Effect of Transdermal Iontophoresis Codelivery of Hydrocortisone on Metoclopramide Pharmacokinetics and Skin-Induced Reactions in Human Subjects

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Abstract □ The effects of transdermal iontophoresis (IP) codelivery of hydrocortisone (HC) on metoclopramide hydrochloride (MCP) pharmacokinetics and on skin-induced reactions were evaluated in a randomized, crossover clinical study. MCP, an antiemetic, low molecular weight, cationic drug intended for systemic delivery, was delivered from the anode of IP systems at a constant current of 100 μA/cm^2. HC, a neutral endogenous antiinflammatory agent, was codelivered from the same electrode, primarily by electroosmotic processes. Each subject ($n = 7$) wore two identical IP systems (MCP alone or MCP plus HC), each supplying 500 μA, one on each upper arm for 4 h. One week later, each subject repeated the procedure with the alternate type of MCP system. HC did not change the pharmacokinetics of MCP: There were no statistically significant differences in MCP plasma concentrations, half-life, area under the curve (AUC), or rate of absorption between the two treatment groups. However, HC significantly decreased erythema and edema scores produced by the IP of MCP. In both groups, a steady-state MCP flux of about 100 μg/(cm^2 × h) was achieved after only 1 h of transport, and input rate dropped dramatically immediately after removal of the system. In vitro, HC flux through human epidermis from an MCP plus HC formulation was 2.8 ± 1.1 μg/(cm^2 × h) after 4 h transport at 100 μA/cm^2, suggesting negligible systemic exposure to hydrocortisone. These data indicate that MCP input rate and its clearance from the skin are unaltered by HC and that the codelivery of HC by IP is an effective strategy for inhibition of local reactions resulting from the transdermal delivery of drugs.

Introduction

Transdermal drug delivery was introduced as a means to deliver drugs intended for systemic therapy more than 20 years ago. Typically, transdermal systems deliver a drug in a zero-order fashion over several days.[1] This mode of delivery is particularly desirable for drugs with a low therapeutic index.[2] For these agents, zero-order delivery may result in reduction of systemic side effects. Unfortunately, local delivery results in high drug concentrations in the delivery site that can result in irritation and sensitization to the drug being delivered.[3] Several clinically available transdermal systems have been reported to produce local irritation or sensitization.[4−6] In addition, reports indicate that many potential candidates for transdermal delivery may be too irritating or sensitizing for development.[7,8] Various strategies have been developed to minimize these local side effects.[9−14] One of the most promising strategies consists of pretreating the skin with a glucocorticoid (GC) or codelivering it with the drug.[15] This pretreatment strategy has been applied to several transdermal systems already on the market.[4,16] To date, there are no commercialized combination products. One of the potential problems associated with the use of the topical delivery of GCs results from their local vasoconstrictive effect.[17] This pharmacological effect is directly dependent on the potency and the flux of the GC[18] and may possibly affect the pharmacokinetics of the drug being delivered.

Surprisingly, there are only a few reports of the effect of GCs on the pharmacokinetics of a drug being delivered transcutaneously. Ito and O′Connor reported that pretreatment with a 0.5% HC cream did not affect the pharmacokinetics of clonidine delivered from Catapres-TTS applied to the same skin site.[16] Unfortunately, this study did not address HC delivery through the skin—in particular if HC was codelivered efficiently during the 7-day patch application. Finally, the effectiveness of HC in reducing the clonidine-induced skin reaction could not be accurately evaluated because the subjects were not previously sensitized to clonidine.

IP offers a means to deliver drugs through the skin with a minimum lag time and an optimal control of drug flux.[19] IP delivery of MCP, an antiemetic drug intended for systemic delivery, was previously found to result in moderate skin irritation at the site of delivery (unpublished data). We decided to use the IP technology to demonstrate that hydrocortisone can be used in transdermal delivery to minimize skin reactions caused by the transdermal delivery of drugs without significant alteration of drug flux and drug clearance from the skin.

Materials and Methods

In Vitro Studies—For in vitro studies, human skin from cadavers was used. The epidermis was separated from the dermis after incubating the skin for about 1 min in water heated to 60 °C. The separated epidermis was mounted in custom-made IP cells (two compartment cells) with the stratum corneum facing the donor compartment. IP cells were assembled with a silver foil anode in the drug donor compartment and a silver/silver chloride cathode in the receptor compartment. The donors were filled with 2 mL of saturated HC (USP clinical grade, Diosynth, Chicago, IL) aqueous solution in Dulbecco's phosphate-buffered saline or 10% (w/w) MCP (USP clinical grade, Lee Lab, Arlington, VA) aqueous solution saturated with HC. The receptors were filled with 1.8 mL of Dulbecco's phosphate-buffered saline. The permeation cells were thermostated at 32 °C. Experiments were run without current or under constant current set at 0.1 mA/cm^2 for 18 h with samples taken every 4 h. Both HC and MCP were assayed by high-performance liquid chromatographic (HPLC) methods.[20,21]

Clinical Study—Electrically assisted delivery of MCP was accomplished with custom-built IP systems. The IP systems had

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a silver anode (donor) and an anodic reservoir gel containing a 10% (w/w) aqueous solution of MCP with or without a 0.5% (w/w) saturated aqueous solution of HC and 3% (w/w) hydroxy ethyl cellulose (HEC, Aqualon, Wilmington, DE) to form a gel. The IP systems also had a silver chloride cathode (counter electrode) and a cathodic reservoir containing a buffered saline gel. The reservoir gels (i.e., both the anodic and cathodic gels) each had a volume of approximately 600 μL and a skin-contacting surface area of about 5 cm^2. The electrodes were connected to a DC power source that supplied a constant level of electric current of 500 μA or 100 μA/cm^2. The study was undertaken in volunteers after approval by the Medical Review Board at ALZA, which, at the time the study was performed, met FDA criteria, and in accordance with the principles of the Declaration of Helsinki. Each study volunteer met all of the following inclusion criteria: male, 18−50 years old; medical history, physical examination demonstrating no clinically relevant abnormalities, SMA 17 blood profile tests (glucose, blood-urea-nitrogen, uric acid, calcium, phosphorus, total protein, albumin, cholesterol, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, sodium, potassium, creatinine, bicarbonate, and chloride), complete blood count, urinalysis, and electrocardiogram; normotensive. Exclusion criteria included dermatological disorders, application sites presenting scar tissue or moles, known hypersensitivity to any component of the IP system, use of antiinflammatory drugs such as steroids, nonsteroidal antiinflammatory drugs, and abnormal clinical laboratory tests. Informed, written consent was obtained from each subject. The IP systems were applied to and removed from the upper arms of subjects by the study investigators. The application site was wiped with 70% isopropyl alcohol pads prior to system application. Each week, each subject wore two identical IP systems simultaneously, one per arm, for 4 h. On the first week, four subjects wore two systems containing MCP and four subjects wore two systems containing MCP plus HC. One week later, each subject repeated the procedure with the alternate type of MCP system. Seven subjects completed this study.

Voltage and current were measured at 0.5, 1, 2, 3, and 4 h after system application. To perform voltage measurements at each individual electrode, an adjacent skin site was lightly abraded using electrocardiogram-grade abrasive tape (One-Step Skin Prep, 3M Canada Inc, London, Ontario). An electrocardiogram electrode (TenderTrace, NDM, Dayton, OH) was immediately applied to this skin site. Voltage was measured between this reference electrode and the anode or cathode of the IP system at each time point. Electrode resistance was extrapolated from current and voltage measurements. Blood samples (10 mL) were drawn at hours 0, 0.5, 1, 2, 3, 4, 4.5, 5, 6, 8, and 20 (systems were removed at hour 4). Blood samples were centrifuged immediately after collection. The plasma was divided into duplicate aliquots and frozen at −20 °C until analysis. MCP analysis was performed by Harris Labs (Lincoln, NE) with a validated HPLC method.[21] The MCP assay quantification limit was 3.0 ng/mL.

Individual plasma concentrations were used for all pharmacokinetic calculations and were summarized by nominal sampling times. Plasma MCP concentrations below the assay quantification limit of 3.0 ng/mL were assigned a value of 0. The maximum observed plasma MCP concentration (C_{max}) and corresponding sampling time (T_{max}), expressed in hours following initial dosing, were determined for each treatment. The plasma MCP apparent elimination rate constant (k) was estimated by linear regression of the log-transformed (natural log) plasma MCP concentrations during the log-linear phase of the data after system removal. Apparent half-life values were calculated as 0.693 divided by k. MCP area under the plasma concentration versus time values (AUC) were determined by the linear trapezoidal method from study hours 0 to 20, and from hour 0 to the last detectable concentration at time t, AUC_t. The AUC value extrapolated to infinity, AUC_{inf}, was determined as the sum of AUC_t plus the area extrapolated to infinity, as calculated by the concentration at time t (C_t) divided by k. The average MCP concentration, C_{avg}, was calculated as $AUC_{(0-20)}$ divided by 20 h. The cumulative amount of metoclopramide absorbed and the rate of MCP absorption was calculated according to the Wagner and Nelson method.[22]

Visual skin inspection following system removal was done to evaluate the presence and extent of erythema, edema, papules, and pustules. Edema, extent of erythema, papules, and pustules were scored using a 0−2 visual scale and rated as follows: 0 = none, 1 = <50% of occluded area, 2 = >50% of occluded area. Scores for erythema: 0 = none, 1 = barely perceptible redness, 2 = definite redness, 3 = beet redness. Subjects were also asked to report any itching. Visual skin site evaluations were conducted by a trained nurse under the supervision of a medical doctor at 0 (within 10 min after system removal), 1, 4, 24, and 48 h following system removal and were continued until skin sites were clear. Skin sites were also evaluated by skin color reflectance using a Chroma meter CR 210 (Minolta, Ramsey, NJ) at 1, 4, 24, and 48 h following system removal.[23] Reflectance measurements were made by taking the mean a^* value of three readings at adjacent untreated sites and subtracting that value from the mean of three readings taken at the treated site.

Table 1—In Vitro Transdermal Flux of HC and MCP 4 Hours after Initiation of Transport. Transdermal Flux Was Evaluated at 32 °C. HC solubility was determined at 25 °C

formulation	current (μA/cm^2)	HC solubility (mg/mL)	flux (μg/(cm^2 h)	
			HC	MCP
HC	0	0.26	0.02 ± 0.00	NA
HC	100	0.26	0.32 ± 0.11	NA
HC + MCP	100	4.0	2.84 ± 1.12	131 ± 27

Table 2—Subject Demographics of the Seven Caucasian Healthy Men Completing the Study

	mean	SEM	range
age (years)	32.3	1.9	25–39
height (cm)	183	3.0	173–198
weight (kg)	76.6	3.7	68–91

Statistical Analysis—All results are presented as the mean with its associated standard error of the mean (SEM). Statistical analysis was performed using the Student's t test. A probability value of $p < 0.05$ was considered statistically significant.

Results

In Vitro Studies—HC flux through human epidermis was found to be 2.8 ± 1.1 μg/(cm^2×h) after 4 h transport at 0.1 mA/cm^2 from a 10% MCP solution saturated with HC. The flux of MCP from the same formulation was 131 ± 27 μg/(cm^2 × h) (Table 1). HC flux from this formulation was almost 1 order of magnitude greater than that from the formulation containing no MCP. A 0.1 mA/cm^2 current increased the passive flux of HC by more than 1 order of magnitude. Under IP conditions, steady-state flux was achieved for both drugs at or before the 4-h time point (data not shown). Solubility of hydrocortisone at 25 °C was increased from 0.26 mg/mL in the solution without MCP to 4 mg/mL in the presence of 10% MCP.

Demographics—Laboratory exams conducted before the study showed that all subjects were healthy. Eight Caucasian men entered the study and seven completed it. One subject dropped out due to an unrelated illness. Subject demographics are summarized in Table 2.

System Functionality—All IP systems reached the desired current setting within 30 min after application. With MCP alone, average current at this time was 470 ± 6 μA, and was not significantly different from 484 ± 3 μA for MCP plus HC. Current remained constant for the remaining application time. At 4 h, current was 478 ± 3 μA for MCP versus 486 ± 5 μA for MCP plus HC. Anode resistance values at the MCP anode 30 min and 4 h after application were 24 ± 3 kΩ × cm^2 and 18 ± 2 kΩ × cm^2, respectively. In the presence of HC, anode resistance values were 21 ± 2 and 14 ± 1 kΩ × cm^2 at the same time points. At 4 h, cathode resistance was 2.0 ± 0.4 kΩ × cm^2 for MCP versus 3.1 ± 1.3 kΩ × cm^2 for MCP plus HC. Resistance

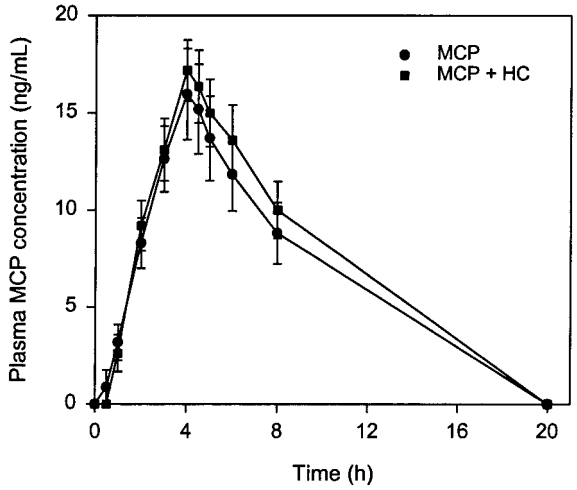

Figure 1—Mean plasma MCP concentrations in subjects receiving IP of MCP or IP of MCP plus HC. Systems were removed at the 4-h time point.

Table 3—Pharmacokinetics Parameters of MCP Delivered by IP from an MCP System or an MCP Plus HC System

	MCP		MCP + HC	
parameter	mean	SEM	mean	SEM
C_{max} (ng/mL)	16.1	2.3	17.3	1.6
T_{max} (h)	4.07	0.07	4.14	0.09
$t_{1/2}$ (h)	4.76	0.38	4.86	0.49
elimination rate constant	0.153	0.015	0.151	0.013
AUC_t (ng × h/mL)	80.1	12.4	86.9	10.6
AUC_{inf} (ng × h/mL)	143	25	163	29
C_{avg} (ng/mL)	4.01	0.62	4.35	0.53

values were not significantly different when MCP alone was compared with MCP with HC.

Plasma MCP Pharmacokinetics—Measurable MCP plasma concentrations were detected in most subjects 1 h after system application. The mean plasma MCP concentrations, with and without HC, are displayed in Figure 1. C_{max} averaged 16 ng/mL for MCP alone, and was not significantly different from the 17 ng/mL C_{max} value for MCP plus HC. T_{max} coincided with the time of system removal in both groups (Table 3). Mean plasma concentrations of MCP, with or without HC, started to drop 0.5 h after system removal (Figure 1). Sixteen hours after system removal, mean plasma drug concentrations were all below the limits of detection. The mean half-life and AUC values of MCP, with and without HC, were equivalent (Table 3). The mean rate of MCP absorption (Figure 2) was not significantly different for the two groups. Steady-state input for MCP of about 100 μg/(cm^2 × h) was achieved by 1 h. Half an hour after removal of the systems, the input rate had dropped by about a factor of 4 to less than 25 μg/(cm^2 × h). The cumulative amount of MCP absorbed per subject is shown in Figure 3. After 4 h IP, about 4 mg MCP had been absorbed, irrespective of the treatment (3.8 ± 0.6 mg for MCP alone versus 4.1 ± 0.7 mg for MCP plus HC). Little absorption was observed following removal of the IP systems.

Topical Effects—all subjects presented some erythema at the anode following system removal. The erythema was homogeneously distributed and limited to the skin-contacting area of the gel (1 h after removal of the system, erythema extent at the anode was 2.0 ± 0.0 versus 1.9 ± 0.1 for MCP and MCP with HC, respectively). Erythema had resolved in all subjects by 72 h. HC significantly decreased erythema scores as assessed visually at all time points except 1 h (Figure 4). Similar results were obtained

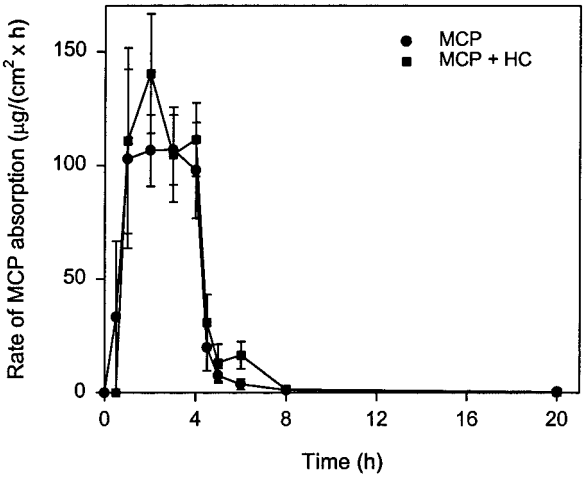

Figure 2—Mean rate of MCP absorption in subjects receiving IP of MCP or IP of MCP plus HC. Systems were removed at the 4-h time point.

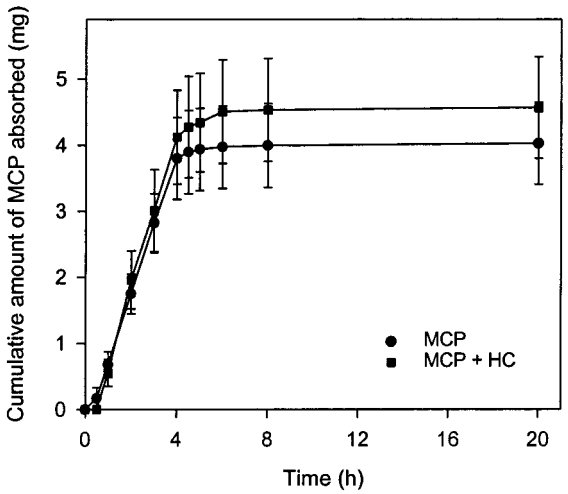

Figure 3—Mean cumulative amount of MCP absorption in subjects receiving IP of MCP or IP of MCP plus HC. Systems were removed at the 4-h time point.

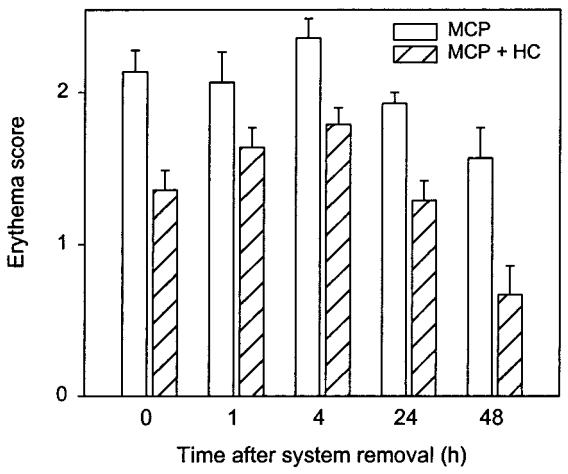

Figure 4—Mean erythema scores at the anode after 4 h IP of MCP or MCP plus HC.

with skin color reflectance measurements: One hour after removal of the system, reflectance values were 2.1 ± 0.3 and 0.8 ± 0.3 for MCP and MCP with HC, respectively. Four hours after removal of the system, reflectance values were 2.7 ± 0.2 and 0.7 ± 0.3 for MCP and MCP with HC, respectively. At 24 and 48 h after removal of the system,

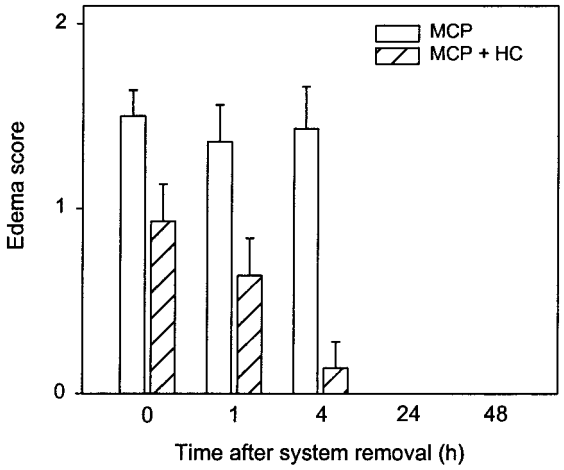

Figure 5—Mean edema scores at the anode after 4 h IP of MCP or MCP plus HC.

reflectance values were below 1 in both groups and were not statistically significant between the two groups.

Edema at the site of system application was observed in most subjects. HC significantly decreased edema score at 0, 1, and 4 h. Four hours after system removal, the mean edema score at the anode delivering MCP was 1.4. HC almost completely inhibited edema at this time point. Edema was resolved in all subjects by 24 h following system removal (Figure 5). There were no papules or pustules observed in any of the subjects and no subjects reported itching.

Discussion

MCP is an antiemetic prescription drug used in the treatment of gastroesophageal reflux and in the prevention of nausea and vomiting. This drug is intended for systemic delivery (iv or oral), and clinical MCP doses range between 10 and 60 mg/d.[24] Subjects in this study wore two 5-cm^2 IP transdermal systems, and input rate was about 1 mg/h at steady state. The cumulative amount of MCP absorbed systemically was about 4 mg after 4 h IP. Steady-state MCP flux of about 100 μg/(cm^2 × h) was achieved after only 1 h of transport, indicating a brief lag time, and input rate dropped dramatically immediately after removal of the systems. The brief lag time observed and the rapid drop in calculated input rate is consistent with a negligible MCP depot or accumulation in the skin. In addition, the calculated MCP half-life is similar to values reported in the literature following iv administration,[24] an outcome also consistent with an absence of skin depot. Collectively, these results indicate that usable MCP therapy could be achieved with an electrode size of about 5 to 30 cm^2.

Although we have demonstrated the feasibility of MCP IP transdermal delivery from an input rate standpoint, local skin irritation has been observed at the delivery site. This local side effect could jeopardize clinical acceptability of this transdermal system. The goal of the present study was to investigate the feasibility of codelivery of HC with MCP and evaluate the inhibitory effect of HC on the skin response. MCP is a low molecular weight, cationic, water-soluble drug salt. Although most MCP transport is accomplished via migration of ionized drug molecules in the electric field, HC transport is mainly the result of passive diffusion and electroosmosis (i.e., migration of nonionized molecules in an electric field).[25] IP through the skin occurs chiefly through aqueous pathways (i.e., sweat glands and hair follicles).[26] As a result, the stratum corneum, which accounts for most of the reservoir effect observed during transdermal steroid delivery,[27] is bypassed; this routing should result in a reduced transport lag time of HC compared with passive delivery. We did not attempt to measure HC flux during this clinical study because theoretical calculations indicated that the resulting HC blood levels would be indistinguishable from endogenous levels. In the in vitro flux experiment, HC steady-state flux was achieved within less than 4 h transport under an anodic current of 0.1 mA/cm^2, indicating that IP effectively bypasses the reservoir effect of the stratum corneum with respect to HC delivery. In addition, we found that HC flux is affected by current and the presence of MCP. A current of 0.1 mA/cm^2 results in a more than 1 order of magnitude increase over the passive flux of HC. This result is consistent with transport of HC by electroosmosis and increased skin permeability resulting from IP, as was demonstrated with other neutral molecules.[28,29] Increase in HC flux in the presence of MCP may be explained by the increase in HC solubility in the presence of MCP. MCP is a very water-soluble drug that does not seem to present significant colloidal properties (in this study, it did not decrease significantly the surface tension of water at up to 0.5 M). Therefore, the observed increase in HC solubility in the presence of MCP cannot be the result of solubilization of hydrocortisone in MCP aggregates as has been observed with surfactants and compounds presenting colloidal properties.[30] Increase in HC solubility is probably the result of a salting-in phenomenon that commonly occurs when organic-substituted ammonium salts are added to aqueous solutions of nonelectrolytes.[31] In any case, the flux of a solute (electrosmotic as well as passive diffusion) has been reported to be directly dependent on its concentration.[28] Consequently, the increase in HC flux observed in the presence of MCP is consistent with the increase in HC solubility.

Neither the plasma concentration profile nor any of the pharmacokinetic parameters of MCP differed when it was delivered by IP, with or without HC, indicating that MCP input rate and its clearance from the skin were unaltered by HC. However, HC inhibited erythema as well as edema resulting from IP delivery of MCP. This result indicates that HC was delivered in vivo at a rate sufficient to exert its local pharmacological effect. Inhibition of erythema was very effective, as assessed visually and by skin color reflectance, and could be the result of the vasoconstrictive effect produced by HC, while the inhibition of edema probably reflects the antiinflammatory action of HC. Vasoconstriction is known to retard drug clearance from the delivery site.[32] Codelivery of HC could therefore impact the pharmacokinetic profile of MCP. No such effect of HC was observed possibly because of the high transport rate of MCP through the skin by IP and saturation of the skin binding sites. Alternatively, this could be explained by the low potency of HC. Indeed, HC is the weakest GC available; stronger GCs could possibly modify the pharmacokinetics of a codelivered drug by increasing local vasoconstriction at the delivery site.

GCs are broad-based antiinflammatory agents; they are expected to exert their activity on any type of inflammation, regardless of the triggering mechanism.[33] As a result, GCs are among the most universal agents for counteracting skin reactions. Using GCs when an inflammation mechanism is unknown or poorly understood provides a definitive advantage compared with using more specific antiinflammatory strategies described in the literature.[9,10,12,13]

The use of topical steroids more potent than HC can be more beneficial from an antiinflammatory standpoint in cases of extreme inflammation.[33,34] However, an increase in potency implies that potential side effects may also be observed. In normal subjects, adrenal suppression did not

occur with high-potency corticosteroid ointment formulations applied to 75% of the body surface once a day for six consecutive days.[35] However, in clinical practice, mild adrenal suppression has been observed after intensive use in patients who required rigorous treatment of their skin disease.[36] This observation indicates that the risk of systemic side effect with high-potency steroids is not completely negligible. Local side effects such as skin thinning resulting from local administration of steroids are also related to potency.[37] The usefulness of high-potency steroids, therefore, may be limited by the potential for systemic and local side effects.

The beneficial effect of HC has been reported only with weak sensitizers or moderate irritants.[15,16] Since IP delivery of MCP results in only moderate inflammation, it is thought that HC is more appropriate than stronger steroids for codelivery with it. The use of HC may be a good alternative to more potent GCs for inhibition of mild to moderate inflammatory responses for three reasons. First, HC is an endogenous compound; the amount needed to produce local antiinflammatory effects is a small fraction of the endogenous production. (In this study, the total calculated flux of HC per subject was about 0.1 mg after 4 h IP delivery, whereas endogenous HC production is reported to be about 10 mg/d.[33] Even if the amount of HC delivered is extrapolated to 24 h, this daily total is still a small fraction of the endogenous HC production. Therefore, systemic activity of HC is probably not responsible for the antiinflammatory effects observed in this study. Second, to the best of our knowledge, local side effects such as skin thinning have never been observed with HC. Finally, water solubility of HC is higher than that of most GCs and, if needed, solubility can be increased by the addition of solvents such as propylene glycol in concentrations compatible with IP delivery.[38] Therefore, the effect observed with MCP can probably be extended to the delivery of other irritating or sensitizing drugs, making this strategy a very powerful tool for achieving safe and acceptable transdermal delivery of drugs.

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