Research Report

# Effects of Iontophoresis Current Magnitude and Duration on Dexamethasone Deposition and Localized Drug Retention

Background and Purpose. Iontophoresis is a process that uses bipolar electric fields to propel molecules across intact skin and into underlying tissue. The purpose of this study was to describe and experimentally examine an iontophoresis drug delivery model. Subjects and Methods. A mechanistic model describing delivery was studied in vitro using agarose gels and was further tested in vivo by evaluation of cutaneous vasoconstriction following iontophoresis in human volunteers. Results. In vitro cathodic iontophoresis at 4 mA and 0.1 mA each delivered dexamethasone/dexamethasone phosphate (DEX/DEX-P) from a 4-mg/mL donor solution to a depth of 12 mm following a 40 mA·minute stimulation dosage. Delivery of DEX/DEX-P to at least the depths of the vasculature in humans was confirmed by observation of cutaneous vasoconstriction. This cutaneous vasoconstriction was longer lasting and greater in magnitude when using low-current, long-duration (~0.1 mA) iontophoresis compared with equivalent dosages delivered by higher-current, shorter-duration (1.5–4.0 mA) iontophoresis. Discussion and Conclusion. From data gathered with the gel model, the authors developed a model of a potential mechanism of drug depot formation following iontophoresis. The authors believe this drug depot formation to be due to exchange of drug ions for chloride ions as the ionic current carriers. Furthermore, diffusion, not magnitude of current, appears to govern the depth of drug penetration. Although the authors did not address the efficacy of the drug delivered, the results of human experiments suggest that current magnitude and duration should be considered as factors in treating musculoskeletal dysfunctions with iontophoresis using DEX/DEX-P at a concentration of 4 mg/mL. [Anderson CR, Morris RL, Boeh SD, et al. Effects of iontophoresis current magnitude and duration on dexamethasone deposition and localized drug retention. *Phys Ther.* 2003;83:161–170.]

**Key Words:** *Cutaneous administration, Dexamethasone phosphate, Iontophoresis, Transdermal drug delivery.*

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Iontophoresis is used as a means of delivering drugs across the skin for the management of a variety of medical conditions, most often, we believe, for localized inflammation and pain.[1–3] There are reports indicating that this mode of drug delivery can be useful, and iontophoresis with dexamethasone phosphate (DEX-P), sodium diclofenac, and acetic acid appears to be effective in treating inflammations in several areas of the body.[4–11] Unfortunately, we believe, the general lack of a strong theoretical foundation for the practice of iontophoresis has hampered its widespread acceptance among all medical professionals. There is, however, literature that we contend can be used to guide the construction and testing of a model that could be useful in understanding the scientific basis for use of iontophoresis. In this article, we address issues affecting the delivery of dexamethasone/dexamethasone phosphate (DEX/DEX-P). Further studies on the efficacy of delivered drugs will be necessary in the future.

After evaluating tissue under the delivery electrode following iontophoresis of dexamethasone (DEX), prednisolone, lidocaine, or salicylic acid, several researchers[12–15] have described a "depot" of drug that is found in the area of the epidermis. This intracutaneous depot represents the highest concentration of the drugs detected. The mechanism of the formation of the depot has not been established. An objective of our study was to determine whether the magnitude of iontophoresis current may influence the proportion and depth of DEX-P delivered. Using an in vitro agarose gel model, depth of penetration following high-current, short-duration (HCSD) delivery (4 mA × 10 minutes) is compared with an equal dosage from low-current, long-duration (LCLD) delivery (0.1 mA × 400 minutes).

The corticosteroid DEX/DEX-P (4 mg/mL) is commonly administered by iontophoresis for the management of local inflammation.[1] Because DEX is uncharged and has a poor solubility in aqueous solutions, the water-soluble DEX-P is generally used in iontophoretic applications. At neutral pH, DEX-P is a negatively charged prodrug that is dephosphorylated into the active form of DEX once it is in the body.[2]

Glass and colleagues[12] found that DEX/DEX-P penetration into tissue of a rhesus monkey following iontophoresis was up to 17 mm and included joint capsules. More recently, however, researchers have been unable to find DEX/DEX-P in equine tibiotarsal joints[16] or in human blood extracted from a vein proximal to the treatment area[17] following iontophoresis. Other objectives of our study were to verify that DEX/DEX-P actually penetrates into human skin at least to the approximate depth of the vasculature underlying the skin and to determine how long the drug is retained locally. In this part of the study, we used a noninvasive vasoconstrictor assay.[18,19] When introduced topically onto the flexor aspect of a forearm, corticosteroids such as DEX/DEX-P induce a cutaneous vasoconstriction that can be seen as a blanching of the skin.[18] This vasoconstriction effect has been used to measure the relative potency of percutaneously absorbed steroids.[19–22] Transdermal penetration of DEX/DEX-P was evaluated qualitatively, through visual observation of blanching, and quantitatively, using infrared temperature measurements as an indirect measure of cutaneous blood flow.[23,24] Equal dosages from HCSD iontophoresis (1.5–4.0 mA) and LCLD iontophoresis (~0.1 mA) were compared.

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Mr Anderson and Dr Sembrowich provided concept/idea/research design. Mr Anderson, Dr Panus, and Dr Sembrowich provided writing. Mr Anderson provided data collection, and Mr Boeh and Dr Sembrowich provided data analysis. Mr Anderson provided project management, and Dr Panus and Dr Sembrowich provided subjects. Dr Morris, Mr Boeh, Dr Panus, and Dr Sembrowich provided consultation (including review of manuscript before submission).

The Institutional Review Board at East Tennessee State University/Veteran's Administration approved the study.

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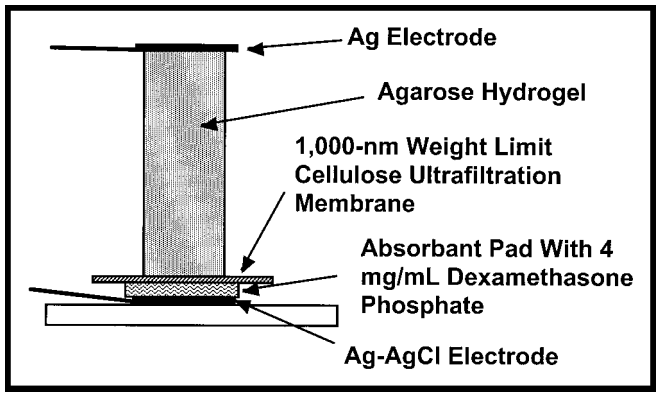


**Figure 1.**
Depth of penetration test apparatus for iontophoretic delivery of dexamethasone/dexamethasone phosphate (DEX/DEX-P).

## Materials and Methods

### *Human Subjects*

Subjects were excluded from the study if they had at any time during the 3 months preceding the study any of the following self-reported conditions: systemic fungal infections; hypersensitivity to sulfites; demand-type cardiac pacemakers; metallic surgical implants in the area of the iontophoretic treatment; skin, liver, kidney, pituitary, pancreatic, or adrenal disorders; any wounds; surgery; fractures; shinsplints or stress fractures; and use of anti-inflammatory medications containing glucocorticoids. These conditions were chosen based on contraindications for DEX/DEX-P described in the 2002 *Physicians' Desk Reference*.[25] Additionally, due to the unknown effects of externally administered weak electromagnetic fields or glucocorticoids, women who were pregnant were excluded from participation in this investigation. The subjects tested were 5 Caucasian men, ranging in age from 34 to 58 years, who reported no impairments or pathologies. All subjects gave written informed consent.

### *In Vitro Depot Formation Studies*

Experiments were performed to quantify the depth of penetration and depot formation of DEX/DEX-P achieved during iontophoresis. The iontophoresis test apparatus is illustrated in Figure 1. Hydrogels were prepared with agarose (SeaKem Gold*) at 1% wt/vol in 1% saline to approximate normal tissue water concentrations of sodium and chloride. The salt-containing hydrogel was formed into a cylinder of 4 cm height and 1.5 cm diameter by heating the solution to near boiling and then allowing it to cool in a mold. A silver-silver chloride electrode† served as the cathode, with the silver wire anode positioned distally against the hydrogel. We have found (unpublished data) that DEX-P is delivered more effectively from the negative electrode if the donor solution is free of competing ions.[26] An absorbent pad saturated with 1.5 mL of 4 mg/mL DEX/DEX-P,‡ pH 7.02, was used as the drug reservoir. To restrict passive drug flow, a cellulose ultrafiltration membrane§ with a nominal molecular weight limit of 1,000 served to separate the donor drug solution reservoir from the hydrogel matrix. Because the molecular weight of DEX/DEX-P is approximately 500, this represents a "restrictive" membrane.

The fixed direct current source was the Iontophor iontophoretic drug delivery instrument (model 6111PM/DX‖). The DEX/DEX-P was iontophoretically administered from the cathode into the hydrogels using the following experimental protocols: (1) iontophoresis of 4 mA for 10 minutes, followed by immediate sampling; (2) iontophoresis of 4 mA for 10 minutes, followed by sampling 400 minutes after iontophoresis, and (3) sampling immediately after iontophoresis of 0.1 mA for 400 minutes. At the conclusion of each iontophoresis application, hydrogels were immediately separated from the donor solution. At the time of sampling, each gel was sliced into equal 2-mm-thick slices cut parallel to the electrode surface and transverse to the hydrogel specimen, and DEX/DEX-P was extracted into 10 mL of distilled water overnight.

Extraction solution aliquots were measured using ultraviolet/visible spectrophotometry# at a wavelength of 243.5 nm, and drug delivery (in milligrams) was determined by comparison of absorbance with reference standards. Net iontophoretic delivery was determined by running a passive system side-by-side, then subtracting the amount of drug delivered passively from the amount of drug delivered as a result of iontophoresis.

### *Human DEX/DEX-P Iontophoresis Experiments*

To ascertain whether DEX/DEX-P could be delivered to local tissue and vasculature and to measure its local retention as a function of time, experiments were conducted on 5 human volunteers. The iontophoretic device used in HCSD testing was a Life-Tec model 6111 PM/DX.‖ The current level was set at the maximum amount tolerable to the volunteer and averaged (average=2.97 mA, SD=0.81, range=1.5–4.0). For LCLD delivery, the IontoPatch,† a wearable self-powered disposable patch that delivers medication at a current of approximately 0.05 to 0.16 mA was used. The IontoPatch is voltage controlled; thus, the actual current levels will

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vary according to skin resistance. Thus, for LCLD iontophoresis, a wear time of 12 hours was used, which is enough time to discharge at least 90% of the 40-mA·min labeled dosage.

The iontophoretic dosage for both the Life-Tec iontophoretic device and the IontoPatch was 40 mA·min, and each device was used in accordance with manufacturer recommendations. The cathodic (negative) delivery electrodes of both devices were loaded with 1.5 mL of 4 mg/mL DEX/DEX-P, and either 1% sodium chloride (IontoPatch) or conductive gel (Life-Tec device) served as the return electrode ion source. Before each treatment, skin sites were cleaned with an isopropyl alcohol (70% by volume) swab, in accordance with electrode manufacturer recommendations. Iontophoresis electrodes were placed on the ventral surface of the forearm. A placebo-controlled, repeated-measures experimental design was used to separate drug effects from current effects. As a placebo, separate iontophoretic applications were repeated on each subject using a buffered saline solution in the cathodic delivery chambers. Each of the 5 volunteers received both HCSD and LCLD iontophoretic administrations of DEX/DEX-P and saline at contralateral locations on the upper extremity. A minimum of 48 hours elapsed between iontophoresis applications.

After completion of the iontophoresis and removal of the electrodes, DEX/DEX-P delivery and its retention in local tissue was monitored by observing evidence of localized cutaneous vasoconstriction under the delivery site. This vasoconstriction was monitored quantitatively by a differential infrared surface temperature measurement. The differential determinations were made by comparing skin surface temperature under the delivery electrode site with that of the immediately adjacent skin. A K-type infrared thermocouple,** calibrated to 37°C, served as the means of measuring surface temperature. The probe is designed to automatically compensate for ambient temperature-related variations associated with emissivity and reflected radiation.

Temperature measurements were made by positioning the probe perpendicular to the skin, using a custom-built fixture to reproducibly position the probe 6 mm from the skin surface and shield it from stray light. Each skin temperature measurement was completed in approximately 1 minute. Temperature measurements were made periodically until thermographic evidence of vasoconstriction had ceased. A minimum of 7 measurements were made in the first 315 minutes following completion of iontophoresis. Cutaneous vasoconstriction was evaluated qualitatively by visual observation of the skin under the delivery site, with researchers looking for skin blanching, or lightening of skin tone,[18,19] within the area of the delivery electrode. If blanching was evident, its time of onset and duration were recorded.

### *Data Analysis*

All data are presented as means and standard deviations. Significance between 2 groups was determined by a paired *t* test. Our main interest was in the comparison of placebo and DEX/DEX-P treatments and in the comparison of LCLD and HCSD treatments. A priori level of significance between 2 groups was established as $P<.05$.

## Results

The quantity of DEX/DEX-P measured as a function of the depth in the agarose gel penetration studies is depicted in Figure 2. These results showed that following a 40-mA·min dosage delivered at 4 mA for 10 minutes, DEX/DEX-P was found nearly exclusively in the top layer of the gel (Fig. 2A). A 10-minute delivery of a 40-mA·min dosage followed by removal of the delivery patch and 400 minutes of passive diffusion resulted in penetration of DEX/DEX-P into the hydrogel to a depth of approximately 12 mm (Fig. 2B). A 40-mA·min iontophoretic dosage of DEX/DEX-P delivered at 0.1 mA for 400 minutes also resulted in penetration of DEX/DEX-P into the hydrogel to a depth of approximately 12 mm (Fig. 2C). Total drug delivery was higher and more variable with the 0.1-mA delivery method. This variability in DEX/DEX-P delivery may be due to the increased contact period between the electrode reservoir and the hydrogel matrix.

The results from our use of in vitro investigation techniques were followed by confirmation of cathodic iontophoresis of DEX/DEX-P in humans. Figure 3 illustrates differential temperature measurements of cutaneous vasoconstriction as a function of time following HCSD iontophoresis. After HCSD placebo iontophoresis, relative skin temperature was elevated, and slowly cooled to normal over the course of approximately 3 hours. After HCSD iontophoresis of DEX/DEX-P, relative skin temperature was initially elevated, rapidly dropped to normal temperatures over the next 2 hours, then became relatively cooler than adjacent skin from approximately hours 2 to 5 after iontophoresis. Figure 4 illustrates differential temperature measurements of the cutaneous vasoconstriction as a function of time following iontophoresis at the lower rates of current flow. After LCLD iontophoresis of DEX/DEX-P, skin temperature was cooler than adjacent skin and warmed to normal skin temperature over the next 5 hours. After iontophoresis of placebo at low currents, skin temperature did not deviate from that of adjacent skin.

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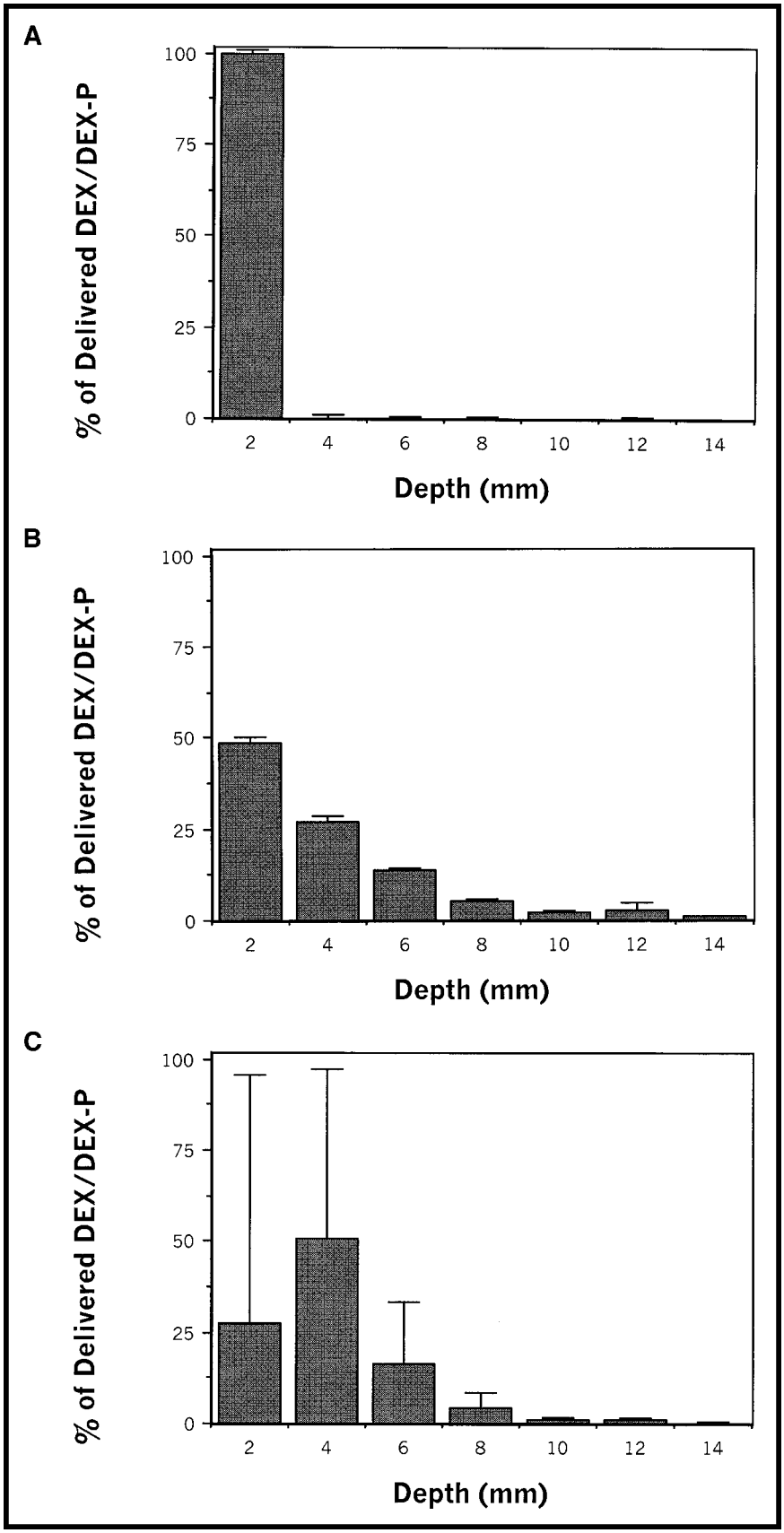


**Figure 2.**
Permeation of 4-mg/mL dexamethasone/dexamethasone phosphate (DEX/DEX-P) into agarose gel. The graphs represent the experimental conditions and time points under which DEX/DEX-P was measured: (1) immediately after iontophoresis at 4.0 mA for 10 minutes (panel A), (2) 400 minutes after iontophoresis at 4.0 mA for 10 minutes (panel B), and (3) immediately after iontophoresis at 0.1 mA for 400 minutes (panel C). Total and passive drug delivery measured for 4.0-mA iontophoresis were 0.42±0.05 mg and 0.04±0.03 mg, respectively. Total and passive drug delivery measured for 0.1-mA iontophoresis were 0.75±0.40 mg and 0.51±0.35 mg, respectively (n=3).

The maximum degree of cutaneous vasoconstriction, as measured by averaging the lowest differential temperatures found after application of a 40-mA·min DEX/DEX-P dose, was approximately −1.86°C (SD=0.47°C, range=−2.44°C to −1.27°C) after LCLD iontophoresis and −0.35°C (SD=0.23°C, range=−0.56°C to −0.22°C) after HCSD iontophoresis (Fig. 5A). These results suggest that the LCLD delivery rate causes greater cutaneous vasoconstriction when compared with an equal dosage applied at the HCSD delivery rate ($P$=.003).

Results based on observation correlated with the quantitative findings. Immediately after completion of HCSD iontophoresis, whether using DEX/DEX-P or placebo, the erythemous skin under the delivery electrode was red rather than blanched. With iontophoresis of DEX/DEX-P at the higher currents, a blanched skin appearance became evident between 165 and 195 minutes following iontophoresis and lasted an average of 415 minutes (SD=187, range=210–708). This cutaneous vasoconstriction was not evident in any subject following placebo iontophoresis. The skin under the delivery electrode site was blanched in all cases immediately following LCLD iontophoresis with DEX/DEX-P. The blanched appearance lasted for an average of 984 minutes (SD=508, range=380–1,500). No blanching at the application site was noted following placebo iontophoresis. Figure 5B illustrates the comparative duration of cutaneous vasoconstriction following LCLD and HCSD ionto-

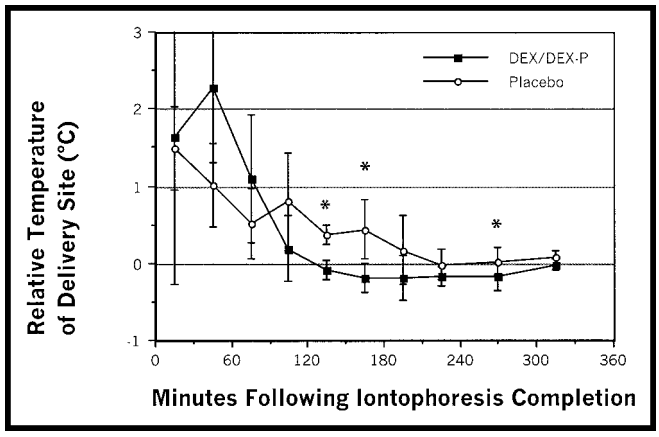


**Figure 3.**
Cutaneous temperature in humans following iontophoresis of 4-mg/mL dexamethasone/dexamethasone phosphate (DEX/DEX-P) and placebo at higher currents. Iontophoresis was as follows: 1.5 to 4.0 mA for a 40-mA·min dose, with current level set to the highest level tolerable to the volunteer. Cutaneous temperature under the delivery electrode was measured by thermography and was reported as the difference compared with the cutaneous temperature of adjacent untreated skin. Significance (denoted by asterisk) was determined by a paired *t* test at each time point, comparing DEX/DEX-P iontophoresis with placebo iontophoresis (N=5 per group).

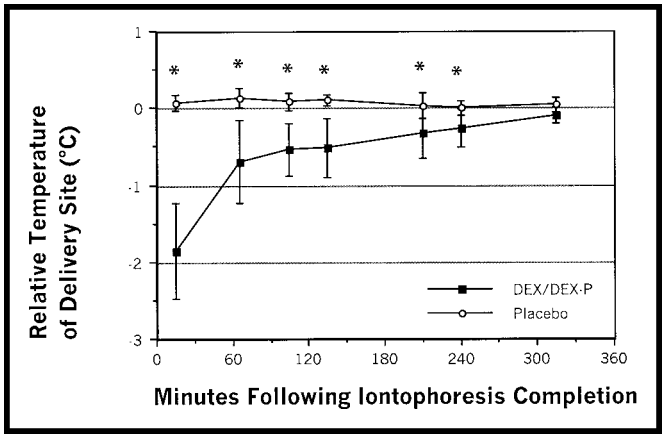


**Figure 4.**
Cutaneous temperature in humans following iontophoresis of 4-mg/mL dexamethasone/dexamethasone phosphate (DEX/DEX-P) and placebo at lower currents. Iontophoresis was as follows: ~0.1 mA for a 40-mA·min dose. Cutaneous temperature under the delivery electrode was measured by thermography and was reported as the difference compared with the cutaneous temperature of adjacent untreated skin. Significance (denoted by asterisk) was determined by a paired *t* test at each time point, comparing DEX/DEX-P iontophoresis with placebo iontophoresis (N=5 per group).

phoresis with DEX/DEX-P as determined by observation. Duration of the skin blanching was approximately two-fold greater following LCLD application than it was with an equivalent HCSD dosage.

## Discussion

Studies designed to evaluate the depth of penetration of the drugs (DEX, prednisolone, salicylate, and lidocaine) into local tissue following iontophoresis have demonstrated that a depot is formed in the area of the epidermis.[12–15] This depot formation appears in contradiction to the general impression that the current flow induced by iontophoresis extends by field lines unabated into tissue well below the epidermis and ultimately to the counter electrode. One objective of our investigation was to construct and study a mechanistic model to determine how drug depot formation may occur during iontophoresis. We hypothesized that once any drug is delivered into tissue, it contacts an environment with a proportionately higher concentration of smaller ions of like charge (ie, competing ions). In the case of DEX/DEX-P iontophoresis, the drug will be introduced into the tissue water, which contains many more, and much smaller, chloride ions. Therefore, we expected that current flow into deep tissue would be dominated by movement of the smaller competing ion.

Based on the results of our research using in vitro agarose gels, we found support for the delivery model that we studied. The active transport process of iontophoresis with DEX/DEX-P does not appear to deliver drug ions deeper than 2 mm in the gels, despite current flow that extended through the entire 40-mm length of the gels. By the second millimeter, the DEX/DEX-P appeared to be immediately overwhelmed by the dilution effects of competing chloride ions. The data suggest that the drug is essentially "dropped off" as soon as it encounters the aqueous saline environment. Deeper penetration of the drug apparently occurs not from iontophoretic current, but from passive diffusion. Passive diffusion is a slower, mass transfer process compared with iontophoresis. Thus, for equivalent iontophoretic dosages, it is time, not current magnitude, that dictates the ultimate local depth of penetration. In living tissue, however, other factors such as local blood flow will determine the ultimate depth of local penetration.

The results of our study also are supported by other published investigations. James et al[13] measured prednisolone levels following iontophoresis across palmar, abdominal, or arm skin of human subjects. Prednisolone was found in the epidermis for up to 4 days following application and was released to the blood for 15 days following application. With other pharmacologic agents such as ketoprofen,[27,28] fentanyl,[29,30] and lidocaine,[14] there is also a depot effect in the skin. Published studies document the formation of an intracutaneous reservoir or depot for a variety of pharmacologic agents following iontophoresis.[13,14,27–30]

The cutaneous vasoconstriction (blanching) and measurable reduction in surface skin temperature that we found suggest that iontophoresis successfully transports DEX/DEX-P across the epidermis in humans, using

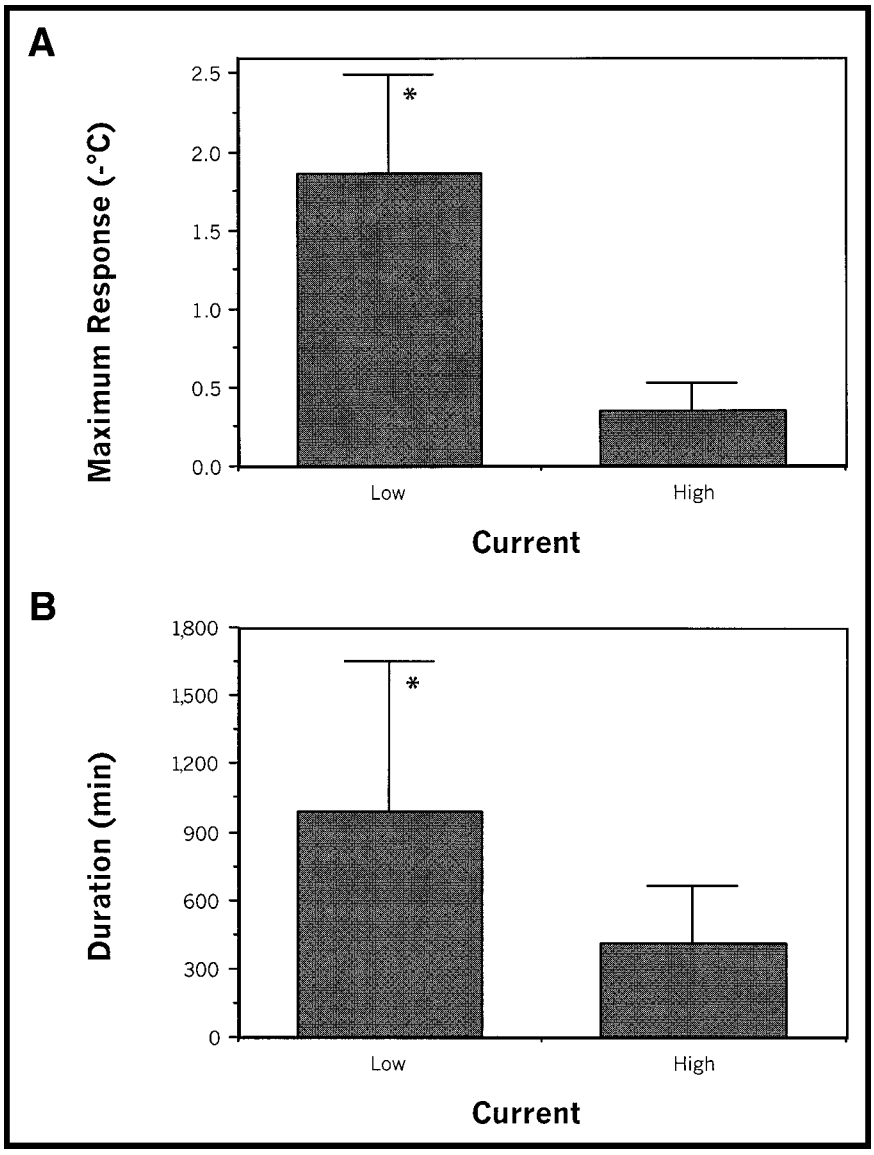


**Figure 5.**
Comparison of magnitude (panel A), and duration (panel B) of apparent vasoconstriction following equivalent dexamethasone/dexamethasone phosphate (DEX/DEX-P) dosages applied using low-current, long-duration (LCLD) and high-current, short-duration (HCSD) iontophoresis. Significance (denoted by asterisk) was determined by a paired *t* test, comparing HCSD iontophoresis of DEX/DEX-P with LCLD iontophoresis of DEX/DEX-P (N=5 per group).

both LCLD and HCSD administration. In a previous report,[20] a general relationship between a vasoconstrictive blanching effect and cutaneous anti-inflammatory action was shown. The presence of DEX/DEX-P–induced vasoconstriction, however, does not in itself guarantee any clinical benefits of subcutaneous applications. The iontophoresis of DEX/DEX-P at high current, 1.5 to 4.0 mA for a 40-mA·min dosage, resulted in erythema lasting for approximately 2 hours following application. Galvanic current-induced cutaneous erythema is well documented,[26,30,31] and this erythemic effect can be seen even after HCSD iontophoresis with the systemic vasoconstrictor NG-monomethyl-L-arginine acetate.[31] In contrast, iontophoresis at low current, ~0.1 mA for a 40-mA·min dosage, demonstrates cutaneous vasoconstriction immediately following completion of the iontophoresis, without the vasodilation phase. These results are consistent with our in vitro results and the data from the theoretical model, in that time, not magnitude of current flow, dictates the physiologic effect of glucocorticoids on this local vasculature. For equivalent doses, low current appears more efficient than high current in the creation of a localized physiologic effect, based on the magnitude and duration of cutaneous vasoconstriction. A possible explanation for this effect is that a greater degree of erythema induced by the HCSD iontophoresis reduces the local drug concentration via loss to the systemic vasculature during the vasodilation phase prior to the vasoconstriction phase. Further studies of DEX/DEX-P delivered under these conditions also are warranted.

Our findings may provide insight into the results obtained in previous studies of DEX/DEX-P iontophoresis. Glass and colleagues[12] reported that DEX/DEX-P could reach deep tissues and joint capsules after iontophoresis, based on their findings using anodal iontophoresis of DEX-P at 5 mA for 20 minutes (current density=0.94 mA/cm$^2$) on a rhesus monkey. Consistent with the depot concept, the highest concentrations of the drug were found in the skin. Although Glass et al[12] demonstrated the ability of iontophoresis to deliver DEX/DEX-P locally to depths and in concentrations that may have some benefit, they studied only one animal and they did not use clinically relevant iontophoresis. Recently, Smutok et al[17] reported that they were unable to find DEX/DEX-P in the effluent venous blood of human volunteers who underwent cathodic iontophoresis of DEX/DEX-P at 4 mA for 10 or 20 minutes. Blood samples were taken prior to, during, and at 5 time points up to 120 minutes after iontophoresis. The results of our investigation may provide a potential explanation for the negative results observed by Smutok et al. First, following 1.5- to 4.0-mA cathodic iontophoresis, a cutaneous erythema devel-

oped and persisted for approximately 2 hours before vasoconstriction was observed. These results suggest that during the 2 hours immediately following HCSD iontophoresis, the absorption of DEX/DEX-P by the vasculature in the tissue during erythema was sufficient to dilute the effluent blood concentrations of DEX/DEX-P below the level of detection for the high-performance liquid chromatography protocol.

The lack of detectable DEX/DEX-P concentrations in the equine tibiotarsal joint, when compared with the detection of 21 $\mu$g/mL in the monkey elbow joint, also may be related to different settings used during iontophoresis.[12,16] The current density used by Glass et al[12] was 0.94 mA/cm$^2$, whereas the current density in the equine investigation[16] was 0.11 mA/cm$^2$. The current density of 0.94 mA/cm$^2$ used by Glass et al[12] exceeds the normal maximum clinical value of 0.50 mA/cm$^2$, as reported by Banga and Panus[1] and Riviere et al,[32] and may cause local tissue damage, decreasing blood flow. A lack of local blood flow may artifactually increase both the drug concentrations in local tissue and the depth of drug penetration at the iontophoretic application site.

An important area of investigation has been the mechanisms that influence the subcutaneous penetration of drug ions such as salicylate and lidocaine from the intracutaneous depot during and following iontophoresis. As the drug diffuses away from the depot and into deeper tissues, it encounters the vascular capillary beds that can move the drug away from the immediate application area. The importance of this vascular clearance has been documented by Singh and Roberts[33] using animals. Iontophoresis of salicylic acid and lidocaine across intact skin and into the tissues was compared with passive delivery into the tissues after removal of the epidermis. Under both conditions, the penetration of salicylic acid and lidocaine were the same. Thus, once a drug transits the epidermis, the forces that distribute it away from the depot are the same. Drugs studied were found in concentrations above those seen in the plasma to a depth of about 4 mm. Drugs also were found as deep as 12 mm but in concentrations below those of the plasma, suggesting delivery to these deeper tissues is the result of circulation.

The effects of local cutaneous vasoconstriction and vasodilation on penetration of iontophoretically and passively delivered drugs into tissue also have been examined. Compared with vasodilation, concentrations of transcutaneously delivered drugs in tissue are greater in the presence of local vasoconstriction.[14,33] Additionally, during local cutaneous vasoconstriction, the penetration of drugs into tissue approached 8 mm. This depth of penetration has the potential to reach subcutaneous muscular and tendinous sites, depending on the anatomic location. When these forms of transcutaneous drug delivery were used in freshly euthanized animals, drug concentrations were even higher at any given tissue depth when compared with those of live animals. These experiments suggest that the cutaneous vasculature is the main modulator of diffusion of drugs into tissue during and following trancutaneous delivery. We believe that our observations of sustained local tissue vasoconstriction following LCLD suggest that the kinetics of DEX/DEX-P in tissue are similar to the characterizations of other drugs in the literature. Verification of these effects across a wider spectrum of drugs is needed.

### *Proposed Model of Iontophoretic Delivery and Depot Formation*

Based on our results and the literature, we propose a general model to explain the mechanism of cutaneous and subcutaneous tissue penetration by drug ions as a result of the iontophoresis of drugs across the skin. The first step involves current flow. Voltage applied to the skin under the proper conditions with a donor electrode filled with ionized drug and a return electrode will cause an ionic current to flow, with the current being carried, in part, by the drug ions. The drug apparently will be transported into the stratum corneum by the current.

The second step involves penetration. The drug penetrates the stratum corneum at a rate proportional to the magnitude of the current. The third step involves depot formation within the epidermis, at the avascular basal epithelial cell layers where drug ions will encounter an aqueous environment dominated by sodium and chloride ions. In the aqueous environment, the drug molecules face competition from the more numerous and more mobile like-charged ions. In the case of DEX/DEX-P iontophoresis, the negatively charged ion, chloride, would be the competing ion. The current is carried by chloride ions leaving the drug molecules behind. Due to this effect, we believe, a reservoir or depot of drug begins to accumulate in the avascular epidermal layer just under the donor electrode. An assumption is that the drug delivery rate exceeds the systemic vascular absorption rate.

The final step is deeper tissue penetration. Drug absorption from the depot and into the surrounding tissues occurs by diffusion. As the drug diffuses into the dermis, it encounters the capillaries of the microcirculation. Drug molecules are distributed from the local tissues under the donor electrode by the blood, decreasing the gradient for deeper penetration. Some drug is returned to the deeper tissues by the circulation, but in relatively low concentrations. The status of the cutaneous microvasculature bed (ie, vasoconstriction or vasodilation) will have the greatest effect on drug penetration into local tissue. Generally, drug penetration will be deeper when

the local cutaneous capillary beds are vasoconstricted, and penetration will be less when the local cutaneous capillary beds are vasodilated. Other factors also appear to operate in the tissues to modulate clearance.[34] They include metabolism of the drug by the tissues and protein binding, each of which would reduce the free drug concentration gradient to the deeper tissue below the donor site.

## Conclusion

Iontophoresis, theoretically, may facilitate the penetration of drugs such as DEX/DEX-P up to 8 to 10 mm into local tissues at pharmacologic concentrations. Thus, any conditions managed with DEX/DEX-P for control of inflammation should be within these known depth limits. In addition, because DEX/DEX-P is a cutaneous vasoconstrictor, this may promote deeper penetration than other vasoneutral or vasodilatory drugs. Finally, we have provided evidence to suggest that comparable iontophoretic doses delivered at low currents over several hours are more effective than those delivered by higher currents over 10 to 30 minutes in the creation of a localized physiologic effect for DEX/DEX-P, based on the magnitude and duration of local cutaneous vasoconstriction. Additional investigations will be needed to determine whether iontophoresis delivers therapeutic concentrations of DEX/DEX-P into the local subcutaneous tissue for effective local anti-inflammatory action.

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