Effects of vehicle and region of application on absorption of hydrocortisone through canine skin

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Objective—To determine the effects of various vehicles on the penetration and retention of hydrocortisone applied to canine skin.

Sample Population—20 canine skin samples obtained from the thorax, neck, and groin regions of 5 Greyhounds.

Procedure—Skin was harvested from dogs after euthanasia and stored at –20°C until required. The skin was then defrosted and placed into diffusion cells, which were maintained at approximately 32°C by a water bath. Saturated solutions of hydrocortisone that contained trace amounts of radiolabelled [^{14}C]-hydrocortisone in each vehicle (ie, PBS solution [PBSS] alone, 50% ethanol [EtOH] in PBSS [wt/wt], and 50% propylene glycol in PBSS [wt/wt]) were applied to the outer (stratum corneum) surface of each skin sample, and aliquots of receptor fluid were collected for 24 hours and analyzed for hydrocortisone.

Results—The maximum flux of hydrocortisone was significantly higher for all sites when dissolved in a vehicle containing 50% EtOH, compared with PBSS alone or 50% propylene glycol, with differences more prominent in skin from the neck region. In contrast, higher residues of hydrocortisone were found remaining within the skin when PBSS alone was used as a vehicle, particularly in skin from the thorax and neck.

Conclusions and Clinical Relevance—Penetration of topically applied hydrocortisone is enhanced when EtOH is used in vehicle formulation. Significant regional differences (ie, among the thorax, neck, and groin areas) are also found in the transdermal penetration and skin retention of hydrocortisone. Variability in clinical response to hydrocortisone can be expected in relation to formulation design and site of application. (*Am J Vet Res* 2005;66:43–47)

Pharmacologic agents are applied topically to avoid hepatic first-pass metabolism, optimize local drug concentrations in the underlying tissue, and improve owner compliance with recommended dose rates and intervals.[1] Ideal drug candidates for topical application are generally lipophilic (log P [an index of lipophilicity based on the partition of drug between octanol and water] between 1 and 3) and unionized and have a low molecular weight.[2] Many commercially available drugs formulated for topical administration are contained within a vehicle specifically chosen to enhance transdermal penetration. Following topical application, a drug will first diffuse out of the vehicle and permeate, together with vehicle components, through the major barrier, the stratum corneum,[3,4] to varying extents depending on its physicochemical properties. Therefore, choice of vehicle components in the formulation has the potential to substantially alter the uptake and subsequent clinical effect of topically applied compounds.

Hydrocortisone is frequently used in veterinary medicine to control local inflammation and has suitable physicochemical properties (log P = 1.426; molecular weight = 362.5 d) to penetrate skin. Hydrocortisone is the active ingredient of a number of topically applied pharmaceuticals, which differ in the concentration of drug (0.5% to 1.0%) and type of vehicle (eg, alcohols and **propylene glycol [PG]**) in each product.[5] Many of the commercially available hydrocortisone products for topical application are based on human studies, yet it is acknowledged in the literature that extrapolation of transdermal penetration among species is highly unreliable.[6] Few studies have investigated the effects of vehicle on movement of hydrocortisone through canine skin.

Several factors may account for species differences in transdermal drug penetration, particularly cutaneous blood flow,[7] skin composition and thickness,[8] and the number and type of appendages of the skin (ie, hair follicles and sweat glands)[9,10] at the site of application. Site of application is reported to affect percutaneous absorption of hydrocortisone in humans.[11]

In the study reported here, we investigated the effect of vehicle composition and site of application on the penetration and retention of hydrocortisone in canine skin. An in vitro diffusion model commonly used in human[1,2,6,8,12] and animal[13] transdermal studies was used to exclude alterations in cutaneous blood flow induced by the vasoactive properties of hydrocortisone.[14]

Materials and Methods

Animals—Dog skin was harvested from 5 Greyhounds that were admitted to the University of Queensland Veterinary School for euthanasia. Dogs were euthanatized by an IV injection of sodium pentobarbital,[a] and the hair was removed by clippers. The skin over the thorax (central thorax, approximately midway between costochondral junction and vertebrae), neck (dorsal part, just cranial to shoulder blades), and groin regions was dissected away, with

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care to trim off subcutaneous fat, and frozen at –20°C until required.[13] This protocol was approved by the Animal Ethics Committee of the University of Queensland.

In vitro skin penetration—Skin was defrosted and cut into circular sections (approx 2 cm in diameter) and mounted in Franz-type diffusion cells with the stratum corneum side uppermost. A measured volume (approx 3.5 mL) of **PBS solution** (**PBSS**; pH 7.4) containing 4% bovine serum albumin[b] (bovine-fraction V) as a receptor fluid was added to the lower reservoir with a magnetic bar for stirring. One milliliter of PBSS was added to the donor reservoir, and the skin cell was placed in a water bath containing a magnetic stirring plate and allowed to equilibrate at 35°C for 60 minutes. The temperature of the skin in the diffusion cell was approximately 32°C. The PBSS was removed from the donor reservoir, and 1 mL of donor solution (PBSS alone, 50% **ethanol [EtOH]** in PBSS [wt/wt], or 50% PG in PBSS [wt/wt]) saturated with hydrocortisone[c] and containing a tracer concentration of radiolabelled [^{14}C]-hydrocortisone[d] with a specific activity of 25 µCi/mmol was added (0.5 to 1.0 µCi; time = 0 hour). A 200-µL sample was collected from the receptor fluid via a side port of each diffusion cell and immediately replaced with fresh solution at 2, 4, 8, 16, 20, 22, and 24 hours. The 200-µL sample was placed in scintillation vials with 2.0 mL of scintillation fluid,[e] and the radioactivity in each vial was measured by use of preset channels of a scintillation counter.[f] An aliquot (20 µL) was collected from the donor reservoir of each diffusion cell at time = 24 hours to determine depletion of the radiolabelled drug, compared with the initial donor solution (donor recovery). At the completion of each study, skin samples were removed from the diffusion cell, rinsed in distilled water, placed in preweighed scintillation vials, and accurately weighed. Two milliliters of tissue solubilizer[g] was added before incubation at 60°C for 24 hours. Two milliliters of scintillation fluid was then added to each sample, and radioactivity was assessed as already described here. The reported values represent a mean of 4 replicates for each data point.

Analysis of hydrocortisone—Saturated solutions of hydrocortisone in each donor phase were made by dissolving excess hydrocortisone in the respective donor phases and then roller-mixing the solutions at 30°C for 24 hours. The resulting solutions were centrifuged (300 × *g* for 10 minutes), and the supernatant was then diluted to 4 concentrations (ie, 1:10, 1:100, 1:500, and 1:1,000) with the respective donor phase. The resulting dilutions of hydrocortisone in donor phase were analyzed for hydrocortisone concentration by use of a high-pressure liquid chromatography system consisting of the following: a pumping system,[h] an autoinjector,[i] a UV detector (254 nm),[j] and a chromatography software package.[k] A steel C18 column[l] (5 µm; 150 × 4.6 mm) was used. The mobile phase was 40% acetonitrile in water that was filtered and degassed through a 0.45-µm-diameter filter at a flow rate of 1.0 mL/min. Inter- and intrarun precisions (coefficients of variation) were 3.4% and 2.3%, respectively.

Data analysis—**Permeability coefficients (k_P**; cm/h) relating solute flux to the concentration gradient across the membrane (ie, how fast a drug molecule travels through skin) were calculated from the pseudo–steady-state portion of the receptor compartment concentration versus time profile, according to the following formula[12]:

$$k_P = V_R \left[\frac{dC/dt}{A \times \Delta C} \right],$$

where V_R is the receiver volume, dC/dt is the steady-state rate of change in the receiver concentration (counts/min), *A* is the exposed cross-sectional area of the membrane, and ΔC is the concentration (counts/min) of radioactivity differential between compartments. **Maximum flux (J_{max}**; mol/cm^2/h) was predicted from k_P multiplied by the solubility in the donor phase. In aqueous solutions, J_{max} estimates the total amount of drug penetration possible per unit time from a saturated solution as the product of skin area, k_P, and aqueous solubility.[15] Radiolabelled alcohol

Table 1—Percentage of donor recovery and mean (± SD) permeability coefficients (k_P) and maximum flux (J_{max}) of hydrocortisone applied in vitro to canine skin harvested from 3 sites.

		Sites		
Variables	**Vehicle**	**Thorax**	**Neck**	**Groin**
Donor recovery (%)	PBSS alone	98.9	98.1	103.4
	50% EtOH	109.8	104.4	106.7
	50% PG	96.1	94.2	97.9
k_P (cm/h × 10^{-5})	PBSS alone	2.06 ± 0.85	13.74 ± 0.99	0.66 ± 0.15
	50% EtOH	1.99 ± 0.19	3.81 ± 1.03	0.78 ± 0.04
	50% PG	2.19 ± 0.51	1.89 ± 0.88	1.12 ± 0.33
J_{max} (mol/cm^2/h)	PBSS alone	0.27 ± 0.11	1.78 ± 0.79*	0.09 ± 0.02
	50% EtOH	3.58 ± 0.46†‡	9.15 ± 2.61†‡	1.87 ± 0.10†‡
	50% PG	1.56 ± 0.36	1.34 ± 0.63	0.79 ± 0.23

*Significantly ($P < 0.05$) greater J_{max} for skin from the neck, compared with skin from the thorax or groin, for PBSS alone. †Significantly ($P < 0.05$) different J_{max} among sites (thorax, neck, and groin) for 50% EtOH. ‡Significantly ($P < 0.05$) greater J_{max} at each site (neck, thorax, and groin) for 50% EtOH, compared with PBSS alone or 50% PG.

PBSS = PBS solution. 50% EtOH = 50% ethanol in PBSS (wt/wt). 50% PG = 50% propylene glycol in PBSS (wt/wt).

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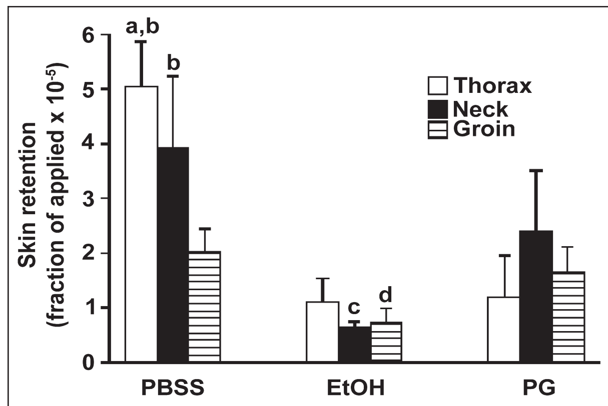

Figure 1—Mean (± SD) skin retention (fraction of applied X 10^{-5}) of hydrocortisone dissolved in PBS solution (PBSS) alone, 50% ethanol (EtOH) in PBSS (wt/wt), or 50% propylene glycol (PG) in PBSS (wt/wt) through canine skin from the thorax, neck, and groin. [a]Significantly (P < 0.05) greater value for PBSS alone, compared with EtOH or PG, for skin from the thorax. [b]Significantly (P < 0.05) greater value for skin from the thorax or neck, compared with skin from the groin, for PBSS alone. [c]Significantly (P < 0.05) lower value for EtOH, compared with PBSS alone or PG, for skin from the neck. [d]Significantly (P < 0.05) lower value for EtOH, compared with PBSS alone or PG, for skin from the groin.

remaining within each skin sample at the completion of the study was divided by the donor recovery fraction to adjust for donor depletion.

Differences in J_{max} and skin retention for each site (mean of 4 replicates/site) from each dog were compared over vehicles and application site via a 1-way ANOVA and the Tukey post hoc test for pairwise comparisons by use of a statistical software program.[m] Values of $P < 0.05$ were considered significant.

Results

The solubility of hydrocortisone in PBSS, 50% EtOH in PBSS (wt/wt), or 50% PG in PBSS (wt/wt) was 1.28, 23.97, and 7.08 mmol/L, respectively. Hydrocortisone recovery in the system approached 100%. Penetration parameters, k_P and J_{max}, from each of the vehicles and through each of the skin sites were determined (**Table 1**). No significant differences in k_P were found among the 3 vehicles when applied to skin from the thorax and groin, although in the neck region k_P had a pattern of PBSS > 50% EtOH > 50% PG.

The J_{max} of hydrocortisone was significantly higher for all sites when applied in the vehicle containing 50% EtOH, compared with PBSS alone or 50% PG (Table 1). This difference was greatest when applied to skin from the neck ($P < 0.001$). In contrast, significantly higher residues of hydrocortisone were found remaining within the skin when PBSS was used as a vehicle (**Figure 1**), particularly in the thorax ($P < 0.001$) and neck ($P = 0.004$).

Discussion

Results of our study reveal a significant difference in transdermal penetration of hydrocortisone among various sites in dogs. Results of previous studies[11,16] also indicate that differences exist in percutaneous absorption of pharmaceutical agents at various sites. For example, Qiao and Riviere[16] reported site differences in the penetration of parathion in the pig, and significant differences are found in hydrocortisone uptake between forearm and vulva in human females.[11] Because variations in skin blood flow can significantly affect drug uptake,[7,16] the efficacy of topically applied hydrocortisone is frequently determined by the blanching (vasoconstriction) effect of the local vasculature.[14,17] In our study, the use of an in vitro diffusion technique eliminated the influence of hydrocortisone on vascular flow and enabled us to study the effects of vehicle and application site on topical penetration and retention in isolation.

An explanation for site differences in the J_{max} of hydrocortisone in dogs may relate to skin appendage density,[9,10,18] stratum corneum thickness,[19] or both. Results of 1 study[20] indicate that skin appendage density may affect transdermal drug penetration, and this may be related to absorption through the ostia of the hair follicle. Hueber et al[10] suggested that loss of skin appendages significantly decreases drug penetration through scar tissue, compared with normal skin, although structural changes in the scar tissue may decrease the validity of this model. The absorption of methylnicotinate correlates with skin appendage density of the human forehead, forearm, and palm,[9] although, again, the effects of cutaneous vascularity cannot be eliminated. In our study, we found that for each vehicle, the J_{max} of hydrocortisone was lowest in the groin, a region of minimal skin appendage density and a relatively thicker stratum corneum.[21]

Differences in skin appendage density are obvious when comparing skin from the groin and neck of a dog. The contribution of skin appendage type and number is less clear between the neck and thorax, although significant differences in J_{max} and residues of hydrocortisone with the various vehicles were measured between the 2 sites. Further research is required before number and type of skin appendages can be related to transdermal hydrocortisone penetration in dogs.

The dependence of transdermal drug transport on the vehicle or carrier medium is well documented in the literature.[4] Optimal penetration of a topically applied drug is achieved by formulating a vehicle-drug combination to maximize the flux.[22] A significantly higher J_{max} was measured in canine skin when hydrocortisone was applied in a 50% EtOH, compared with PBSS alone or 50% PG. In a previous study of 4 commercially available human cortisol creams, it was reported that a 16-fold difference in cortisol delivery can be found across human skin.[23] Similarly, a significant difference was found in the human skin uptake of topically applied ibuprofen in relation to changes in vehicle type (spray vs gel vs cream).[24] An optimized vehicle for topical application of hydrocortisone to dogs has not been reported, and veterinary clinicians are limited to products developed for topical use in humans. We have already stated that extrapolation of transdermal drug penetration among species is unreliable.[6,25] It should also be mentioned that a cream developed for topical application of hydrocortisone usually contains ≤ 1% of the active drug, a factor determined from maximum blanching of cutaneous vessels.[26] The

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ideal concentration of hydrocortisone in topical creams for dogs does not appear to have been investigated.

Vehicle effects on skin penetration kinetics are attributed to either changes in drug partitioning between the vehicle and the skin or changes in the diffusivity of the drug within the skin caused by the presence of vehicle components within the skin.[1] However, the former effect on partitioning into the skin appears to be the dominant effect in most instances for human skin.[27] Generally, only the solubilized drug can diffuse freely within the vehicle and contribute substantially to release rate.[28] Hydrocortisone is more soluble in EtOH, compared with PBSS, increasing the amount of hydrocortisone capable of partitioning between the vehicle and the canine stratum corneum. It is also reported[29] that hydrocortisone-17-butyrate penetrates human skin better from an ethanolic solution, compared with an oil-in-water cream, although that study was not performed with saturated solutions and may reflect thermodynamic activity of the steroid in solution and not be related to an effect of the vehicle. Results of our study indicate that vehicles containing EtOH have the potential to produce a significantly higher J_{max} than those containing PG, which, in turn, appeared superior to PBSS (representing aqueous-based vehicles) in the ability to facilitate hydrocortisone penetration, particularly through the thorax and neck region of dogs. However, the flux of hydrocortisone varies inversely with PG concentration in the applied solution;[30] whether our observed effects are the result of changes in vehicle-skin partitioning, differences in solubility and therefore thermodynamic activity at the hydrocortisone concentration studied, or changes in the diffusion of hydrocortisone within the skin is not known.

The effect of vehicle on drug penetration cannot be considered in terms of drug solubility changes alone because many vehicles act by disrupting the skin surface, with a decreased barrier function as a result.[31] Ethanol is known to irritate skin and dilapidate surface membranes,[2,32] which may contribute to the enhanced penetration of dissolved substances through the skin. Hydration of skin will also disrupt the stratum corneum by corneocyte swelling, and this contributes to the mechanism by which transdermal patches enhance drug penetration.[33] In our study, this may also explain the higher residues of hydrocortisone remaining within the skin following the use of PBSS, compared with EtOH, as the drug and vehicle permeate lipids within the stratum corneum. Similarly, PG diffuses into skin and improves the solubility of skin lipids.[15]

In conclusion, results of our study indicate that regional and vehicle differences exist in transdermal hydrocortisone penetration, with EtOH-containing vehicles appearing superior to vehicles containing PBSS alone or 50% PG, particularly in the neck region. Findings in our study indicate that variability in clinical response to hydrocortisone can be expected with formulation design and site of application.

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a. Lethabarb, Virbac, Peakhurst, NSW, Australia.
b. Bovine serum albumin (fraction V-A7906), Sigma Chemical Co, St Louis, Mo.
c. Hydrocortisone (H4001), Sigma Chemical Co, St Louis, Mo.
d. [^{14}C]-hydrocortisone, American Radiolabeled Chemicals Inc, St Louis, Mo.
e. Emulsifier Safe, Packard Bioscience Corp, Meriden, Conn.
f. TriCarb 2700TR liquid scintillation analyzer, Packard Biosciences Corp, Meriden, Conn.
g. Tissue solubilizer, Packard Bioscience Corp, Meriden, Conn.
h. Shimadzu 10A pumping system, Shimadzu Scientific Instruments, Rydalmere, NSW, Australia.
i. Shimadzu 9A auto-injector, Shimadzu Scientific Instruments, Rydalmere, NSW, Australia.
j. Shimadzu 10AXL UV/VIS detector, Shimadzu Scientific Instruments, Rydalmere, NSW, Australia.
k. Shimadzu VP software, Shimadzu Scientific Instruments, Rydalmere, NSW, Australia.
l. Phenomenex Luna, Waters Australia, Rydalmere, NSW, Australia.
m. Minitab v13, Minitab Inc, State College, Pa.

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