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Iontophoretic Transdermal Delivery of Salicylic Acid and Lidocaine to Local Subcutaneous Structures

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Abstract □ The depth of penetration of solutes into underlying tissues after transdermal iontophoresis has been evaluated with salicylic acid and lidocaine as model compounds. Concentrations of salicylic acid and lidocaine were measured in plasma and tissues below the donor electrode after iontophoresis in rats. The concentrations obtained were then compared with those obtained after passive delivery (without iontophoresis) of the drugs applied either to intact epidermis or to the exposed dermis (epidermis removed) of rats. Iontophoresis yielded high concentrations of lidocaine in each underlying tissue when compared with passive application to rat epidermis or dermis. Negligible concentrations of lidocaine in plasma were found for each mode of delivery. Similar concentrations of salicylic acid were found in each of the underlying tissues after delivery of salicylic acid either by iontophoresis through intact epidermis or after passive application to the exposed dermis. Negligible concentrations of salicylic acid in underlying tissues were obtained after passive application to intact epidermis. The plasma salicylic acid concentrations observed after both iontophoretic epidermal and passive dermal (epidermis removed) treatments were approximately the same as the tissue salicylic acid concentrations observed at ~3–4 mm below the application site. It is concluded that transdermal iontophoresis allows salicylic acid and lidocaine to be effectively delivered across the stratum corneum. Local direct deep tissue penetration of lidocaine is facilitated by iontophoresis. The concentrations of salicylic acid in deeper underlying tissues (>3–4 mm) tend to be similar to the concentrations in plasma after either iontophoresis or passive dermal application, a result indicating that direct penetration of salicylic acid occurs only to a depth of 3–4 mm.

There is an increasing interest in the possible treatment of osteoarthritis, soft-tissue rheumatism, tendonitis, and other local inflammatory conditions with topically applied drugs.[1,2] The major barrier to any topically applied compound is the stratum corneum.[3] Transdermal iontophoresis is defined as the transfer of drugs across the skin under an applied electrical potential difference.[4] The therapeutic applications and principles underlying this technique have been discussed elsewhere.[4–6] We are particularly interested in the local levels of drugs in tissues after transdermal iontophoretic application. Iontophoresis has been shown to localize dexamethasone in the tissues below the application site.[7] Evidence also exists for the noninvasive iontophoretic administration of other corticosteroids to inflamed joints and tendons[8,9] and lidocaine for local anesthesia of skin.[10–12]

In this work, we examined the effect of iontophoresis on the depth of penetration of salicylic acid and lidocaine in rats after topical application and compared the observed concentrations in underlying tissues with those obtained after passive (without iontophoresis) application of these drugs. Tissues below the receptor electrode site of application were also examined to measure the extent of lateral spread and "back extraction" of iontophoretically driven drug by the receptor or passive electrode.[13,14] In addition, tissues below a site on the contralateral side and the blood were also analyzed for solute concentrations. Salicylic acid and lidocaine were chosen for this study as representative anionic and cationic solutes. Both salicylic acid and lidocaine are common ingredients of a number of topical products.[15,16]

Experimental Section

Chemicals and Instruments—[^{14}C]Salicylic acid (specific activity, 56 mCi/mmol; purity, >98.0%) was a gift from Hamilton Labs (Australia) Pty. Ltd. [^{14}C]Lidocaine hydrochloride (specific activity, 48 mCi/mmol; purity, >97.0%) was purchased from New England Nuclear. Salicylic acid was purchased from Sigma Chemical Co., and lidocaine hydrochloride was a gift from Astra Pharmaceuticals (Australia) Pty. Ltd. A model 901 Zimmer electrodermatome was used for removing rat epidermis. The constant current used in the iontophoretic experiments was generated by a custom-made constant-current source. Silver–silver chloride electrodes (purity, 99.99%) were used. Tissue solubilizer and liquid scintillation cocktails (organic counting scintillant and biodegradable counting scintillant for tissue and aqueous samples, respectively) were purchased from Amersham International. Sodium acid phosphate ($NaH_2PO_4 \cdot 2H_2O$), disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$), and HEPES (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid), used to prepare buffers, were of analytical grade. A liquid scintillation counter (Tri-carb 4000 series; United Technologies Packard) was used to determine the radioactivity in the samples.

Animals—Male Wistar rats (300–350 g) were used. The animals were housed under standard laboratory conditions (20.0 ± 0.5 °C; relative humidity, 55–75%) and supplied with a normal pellet diet and water ad libitum. All experiments had previously been approved by the Animal Experimentation Committee of The University of Queensland and Princess Alexandra Hospital.

In Vivo Epidermal Penetration and Local Tissue Uptake Studies (with Iontophoresis)—The rats were lightly anesthetized with pentobarbital (35 mg/kg), and their body temperature was maintained at 37 °C by placing them on a heating pad. The hair on the dorsal area was clipped, and any residual hair was removed by application of a depilatory[17] [Nair; Carter-Wallace (Australia) Pty. Ltd.]. The depilated area was swabbed with methyl alcohol[7,9,12] to remove any traces of the depilatory, and a donor glass cell (internal diameter, 1.8 cm) was affixed to the epidermis. A receptor glass cell of similar dimensions was affixed 2–3 cm from the donor glass cell. The glass cells were warmed to 37 °C by means of an external heating device.[18]

Solutions of either salicylic acid (1 mM, spiked with 12 μCi of [^{14}C]salicylic acid, in 20 mM HEPES buffer [pH 7.4]) or lidocaine (10 mM, spiked with 12 μCi of [^{14}C]lidocaine hydrochloride, in 20 mM HEPES buffer [pH 6.3]) previously warmed to 37 °C were introduced into the donor glass cell. Isotonic HEPES buffer (20 mM; pH 7.4) was used as the receptor solution. The donor solution was stirred with a glass stirrer driven by an external motor.

Iontophoretic studies were conducted by placing a silver chloride electrode (cathode) in the donor cell and a silver electrode (anode) in the receptor cell for salicylic acid (cathodal iontophoresis) and a silver electrode (anode) in the donor cell and a silver chloride electrode (cathode) in the receptor cell for lidocaine (anodal iontophoresis). A

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current of 0.38 mA/cm^2 was applied between the two electrodes. The upper limit of current before a person feels perceptible physical discomfort is believed to be 0.5 mA/cm^2.[19] Samples (10 μl) were removed from the donor cell at 5, 10, 15, 30, 45, 60, 75, 90, and 120 min and placed in preweighed scintillation vials. Samples were removed from the receptor cell at the beginning and at the end of the experiment. The glass cells were removed from the rat skin at 2 h postapplication, and the application areas were wiped dry with blotting paper. A blood sample was then taken from the tail vein, and the animals were sacrificed with an overdose of anesthetic ether. Immediately thereafter, the tissues below the treated site, i.e., skin, subcutaneous tissue, fascia, muscle lining or superficial muscle, muscle, fat pad, and deep muscle, were removed by dissection and placed in preweighed scintillation vials. The dissecting scissors and forceps were thoroughly cleaned after each tissue separation to prevent any cross contamination between different tissue layers. Similarly, the tissues below the receptor electrode and the contralateral side were also removed. Tissue and plasma samples were stored at −20 °C until analysis.

In Vivo Epidermal Penetration and Local Tissue Uptake Studies (without Iontophoresis)—The experimental conditions were the same as those for the in vivo epidermal studies with iontophoresis, except that no current was applied between the two cells. Tissues were collected from below the treated site, the receptor electrode, and the contralateral side as described above.

In Vivo Dermal Penetration and Local Tissue Uptake Studies—The epidermis was removed from the dorsum of anesthetized rats by means of an electrodermatome set at a thickness of 80 μm. Solutions of either salicylic acid or lidocaine in a glass cell were then applied to the exposed rat dermis.[18] Tissues below the treated site and similar tissues below the contralateral side were removed in the manner described above.

In Vitro Human and Rat Dermal Absorption Studies—Human skin was obtained from the mid-abdominal region of cadavers, and rat skin was excised from the dorsal region of male Wistar rats. The epidermis was separated from the dermis by the heat method.[20] Isolated human or rat dermis was mounted in side-by-side glass diffusion cells and submerged in a water bath at 37 °C. A solution of drug in isotonic phosphate buffer (pH 7.4) was introduced into the donor compartment, and isotonic phosphate buffer (pH 7.4) was used as the receptor solution. Samples were removed from the receptor side at predetermined times and analyzed for either salicylic acid or lidocaine.

Sample Treatment—Aqueous samples removed from the glass cells were directly mixed with 5 mL of biodegradable counting scintillant, and the radioactivity was counted in a liquid scintillation counter. The tissue samples were solubilized with 50 μL of water and 1 mL of tissue solubilizer at 50 °C for 6–8 h. After the digested samples were cooled to room temperature, 0.03% glacial acetic acid and then 10 mL of organic counting scintillant were added to each tissue sample. The plasma samples were solubilized with tissue solubilizer (5 parts to 1 part plasma) at room temperature and treated with glacial acetic acid and then organic counting scintillant. The radioactivity of each sample was then counted in the liquid scintillation counter for 10 min.

Analysis—Zero-time samples from the cell were used to represent the initial solution concentration, and ^{14}C activity in the tissues and plasma was converted to a fraction of the initial solution concentration (concentration fraction). In isolated dermal penetration experiments, the cumulative amount of salicylic acid or lidocaine appearing on the receptor side was plotted against time. The slope of the linear portion of the plot yielded the steady-state flux which, when divided by the initial concentration, yielded the permeability coefficient.[21]

Salicylic acid or lidocaine clearance was estimated as $k \cdot V$, where k is the rate constant for disappearance from volume V and is estimated by least-squares regression of the exponential decline in the concentrations applied to either rat epidermis or rat dermis.[18,22,23] The permeability coefficient can be deduced by dividing the clearance by the area of the application of the solution.

The t test was used to determine the statistical significance of differences when required. Each observation is the mean ± SD for three or four determinations.

Results and Discussion

Kinetics of Disappearance from the Application Site—The amounts of salicylic acid (<1%) and lidocaine (<3%) lost from diffusion cells after passive epidermal application to rats were small. A similar loss was observed when salicylic acid and carbinoxamine (a base) were applied topically to guinea pigs.[24] A greater loss of lidocaine is not unexpected, given that lidocaine is 25% nonionized at pH 7.4, whereas salicylic acid is almost completely ionized at this pH. It has been reported that nonionized compounds penetrate the stratum corneum better than ionized compounds.[25]

Figure 1 shows the percentages of salicylic acid and lidocaine remaining to be absorbed after 2 h of passive dermal and iontophoretic epidermal treatments. Comparable rate constants and clearances were obtained for salicylic acid and lidocaine after iontophoretic epidermal application (Table I). Both compounds were applied to the skin at a pH at which they were almost completely ionized: lidocaine at a pH of 6.3 and salicylic acid at a pH of 7.4. These conditions were chosen because a decreased iontophoretic flux resulted when ionization was suppressed for both lidocaine[26] and salicylic acid.[27] Comparable clearances were also found after passive dermal and iontophoretic epidermal treatments for both salicylic acid ($p > 0.6$) and lidocaine ($p > 0.5$) (Table I). The in vivo dermal model enabled the potential deep tissue penetration provided by epidermal iontophoresis across intact skin to be compared with tissue penetration of solutes applied to the dermis. The permeability of skin after the removal of the epidermis has been reported to increase considerably.[28] The similarity of the passive dermal and iontophoretic epidermal clearances obtained in this study suggests that iontophoresis allows solutes to be delivered across intact skin at a rate that is comparable to the passive delivery of compounds applied directly to the exposed dermis. It was also observed that the clearances obtained for salicylic acid and lidocaine were not significantly different ($p > 0.2$) from those from anesthetized rat dermis in vivo.

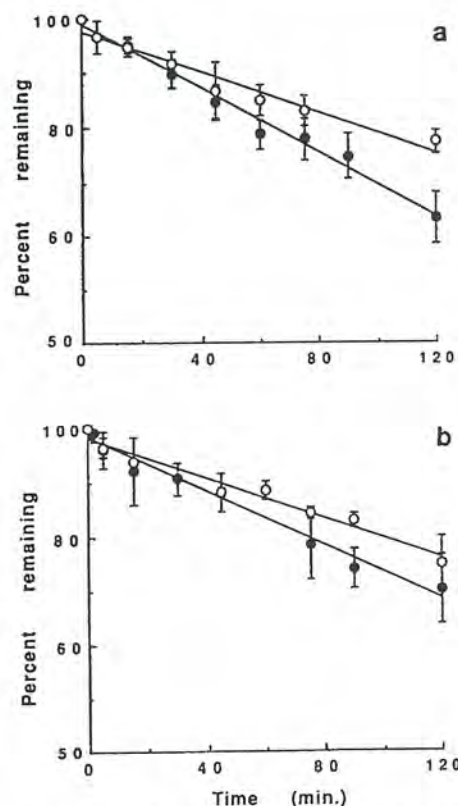

Figure 1—Disappearance of salicylic acid (a; n = 3) and lidocaine (b; n = 4) in rats after application to dermis (●) or iontophoretic application through epidermis (O). Values are reported as the mean ± SD.

Table I—Passive Dermal Absorption (D) and Transepidermal Iontophoretic (I) Kinetic Parameters for Salicylic Acid and Lidocaine[a]

Drug	Treatment	Rate Constant, min^{-1}	Clearance, mL/h	Percent Dose Absorbed
Salicylic acid	D	0.0032 ± 0.0004	0.58 ± 0.08	34.3 ± 3.68
	I	0.0028 ± 0.0007	0.50 ± 0.12	22.7 ± 2.29
Lidocaine	D	0.0028 ± 0.0009	0.51 ± 0.13	28.8 ± 5.25
	I	0.0023 ± 0.0003	0.39 ± 0.06	25.0 ± 4.47

[a] Data are given as mean ± SD.

The in vitro human dermal permeability coefficients for the two drugs were comparable [0.013 ± 0.0021 cm/h (r^2 = 0.999) for lidocaine and 0.017 ± 0.001 cm/h (r^2 = 0.998) for salicylic acid; n = 4]. Permeability coefficients of a similar order were obtained for rat dermis [0.009 ± 0.001 cm/h (r^2 = 0.999) for lidocaine and 0.013 ± 0.002 cm/h (r^2 = 0.998) for salicylic acid; n = 3]. The similar penetration fluxes for lidocaine and salicylate for both human dermis and rat dermis suggest that rat dermis is a suitable model for human dermis. The permeability coefficients for rat dermis in vivo, i.e., 0.23 ± 0.03 cm/h for salicylic acid and 0.20 ± 0.05 cm/h for lidocaine, were one order higher than those obtained with isolated human or rat dermis. The difference between in vitro and in vivo permeability coefficients probably reflects the contribution of dermal blood supply in removing topically applied compounds.[18]

Tissue Penetration of Salicylic Acid—Figure 2 shows the tissue distribution of salicylic acid after dermal application and iontophoresis through the epidermis. Detectable levels in tissue (except in the skin) were not obtained after passive application to rat epidermis. The low concentrations of salicylic acid observed are consistent with the findings of Hlynka et al., who applied [^{14}C]salicylic acid to the dorsum of guinea pigs and detected appreciable levels only up to a depth of 250 μm from the epidermis.[29] Washitake et al. have also reported the presence of small amounts of salicylate in the skin of guinea pigs after topical application of an aqueous solution (pH 6.0).[30]

Iontophoresis yielded significant concentrations of salicylic acid in the underlying tissues, the levels being comparable to those obtained when salicylic acid was applied to exposed rat dermis (Figure 2). The concentrations of salicylic acid in skin, dermis, and subcutaneous tissue below the treated site were higher than those in plasma (Figure 2b) and contralateral tissues to a depth of 3–4 mm (Figure 2a). Concentrations in deeper underlying tissues were always lower than concentrations in plasma but higher than, although comparable with, concentrations in contralateral tissue, a fact suggesting that the drug is first absorbed into the bloodstream and then distributed to different tissues. It is therefore suggested that direct penetration of salicylic acid occurs only to a depth of 3–4 mm. Dawson et al.[31] and Radermacher et al.[32] studied percutaneous penetration of biphenylacetic acid and diclofenac, respectively, in patients with bilateral knee effusions. Both groups concluded independently that the drugs were absorbed first into the blood and subsequently into the deeper tissues, such as synovium.[31,32]

The tissues below the receptor cell showed concentrations of salicylic acid similar to those in contralateral tissue after iontophoretic treatment. This result suggests that no salicylic acid is carried laterally by the current flowing between the two electrodes and that salicylic acid is delivered by the systemic blood supply. Table II shows the amount of salicylic acid recovered in underlying tissues as a percentage of the amount absorbed. Only 30% of the amount absorbed was

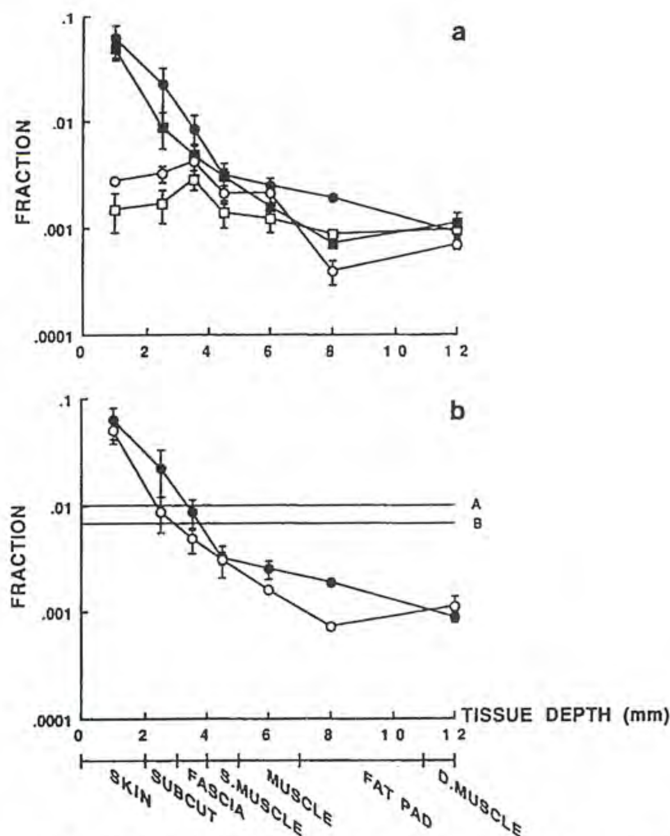

Figure 2—(a) Tissue distribution of salicylic acid in rats after application to dermis [treated site (●) and contralateral site (○)] and iontophoresis through epidermis [treated site (■) and contralateral site (□)]. Values are reported as the mean ± SD (n = 3). (b) Tissue concentrations of salicylic acid in rats. Key: (●) application to dermis; (○) iontophoresis through epidermis; (A) levels in plasma after dermal application; (B) levels in plasma after iontophoresis through epidermis. Values are reported as the mean ± SD (n = 3). SUBCUT, subcutaneous tissue; S.MUSCLE, superficial muscle; D.MUSCLE, deep muscle.

present in underlying tissues, the majority being present in the skin, subcutaneous tissue, and fascia. High levels of salicylic acid in the skin after iontophoretic treatment as compared with passive epidermal application are consistent with the findings for other compounds.[17,33]

Tissue Penetration of Lidocaine—Figure 3 shows the tissue distribution of lidocaine with various treatments. We previously reported that lidocaine can penetrate directly into underlying tissues after topical application and that the levels obtained are higher than those in plasma and contralateral tissue.[34,35] Passive epidermal application of lidocaine to rat epidermis yielded appreciable levels in skin but lower levels in deeper underlying tissues. Application by iontophoresis yielded high concentrations of lidocaine in all the underlying tissues to a depth of 1.2 cm (Figure 3). Russo et al. previously reported the penetration of iontophoretically applied lidocaine to the depth of subcutaneous tissue (observed by the placement of sutures) in humans,[10] consistent with our early communication.[35] More recently, Riviere et al. also reported deep tissue penetration of lidocaine after transdermal iontophoresis in pigs.[36] Murray et al. also demonstrated the safety of steroid iontophoresis in diseases of subcutaneous tissue at an estimated depth of 1.25 cm.[37] In the present work, appreciable levels of lidocaine were observed as deep as underlying muscle in rats (Figure 3).

Lidocaine could not be detected in contralateral tissue after iontophoresis, and only low concentrations of lidocaine were observed in the blood (Figure 3b). Earlier studies by Glass et

Table II—Salicylic Acid and Lidocaine Recovered in Underlying Tissues and Plasma[a]

Tissue	Recovery[a] of: Salicylic acid		Lidocaine	
	D	I	D	I
Dermis	15.3 ± 3.88	18.8 ± 2.14	41.2 ± 13.5	50.9 ± 17.1
Subcutaneous tissue	7.13 ± 2.10	6.33 ± 1.81	25.6 ± 6.20	31.1 ± 10.1
Fascia	2.80 ± 0.72	2.18 ± 0.72	19.8 ± 4.70	23.8 ± 4.91
Superficial muscle	0.82 ± 0.26	1.00 ± 0.31	7.40 ± 2.46	9.37 ± 3.26
Muscle	0.57 ± 0.19	0.89 ± 0.25	2.65 ± 0.71	3.48 ± 1.25
Fat pad	0.21 ± 0.04	0.34 ± 0.09	1.67 ± 0.41	0.34 ± 0.11
Deep muscle	0.12 ± 0.04	0.21 ± 0.07	1.66 ± 0.47	0.48 ± 0.14
Plasma	2.07 ± 0.29	2.43 ± 0.56	0.37 ± 0.07	0.11 ± 0.02

[a] Given as a percentage (mean ± SD) of the amount absorbed after passive dermal application (D) and iontophoretic epidermal application (I).

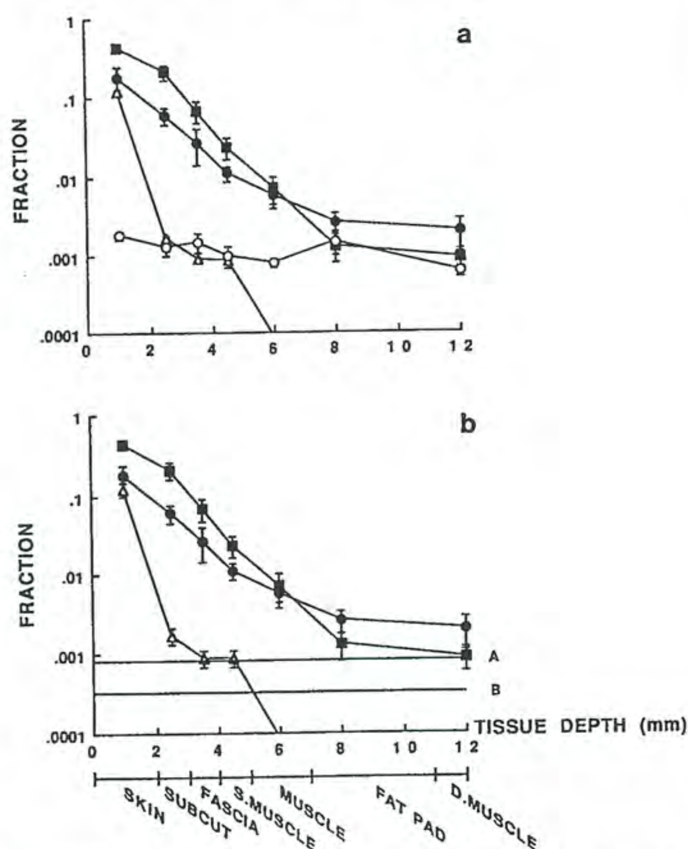

Figure 3—(a) Tissue distribution of lidocaine in rats after application to dermis [treated site (●) and contralateral site (○)], iontophoresis through epidermis [treated site (■)], and application to epidermis [treated site (△)]. Values are reported as the mean ± SD (n = 4). (b) Tissue concentrations of lidocaine in rats. Key: (●) application to dermis; (■) iontophoresis through epidermis; (△) application to epidermis; (A) levels in plasma after dermal application; (B) levels in plasma after iontophoresis through epidermis. Values are reported as the mean ± SD (n = 4). Abbreviations are as defined in the legend to Fig. 2.

al. revealed that <0.4% dexamethasone was absorbed into the total blood volume after iontophoretic application in monkeys.[7] Percutaneous iontophoresis of prednisolone has also been shown to yield levels in plasma that are about one-third those produced by oral administration of prednisolone.[38] It is therefore apparent that transdermal iontophoresis is a useful technique for enhancing the local delivery of drugs without exposing the rest of the body to unwanted side effects.

The tissue lidocaine levels after iontophoretic epidermal treatment were higher than the levels in similar tissues after passive dermal application, a result highlighting the efficacy of iontophoretic delivery (Figure 3). Table II shows the distribution of lidocaine in underlying tissues as a percentage of the amount absorbed. Almost all of the lidocaine absorbed could be recovered in underlying tissues, providing evidence for the direct penetration of lidocaine after topical application.

Figure 4 shows the iontophoresis/dermal absorption concentration ratios estimated for salicylic acid and lidocaine from the data in Figures 2 and 3. An iontophoresis/dermal absorption concentration ratio exceeding unity is consistent with iontophoresis-facilitated transport. An examination of Figure 4 suggests that iontophoresis facilitated lidocaine penetration to a depth of 8 mm. The lidocaine levels in skin, subcutaneous tissue, fascia, and underlying muscle were 2–3.5 times higher than those obtained after passive dermal application. Facilitation was supported by an iontophoresis/dermal absorption concentration ratio for plasma of 0.51 ± 0.15. A low ratio would have been consistent with a higher deep tissue penetration flux of lidocaine after iontophoresis relative to dermal diffusion for the same blood removal rate. In contrast, both the tissue and the plasma salicylic acid concentration ratios (iontophoresis/dermal absorption) were not significantly different from unity (the concentration ratio for plasma was 0.82 ± 0.17).

No lateral spread of salicylic acid or lidocaine was observed after iontophoresis. Lidocaine was not detectable in any of the tissues below the receptor electrode, whereas the concentrations of salicylic acid at this site were similar to those at a site on the contralateral side. In addition, no detectable salicylic acid or lidocaine was found in the receptor solution containing

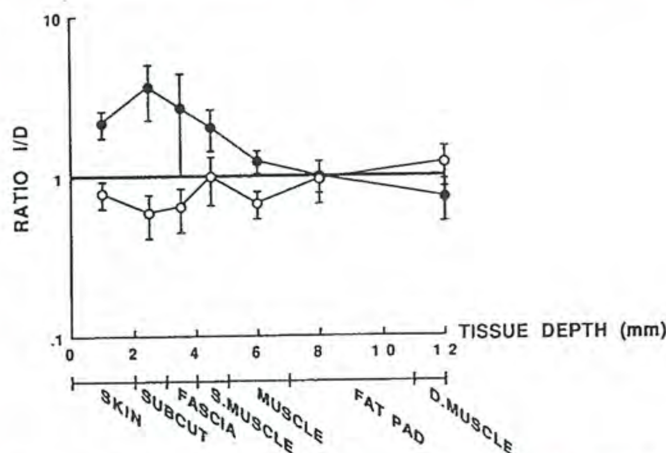

Figure 4—Concentration ratio (I/D) in tissues following iontophoretic (I) and dermal (D) treatments. Key: (●) lidocaine; (○) salicylic acid. Values are reported as the mean ± SD (n = 3 or 4). Abbreviations are as defined in the legend to Fig. 2.

the receiving electrode. Glikfeld et al. reported no lateral spread of morphine or clonidine after iontophoretic application to hairless mouse skin in vitro.[13] Russo et al. also found no evidence of lateral spread of iontophoretically applied lidocaine in human volunteers.[10] However, significant concentrations of morphine, clonidine, and theophylline have been observed at the receptor electrode in vitro,[13,14] in contrast with the present in vivo results. The differences are likely to reflect the sink conditions offered by the dermal blood supply in vivo and the close proximity of the electrodes and receptor solution in the in vitro studies of Glikfeld et al.[14]

In conclusion, the present study confirms that iontophoresis is an effective way of delivering certain drugs across the stratum corneum. Evidence is presented that the penetration of lidocaine into the superficial underlying tissues may be facilitated by iontophoresis. In contrast, the concentrations of salicylic acid in underlying tissues are similar after iontophoretic delivery through skin and dermal delivery.

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