

## Physical enhancement of dermatologic drug delivery: Iontophoresis and phonophoresis

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Iontophoresis and phonophoresis are emerging technologies capable of enhancing drug penetration through the stratum corneum, the principal barrier to percutaneous absorption. With utilization of applied electric current or ultrasonic waves, respectively, iontophoresis and phonophoresis have shown efficacy in an increasing number of clinical applications. This article reviews the underlying principles, current status, and potential of iontophoresis and phonophoresis in dermatologic therapy. (*J AM ACAD DERMATOL* 1996;34:657-66.)

Many drugs are poorly absorbed through the skin by passive diffusion alone. The use of topical agents often requires vehicle formulations or chemical penetration enhancers that are potential irritants or sensitizers.<sup>1,2</sup> Iontophoresis and phonophoresis are methods of driving topically applied substances across tissues by utilization of electric current or ultrasound, respectively. These physical modalities offer methods for enhancing the percutaneous absorption of selected drugs.

### IONTOPHORESIS

#### Historical background

Iontophoresis is the use of an electromotive force to enhance percutaneous absorption of a drug or chemical. Iontophoresis usually employs a direct current between 0.5 and 20 mA.

In 1747, Veratti described the application of an electric current to increase the penetration of drugs into surface tissues (from Turnell<sup>3</sup>). In 1900, Leduc<sup>4</sup> reported the first controlled iontophoresis studies in his oddly named "ionotherapy" experiments. He applied iontophoresis of strychnine and cyanide ions into rabbits and produced tetanic seizures and cyanide poisoning.<sup>4</sup>

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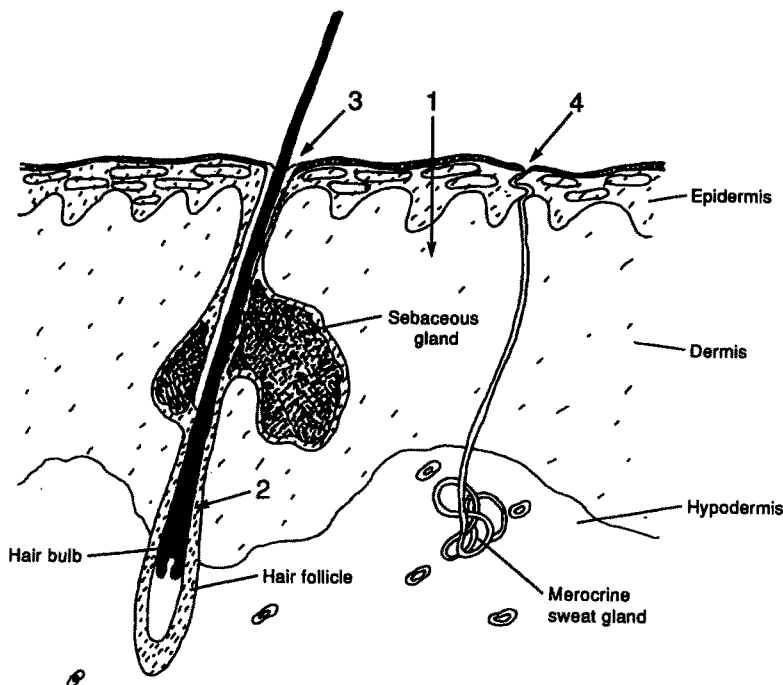
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In 1936, Ichihashi observed that iontophoresis of certain applied solutions reduced sweating. He also induced sweating by pilocarpine iontophoresis.<sup>5</sup> Conversely, Gibson and Cooke<sup>6</sup> induced sweating through the iontophoresis of topically applied pilocarpine. This procedure, which was done to measure sweat sodium and chloride concentrations, is the basis of the "sweat test," which is used to diagnose cystic fibrosis. Although Gibson and Cooke were among the first to use this technique, they cannot be given credit for its development.<sup>7</sup>

#### Technical characteristics and mechanism of action

The stratum corneum, the primary barrier to percutaneous absorption, is composed of approximately 20% lipids, 40% proteins (mostly keratin), and 40% water.<sup>8,9</sup> The electric potential gradient used in iontophoresis may alter the permeability of the skin by inducing changes in the arrangement of lipid, protein, and water molecules.<sup>10</sup> Iontophoretic transport may occur through discrete pores in the skin.<sup>11-14</sup> The "flip-flop gating model" is one proposed mechanism by which iontophoretic currents induce pore formation in the stratum corneum. According to this theory, an electric potential applied across the stratum corneum causes  $\alpha$ -helical keratin polypeptide molecules to reorient (or flip-flop) into a parallel arrangement. Pores are formed between neighboring keratin helixes as a result of molecular realignment and repulsion of neighboring dipoles.<sup>15</sup> Hair follicles and sweat gland ducts act as diffusion shunts, offering paths of reduced resistance for iontophoretic transport (Fig. 1).<sup>13</sup> In many instances



**Fig. 1.** Iontophoresis is thought to induce charged substances to travel across the skin along diffusion shunts, including pores (1), hair follicles (2), sebaceous ducts (3), and sweat ducts (4).

these diffusion shunts are more important than pore formation.<sup>16</sup>

Behl et al.<sup>16</sup> explored factors that influence iontophoretic drug delivery of benzoic acid and butyric acid. The iontophoretic flux increased linearly with respect to both drug concentration and applied current. In addition, increased rates of drug delivery were achieved by minimizing the presence of counterion salts such as potassium chloride. The rate of absorption declined almost exponentially with increased counterion salt concentration. This is consistent with the observations of Phipps et al.,<sup>15</sup> who noted that production of new ions at the anode and cathode through oxidation-reduction reactions contaminated the donor reservoir, requiring increased levels of current to maintain a steady delivery rate. Careful selection of electrode material and drug counterion can reduce these problems.

Intact stratum corneum is essential for successful iontophoretic transport. Stripping the stratum corneum from nude rat skin decreased the iontophoretic delivery of acetic acid, pentenoic acid, and octanoic acid by a factor of three to four.<sup>16</sup>

Iontophoresis can be used to deliver drugs not only to the cutis and subcutis but also to tendon, cartilage, and even the systemic circulation. Glass et

al.<sup>17</sup> used rhesus monkeys to demonstrate that the glucocorticoid dexamethasone phosphate could be applied by iontophoresis in significant quantities from the positive electrode to skin and also to tendon and cartilage. Chien et al.<sup>10</sup> developed an iontophoretic system (transdermal periodic iontophoretic system) capable of delivering insulin transcutaneously by iontophoresis into the diabetic rabbit. This method yielded more precise control of blood glucose levels than use of parenteral insulin. These investigators have also used iontophoresis to enhance percutaneous absorption of the nine-amino acid peptide, vasopressin.

Passive diffusion of polar (ionic) compounds through the stratum corneum is often slow and incomplete.<sup>17</sup> Iontophoretic penetration enhancement is greatest for these polar (ionic) compounds. Iontophoresis may actually decrease transport of highly lipophilic drugs.<sup>16</sup> Enhancement ratios, the ratio of the degree of absorption with and without iontophoresis, decline almost linearly as the alkyl chain length (i.e., increased lipophilicity) is increased in both alkanols and corticosteroids. Lipophilic substances are least suitable for iontophoretic delivery. Gangarosa, Park, and Fong<sup>18</sup> argued that the specific conductivity, a measure of the ability of

**Table I.** Iontophoresis of lidocaine

Procedure	Current	Result	Study design
Pulsed dye laser treatment of port-wine stains <sup>25</sup>	20-30 mA/min	10 of 11 patients satisfied	11 patients, double-blind, placebo-controlled
Needle prick <sup>24</sup>	0-4 mA × 7 min	Increased duration of anesthesia	27 patients, double-blind, placebo-controlled
Shave biopsy on nose <sup>21</sup>	3 mA	Efficacious	Case report
Various dermatologic procedures <sup>20</sup>	2-4 mA × 5-12 min	80% to 100% efficacy for epidermal procedures	94 procedures in 64 patients
Dialysis needle insertion <sup>23</sup>	3 mA × 10 min	Iontophoresis preferred over injection	13 patients, served as own controls
Cauterization of spider veins <sup>22</sup>	3 mA × 7 min	16 of 16 patients satisfied	16 subjects, unblinded

a compound to transmit electricity, is directly proportional to iontophoretic potential. They believed that conductivity measurements could be used to predict which drugs would be candidates for iontophoresis. Conductivity attempts to predict iontophoretic efficacy, whereas enhancement ratios simply indicate the degree of enhancement of percutaneous penetration once a comparison with passive diffusion has been performed. Gangarosa, Park, and Fong<sup>18</sup> compiled a ranked listing of conductivity values for a variety of drugs, including anesthetics, antiinflammatory corticosteroids, and anticancer and antiviral agents.

Nonionic molecules can sometimes be iontophoretically delivered. Gangarosa, Park, and Hill<sup>19</sup> demonstrated increased penetration of the nonpolar compound idoxuridine after anodal iontophoresis. They attributed this to water movement associated with sodium ion transfer and hypothesized that nonionic drugs in ionic solutions were delivered iontophoretically through a process termed *iontohydrokinesis*.<sup>19</sup> When this occurs, ions and water molecules carry nonionic substances such as idoxuridine through a mass transport effect.

### Clinical applications of iontophoresis in dermatology

The principles of iontophoresis have been used to enhance drug delivery in a wide variety of cutaneous conditions. The lack of standardized experimental conditions with respect to intensity of current, frequency, waveform, on/off ratio of current, and tissue pH and failure to use adequate controls makes it difficult to assess many of the studies.

**Cutaneous anesthesia.** The application of iontophoresis for induction of local anesthesia has been

successful (Table I). Maloney et al.<sup>20</sup> delivered 4% lidocaine with epinephrine, 1:50,000, by iontophoresis before performing 94 painful cutaneous office procedures. This technique had an efficacy rate of 80% to 100% for relieving pain caused by injections, dermabrasions, laser surgery, and cautery. Fifty-one percent of procedures with this type of anesthesia were recorded as "painless," 36% produced "minor pain," and 14% caused "moderate to severe pain." Iontophoresis was less effective (56% level of acceptability) for relieving pain associated with excisions, especially for larger lesions and lesions on the hands and feet.

Iontophoresis of lidocaine with epinephrine is advantageous for regions in which injection of local anesthetics is especially painful. Maloney<sup>21</sup> used lidocaine iontophoresis to perform a painless shave biopsy of a dermal nevus from the nose of a 13-year-old patient. No pain, bleeding, or tissue distortion occurred with use of this technique.

Bezzant et al.<sup>22</sup> used iontophoresis to deliver lidocaine before electrocoagulation of spider veins. Iontophoresis of 4% lidocaine with epinephrine (1:50,000) produced "total" anesthesia in 94% of patients and "adequate" anesthesia in the remainder without the adverse effects of conventional local anesthesia such as pain, burning, distortion of tissues, and the risk of systemic absorption.

Zeltzer et al.<sup>23</sup> compared children's responses to subcutaneous lidocaine injection and to lidocaine iontophoresis used as local anesthesia before insertion of a dialysis needle. Lidocaine injection, although more painful and anxiety provoking than iontophoresis, was more effective. In addition, some patients experienced cutaneous burning and tingling with iontophoresis.

Russo et al.<sup>24</sup> studied the duration and depth of anesthesia produced by lidocaine administration delivered through iontophoresis, intradermal injection, and swabbing in a placebo-controlled study of 27 patients. Lidocaine iontophoresis produced local anesthesia of significantly longer duration than topical application but of significantly shorter duration than injection. The depth of anesthesia achieved with lidocaine iontophoresis was the same as with injection. The shorter duration of anesthesia associated with iontophoresis may be related to iontophoresis-induced capillary dilation, resulting in increased regional blood flow and the removal of lidocaine from the site.<sup>26</sup> The addition of epinephrine as a vasoconstrictor in the preparation might have prolonged anesthesia.

These findings suggest that lidocaine iontophoresis without epinephrine is an effective means of achieving local anesthesia for approximately 5 minutes.<sup>24</sup> This method may be especially advantageous in avoiding trauma to tissues, for example, around an abscess before incision or removal of a foreign object.

**Hyperhidrosis.** Management of palmo-plantar hyperhidrosis was the first dermatologic application of iontophoresis. Hyperhidrosis of the palms, soles, and axillae is a common, often disabling condition.<sup>24, 27, 28</sup> Topical application of aluminum chloride, formaldehyde, or glutaraldehyde produces only short-term relief and may be irritating.<sup>27</sup> Surgical sympathectomy, although effective, is associated with serious side effects.<sup>29</sup> It was first observed in the 1930s that iontophoresis of various solutions was effective in reducing production of sweat.<sup>5, 30</sup>

In 1969, Gordon and Maibach<sup>31</sup> showed a 40% to 97% inhibition of sweat production with tap water iontophoresis. They demonstrated that raising the current increased the degree and duration of anhidrosis.

Additional studies have demonstrated a therapeutic effect of tap water iontophoresis on hyperhidrosis of the axillae, palms, and soles.<sup>26-28, 32-35</sup> Holze and Ruzicka<sup>33</sup> achieved complete control of severe palmo-plantar hyperhidrosis after 10 to 12 treatments, as documented by quantitative gravimetric measurements of sweat rates and starch iodine paper imprints. The only side effect was mild, temporary skin irritation. An average of 1.3 treatments per week was necessary to maintain complete control.

Stolman<sup>32</sup> reported that 15 of 17 patients treated

for palmar hyperhidrosis by tap water iontophoresis became euhydrotic. Mild side effects, including intermittent dysesthesia that lasted up to several days in the treated hand of one patient and cutaneous erythema, did not prevent patients from continuing iontophoresis.

Abell and Morgan<sup>26</sup> showed that iontophoresis with anticholinergic agents was more effective than with tap water. However, this resulted in systemic side effects. More recently, Shen et al.<sup>27</sup> combined iontophoresis of an anticholinergic agent with aluminum chloride in an effort to produce both inhibition of sweat gland secretion and duct blockage. The average remission was 3.5 days with tap water and 20 days with the combined method. The only side effect of the combined method was transient dryness of the mouth.

The mechanism of iontophoretic treatment of hyperhidrosis is unclear. Gordon and Maibach<sup>31</sup> hypothesized that iontophoresis inhibited sweat production by producing epidermal injury, resulting in abnormal keratinization and plugging of the segment of the sweat duct in the stratum corneum. Dobson and Lobitz<sup>36</sup> had previously produced miliaria crystallina and miliaria rubra in skin of normal volunteers treated with iontophoresis. They demonstrated plugging of sweat ducts by periodic acid-Schiff-positive, diastase-resistant material in all patients. Surprisingly, other studies failed to reveal changes in eccrine glands or mechanical obstruction of eccrine ducts.<sup>33, 34</sup> Holze and Ruzicka<sup>33</sup> suggested that iontophoresis works by means of blockage of neuroglandular transmission or inhibition of the secretory mechanism at the cellular level.

**Antibiotics.** There have been several reports of successful iontophoresis of antibiotics through both injured and intact tissue. Rapperport et al.<sup>37</sup> showed that iontophoresis enhanced the transport of penicillin through burn eschar into underlying avascular tissues, yielding concentrations far exceeding those to which no electric current was applied (200-fold increase). Bactericidal levels of antibiotic were achieved in areas thought to be major sites of the origin of bacteremia and septicemia in patients with burns.

Rigano et al.<sup>38</sup> examined the effect of gentamicin or penicillin iontophoresis on the management of ear burns in 145 patients. The incidence of ear infection and need for chondrectomy were virtually eliminated by antibiotic iontophoresis.

**Herpes simplex and aphthous stomatitis.** Le-

kas<sup>39</sup> treated 15 cases of recurrent oral herpes simplex with iontophoresis of a 0.1% solution of idoxuridine, an antiviral drug that inhibits the incorporation of thymidine into DNA. Treatment of lesions at the mucocutaneous junction with 0.5 to 0.8 mA of iontophoresis for 10 minutes resulted in rapid relief of discomfort. Oral lesions on the inner surface of the lips and tongue that were treated with only 0.2 mA of iontophoresis for 10 minutes healed within 36 hours, as opposed to the expected course of 10 to 14 days.

Boxhall and Frost<sup>40</sup> observed similar results in another uncontrolled study that used 0.5 mA of 0.1% idoxuridine iontophoresis for 7 minutes to treat recurrent oral herpes. They reported prompt pain relief and an estimated 70% reduction in healing time. A high level of patient satisfaction was reported; 43 of 54 patients ranked idoxuridine iontophoresis superior to all previously tried therapeutic modalities.

Henley-Cohn and Hausfeld<sup>41</sup> reported that 26 of 28 patients with recurrent herpes labialis showed a major response (defined as scab formation and healing of lesions within 24 hours) to 0.1% idoxuridine iontophoresis at 0.6 mA for 15 minutes. In another group of patients with multiple lesions, random noncontiguous lesions were treated with iontophoresis. All treated lesions showed a "major response" compared with the untreated lesions, of which six showed no response and two showed "some response" (defined as some improvement, but it is unclear whether this was significant). Henley-Cohn and Hausfeld<sup>41</sup> also successfully treated four patients with iontophoresis of 5% acyclovir ointment.

Gangarosa et al.<sup>42</sup> successfully treated two cases of herpetic whitlow with idoxuridine iontophoresis. Treatment resulted in rapid relief of discomfort and swelling, rapid appearance and coalescence of vesicles, and rapid healing. No recurrences were noted in these two patients after 42 and 38 months, respectively.

Lekas<sup>39</sup> successfully treated aphthous stomatitis with iontophoresis of triamcinolone acetonide suspension, 40 mg/ml, with 0.2 mA for 10 minutes. Five patients in the prodromal stage experienced immediate relief of discomfort, whereas one patient with lesions beyond the prodromal stage required 36 hours to achieve relief.

**Miscellaneous applications.** Iontophoresis has been used in the treatment of other cutaneous con-

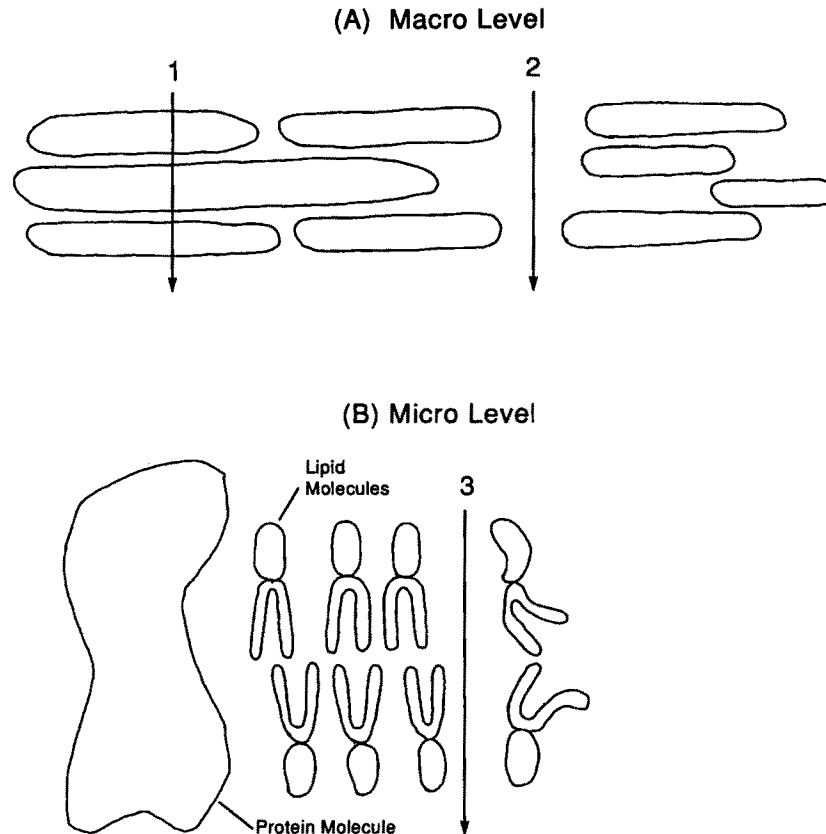
ditions. Cornwall<sup>43</sup> used zinc iontophoresis to treat ischemic leg ulcers in a patient with diabetes who had peripheral vascular disease. More than 98% wound closure was achieved after 20 days of iontophoretic application of a 0.1 mol/L solution of zinc oxide at a direct current between 4 and 5 mA.

Other reports of iontophoresis include hyaluronidase for treating scleroderma,<sup>44</sup> salicylic acid for treating plantar warts,<sup>45</sup> acetic acid for treating calcinosis cutis,<sup>46</sup> and iodine ointment for reducing scar tissue.<sup>47</sup>

### Iontophoretic devices

Several iontophoretic devices with different types of power sources are available. Iontophoretic devices are simple; they consist of two electrodes and a power source, which is either a battery (9 volt or 45 volt) or an on-line unit with a voltage regulator. Most units contain electronic timers and a meter for measuring current output. The Drionic unit (General Medical Co., Los Angeles, Calif.) is a widely accepted compact iontophoretic device.<sup>27, 28, 33</sup> Developed in 1984, the Drionic unit has been approved by the Food and Drug Administration for home treatment of hyperhidrosis. A battery-generated direct current is sent through two tap water-saturated wool pads that are placed on treatment sites, thus completing the circuit. Efficacy has been shown in several studies.<sup>27, 28, 33</sup>

The Phoresor II (Motion Control Inc., division of Iomed Inc., Salt Lake City, Utah) is widely used in physical therapy, medicine, and dentistry to treat musculoskeletal and inflammatory disorders through the delivery of drugs such as lidocaine and dexamethasone.<sup>21</sup> This device, powered by a 9 volt battery, has the added safety benefit of delivering a constant current achieved by automatically adjusting to changes in resistance that occur during iontophoresis. The Drionic unit and the Phoresor II are the two most widely used iontophoretic units. These ready-made units have the disadvantage of not allowing the operator to alter the physical characteristics of the electromotive signal, such as the frequency, shape of the wave, intensity of current, or on-off ratio of current. Different drugs might respond better to different iontophoretic stimuli. In addition, these systems do not permit the user to modify the composition and shape of the electrodes. Such modification may be desirable, depending on the drug being used and the anatomic site being treated. The commercially available devices are



**Fig. 2.** At the macro level (A), phonophoresis is thought to enhance drug penetration through the stratum corneum transcellularly (1), in a process termed *acoustic streaming*, or through increased pore size (2), in a process termed *ultrasonic stirring*. At the micro level (B), an alteration in lipid bilayer lipids results in enhanced drug diffusion through pores in the cell membrane.

portable and work well for most intended applications.

### PHONOPHORESIS

#### Technical characteristics and mechanism of action of phonophoresis

The term *ultrasound* refers to sound waves with frequencies beyond the human audible range of 20 kHz.<sup>48</sup> High-frequency waves, typically in the range of 800 to 1000 kHz, are generated by applying alternating current to a crystal, such as silicone dioxide or quartz. Through a phenomenon known as the piezoelectric effect, the electric current causes the crystal to undergo rhythmic deformation, producing ultrasonic vibrations. These vibrations, or pressure waves, are then transferred through a coupling medium to the tissue surface.<sup>49, 50</sup> In therapeutic phonophoresis, the coupling agent (i.e., gel or water) used to maximize energy transmission to tissues is replaced with the drug to be delivered.

Although the mechanism of action is not clear, ultrasound is thought to enhance drug delivery through the induction of thermal, chemical, and/or mechanical alterations in the involved tissues. Brown<sup>51</sup> suggested that ultrasound increased cell permeability and drug absorption by raising skin temperature.<sup>52</sup> Tissue warming is directly proportional to wave reflection and occurs between tissues of different impedance. Differences in impedance are minimal between skin, fat, and muscle, with a more significant difference existing between soft tissue and bone. Therefore the latter experiences the greatest warming.<sup>52</sup> Recent studies suggest that the small (1° to 20°) increase in skin temperature observed after ultrasound application is not the sole factor causing the changes in cutaneous permeability.<sup>53, 54</sup>

Chemical changes reported to occur during phonophoresis include the induction of an increased number of oxidation reactions,<sup>50</sup> inactivation of en-

**Table II.** Phonophoresis of topical anesthetics

Anesthetic	Frequency (kHz)	Energy (W/cm <sup>2</sup> )	Duration of treatment (min)	Test method	Effect on drug delivery
4% Lidocaine in oil <sup>67</sup>	Not documented	2	5	Homogenize tissue and optical density measurement	Increased
25% Lignocaine cream <sup>66</sup>	870	2	5	Needle prick	Insignificant
Aqueous lidocaine <sup>68</sup>	48	0.17	5	Reaction to voltage	Increased

zymes,<sup>50</sup> and formation of small gaseous bubbles induced by molecular splitting within cells, known as cavitation.<sup>53-55</sup> Increased adenosine triphosphate activity and increased cell membrane permeability are possible mechanisms.<sup>52</sup>

Increased tissue permeability has also been attributed to mechanical ultrasonic "stirring" and increased pore size.<sup>50</sup> Other studies suggest that ultrasound increases percutaneous absorption by inducing changes in stratum corneum lipid structure.<sup>48</sup> Ultrasound may increase cellular and vascular permeability by promoting movement of fluid across cell membranes, a process referred to as acoustic streaming (Fig. 2).<sup>56</sup>

### Historical background

Phonophoresis, the use of ultrasound to enhance the percutaneous absorption of drugs, was first reported by Fellingner and Schmid<sup>57</sup> in 1954. They demonstrated successful treatment of polyarthritis of the hand by driving hydrocortisone ointment into the inflamed area with ultrasound.

In 1963 Griffin and Touchstone<sup>58,59</sup> demonstrated that cortisol could be driven percutaneously into skeletal muscle and paravertebral nerve by ultrasound. The application of ultrasound increased the concentration of hydrocortisone by 100% in muscle and by 145% in neural tissue.<sup>60</sup> The concentration of hydrocortisone that penetrated the tissue was proportional to the intensity of ultrasound applied.<sup>58</sup> Phonophoresis has been used in a variety of nondermatologic conditions, most notably for the treatment of musculoskeletal disorders.<sup>48-50, 52, 55, 56, 61</sup> Hydrocortisone phonophoresis has been used successfully to treat strains, sprains, tendonitis, bursitis, and epicondylitis.<sup>62</sup> Recent reports have included successful phonophoresis of iodide bromide solution for treating osteoarthritis associated with gout attacks,<sup>63</sup> trolamine salicylate cream for muscle soreness,<sup>64</sup>

**Table III.** Advantages and disadvantages of iontophoretic and phonophoretic drug delivery

<b>Advantages</b>
Enhanced drug penetration (of selected drugs) over passive transport
Allows strict control of transdermal penetration rates
Permits rapid termination of drug delivery through termination of current or ultrasound
Skin remains intact, therefore low risk of introducing infection
Less anxiety provoking or painful than injection
Not immunologically sensitizing
In many cases, greater patient satisfaction
Home units available for iontophoresis
Less risk of systemic absorption than injection
<b>Disadvantages</b>
Can be time-consuming to administer
Minor tingling, irritation, and burning have been reported (these effects can often be minimized or eradicated with proper technique or current adjustment <sup>20</sup> )
Stratum corneum must be intact for effective drug penetration
Lowered efficacy with nonpolar drugs (iontophoresis only)

and interferon for herpetic keratitis.<sup>65</sup> Several workers have investigated the use of phonophoresis in the treatment of dermatologic disorders.

### Dermatologic applications of phonophoresis

**Anesthetics.** Most local anesthetics have poor topical skin penetration. Novak observed an increase in the concentration of lidocaine transmitted into rabbit subdermal tissues when topical application was followed by use of ultrasound.<sup>49</sup> In a double-blind, vehicle-controlled, crossover trial in healthy volunteers, McElnay et al.<sup>66</sup> reported no increase in absorption of lignocaine cream. There are several explanations for these contrasting results. McElnay et al. used lidocaine in a cream vehicle, whereas Novak<sup>67</sup> used lignocaine in oil. Other variables in-

clude differences in ultrasound frequencies and drug concentrations. Griffin and Touchstone<sup>60</sup> found that 250 kHz induced the highest penetration of drug, whereas 1000 kHz consistently resulted in the least amount of recovered cortisol. McElnay et al. did not state why they chose 870 kHz, a frequency closer to 1000 than 250 kHz. In addition, the method that McElnay et al. used to test absorption (pin prick) may not have been sensitive enough to detect differences in absorption.

Tachibana and Tachibana<sup>68</sup> showed that ultrasound in conjunction with a topical aqueous lidocaine solution was rapidly effective in inducing an anesthetic effect in the legs of hairless mice. Immersion in lidocaine without ultrasound did not produce analgesia. Similarly, use of ultrasound without lidocaine had no anesthetic effects.

These findings differed from those of Williams,<sup>69</sup> who used an electrical sensory perception threshold technique to study phonophoresis of topical benzocaine and dibucaine. With low-intensity ultrasound (0.25 W/cm<sup>2</sup>) and a high frequency (1.1 MHz), Williams found no detectable increase in the rate of anesthetic penetration.

In light of the differences in experimental variables and methods in these studies (Table II), more research is necessary to elucidate the factors that affect phonophoresis of anesthetics.

**Fluocinolone acetonide.** McElnay et al. investigated the influence of ultrasound on the percutaneous absorption of fluocinolone acetonide gel in a double-blind crossover trial (cited in Saxena et al.<sup>50</sup>). Percutaneous absorption, as measured by vasoconstrictor assay, was enhanced by ultrasound treatment, but the change in absorption was probably too small to be of clinical use.

**Amphotericin B.** Romanenko and Araviiskii<sup>70</sup> studied the effect of ultrasound on the delivery of topically applied amphotericin B ointment in guinea pigs. They found that amphotericin B content in the skin and subcutaneous fatty tissues was much higher when the drug was delivered in the presence of ultrasound. The highest levels of drug delivery produced involved preliminary treatment with dimethyl sulfoxide in combination with ultrasound.

**Suppurative wounds.** Phonophoresis has also been studied in the treatment of suppurative wounds. Levenets, Shuvalov, and Poliakov<sup>71</sup> found that the phonophoresis of ethylenediaminetetraacetic acid with the quinoxaline antibiotic dioxidine (2,3-diquinoxaline-1,4-dioxide)<sup>72</sup> was effective in acceler-

ating wound purification and elimination of necrotic tissues. Matinian et al.<sup>73</sup> similarly reported that the phonophoresis of a 1% papain solution together with dimethyl sulfoxide was an effective method for treating purulent wounds and inflammatory infiltrates. They found that phonophoresis of the aforementioned solutions almost halved the healing time.

**Keloids.** Ultrasound therapy with a water-based gel alone was reported to result in "complete flattening" of keloids in two young men when 1 MHz at 0.8 W/cm<sup>2</sup> was applied for approximately 4 minutes.<sup>74</sup> Long-term follow-up and controlled studies, however, must be done to further evaluate the efficacy of such treatment.

## CONCLUSION

Current evidence suggests that iontophoresis and phonophoresis are promising methods of enhancing topical delivery of both dermatologic and nondermatologic drugs (Table III). These methods may enable precise control of transdermal drug delivery rates by varying electrical current or ultrasound frequency.

Further controlled studies of these modalities are necessary to determine optimal techniques and conditions for safe and efficacious utilization. Future interest may also focus on systemic iontophoretic and phonophoretic delivery of peptide and protein drugs. Insulin and vasopressin have been delivered iontophoretically without the pain and side effects associated with traditional subcutaneous injection.<sup>5, 10</sup>

## REFERENCES

1. Ranade VV. Drug delivery systems: transdermal drug delivery. *J Clin Pharmacol* 1991;31:401-18.
2. Franz TJ. Transdermal delivery. In: Kydonieus A. Treatise on controlled drug delivery. New York: Marcel Dekker, 1992:364-72.
3. Tumell WJ. Therapeutic action of constant current. *Proc Royal Soc Med* 1921;14:41-52.
4. Leduc S. Introduction of medicinal substances into the depth of tissues by electric current. *Ann D'electrobiol* 1900;33:545-60.
5. Chien YW, Banga AK. Iontophoretic delivery of drugs. *J Pharm Sci* 1989;78:353-4.
6. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959;23:545-9.
7. Hall SK, Stableforth DE, Green A. Sweat sodium and chloride concentrations: essential criteria for the diagnosis of cystic fibrosis in adults. *Ann Clin Biochem* 1990;27:318-20.
8. Shaw JE, Prevo M, Gale R, et al. Percutaneous absorption. In: Goldsmith LA, ed. *Physiology, biochemistry, and mo-*

- lecular biology of skin. New York: Oxford University Press, 1991:1448.
9. Elias PM. Epidermal lipids, barrier function, and desquamation. *J Invest Dermatol* 1983;80(suppl):44S-9S.
  10. Chien YW, Siddiqui O, Shi M, et al. Direct current iontophoretic transdermal delivery of peptide and protein drugs. *J Pharm Sci* 1989;78:376-83.
  11. Abramson HA, Engel MG. Patterns produced in the skin by electrophoresis of dyes. *Arch Dermatol Syphilol* 1942;44:190-200.
  12. Grimnes S. Pathways of ionic flow through human skin in vivo. *Acta Dermatol Venereol (Stockh)* 1984;64:93-8.
  13. Burnette RR, Marrero D. Comparison between the iontophoretic and passive transport of thyrotropin releasing hormone across excised nude mouse skin. *J Pharm Sci* 1986;75:738-43.
  14. Cullander C, Guy RH. Sites of iontophoretic current flow into the skin: identification and characterization with the vibrating probe electrode. *J Invest Dermatol* 1991;97:55-64.
  15. Phipps JB, Padmanabhan RV, Lattin GA. Iontophoretic delivery of model inorganic and drug ions. *J Pharm Sci* 1989;78:365-9.
  16. Behl CR, Kumar S, Malick AW, et al. Iontophoretic drug delivery: effects of physicochemical factors on the skin uptake of nonpeptide drugs. *J Pharm Sci* 1989;78:355-60.
  17. Glass JM, Stephen RL, Jacobson SC. The quantity and distribution of radiolabeled dexamethasone delivered to tissue by iontophoresis. *Int J Dermatol* 1980;19:519-25.
  18. Gangarosa LP, Park NH, Fong BC. Conductivity of the drugs used for iontophoresis. *J Pharm Sci* 1978;67:1439-43.
  19. Gangarosa LP, Park NH, Hill JM. Increased penetration of nonelectrolytes into mouse skin during iontophoretic water transport (iontohydrokinesis). *J Pharm Exp Ther* 1980;212:377-81.
  20. Maloney M, Bezzant JL, Stephen RL, et al. Iontophoretic administration of lidocaine anesthesia in office practice. *J Dermatol Surg Oncol* 1992;18:937-40.
  21. Maloney MJ. Local anesthesia obtained via iontophoresis as an aid to shave biopsy. *Arch Dermatol* 1992;128:331-2.
  22. Bezzant JL, Stephen RL, Petelenz TJ, et al. Painless cauterization of spider veins with the use of iontophoretic local anesthesia. *J AM ACAD DERMATOL* 1988;19:869-75.
  23. Zeltzer L, Regalado M, Nichter LS, et al. Iontophoresis versus subcutaneous injection: a comparison of two methods of local anesthesia delivery in children. *Pain* 1991;44:73-8.
  24. Russo J, Lipman A, Comstock TJ, et al. Lidocaine anesthesia: comparison of iontophoresis, injection, and swabbing. *Am J Hosp Pharm* 1980;37:843-7.
  25. Kennard CD, Whitaker DC. Iontophoresis of lidocaine for anesthesia during pulsed dye laser treatment of port-wine stains. *J Dermatol Surg Oncol* 1992;18:287-94.
  26. Abell E, Morgan K. The treatment of idiopathic hyperhidrosis by glycopyrronium bromide and tap water iontophoresis. *Br J Dermatol* 1974;91:87-91.
  27. Shen J-L, Lin G-S, Li W-M. A new strategy of iontophoresis for hyperhidrosis. *J AM ACAD DERMATOL* 1990;22:239-41.
  28. Akins DL, Meisenheimer JL, Dobson RL. Efficacy of the Drionic unit in the treatment of hyperhidrosis. *J AM ACAD DERMATOL* 1987;16:828-32.
  29. Gruszkiewicz J, Doron Y, Guilburd JN, et al. Hyperhidrosis and its surgical treatment. *Acta Neurochir* 1986;81:128-31.
  30. Sloan JB, Soltani K. Iontophoresis in dermatology. *J AM ACAD DERMATOL* 1986;15:671-84.
  31. Gordon BI, Maibach HI. Eccrine anhidrosis due to glutaraldehyde, formaldehyde, and iontophoresis. *J Invest Dermatol* 1969;53:436-9.
  32. Stolman LP. Treatment of excess sweating of the palms by iontophoresis. *Arch Dermatol* 1987;123:893-6.
  33. Holze E, Ruzicka T. Treatment of hyperhidrosis by a battery-operated iontophoretic device. *Dermatologica* 1986;172:41-7.
  34. Hill AC, Baker GF, Jansen GT. The mechanism of action of iontophoresis in the treatment of palmar hyperhidrosis. *Cutis* 1981;28:69-72.
  35. Holze E, Alberti N. Long-term efficacy and side effects of tap water iontophoresis of palmoplantar hyperhidrosis: the usefulness of home therapy. *Dermatologica* 1987;175:126-35.
  36. Dobson RL, Lobitz WC Jr. Some histochemical observations on the human eccrine sweat glands: II, pathogenesis of miliaria. *Arch Dermatol* 1957;75:653-66.
  37. Rapperport AS, Larson DL, Henges DF, et al. Iontophoresis: a method of antibiotic administration in the burn patient. *Plast Reconstr Surg* 1965;36:547-52.
  38. Rigano W, Yanik M, Barone FA, et al. Antibiotic iontophoresis in the management of burned ears. *J Burn Care Rehabil* 1992;13:407-9.
  39. Lekas MD. Iontophoresis treatment. *Otolaryngol Head Neck Surg* 1979;87:292-8.
  40. Boxhall M, Frost J. Iontophoresis and herpes labialis. *Med J Aust* 1984;140:686-7.
  41. Henley-Cohn J, Hausfeld JN. Iontophoretic treatment of oral herpes. *Laryngoscope* 1984;94:118-21.
  42. Gangarosa LP, Payne LJ, Hayakawa K, et al. Iontophoretic treatment of herpetic whitlow. *Arch Phys Med Rehabil* 1989;70:336-40.
  43. Cornwall MW. Zinc iontophoresis to treat ischemic skin ulcers. *Phys Ther* 1981;60:359-60.
  44. Popkin RJ. The use of hyaluronidase by iontophoresis in the treatment of generalized scleroderma. *J Invest Dermatol* 1951;16:97-102.
  45. Gordon AH, Weinstein MV. Sodium salicylate iontophoresis in the treatment of plantar warts. *Phys Ther* 1969;49:869-70.
  46. Kahn J. Acetic acid iontophoresis for calcium deposits. *Phys Ther* 1977;57:658-9.
  47. Tannenbaum M. Iodine iontophoresis in reducing scar tissue. *Phys Ther* 1980;60:792.
  48. Tyle P, Agrawala P. Drug delivery by phonophoresis. *Pharm Res* 1989;6:355-61.
  49. Wells PN. Biomedical ultrasonics. New York: Academic Press, 1977:421-30.
  50. Saxena J, Sharma N, Makoid MC, et al. Ultrasonically mediated drug delivery. *J Biomater Appl* 1993;7:277-96.
  51. Brown SA. Transdermal delivery of drugs I: relationship of drug agents and carriers in skin penetration. *Dermatol Rep* 1987;6:1, 2, 8.
  52. Newman JT, Nellermeoe MD, Carinett JL. Hydrocortisone phonophoresis. *J Am Podiatr Med Assoc* 1992;82:432-5.
  53. Knutson K, Potts RO, Guzek DB, et al. Macro and molecular physical-chemical considerations in understanding drug transport in the stratum corneum. *J Controlled Release* 1985;2:67-87.
  54. Mumtaz AD, Lawrence AC, Crum A, et al. The effect of therapeutic ultrasound on electrophysiological parameters of frog skin. *Ultrasound Med Biol* 1989;5:461-70.

55. Nelson PA, Herrick JF, Krusen FH. Ultrasonics in medicine. *Arch Phys Med Rehabil* 1950;31:6-19.
56. Wyper DJ, McNiven DR, Donnelly TJ. Therapeutic ultrasound and muscle blood flow. *Physiotherapy* 1978; 64:321.
57. Fellinger VK, Schmid J. Intraarticulare cortisontherapie. *Wien Klin Wochenschr* 1952;64:377-9.
58. Griffin JE, Touchstone JC. Ultrasonic movement of cortisol into pig tissue: I, movement into skeletal muscle. *Am J Phys Med* 1963;42:777-85.
59. Griffin JE, Touchstone JC. Ultrasonic movement of cortisol into pig tissue: II, movement into paravertebral nerve. *Am J Phys Med* 1965;44:20-5.
60. Griffin JE, Touchstone JC. Effects of ultrasound frequency on cortisone into swine tissue. *Am J Phys Med* 1972;51:62-78.
61. Pottenger FJ, Karalfa BL. Utilization of hydrocortisone phonophoresis in United States Army Physical Therapy Clinics. *Mil Med* 1989;154:355-8.
62. Griffin JE, Eternach JL, Price RE. Patients treated with ultrasound driven hydrocortisone and with ultrasound alone. *Phys Ther* 1967;47:594-601.
63. Kamenskaia NS, Fedorova NE. The therapeutic use of iodide-bromide-sodium chloride baths combined with hydrocortisone phonophoresis in patients with osteoarthritis and gout. *Vopr Kurorto Fizioter Lech Fiz Kult* 1990;6:47-50.
64. Ciccone CD, Leggin BG, Callamaro JJ. Effects of ultrasound and trolamine salicylate phonophoresis on delayed-onset muscle soreness. *Phys Ther* 1991;71:666-75.
65. Vin'Kova GA. The combined treatment of recurrent forms of herpetic keratitis. *Oftalmologicheskii Z* 1989;4:221-4.
66. McElnay JC, Mathews MP, Harland R, et al. The effect of ultrasound on percutaneous absorption of lignocaine. *Br J Clin Pharmacol* 1985;20:421-4.
67. Novak FJ. Experimental transmission of lidocaine through intact skin by ultrasound. *Arch Phys Med Rehabil* 1964; 64:231-2.
68. Tachibana K, Tachibana S. Use of ultrasound to enhance the local anesthetic effect of topically applied aqueous lidocaine. *Anesthesiology* 1993;78:1091-6.
69. Williams AR. Phonophoresis: an in vivo evaluation using three topical anaesthetic preparations. *Ultrasonics* 1990; 28:137-41.
70. Romanenko IM, Araviiskii RA. Comparative levels of amphotericin B in the skin and subcutaneous fatty tissue after cutaneous application of amphotericin ointment by phonophoresis and with preliminary treatment by dimethyl sulfoxide. *Antibiot Khimioter* 1991;36:29-31.
71. Levenets AA, Shuvalov SM, Poliakov AV. The effect of the disodium salt of ethylenediaminetetraacetate on the healing of experimental suppurative wounds. *Stomatologiya (Mosk)* 1989;68:14-6.
72. Abilev SK, Abdrazakov MM. Organ specificity of DNA damaging activity of dioxidine. *Genetika* 1991;27:2039-41.
73. Matinian AL, Nagapetian KH, Amirian SS, et al. Papain phonophoresis in the treatment of suppurative wounds and inflammatory processes. *Khirurgiya (Mosk)* 1990;9:74-6.
74. Walker J. Ultrasound therapy for keloids [Letter]. *S Afr Med J* 1983;64:270.

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