Iontophoresis- A New Generation Approach Through Transdermal Route

V. Ravi Sankar1*, Y. Dastagiri Reddy1, N. Vijaya Bhaskar1, Audi Naryana2, N. Prathyusha1, Sophia1

Abstracts: This technique facilitates the movement of ions across a membrane under the influence of an externally applied electric potential difference, is one of the most promising physical skin penetration enhancing method. The rationale behind using this technique is the capability of this method to increase the systemic delivery of high molecular weight compounds with controlled input kinetics and minimum inter-subject variability, which is otherwise achieved only when parenteral route of administration is used. Recently, good permeation of larger peptides like insulin has been achieved through this technique in combination with chemical enhancers. This review briefly describes the factors which affect Iontophoretic drug delivery and summarizes the studies conducted recently using this technique in order to achieve higher systemic absorption of the drugs having low passive diffusion otherwise. The effect of permeation enhancers (chemical enhancers) on Iontophoretic flux of drugs has also been described. Present review also provides an insight into reverse Iontophoresis. Various parameters which affect the transdermal absorption of drugs through Iontophoresis like drug concentration, polarity of drugs, pH of donor solution, presence of co-ions, ionic strength, electrode polarity etc. have also been reviewed in detail.

Key Words: Iontophoresis, electric current, potential difference, transdermal, permeation enhancers.

INTRODUCTION

The Iontophoresis is a process which involves increased transport of solute molecules into a tissue using an electric current. This technique has been employed for the delivery of ionic drugs for local and systemic therapeutic effects in clinical settings. Transdermal administration of drugs is rapidly assuming an important place in modern drug therapy and is primarily used for non-ionized drugs requiring a relatively small dosage (1, 2). Transdermal administration can be passive or facilitated. In passive administration, the drug traverses the skin governed primarily by the laws of passive diffusion of the non-ionized drug through the rate-limiting membrane, the stratum corneum. Often times a chemical penetration enhancing system is incorporated. Ionized drugs, however, do not easily penetrate this barrier and are not suitable for routine transdermal dosage forms unless an external source of energy is provided to drive the drug across the skin. Facilitated diffusion can utilize either ultrasound (phonophoresis) or electrical (Iontophoresis) energy.

In Iontophoresis (IP), this external source of energy is in the form of an applied direct electrical current. Electrical energy assists the movement of ions across the stratum corneum according to the basic electrical principles of “like charges repel each other and opposite charges attract.” In practice, a solution of the drug in a pad or a gel is placed on the skin. An active electrode is placed on this pad or gel and the return electrode placed elsewhere on the body. A small electric current, usually less than 1 mA, is applied for a time period, usually 15 to 20 minutes. The drug travels through the tissue and is available for its local effect or is picked up by the microcirculation for an eventual systemic effect. Advantages of IP include (1) providing for controlled delivery rates (through variations of current density, pulsed voltage, drug concentration and ionic strength), (2) eliminating gastrointestinal incompatibility, erratic absorption, and first pass metabolism, (3) reducing side effects and interpatient variability, (4) avoiding the risks of infection, inflammation, and fibrosis associated with continuous injection or infusion since it is non-invasive and (5) enhancing patient compliance with a convenient and non-invasive therapeutic regimen. Iontophoresis creates a potential gradient through the skin tissue with an applied electrical current or voltage and induces an increased migration of ionic drugs into the skin by electrostatic repulsion at the active electrode: negative ions are delivered by the cathode and positive ions by the anode (1, 2). A typical Iontophoresis device consists of a battery, microprocessor controller, drug reservoir and electrodes. Most commonly, batteries in today’s devices are 9 volt. Drug reservoirs may consist of a gauze/ cloth or gel pad to which the solution is applied, or more commonly, the solution is injected through a port into the reservoir: electrode combination. Wires are then connected between the microprocessor unit and the active and passive electrodes, and the unit set for current and time. In the Iontophoresis process, the current, beginning at the device, is transferred from the electrode through the ionized drug solution as ionic flow. The drug ions are moved to the skin where the repulsion continues moving the drug through whatever pathways are available, namely pores and possibly through a disrupted stratum corneum. The drug-containing electrode is termed the active electrode and the other electrode is the passive electrode, which is placed elsewhere on the body. Current densities up to 0.5 mA, can be tolerated by the body with little or no discomfort. The larger the electrode surface, the greater the current the device must supply to provide a current density for moving the drug. Devices used for Iontophoresis formerly were large and cumbersome.

Today, however, the size of these devices ranges from the size of a penlight flashlight to the size of a Walkman radio. Some of the newer units incorporate the electrodes into the unit itself, thus eliminating the need for additional wiring. Projected for the near future will be small, flat units with self-contained batteries incorporated into a dosage unit the size of a “transdermal patch”. Miniaturization is now possible with smaller, more powerful batteries and electronics. The next generation Iontophoresis patch may also include an electronic record of the date, time and quantity of each dose delivered; providing information for determining patient compliance. Currently, however, Iontophoresis today involves the use of an Iontophoretic device attached to electrodes containing a solution of the drug. Rachna Prasad et al has studied on Transdermal Iontophoretic Delivery of Methotrexate: Physicochemical Considerations and concluded that The use of low energy electrical current is very effective in increasing the skin permeability to methotrexate. The methotrexate permeation was found to be more with poly (acrylamide) patch as compared to poly (acrylamide-acrylic acid). Changing the crosslinking density of hydrogel can be used for controlling the drug permeation. Ethanol when used with Iontophoresis showed 61% enhancement as compared to passive control. Mohammad Al-Khalili et al has studied on Iontophoretic Transdermal Delivery of Buspirone Hydrochloride in Hairless Mouse Skin and conclude that and concluded that terpenes were more effective than Iontophoresis alone in enhancing BH transdermal delivery across hairless mouse skin. However, the combination of terpenes and Iontophoresis generally resulted in a synergistic increase in BH flux. Moreover, menthol was the most effective enhancer relative to cineole and terpineol where the combination of Iontophoresis with menthol delivered 10 mg/
cm²/day from HPMC gel. At this delivery rate, it is possible to easily achieve a daily dosage of BH of 50 mg/day with a 5cm² patch on the skin (2, 3). Although the daily dose of BH is much lower than this, at this point this high delivery rate may be justified, given that human skin is known to be several times less permeable than hairless mouse skin. Sang Youl Rhee et al studied on Clinical Experience of an Iontophoresis Based Glucose Measuring System and concluded that the present study shows that as yet RIGMD is not sufficiently reliable or accurate enough to replace conventional methods of monitoring glucose. However, if the device could be made more accurate and convenient we believe that it would offer a highly effective means of glucose level self-testing Vikram Kotwal et al studied on Enhancement of Iontophoretic Transport of Diphenhydramine Hydrochloride Thermosensitive Gel by Optimization of pH, Polymer Concentration, Electrode Design, and Pulse Rate and concluded that Lutrol F-127 could be used to formulate a thermosensitive gel for iontophoresis that will gel upon application to skin. Because of neutralization of skin charges and complete ionization of DPH, permeation was significantly enhanced at pH 4.2. Because of an increase in surface repulsion and periodic depolarization of skin, pulsed iontophoresis using a disk electrode showed better flux enhancement, and iontophoretic transport of DPH was almost twice as much as for passive transport. The present study demonstrated the feasibility of DPH transdermal transport through Lutrol gel

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<tr>
<th>Medication</th>
<th>Polarity</th>
<th>Indications for Use</th>
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<tbody>
<tr>
<td>Dexamethasone (0.4%)</td>
<td>Negative</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Acetic Acid (4%)</td>
<td>Negative</td>
<td>Calcium deposits, keloid scarring, myositis Ossificans, calcific tendinitis</td>
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<tr>
<td>Lidocaine</td>
<td>Positive</td>
<td>Pain</td>
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<tr>
<td>Ketoprofen (10%)</td>
<td>Negative</td>
<td>Chronic Inflammation</td>
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<td>Sodium Diclofenac</td>
<td>Negative</td>
<td>Inflammation</td>
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<tr>
<td>Sodium Salicylate</td>
<td>Negative</td>
<td>Plantar Warts, Inflammation</td>
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<tr>
<td>Sodium Chloride</td>
<td>Negative</td>
<td>Scar Tissue, Adhesions</td>
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<tr>
<td>Potassium Iodide (10%)</td>
<td>Negative</td>
<td>Scar Tissue</td>
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<td>Zinc Oxide</td>
<td>Positive</td>
<td>Slow Healing Ulcers</td>
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<td>Naproxen Sodium</td>
<td>Positive</td>
<td>Inflammation</td>
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<td>Magnesium Sulfate</td>
<td>Positive</td>
<td>Muscle Spasm</td>
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<td>Copper Sulfate</td>
<td>Positive</td>
<td>Fungal Infections</td>
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Table 1: List of drug with their polarity and usage

Figure 1: Iontophoresis mode of working

Figure 2: Iontophoretic moment of drug through skin

Figure 3: Moment of drug influenced by the Iontophoretic current

Figure 4: Different shapes of transdermal patches
by iontophoresis. Arzu kaya et all has studied on Direct current therapy with or without lidocain in mayofacial pain syndrome and concluded that the method is cheap, easily applicable and non-invasive with the potential to induce less side effects. Muneeza Rizwan has studied on Treatment of idiopathic facial hirsutism with medroxyprogesterone acetate iontophoresis and concluded that iontophoretic administration of MPA is a potentially simple, cost effective, safe and reasonably effective method for the treatment of hirsutism. Since this is a pilot study, results can potentially be improved by any or all of the following measures

- By increasing the concentration of MPA
- By increasing the frequency of application of the drug
- By increasing the time duration of iontophoresis in each sitting
- By reversing the polarity of the electrodes periodically so as to benefit both the treatment sites.

This relatively simple methodology can be utilized in future to treat a very common problem among the females belonging to every subset of the community. Sibel Lbasmifi tamer has studied on Passive and Iontophoretic Delivery of Sildenafil Through the Skin and it was concluded that there are several factors affecting sildenafil penetration. The Clear gel may affect the skin cells. All observations suggest that the main penetration process for sildenafil occurs mainly via electro osmosis, but other mechanisms may also be involved. It was concluded that the dermal application of sildenafil and application of Iontophoretic delivery may be useful; it was found to be an effective and safe alternative route. Yannic B. Schuetz et all has studied on Iontophoretic delivery of peptides: structure-permeation relationships and concluded that The donor formulation, as well as the amino acid sequence, strongly influence the Iontophoretic transport of peptides through the skin. The computational assessment of peptide physicochemical properties enables the prediction of the relative impact of molecular properties affecting transdermal Iontophoretic peptide transport and this may prove useful in determining the optimal sequence of a therapeutic candidate for Iontophoretic delivery. Vinod labhasetwar et all has studied on Iontophoresis for modulation of cardiac drug delivery in dogs and concluded that is advantageous compared with other Iontophoresis protocols in which electrical current is passed through cardiovascular tissues, raising the possibility of electrically induced trauma or electro physiologic stimulation. Other controlled-release methods, electromagnetism and ultrasound, have also been demonstrated to successfully regulate implant drug release kinetics. However, HCM Iontophoresis is particularly well suited for long-term and self-contained arrhythmia-related implants, because of the low energy requirements with this form of delivery. Furthermore, HCM Iontophoresis offers the possibility of electrical control both the Iontophoresis system and a feedback-related ant arrhythmic device, such as a pacemaker or implantable defibrillator.

History
There has been a resurgence of interest in Iontophoresis in the medical profession. Why call it a renaissance of Iontophoresis in this day and age? We’ve known about galvanic current for about 200 hundred years and Iontophoresis (a word derived from Greek meaning the transport of electrically charged chemicals called ions) through skin was
Drug delivery begins when the electrical current is applied to the transdermal system. This happens after the patient presses the dosing button twice within 3 seconds. Once activated, the system cannot deliver additional doses and drug delivery cannot be interrupted or extended. The system is designed to operate for 24 hours after the first activation and allow up to 6 doses per hour for a maximum of 80 doses, after which the system shuts off and a new transdermal system will need to be applied if this type of fentanyl therapy is to be continued. Once activated, the system provides audible (beep) and visual (red light) indications that a dose has begun. The light turns off momentarily when the dose has been completed, then flashes to indicate the approximate number of doses delivered. One flash represents delivery of 1 to 5 doses, 2 flashes represent delivery of 6 to 10 doses, etc. The maximum number of doses allowed by this Transdermal system is 80; therefore, the maximum number of flashes is 16.8. The Transdermal system uses a series of audible alerts to indicate a malfunction. A short series of beeps indicates the system should be restarted. A continuous beeping indicates the system has shut down and should be removed.

With titration to analgesic effect with the fentanyl 40 mcg Iontophoretic system, serum concentrations were in the range of 0.4 to 1.5 ng/mL over the 24-hour dosing period. Administration of the maximum number of doses over the shortest possible time (90 doses delivered over approximately 13 hours) resulted in serum fentanyl concentrations in the range of 1.51 to 2.37 ng/mL.

### Pharmacokinetics

The site of application can influence the pharmacokinetic profile of this transdermal system. However, the pharmacokinetic parameters are similar when the transdermal system is applied to the recommended sites of application, the upper outer arm or chest. Application at the lower inner arm resulted in 20% reduced delivery. Other application sites were lower when the system was applied to the chest. Both peak concentration and AUC24-25 were lower when the system was applied to the lower inner arm (peak concentration, 2.3 mcg/h, AUC, 0.757 mcg•h/L) compared to application to the upper outer arm and 1.176 mcg/L when the system is applied to the chest. The area under the curve at 24 to 25 hours (AUC24-25) was 1.033 mcg•h/L with application to the upper outer arm and 1.105 mcg•h/L with application to the chest. Both peak concentration and AUC24-25 were lower when the system was applied to the lower inner arm (peak concentration, 0.859 mcg/L; AUC, 0.757 mcg•h/L). The amount of fentanyl absorbed is proportional to the amount of current applied. A current of 170 mcA resulted in absorption of fentanyl 39.5 mcg during a 10-minute period of activation. The amount of fentanyl absorbed from this system increases as a function of time and is independent of both dosing frequency and the total number of doses. The reason for the increase in absorption is not known, but it has been suggested that it may be related to alterations in the electric conduction properties of the skin, which may occur as the skin adapts to the current from the system.

Administration of a 40 mcg dose with a 10-minute electrical current resulted in levels below quantification in some subjects during the first hour of administration, but all participants had measurable levels at 12 to 13 and 23 to 24 hours after application. With repeated administration of the 40 mcg dose over 1 to 3 days, the time-to-peak concentration was 1 to 2 hours and the half-life was 11.4 to 14.2 hours. A lag of approximately 5 minutes has been observed between the end of the dose from the Transdermal system and the onset of a decline in serum fentanyl concentration.

The rate of decline is also slower than that observed after discontinuation of intravenous (IV) administration but substantially quicker than that observed with the fentanyl transdermal patch, which creates a subcutaneous depot that slowly releases the drug. When the system has been applied without activating the current, the mean absorption rate for fentanyl over 24 hours was 2.3 mcg/h. Fentanyl has exhibited a 3-compartment disposition model, with an initial distribution half-life of about 6 minutes, a second distribution half-life of about 1 hour, and a terminal elimination half-life of about 16 hours.

### Warnings and Precautions

The warnings and precautions for this dosage form are similar to those with other fentanyl dosage forms. Unlike the transdermal patch and transmucosal lozenge, this dosage form is not restricted to patients with pre-existing opioid tolerance. The dose released with this dosage form is for the treatment of acute pain and may not provide adequate analgesia for patients with pre-existing opioid tolerance. Patients on chronic opioid therapy or with a history of opioid abuse should be evaluated frequently to make sure they are receiving adequate analgesia.
adequate analgesia with the transdermal system. Patients undergoing treatment with the fentanyl iontophoretic system should be under supervision of medical personnel with expertise in the detection and management of hyperventilation, including airway management and the use of opioid antagonists. Patients experiencing adverse reactions, including overdose, will require continued monitoring after removal of the system because serum fentanyl levels gradually decline, with a mean terminal elimination half-life of 11 hours. As with other forms of PCA, only the patient should activate the fentanyl iontophoretic transdermal system to avoid potential overdosing. More than one system should not be applied to a patient at the same time. Use of the fentanyl system resulting in ingestion or contact with mucous membranes, or unintended exposure to the fentanyl hydrogel, could lead to absorption of a potentially lethal dose of fentanyl. The hydrogels should not come into contact with fingers or mouth. If the fentanyl hydrogel becomes separated from the system, contact can be harmful. If the hydrogel becomes separated from the system during removal, gloves or tweezers should be used to remove the hydrogel from the skin. The skin area that had been in contact with the hydrogel should be thoroughly flushed with water. Soap, alcohol, or other solvents should not be used to remove the hydrogel, because they may enhance the ability of fentanyl to penetrate the skin. If the system falls off, the entire system should be collected and properly disposed.

Prior to patient discharge from the hospital, medical personnel must remove the system and dispose of it properly. Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations and may occur at any time during therapy, particularly in patients with an underlying pulmonary condition or who are receiving doses of opioids or other CNS drugs associated with hypoventilation in addition to fentanyl. The respiratory effects of fentanyl should be monitored by clinical evaluation, including oxygen saturation, respiratory rate, and degree of sedation. Fentanyl iontophoretic should be used with caution in patients with pre-existing medical conditions predisposing them to hypoventilation. The fentanyl iontophoretic system should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention, such as patients with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. The fentanyl system should be used with caution in patients with brain tumours. Fentanyl may produce bradycardia in some patients. Fentanyl iontophoretic should be used with caution in patients with brady1080 Volume 41, November 2006 arrhythmias. Limited information is available on the use of fentanyl iontophoretic in patients with renal or hepatic function impairment; the fentanyl system should be used with caution in such patients. The system should be applied to intact, nonirritated, and nonirritated skin on the upper outer arm or chest. Application to the inner lower arm results in less fentanyl absorption. Applications to other sites, such as the legs or abdomen, have not been studied. Care should be taken to avoid contact of the system with water. Exposure to water may cause the system to fall off or stop working. Topical skin reactions (eg, erythema, sweating, vesicles, papules/pustules) may occur after removal of the fentanyl system. Such reactions are typically limited to the application-site area and resolve without treatment. If a severe skin reaction is observed, it should be treated with a topical antiseptic/antibiotic as appropriate. Because the system uses a series of audible signals to alert patients or caregivers when a dose is not being delivered in response to a patient’s attempt to activate a dose, the system should be used with caution in patients with high-frequency hearing impairment. Testing instructions should be used to demonstrate the audible tone for patients if there is a question regarding the patient’s ability to hear the tone. The fentanyl system contains metal parts and should be removed prior to a magnetic resonance imaging procedure, cardioversion, or defibrillation to avoid damage to the system. The system also contains radiopaque components and may interfere with an x-ray or computerized axial tomography scan. The low-level electrical current provided by the system does not result in electromagnetic interference with other electromechanical devices, such as pacemakers or electrical monitoring equipment. In elderly patients 65 years of age and older, no overall differences in safety or effectiveness were observed with the fentanyl system compared with younger subjects. The incidence of hypotension, confusion, hypokalemia, hypoxia, and hypoventilation was increased in the elderly population compared with subjects 18 to 64 years of age. The fentanyl iontophoretic system is not recommended for use in children. Safety and efficacy have not been adequately studied in patients younger than 18 years of age. Preliminary studies with a lower iontophoretic dose suggested children were more vulnerable to application-site reactions. The reactions tended to be more severe than in adults. Fentanyl is in Pregnancy Category. There are no studies assessing the fentanyl iontophoretic system in pregnant women. The fentanyl system should only be used if the potential benefit justifies the potential risk to the fetus. Use of the system is not recommended for analgesia during labor and delivery, because fentanyl readily passes across the placenta to the fetus. Fentanyl is excreted in human milk. The fentanyl iontophoretic system is not recommended for use in breast-feeding women because of the risk of sedation and/or respiratory depression in the breastfeeding infant.

BIOCYCLIC TRANSCEREBRAL IONTOPHORESIS

Bioccular transcerebral iontophoresis (BTI) is a treatment that was developed around 1920 by Georges Bourguignon, M.D., D.Sc., who was a neurologist and neuropathologist and a member of the French Academy of Medicine. It was first used to treat World War I soldiers who were suffering from sequelae of head injuries. BTI treatments have been successfully used with those who have affections of the brain not only following head trauma (such as epilepsy or paralysis), but also due to inflammation (such as multiple sclerosis), infection (encephalitis and Bell’s palsy), stroke (hemiplegia) and hypoxia (cerebral palsy or due to respiratory arrest). Other conditions that have also been helped are sequelae from damage to the eyes (such as retinitis and optic neuritis) and spinal cord (such as following spinal cord injury, or inflammation, like transverse myelitis). Dr. Joseph Saine who learned this method of treatment from Professor Bourguignon supervised thousands of BTI treatments over a period of 50 years in his clinic in Montreal. In particular, he treated many patients with multiple sclerosis and epilepsy with marked improvement.

Principles of Treatment

A tiny, painless and barely perceptible direct electrical current is transmitted from the eyes through the brain to the neck and back. This micro-electrical current carries different ions (ie, calcium, magnesium, iodide, etc.) through the brain and spinal cord from one electrode to the other. The rehabilitation of neural tissue and restoration of function are likely achieved by decreasing scar tissues in the eyes, brain or spinal cord and improving circulation which helps to regulate function and repair neural tissue. Bio-medical researchers have also demonstrated that DC electrical fields can stimulate regeneration of nerve cells.

Method

The duration of the treatment is approximately 30 minutes and is performed at first once or twice a day for 5 consecutive days. The frequency of treatment is decreased afterwards to 3 times a week, then once a week to once a month. During a BTI treatment, patients must lie quietly for the length of the treatment and therefore it is not always well-suited to children under 5, unless the child is particularly cooperative or when the treatment can be administered during sleep.
Prognosis
Positive results following BTI treatments are usually noticed within the first few treatments and are, as a rule, cumulative and lasting. Treatments are continued as long as the patient is improving. What improves in any individual patient is not predictable beforehand, as benefits are limited by the degree of the permanency of the neural tissue lesions.

Side Effects
BTI treatments have been used on many thousands of patients since 1920. Side effects from BTI treatments when administered by a well-trained person are minimal to none and, most commonly, only mild and short-lasting skin irritations.

Iontophoresis: Maximizing Treatment Effectiveness
For physically active people, exercise inevitably leads to muscle soreness and joint stiffness. This is normal and expected. But when soreness gives way to inflammation and pain, clinicians look for a quick fix to get people back in action. To do so, we have numerous treatment options, one of which is iontophoresis. Unfortunately, many clinicians undervalue this modality. Some feel their training is outdated or inadequate, while others believe it’s too costly when treating conditions such as tendinitis, bursitis, fasciitis, neuritis and synovitis. However, new research shows iontophoresis is both an efficacious and cost-effective method for treating these conditions. Iontophoresis is indicated for acute and chronic inflammation, localized pain, fungal infection, small ulcers, calcium deposits, trigger points and even plantar warts. It’s most widely used to control inflammation and pain associated with tendinitis, bursitis and other common inflammatory conditions. It also can be used to treat calcification in muscles and tendons. Numerous reports, in fact, have demonstrated decreased size of calcifications, such as bone and heel spurs, and myositis ossificans. Iontophoresis introduces a topically applied, physiologically active ion into the epidermis and mucous membranes of the body using continuous, low-volt, direct current.1 The analogy of the magnet is a good one to envision how iontophoresis works. Like a magnet, negatively charged ions are repelled by the negative electrode, while positively charged ions are repelled by the positively charged electrode. The notion of driving the medication into the skin, like an injection, is unfounded. The process by which iontophoresis occurs relies much more on the laws of passive diffusion. With this modality, we can administer medications to target tissues up to a depth of 1 centimeter to 3 centimeters.2, 3 New versatile iontophoretic drug delivery units and newly designed electrodes have made iontophoresis safer and more effective than ever before.4 And recent research has indicated that iontophoresis is a safe and cost-effective alternative to injection therapy.

EFFICACY AND TREATMENT OPTIONS
Before using iontophoresis, we need to consider several factors. These include treatment goals, patient allergies to the proposed medication, drug interactions with other medications the patient is using, and the potential for effective depth of penetration, based on ion size and treatment parameters. To determine the risk of allergic reactions and drug interactions, we must be thorough in gathering a subjective history from the patient. We also must enlist the help of attending physicians and pharmacists to select the most appropriate medication. Finally, we must consider the size of the ion being used during treatment. Because iontophoresis therapy moves drug ions by electric current, the formulations must not contain competing ions, such as preservatives, antioxidants and buffering agents. Competing ions will alter polarity of the formula and decrease treatment effectiveness. If the solution contains active ingredients without competing ions, iontophoresis treatment will be more effective. Most commercially available injectable dexamethasone contains competing ions. Additionally, larger ions, such as cortisone and dexamethasone, are harder to deliver transcutaneously than smaller ions, such as ketoprofen.6 Dexamethasone, the gold standard for iontophoresis application, is an anti-inflammatory drug that can be used to treat various acute and chronic inflammatory conditions, including carpal tunnel syndrome,10 bicipital tendinitis, sub-acromial bursitis, patellar tendinitis, plantar fasciitis and iliotibial band friction syndrome. In fact, studies have found that iontophoresis using dexamethasone is 80 percent to 100 percent effective in reducing pain associated with carpal tunnel syndrome and shoulder tendinitis. Another study found iontophoresis using dexamethasone to be more effective than other modalities (including cross-friction massage) in decreasing pain, reducing inflammation and promoting tissue healing in patients with infrapatellar tendinitis. Additional authors advocate iontophoresis using dexamethasone to relieve pain and inflammation associated with plantar fasciitis and iliotibial band syndrome. Pain relief with dexamethasone is quick and often long-lasting. Unlike injection therapy, tissue trauma and systemic effects are eliminated. On average, conditions resolve in fewer than six treatment sessions. Along with dexamethasone, we can use other medications, including sodium salicylate, sodium diclofenac and ketoprofen. One study found sodium diclofenac more effective than sodium salicylate in treating patients with lateral epicondylitis. Sodium salicylate has been advocated in diminishing the size of plantar warts and the pain associated with the lesion.14 Sodium chloride can decrease scar tissue and promote increased scar mobility when combined with scar massage in clinical trials. Finally, lidocaine can temporarily relieve pain that’s unrelated to inflammation. In these cases, lidocaine can be delivered to a small painful region with effective, temporary pain relief. Consequently, many clinicians widely used iontophoresis to treat trigger points, using either lidocaine or dexamethasone. But one study investigating the effect of the modality on trigger point pain and pressure sensitivity found little difference between lidocaine iontophoresis and sham iontophoresis.

Maximizing Treatment Effectiveness
To get the best effects from iontophoresis, we should inspect the integrity and sensation of the skin to minimize the risk of burns. Skin that has abrasions or cuts will provide less resistance to the electrical current and, therefore, may require lower treatment intensities. Skin with altered or no sensation is a precaution as well. There’s a risk of tissue burns and blistering with iontophoresis. This occurs most commonly when high intensities are used and when the skin hasn’t been properly cleaned before applying iontophoresis. In most cases, when skin lesions occur, they’re small histamine blisters that aren’t painful and resolve within hours of the treatment. Be sure to clean the area with an alcohol wipe to decrease tissue resistance. Lightly abrading the skin or shaving the skin in the treatment area will further decrease tissue resistance. Dirt, oil, lotion and hair will increase the superficial tissue resistance and decrease the amount of medication that reaches the target tissue. Finally, for chronic conditions, apply moist heat prior to treatment in order to increase tissue permeability. Just like a hot shower opens the skin’s pores, using a moist hot pack before treatment will make the skin more permeable to medication. Manufacturers discourage the simultaneous use heat or ice when applying iontophoresis. When setting up the treatment, follow these steps to maximize effectiveness. First, be sure the polarity of the medication matches the polarity of the active electrode. Failing to match polarities will attract the medication to the active electrode, and little to no medication will be transferred to the skin. Next, look at treatment parameters, including medication dose, treatment intensity and treatment time. The typical treatment dose is 40 milliamper-minute, with the exception of acetic acid, which is typically 80 milliamper-minute.
are able to perform their own tenolysis by often indicated, although occasionally patients exercise does not always mobilize the tendon. Complication of tendon repairs because active surrounding tissues and prevents gliding of heals also causes it to adhere to the tendon gliding is often difficult for patients. TENDON ADHESIONS SD AND TIME. Current density is an important factor in determining treatment intensities. Normal skin can withstand 1 milliamp per centimetre squared, while fair skin can withstand less. Lower treatment intensities allow for the least amount of skin resistance and the greatest depth of penetration. Treatment intensities that are too high will lead to increased tissue resistance and an increased risk of burns and blistering. Depth of penetration of the medication is time dependant. As treatment time increases, skin resistance decreases and, therefore, a greater percentage of medication reaches deeper, target tissues. Select treatment intensities with the idea of maximizing depth of penetration. In general, the lower the intensity, the better the depth of penetration of the medication. Determine treatment intensities by the quality of the skin overlying the target tissues. Rough, calloused skin will provide more resistance to electrical flow than moist, supple skin. Therefore, when treating the plantar surface of the foot or the palmar surface of the hand, use lower intensities to enhance medication transfer. Because time and intensity are related, treatment time can be easily calculated, once you select an intensity. A 40 milliamp-minute dose delivered with a 1.0 milliamp intensity will require a 40-minute treatment. The same medication dose delivered at 2.0 milliamp intensity will require a 20-minute treatment time. Remember, higher intensities and shorter treatment times will most likely lead to a less effective treatment outcome. After traditional iontophoresis treatment, leave the active electrode and the medication in place for several hours. This allows for passive diffusion after the current has been removed. Using ice after treatment also can keep the medication in the area and further maximize the modality’s effects. For this same reason, it’s best to perform exercise, other modalities and massage before applying iontophoresis. These activities will increase localized blood flow, spreading the medication away from the target area and decreasing the effectiveness of the medication at the delivery site.

IONTOPHORESIS TO AID IN REDUCING TENDON ADHESIONS

Tendon gliding is often difficult for patients after they have had divided tendons repaired. The very process by which an injured tendon heals also causes it to adhere to the surrounding tissues and prevents gliding of the tendon. Adhesions are a frequent complication of tendon repairs because active exercise does not always mobilize the tendon. Surgical tenolysis to free the adhered tendon is often indicated, although occasionally patients are able to perform their own tenolysis by active and resistive exercises. Iontophoresis on one of our patients as an adjunct to active and resistive exercises to aid in reducing scar tissue from repair of the extensor digitorum tendons to the right middle finger. Some authors have written about the physical effects of the galvanic current used in iontophoresis. Clinicians must have an understanding of these effects before attempting to use iontophoresis. The human body may be considered from the viewpoint of electrotherapy as a bag made of skin holding a solution of common salt (NaCl). The flow of a direct current through the salt solution causes the positively charged sodium ions to migrate toward the negative electrode and the negatively charged chlorine ions to migrate toward the positive electrode. The ions cause a secondary chemical reaction at the electrodes. They form sodium hydroxide at the negative electrode and hydrochloric acid at the positive electrode, which may be described as a polar effect because it occurs only under the electrodes. The physiological effects include hardening of tissues under the positive electrode and softening of tissues under the negative electrode. The patient who received iontophoresis was a 29-year-old male music teacher who had difficulty playing the piano because of his inability to hyperextend adequately the metacarpophalangeal (MCP) joint to the middle finger on the involved hand. Seven weeks after tendon repair, the patient had 260 degrees total passive motion of the middle finger (ie, motion of three joints of one finger added together). With the hand of the patient resting on the tabletop and the volar surface down, the therapist could passively hyperextend the MCP joint of the middle finger 4 cm from the surface of the tabletop. With his hand in the same position, the patient only had adequate hyperextension to lift the finger 2 cm from the tabletop. The patient’s total active motion was 235 degrees. The patient had slight manual resistance to extension of the MCP joint. The additional tendon gliding required for hyperextension of the MCP joint appeared to be limited because of peritendinous adhesions. The ion I used for iontophoresis was iodine in the form of Iodex® with methyl salicylate ointment because it is sclerolytic and effective in reducing scar tissue. The iodine increases the extensibility of the scar and therefore increases the effectiveness of stretching following iontophoresis. The patient was positioned supine with his right leg supported on a pillow for comfort. Iodex® was massaged over the scar and surrounding area after cleaning the dorsal surface of the hallux and forefoot. Gauze pads (4 in X 4 in) were moistened in warm water and were applied evenly over the treatment area. Five folded moist paper towels were placed over the gauze. A tin electrode was molded to fit the contour of the toe and was held in place by an elastic strap. Care was taken to avoid folds in the towelling under the electrode that could cause areas of excessive current and subsequent burns. The tin electrode was connected to the negative pole of a low-volt generator with an alligator clip. The positive electrode was about one half the size of the negative electrode and was prepared in a similar manner but without the iodine ointment. The electrode was secured over the right anterior thigh. Firm contact was maintained with a light weight sandbag. The galvanic current flow was gradually increased to 5mA and held constant for 20 minutes. The patient experienced a mild tingling and warmth under both electrodes. After 20 minutes the current was slowly reduced, the electrodes removed, and the underlying skin inspected for irritation. The skin was massaged gently with Alkolave Gel and dusted with talcum powder to soothe the skin and control itching. Following iontophoresis, passive stretching and active flexion and extension of the distal interphalangeal joint was begun.
extension were employed to achieve additional range of motion while taking advantage of the loosened scar. The patient was instructed in a home program of range-of-motion exercises and proper heel-toe gait activities to be performed several times daily. Iontophoresis was administered for five consecutive days. Evaluation at the final treatment session revealed normal range of motion in flexion and extension of all joints of the great toe and a significant increase in muscle strength to a good grade. The patient was discharged with a home program of daily exercises to increase strength further. A six-month follow-up examination of the great toe revealed normal range of motion of all joints and normal strength of flexor and extensor muscles, with a gait pattern free of deviations.

**TREATING DAMAGED SKIN**

There has been a resurgence of interest in iontophoresis in the medical profession. Why call it a renaissance of iontophoresis in this day and age? We’ve known about galvanic current for about 200 hundred years and iontophoresis (a word derived from Greek meaning the transport of electrically charged chemicals called ions) through skin was demonstrated almost 100 years ago. Skin care therapists have used galvanic currents to treat skin for about 70 years -so what can be new? First activate the skin on negative current, then massage and finally soothe the skin on positive for a refreshed appearance. Right? No! Wrong! Of course these ideas are wrong because they ignore the basic scientific principles. First of all one has to understand that iontophoresis will only occur if the targeted active chemicals have an electrical charge (i.e. they are ions carrying either a positive or negative electrical charge, or will ionise with electricity). When a low intensity galvanic current is applied to a molecule that can dissociate into a positive ion (cation) and a negative ion (anion), then it dissociates more readily in the presence of water and salts. Negative ions move towards the positive pole, and positive ions move towards the negative pole. As a result ions can be carried to deeper layers of the skin and concentrated there. If a positive current is applied to the skin together with appropriate gels, then the positive pole will act exactly like a magnet (North Pole repels North Pole and alternately South Pole and vice versa) and repel cations and attract anions. Therefore, if one wants to facilitate the penetration of a cation then one has to apply a positive charge to the skin. However, if one wants to make an anion penetrate deeper into the skin, then one has to apply a negative charge. To understand iontophoresis better, then one must go back to the very first demonstration of its power. Two rabbits were selected and one poison that has a positive charge was applied to one ear and a poison with a negative charge was applied to the other ear. Only one ear was treated with an electrical current. When the positively ionised poison was treated with a negative current, nothing happened. When positive current was used then the rabbit died! So either positive current was responsible, or the positive poison ions moved through the skin into the blood and killed the rabbit (8). The second rabbit then proved that it was the ions because when a positive current was used, nothing happened, whereas when a negative current was used, the rabbit died! The only explanation was that the positive and negative ions had been repelled by their similar charges and had gone through the skin. This was a magnificent demonstration but unfortunately not enough people paid attention to it and it was lumped together with things like hypnosis and ignored by the medical profession. In recent years, research workers have looked again at iontophoresis and have tried to define its mysteries. As a result we’ve learned a great deal about iontophoresis and today research workers believe that iontophoresis can very often be as effective as injections into the skin or muscles. Diabetics may one day wear only a simple instrument like a watch and in that way dose themselves with enough insulin to keep them selves healthy. Other powerful medicines can even be taken more than 2 cms. Into the body by simple electrical currents. Iontophoresis promises to become a major method for treating people without the use of injections and other invasive techniques. The research workers have realised that we have to know certain properties about ions not merely that they can ionise. When a molecule that can be ionised at an appropriate pH is subjected to a galvanic current, the molecule ionises into its anion and cation. We have learned that the concentration of the ions is important. The strongest solution is not always the best. We also know now that the properties of the current are important. Certain wave shapes and intermittent application of the current are better than continuous galvanic current.

**There are Some Very Important Rules that have to be Followed when doing Iontophoresis**

- The selected molecule must be ionised into positive and negative components and be maintained as ions during the treatment. You cannot iontophorese chemicals that are not ionised.
- The size of the ion is important. For example even though a complex protein like collagen may be possible to ionise, the size of the important ion of collagen is so large that it cannot be transported through skin.
- There is a limit to the number of polar substances that can be used simultaneously. We believe that during iontophoresis "Pores" open up through membranes and the charged particles can move through them. If there are too many charged particles then the "pores" may be "blocked" by the crowd of ions converging all at once.
- The ion must be water-soluble because electricity is only conducted through water and not lipids.
- The pH of the active gel is of fundamental importance. The right ingredient at the right concentration won’t work properly if the pH is wrong. Each ion has its own ideal pH at which it will be ionised best.
- The current used must be appropriate. You cannot use any current you like.
- The current used should be high enough to be effective and still safe. The higher the current, the faster the ions will move.
- Intermittent current works better than continuous current because as the ion moves into the skin it will react with other chemicals and needs to be re-ionised. I have used the Environ® Ionzyme DF 1998 machine for the work that I have done.
- The treatment period should be at least 10 minutes and probably not longer than 30 minutes. Most of the ions pass
- Through the skin at about 8 to 15 minutes and then relatively little passes through after 30 minutes. I prefer to use a “field” of electrical charge rather than use rollers which produce rather localised effects. I use specialised gauze that retains moisture (Hazelgauese®) more effectively than any other gauze I have used.
- It is possible, maybe even highly desirable to treat skin with only one polarity. It is not necessary to treat the skin with
- The opposite current after doing the active treatment. If you do that then you will reverse the beneficial effects of the active treatment!
- Of course, the ion will only have positive effects if in fact scientific research has proved that it is effective. Ionising salt water into skin cannot have the same effects as ionising a proven rejuvenating vitamin ion into the skin.
- Iontophoresis when correctly used is proving to be a powerful tool. However, it does have problems. First of all it can only used on molecules that can be ionised. Not all molecules can be ionised at physiological levels and some cannot be ionised. Secondly, if strong currents are used and the current has built up too quickly when using simple galvanic current, then a burn may occur. One has to remember that in fact some very complex chemical changes occur at the exact site of the iontophoresis contact points. Strong
alkalis may be formed or strong acids may damage the skin. Modern iontophoresis has been used to minimise wrinkles, to eliminate pigment blemishes, soften scars and normalise skin. However, this only happens when the gels used contain the right ingredients, at the right pH, with the right concentration, treated with the correct current properties for the correct amount of time. Change only one of these important points and the treatment becomes a simple complex manipulation of skin and the client's purse\(^{(10,11)}\). With properly controlled iontophoresis up to 400% better penetration can be achieved under ideal conditions and the improvement of skin can be hastened quite dramatically. Schmidt published the results of iontophoresing retinoic acid or Estriol into skin scarred by acne. This gave results that are comparable with dermabrasion of the skin. Dermabrasion thins the skin and results in an artificial looking surface whereas iontophoresis of the skin nutrients actually makes the skin thicker, healthier and more beautiful. I have used both vitamin C and A to achieve this result in about 30 treatments done twice a week initially and then later once a week for 20 minutes on each occasion.

**CONCLUSION**

Iontophoresis is a process which involves increased transport of solute molecules into a tissue using an electric current has greater advantages not only in transdermal drug delivery but it has a wide scope in using for the treatment of Bioccular Transcerebral treatment, aids in releasing tissue adhesions, reducing scar tissue and treatment of damaged skin and also presently still there are number of researches going over the iontophoresis from this we conclude that iontophoresis is a third generation drug deliver and one of the most important drug delivery and many more researches to be under process.

**REFERENCES AND NOTES**