relative to skin. Other factors including first pass metabolism by the skin and the ability of the skin to act as a reservoir for transdermal agents may also play an important role in absorption.

The physicochemical characteristics of the transdermal agent will also impact absorption. The ideal compounds are low molecular weight, lipophilic, soluble in oil and water, and have a high partition coefficient and melting point. Other properties including drug stability, use of solvent carriers or vehicles, use of penetration enhancers and use of delivery devices may dramatically affect absorption.

ADVANTAGES/DISADVANTAGES

The advantages of using transdermal drug delivery include bypassing the gastrointestinal tract and hepatic first-pass biotransformation and metabolism, control of absorption and the availability of multiple sites for application. Avoiding the gastrointestinal environment which may significantly affect bioavailability would seem intuitive. The use of transdermal administration may also reduce hospitalization time and be utilized in home care.

The disadvantages of using transdermal drug delivery include localized cutaneous reactions, systemic toxicity and the time required for drug diffusion. In addition, at this point in time, the efficacy of veterinary applications is unknown.

COMPOUNDS AVAILABLE

A current Internet search listed over 100 compounding pharmacies in the United States. The majority of these pharmacies offer compounding for veterinary use. The list of available agents in a transdermal application for dogs and cats includes the following agents; aminophylline, amitriptyline, amoxicillin, aspirin, azithromycin, buprenorphine, buspirone, chloramphenicol, chlorpromazine, cisapride, clindamycin, cyproheptadine, dexamethasone, diclofenac, diltiazem, diphenhydramine, doxycycline, enalapril, enrofloxacin, famotidine, furosemide, hydroxyzine, ibuprofen, itraconazole, ivermectin, ketoprofen, lorazepam, methimazole, metronidazole, phenylbutazone, phenylpropanolamine, prednisolone, prednisone, and ursodiol. Most of these agents have had little or no work done on pharmacokinetics.

TRANSDERMAL VEHICLES

The most common transdermal vehicle is Pluronic lecithin organogel (PLO). Pluronic F127 is a polymeric surfactant which allows the formation of drug micelles in a gel matrix. PLO has been shown *in vivo* and *in vitro* to modulate the release and permeation of drugs applied transdermally. Lecithin is another component of the PLO and is an emulsifying agent that forms a viscous gel with the addition of water. Lecithin may act by increasing the fluidity of the stratum corneum and thus is thought to be a permeation enhancer. Lecithin containing gels have been shown *in vivo* to increase transdermal penetration of many different agents. One known disadvantage of the PLO is its property to separate in cold temperatures, which precludes refrigeration. The Professional Compounding Centers of America estimates the shelf life of methimazole in a PLO to be approximately 15 days.

Another vehicle available is Lipoderm® and can be used for delivery of water soluble and lipophilic molecules. Lipoderm® contains lecithin and is less greasy than PLO and can be refrigerated. Vanpen® is another commercially available vehicle which has been used for delivery of lipophilic drugs. DMSO has been used in several formulations but is not recommended for repeated applications.

METHIMAZOLE EFFICACY STUDY

A recent retrospective study evaluated 13 hyperthyroid cats that were treated with transdermal methimazole (Tapazole®).[4] The cats were diagnosed based on clinical presentation, serum total thyroxine concentrations and or serum free thyroxine concentrations. Ten cats in this study were evaluated approximately 1 month after initiating therapy and 8 cats were evaluated approximately 6 months after initiating therapy. Methimazole was formulated in a pluronic lecithin organogel (PL0) with a concentration of 5.0 mg/0.1 ml and was applied to the pinna of the

ear. The dosage of methimazole used ranged from 2.5 mg/cat to 10.0 mg/cat BID. Clinical signs appeared to improve in all cats and there were statistically significant differences in total thyroxine concentration between pretreatment and posttreatment values. Seven of the 8 cats reevaluated after 6 months of therapy had normal serum thyroxine concentrations. Although this project did not look at the pharmacokinetics of methimazole, this work has recently been completed and published by Dr. Lauren Trepanier at the University of Wisconsin.[8] Unfortunately, these results indicated that methimazole was not well absorbed via the transdermal route.

FUTURE DEVELOPMENTS

Currently studies evaluating the transdermal administration of several agents including amitriptyline, buspirone, lidocaine, diltiazem, ondansetron are in progress or being completed at several institutions around the country.

The future of this area of study seems bright with many therapeutic agents seemingly meeting criteria in human medicine having utility in veterinary practice. The controlled, objective studies must be performed to compliment the anecdotal information that is currently available.

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