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Rapid Communication

What is the transport-limiting barrier in iontophoresis?

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Summary

We document evidence that the major rate-limiting step in iontophoretic drug delivery of low molecular weight charged solutes can be dermal perfusion at the site of application; for high molecular weight solutes, on the other hand, transport to the site of microcirculation uptake may, in some circumstances, become the slowest step.

The stratum corneum, the outermost layer of skin, is believed to be the principal barrier to the percutaneous penetration of most chemicals. The need to include an aqueous layer (viable epidermis and a portion of dermis) in determining the overall skin resistance for highly lipophilic compounds has been recognized (Flynn, 1990; Kasting et al., 1992; Kasting and Robinson, 1993). In addition, others have reported the potential for blood flow limitations in overall dermal transport (Nakashima et al., 1987; Benowitz et al., 1992; Riviere and Williams, 1992; Kasting and Robinson, 1993; Singh and Roberts, 1994). Transdermal iontophoresis may be defined as the facilitation of drug delivery across the skin by mobilization of drug ions under the influence of an appropriate applied potential gradient. Although not yet conclusive, recent iontophoresis data suggest that electrotransport can circumvent the stratum corneum barrier, such that either clearance by the cutaneous blood supply or tissue diffusion to this site of uptake becomes the rate-limiting step.

In a recent study, apparent dermal clearances of salicylic acid and lidocaine were estimated in rats from the disappearance-time profiles obtained after either epidermal iontophoretic (EI) or passive dermal (PD) (epidermis removed) application (Singh and Roberts, 1993a). Both compounds were applied to the skin at a pH at which they were almost completely ionized. The estimated clearances in the presence of viable blood supply were comparable after both modes of application for both drugs (Singh and Roberts, 1993a). Thus, iontophoresis, in this case, allowed drug delivery across intact skin at a rate comparable to the passive permeation of compounds following their direct application to exposed dermis. The dermal clearances of salicylic acid and lidocaine were self-consistent for both EI and PD

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applications. In vitro permeability coefficients for the two compounds across isolated human dermis were also comparable (0.013 cm/h for lidocaine and 0.017 cm/h for salicylic acid). The permeability coefficients calculated for rat dermis in vivo (0.23 cm/h for salicylic acid and 0.20 cm/h for lidocaine) were an order of magnitude higher than those obtained with isolated human or rat dermis in vitro. This difference presumably reflects the contribution of the dermal blood supply in removing topically applied compounds in vivo (Singh and Roberts, 1993a).

The microcirculation in the absorption zone is considered to play an important role in the uptake of solutes particularly for low molecular weight compounds (Schou, 1961, 1971; Selye, 1967; Patel and Levy, 1974; Singh and Roberts, 1993b). For high molecular weight solutes, the rate-limiting step has been suggested to be tissue diffusion (Schou, 1971). The efficacy of tissue clearance through absorption and diffusion is important in determining the activity of the compound with respect to its local action/toxicity relative to systemic action/toxicity. The use of vasoactive chemicals to alter the tissue clearance of compounds has been reported (Seyle, 1967; Patel and Levy, 1974; Riviere et al., 1991; Singh and Roberts, 1994). Vasoconstrictors such as epinephrine, norepinephrine, vasopressin and octapressin have been shown to delay significantly the absorption of intracutaneously injected phenolsulfonphthalein in the rat (Selye, 1967). The use of vasoconstrictors to prolong the duration of local anesthesia is well documented (Tucker and Mather, 1988). On the other hand, the use of local vasodilators has been found to increase the subcutaneous tissue clearance of local anesthetics in rats in vivo (Patel and Levy, 1974).

The effects of the local vasoconstrictor phenylephrine on the dermal clearance and tissue distribution of lidocaine, salicylic acid and tritiated water were studied (Singh and Roberts, 1994) in a rat model (Singh and Roberts, 1993a). There was an apparent linear decrease in the dermal clearance of salicylic acid with increasing concentrations of phenylephrine. The local underlying tissue concentrations of salicylic acid increased, while the corresponding contralateral tissue levels and the systemic plasma levels declined, in the presence of phenylephrine (Singh and Roberts, 1994). Similar effects were also observed for lidocaine and tritiated water. The observed blood flow-limited effects were attributed to the local vasoconstriction and the resulting decreased dermal blood flow in the area of application (Singh and Roberts, 1994).

The tissue levels of salicylic acid after EI and PD application were comparable in the experiments of Singh and Roberts (Singh and Roberts, 1993a); likewise, the plasma levels following the two administration strategies were similar. The tissue levels of lidocaine were higher (though comparable) after EI application relative to dermal delivery. This supports the hypothesis that iontophoresis circumvents the stratum corneum barrier such that systemic uptake and tissue distribution parallel the behaviour observed following direct passive delivery to the dermis. Russo et al. (1980) have reported the penetration of iontophoretically delivered lidocaine to the subcutaneous tissue in humans. It was also observed that the depth of anesthesia achieved was the same as with lidocaine infiltration (Russo et al., 1980) again suggesting the equal efficacy of the two different routes of application. Similar results comparing iontophoretic and subcutaneous drug delivery have also been reported (Meyer et al., 1990; Kumar et al., 1992). The observation that transdermal iontophoresis facilitates drug delivery across the stratum corneum is further supported by the finding that the plasma concentrations of formoterol fumarate were statistically indistinguishable following passive and iontophoretic application to the stripped skin (i.e., sc-less) of guinea pigs (Sudeji et al., 1989).

If the efficacy of transdermal iontophoresis is comparable to direct delivery to the dermis (Singh and Roberts, 1993a), and blood flow-limitation considerations in passive dermal application (or compromised skin) are valid (Kasting and Robinson 1993; Singh and Roberts, 1994), the coadministration of vasoactive chemicals with transdermal iontophoresis should be expected to influence the iontophoretic flux of a compound. Riviere et al. (1991) studied the effects of coadministered vasoactive chemicals (namely tolazoline, a vasodila-

tor, and epinephrine, a vasoconstrictor) on the transdermal iontophoretic flux of lidocaine (a) in vitro, (b) in the isolated perfused porcine skin flap (IPPSF), and (c) in vivo in pigs. In vitro, the vasoactive species had no impact on diffusion. In the IPPSF, on the other hand, the presence of tolazoline significantly increased lidocaine flux, whereas norepinephrine had the opposite impact, presumably due to local vasodilatation and vasoconstrictor effects, respectively. Tolazoline also significantly increased lidocaine flux in vivo in pigs. Epinephrine prolonged the fractional absorption time, delayed the time to peak and reduced the overall and peak fluxes of lidocaine (Riviere et al., 1991). Consistent with the results of Singh and Roberts (1994), the above observations lend support to the dominant transport-controlling role of the intact microcirculation in the IPPSF and in vivo and highlight drug-induced alterations in the cutaneous microcirculation as the mechanism by which the transdermal iontophoretic delivery of lidocaine is altered.

Epinephrine was found to increase the local skin concentration of lidocaine, elevate lidocaine mass-depth profiles, and to increase the percentage of dose delivered; conversely tolazoline decreased the cutaneous reservoir of lidocaine after transdermal iontophoresis (Riviere et al., 1992). Similar effects were obtained when phenylephrine was coapplied with either salicylic acid, lidocaine or tritiated water to the exposed rat dermis (without iontophoresis) (Singh and Roberts, 1994). The coadministration of epinephrine to increase the duration of local, lidocaine-induced anesthesia following transdermal iontophoresis has also been reported (Russo et al., 1980; Gangarosa et al., 1981; Bezzant et al., 1988). Once again, it can be argued that iontophoresis effectively overcomes the stratum corneum barrier such that subsequent drug absorption and distribution is blood flow-limited.

The observed absorption rate constants of 0.19 and 0.17 h^{-1} for salicylic acid and lidocaine, respectively, after PD application to rats in vivo (Singh and Roberts, 1993a) (a) are similar in order to lidocaine subcutaneous absorption rate constants reported by Levy and Rowland (1974) and Menczel et al. (1977) in rats and rabbits, respectively, and (b) compare favourably with the experimentally determined in vivo rate constants of 0.17 and 0.14 h^{-1} for salicylic acid and lidocaine, respectively, after transdermal iontophoresis (Singh and Roberts, 1993a), again highlighting the similarities between the kinetics of drug absorption following either transdermal iontophoresis or PD or subcutaneous administration. Consistent with blood flow-limited kinetics, an apparent linear decline in salicylic acid dermal clearance was observed in rats with increasing concentrations of vasoconstrictor phenylephrine (Singh and Roberts, 1994). Similar reduction in the dermal clearance of lidocaine and tritiated water in the presence of phenylephrine, has also been observed (Singh and Roberts, 1994).

The similarity between the absorption rate constants for several drugs following either transdermal iontophoresis or passive delivery directly to the exposed dermal surface suggests a similar rate-controlling mechanism. When a drug is applied to the dermal surface, diffusion to the microcirculation and capillary uptake are the only physical processes which can impede the absorption process ('diffusion' in this context, may include protein binding). It follows, then, for the compounds which have been studied, that iontophoresis can move the penetrant efficiently across the epidermis at a rate which exceeds that of diffusion/uptake in the dermis. Certainly, the reports in the literature that the mechanism of iontophoretic delivery through the epidermal barrier involves significantly the participation of appendageal shunts is consistent with this conclusion (Abramson and Gorin, 1940; Grimnes, 1984; Burnette and Ognpipattanakul, 1988; Cullander and Guy, 1991; Cullander, 1992; Cornwell and Barry, 1993).

If the above deduction is sound, then one would expect the absorption process to exhibit a molecular size dependence, and that the dependence should be similar for compounds of diverse properties. With reference to iontophoretic delivery, Yoshida and Roberts (1993) related the experimentally determined permeability coefficients (K_p) of series of (a) anions, (b) cations and (c) uncharged species (delivered from the anode) to the corresponding molecular volumes (MV) using

an exponential relationship (consistent with a 'free volume' mechanism of diffusion (Potts and Guy, 1992)). The results obtained were as follows:

$$\text{anions: } \log K_p = -1.02 - 0.0035\text{MV} \quad (1)$$

$$\text{cations: } \log K_p = -0.76 - 0.0020\text{MV} \quad (2)$$

$$\text{uncharged: } \log K_p = -1.60 - 0.0028\text{MV} \quad (3)$$

As expected, given the permselectivity of skin to positively charged ions, the relationships above indicate that, at fixed MV, a cation will have higher K_p value than an anion which, in turn, will permeate more readily than a neutral compound (which can only be transported by electroosmosis). Significantly, however, the exponents multiplying MV in the above correlations are essentially identical. Furthermore, examination of other data in the iontophoresis literature reveals, once again, comparable values of the MV exponent when correlated with transport. For example: (i) the anionic data of Green et al. (1991) yield a slope of -0.0017; (ii) for the alkanoic acids of Del Terzo et al. (1989), the gradient is -0.0062; and (iii) results for cationic transport (Phipps et al., 1990) are fit by a slope of -0.0032.

It is also interesting to note that a gradient of similar magnitude (-0.0016) is obtained when cationic mobility in aqueous solution is plotted as a function of molecular size (Yoshida and Roberts, 1993). Additionally, to further emphasize the similarity between the absorption kinetics of compounds following either EI or PD delivery, performance of a similar analysis on the permeability coefficient data of Scheuplein and Blank (1973) for *n*-alkanols across isolated human dermis yields a slope of -0.0036. Likewise, for a different set of solutes (including acids, bases, steroids and polar non-electrolytes), Singh (1992) has determined a slope of -0.0020.

The form of Eqns 1–3, and of the other correlations detailed above, implies that, for compounds of relatively small MV (or molecular mass), EI and PD absorption kinetics are likely to be similar in magnitude. As molecular mass increases above about 500 Da, however, the impact of molecular size upon EI/PD absorption will become increasingly important.

In summary, the work reviewed here implies that, for relatively low molecular weight compounds at least, the kinetics of absorption following iontophoretic delivery are controlled by a combination of (a) diffusion through an essentially aqueous environment, and (b) capillary uptake. Analysis of currently available data suggests that the kinetics of absorption will become significantly molecular size-dependent for compounds > 500 Da. The importance of the presence of intact microcirculation in experiments designed to examine iontophoresis is therefore emphasized (Sage et al., 1992). Furthermore, strategies involving the coadministration of local vasoactive agents to enhance either the local concentration, or the systemic uptake of iontophoretically delivered drugs, warrant further examination.

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