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REVIEW ON: IONTOPHORETIC DELIVERY OF DRUGS

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ABSTRACT

Iontophoresis is a safe and effective method of reducing excessive sweating of the hands and feet (hyperhidrosis) by using an electric current. The treatment involves immersing hands and/or feet in baths of shallow water. The machine discharges an electronic current through the water, which is produced by placing two electrodes in contact with the patient to form a current Iontophoretic drug delivery is now an accepted method of drug therapy which is gaining wide popularity especially in the area of pain relief. This technique provides a means for regulated non-invasive systemic administration of minute amounts of drug transdermally which is especially useful in patients who require long-term medication as in chronic pain, diabetics, hypertensives, rheumatoids etc. It negates the need for needle sticks, the pain and anxiety involved and minimises the trauma and risks of infection associated with it. This mode of drug delivery is simple, versatile, effective, reliable and can be tailored for individual needs.

Keywords: Iontophoresis, Dermatology, Hyperhidrosis, Neuropharmacology

INTRODUCTION

Iontophoresis is the method where the movements of ions across a membrane enhanced using an externally applied potential difference. When the Membrane under consideration is skin, the method is called transdermal iontophoresis. The principle barrier to the transport of the molecules into an across the skin is stratum corneum (SC),

this is the uppermost layer of the epidermis with a thickness of between 10-100 µm. The SC consists of several layers of corneocytes (a nucleate keratin filled cells) inlaid in a lipid matrix, a continuous medium through the SC, arranged mainly in bilayers **[1, 2]**. The intercellular lipids consist of approximately equal quantities of ceramides, cholesterols and free fatty acids **[3]**.

Iontophoresis is the passage of an Electrical current onto the skin. Iontophoresis has a variety of uses in medicine. This article discusses the use of iontophoresis to decrease sweating by turning off a sweat gland or glands The area to be treated is placed into water. A gentle current of electricity passes through the water. A technician carefully and gradually increases the electrical current until you feel a light tingling sensation. The therapy lasts about 10-20 minutes and requires several sessions. The maximum current to be given to adults is 20Ma.The Maximum current to be given to children is 15Ma.Children must always be accompanied by an adult, how iontophoresis works isn't exactly known, but it's thought that the process somehow plugs the sweat glands and temporarily prevents you from sweating. Iontophoresis units are also available for home use.

What Is Iontophoresis?

Different investigators have given different definitions because one simple definition cannot explain all the mechanisms involved. But for the sake of simplicity, Iontophoresis is a process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity." This means it would involve an electromotive force. In the body, ions with a positive charge (+) are driven into the skin at the anode and those with negative charge (-) at the cathode. Iontophoresis is sometimes confused with electrophoresis and electro-osmosis, the former involving movement of the colloid (dispersed phase) and the latter involving the liquid (dispersion medium), which are quite different.

Iontophoresis may however cause an increased transport of method of penetration of non electrolytes through tissues. Method of delivery when applied topically, the current is applied through a moist electrode, the size depending on the skin region to be treated. The drug is administered through an electrode (active) which has the same charge as the drug. This is very important; if the polarity of the electrode is not the same as the ions, then penetration through the skin may not occur. The oppositely charged electrode (return) is

placed some distance away at a neutral site, the size and distance of the 2 electrodes would also affect the transport of ions. A current intensity below the pain threshold that is comfortably tolerated by the patient is passed for an appropriate length of time (usually below 5Ma/cm2). The current intensity should be gradually increased in the beginning and slowly decreased towards the end. The Current can be given in any of the different waveforms, square, sinusoidal, triangular etc. The current density is the current intensity per unit cross sectional area. In practice, the density will vary from point to point and the value calculated would be an average value at the electrode surface.

Iontophoretic Devices

The main manufacturing concerns as in any equipment should include safety, convenience, reliability and reproducibility of the device. The components of the equipments are:

a) DC power supply
b) A milliammeter
c) A timer
d) A rheostat
e) The 2 electrodes +ve and –ve

Factors Affecting Iontophoretic Drug Delivery

1. **Presence of extraneous ions:** other ions of the some charge can decrease the Iontophoretic delivery of the drug ions because these ions compete with the drug for the iontophoretic flux.
2. **Ionic strength:** Higher ionic strength of the solution subjected to iontophoretic current resulted in decreased iontophoretic transport of the drug into the tissues as increase in ionic strength yields higher concentration of extraneous ions which compete for the electric current.
3. **Concentration:** increased concentration of the charged molecule yields greater molecules in the tissues.
4. **Current intensity:** higher the intensity, greater then transport
5. **Polarisation:** Direct current can cause polarisation whilst pulsed current can decrease tissue polarisation.
6. **Shifts in pH in Tissue and Drug Solutions:** With metallic electrodes, shifts in pH are noted which can affect ionisation of the drug. pH changes in the tissue can use injury due to migration of hydronium and hydroxyl ions produced by electrolysis. Separate buffered electrolyte solutions can be used which can prevent flow of ions into the tissue. Like charges repel each other while opposite charges attract. So to assist the positively

charged lidocaine ions to be transported to the skin, the ionic form must be applied under a positively charged electrode which then moves to the cathode.

7. Influence of pH

The pH is of importance for the iontophoretic delivery of drugs. The optimum is a compound that exists predominantly in an ionized form. When the pH decreased, the concentration of hydrogen ion increases and a vascular reaction (vasodilatation) is initiated because of C-fiber activation, thus it is important to keep the pH as close as possible to and, at least when working with vasodilators, at pH 5.5 and below. There is an increasing risk for vascular reaction due to the high concentration of hydrogen ions rather than the compound used. Since hydronium ions are small they penetrate the skin more easily than larger drug ions. Laboratory findings vary on the effect of pH and drug behavior. According to the Henderson-Hasselbalch equation, pH is the determining factor governing the amount of drug present in the ionized state. For optimum IP, it is desired to have a relatively large proportion of the drug in the ionized state. However, this must be counterbalanced with delivery of a drug at a pH that is tolerable and safe for the patient **[4]**.

8. Current Strength:

There is a linear relation between the observed fluxes of a 1-cm ^{2} , the current is limited to 1 mA due to patient comfort considerations. This current should not be applied for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non specific vascular reactions (vasodilatation) increases. At a current of 0.4-0.5 mA/cm ^{2,} such a vascular reaction is initiated after a few seconds of iontophoresis with deionised or tap water. This latter effect is probably due to current density being high enough a small area to stimulate the sensory nerve endings, causing reactions such as the release of substance P from C-fiber terminals **[5]**.

9. Ionic Forms of drug

In a solution of sodium chloride, there is an equal quantity of negative (Cl^-) and positive (Na^+) ions. Migration of a sodium ion requires that an ion of the

opposite charge is in close vicinity. The latter ion of opposite charge is referred as a counter-ion. An ion of equal charge but of different type is referred as a co-ion. When using iontophoresis, it is important to know that pH adjustment is performed by adding buffering agents. The use of buffering agents as co-ions, which are usually smaller and more mobile than the ion to be delivered results in a reduction of the number of drug ions to be delivered through the tissue barrier by the applied current. In our example, this means that when a positively charged drug is diluted in saline, the sodium ions will compete with the amount of drug ions to be delivered. Ideally, the use of a buffer system should be avoided in iontophoresis, but if this is not possible, alternative buffers, consisting of ions with low mobility or conductivity are preferred **[6]**.

10. Molecular Size

It has been shown that the permeability coefficients in positively charged, negatively Charged and uncharged solutes across human skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases. However, there are certain solutes with a relatively high molecular size (e.g. insulin, vasopressin and several growth hormones), which have also been to penetrate the skin barrier into the systemic circulation **[7]**.

11. Connective or Electro-osmotic Transport

When performing iontophoresis with a specific current, the flow of ions across the membrane induces a flow of solvent called electro-osmosis. Compared to the ion transport, the electro-osmotic contribution is small. The penetration of uncharged substances (e.g. bovine serum albumin) has been shown to be facilitated by the volume flow effect induced by an applied potential difference across the membrane. Iontophoresis has also been observed to enhance the penetration of a number of dipolar ions (zwitter ionic substances like phenylalanine). Most of these substances have been shown to be delivered in significantly higher amounts by anodic delivery than by cathodic delivery. In general, iontophoresis is more effective for

charged compounds, especially monovalent ions.

12. Current-Continuous Vs Pulsed Mode

Application of a continuous current over a long period of time can modulate iontophoresis delivery. Continuous DC current may result in skin polarization, which can reduce the efficiency of iontophoretic delivery in proportion to the length of current application. This polarization can be over come by using pulsed DC, a direct current that is delivered periodically. During the 'off time'' the skin becomes depolarization using pulsed DC can, however, decrease the efficiency of pulsed transport if the frequency is too high. Enhanced iontophoretic transport has been reported for peptides and proteins by using pulsed Dc compared to convenient DC. Most of the drug ions used for diagnostic purposes in combination with iontophoresis and LDPM are small in size. As a result, the time needed for an effect is relatively short (5-20 s) compared to when iontophoresis is used for therapeutic purposes (20-40 min).

13. Physical Factors

Iontophoresis reduces intra and inter-subject variability in the delivery rate. This is an inherent disadvantage with the passive absorption technique. Experiments *in vivo* iontophoretic give support for clinical findings that there are small differences in the flux rate following transdermal iontophoresis between males and females, as well as between hairy and hairless skin. The status of the vascular bed is also important; for instance, a pre-constricted vascular bed decreases the flux through the skin while a dilated vascular bed increases the yield of the drug through the skin.

Drug Salt Form

It has been reported that different salt forms have different specific conductivities and that conductivity experiments *in vitro* will provide information concerning the general suitability of a drug for IP. The salt form of drugs must be considered along with the pH of the solution for determining the amount of drug in the ionized state **[8]**.

14. Patient Anatomical Factors

Patient anatomical factors that influence the depth of penetration that

is variable from patient to patient include skin thickness at the site of the application, presence of subcutaneous adipose tissue and the size of other structures, including skeletal muscle. Additionally, the presence and severity of inflammation can influence drug penetration due to the increased temperature (which may increase and may serve to transport the drug throughout the body).

Iontophoresis for Physical Therapy

Iontophoresis is a treatment for inflamed joint and muscle troubles, is regaining recognition as a substitute to injections and other treatments. The practice, was first developed in the mid 1700's, and involved introduction to various medications (in the form of ions) through the skin by means of electricity. Using a low-volt direct electrical current, an ion, acting as an anti-inflammatory or pain-relieving medicine, penetrates the skin into the painful area and cures the troubled area. Iontophoresis has many rewards. It is a cost-effective and portable method, though the machinist must be a licensed health professional. There is often less danger and uneasiness than an injection. In contrast to pills, it removes the incorporation and loss of medication into the digestive tract. Also, less medication needs to be handled by the liver, and there is a much lower chance of overdose. Although iontophoresis has many advantages, it may not be favorable for everyone. It should not be used on people who have very susceptible skin or are sensitive to any ion that is projected for treatment. Sporadically, skin irritation, even small blisters can occur on the area where the treatment is applied. In addition, the treatment often requires a series of applications, rather than just one appointment. Even very elderly people who cannot take in the ion treatment should not opt for such treatment.
This kind of treatment has been used productively to treat tendonitis, bursitis, and arthritis, even gout. It has also been revealed to help reduce calcium deposits in muscle that sometimes occurs after an injury to a muscle. It works best for inflamed tissues that is not too deep below the skin's surface, since most anti-inflammatory ions can penetrate only about ½ inch. The process is most often performed by licensed physical therapists, following referral from the physician. The therapist and physician determine which ion would be most beneficial for each condition. Some physicians also perform intophoresis treatments. If we suffer from one of these problems which have not responded

adequately to injections or medication, we can ask our doctor about iontophoresis.

It is known that as iontophoresis progresses in conservative iontophoresis systems, the electrolysis of water occurs to produce hydrogen or hydroxyl ions at the interface of the electrode and medicament medium. Since these ions are highly mobile, they are elated directly into the skin of a patient in preference to the larger medicament ions. Thus, extreme changes in pH are experienced which result in burns due to the acidification or alkalinization of the medicament medium and passage of electric current through the skin. In addition, the efficiency of iontophoresis decreases over time. The present invention avoids extremes in pH by removing the hydrogen or hydroxyl ions which are created during iontophoresis and create conditions for constant delivery over prolonged periods of time. In the present discovery, the medicament ions are attached to an ion exchange matrix, such as an ion exchange resin. When the medicament leaves the ion exchange matrix, the vacated active site is filled by the produced electrolysis products, thereby allowing iontophoresis to progress at a relatively constant pH.

Side Effects of Iontophoresis:

1. The treatment can cause a tingling sensation to hands/feet (or even limbs) treated on the day.
2. If you have eczema, it may worsen the condition.
3. You could suffer some slight bruising if the intensity of the treatment is too great.
4. Moderate temporary thickening of the skin (hyperkeratosis) could occur if the treatment sessions are too frequent.

Reasons Why You May be Unable to Have This Treatment

You should not have Iontophoresis if:

1. You are pregnant
2. Have a cardiac pacemaker
3. Have any metal orthopaedic implants
4. Have fixed mouth braces.

Duration of Treatment

The treatment consists of seven 20 or 30 minute sessions over a four weeks period. Appointments must be kept to the days stated below, so please inform staff if you are likely to be away for any of this period, as it will

affect your treatment. In this case, it would be best to start treatment at a later date.

Week 1 - Day 1, 2 & 4 (Tuesday, Wednesday & Friday)

Week 2 - Day 7 & 10 (Monday & Thursday)

Week 3 - Day 15 (Tuesday)

Week 4 - Day 22 (Tuesday)

Following the course of treatment, a maintenance treatment may be required if sweating persists.

Biomedical Application

Iontophoresis has wide applications in Dermatology, Ophthalmology, ENT, Allergic conditions even in Cardiac and Neurological situations, but its greatest advantage is in the transport of protein or peptide drugs which are very difficult to transport trasdermally due to their hydrophilicity and large molecular size.

Dermatology:

- In hyperhidrosis, especially palmar and plantar – probably by obstructing the sweat ducts. No side effects when compared to anti- cholinergics.
- Copper- iontophoresis for fungal infection and male contraception, zinc for ulcers, iodine for reduction of scar tissues, iron/titanium oxide for tattoo removal.
- Histamine in allergy testing.
- In the diagnosis of cystic fibrosis to increase sweating by pilocarpine and confirm diagnosis by the concentration of sodium and chloride in the sweat.
- In scleroderma, for iontophoretic delivery of hyaluronidase.

Ophthalmology:

- Iontophoretic induction of various drugs like atropine, scopolamine, sulfadiazine, fluorescein, gentamycin etc.

ENT:

- For providing anaesthesia of the external ear canal and middle ear and in maxillo facial prosthetics surgeries.

Dentistry:

- To prevent dentin hypersensitivity and for providing local anaesthetic for multiple tooth extraction.

Neurophysiological and Neuropharmacological Studies:

- As a research tool, micro-iontophoresis can be used to study neuro muscular junction, peripheral and central nervous system and smooth muscle preparations.

Delivery of Drugs:

- Antihypertensives, anti-diabetics, anti-rheumatoids, hormones, vasodilators: Metaprolol,propranolol, insulin,

methylcholine, bleomycin, steroids have all been introduced iontophoretically. *Musculo skeletal disorders*

- Magnesium sulphate for bursitis, Calcium for myopathy, Silver for c/c osteomyelitis, local anaesthetics and steroids into elbow, shoulder and knee joints. *Cardiology*
- Iontophoretic transmyocardial drug delivery of anti-arrhythmic drugs which would avoid high systemic toxic levels is being done in animals.

For Relief of Pain:

- Iontophoretic histamine delivery as counter-irritant
- In painless venipuncture
- For post-operative pain relief
- For iontophoretic delivery of local anaesthetics for referred pain.
- Anti-inflammatory drug delivery This is an area which has wide scope for expansion. We have seen the varied applications and the potential for improvement for this method of drug delivery. Further research is required to perfect this technique. There are several devices now available in all sizes and shapes to suit individual needs and ensure absolute safety. With even pencil shaped transdermal applicators now available for self administration, iontophoresis may prove to be an important alternative method

Iontophoresis Therapy:

One of the most embarrassing medical conditions is called hyperhidrosis or, more commonly, excessive sweating. It affects about three percent of people around the world, which may not sound like much, but it turns out to be a good number of people when you do the math. Hyperhidrosis can affect different people in different ways. For some, they have excessive sweating under the arms. For others, it's the feet. Still others find that their hands become covered in sweat often. There are a number of different attempted cures for hyperhidrosis, one of which is called iontophoresis therapy. This therapy is successful in many cases, and it doesn't make use of any drugs or surgery. Iontophoresis therapy also has very few side effects, although it does have a few downsides that may make you elect to go with a different type of therapy.

Iontophoresis therapy involves using a weak electrical currency that stimulates the mineral carrying ions. These ions are passed through the feet or the palms. You simply place your

hands or your feet into special metal trays that are filled with water. These trays are connected to a weak electrical device. Once you've placed your hands or feet in the water, a technician slowly increases the output of the electrical charge. The entire procedure sounds very painful—after all, you are running an electrical charge through your body—but it is actually completely painless. You won't feel a thing because the current is very, very low.

So how does iontophoresis therapy work? The concept behind the treatment is that the mineral that the ions bring into your skin temporarily fill up your sweat pores. They form thick deposits inside the pores of the hands and feet. These minerals prevent sweating by blocking up the sweat pores. This means you won't suffer any sweating at all. The results of iontophoresis are very similar to botox or other types of hyperhidrosis.

Of course, there are a few downsides to iontophoresis therapy. First of all, it only works on excessive sweating of the hands and feet. If you suffer from sweating under the arms or other areas, you'll need to seek other treatments, such as botox injections. Also, it's not a permanent treatment. You will have to get repetitive iontophoresis treatments on a regular basis. Some people have to have treatments once a week, sometimes twice. This can eventually add up, costing you a good amount of money. Iontophoresis is one of the more expensive hyperhidrosis treatments, so be ready to pay extra if this is the treatment you want to pursue for your excessive sweating.

As far as side effects go, there are only a few to iontophoresis. Besides the fact that you must have the treatments several times a week, some people have reported feeling a bit of irritation around the skin where it meets the water. This irritation generally only happens during the actual therapy, and it can generally be avoided by rubbing a bit of Vaseline on the skin before you start the therapy. This will completely negate the irritation. Other than this side effect, iontophoresis therapy has no other painful downsides.

To begin iontophoresis therapy, simply speak to your dermatologist or doctor and ask about the therapy. He or she will be able to tell you about iontophoresis options in your area and about the cost. However, in recent years, many doctors have started prescribing more powerful antiperspirants and other hyperhidrosis treatments instead of iontophoresis because of the expensive and the fact that the treatments have to be done several times a week. There are better

treatments out there that will last longer and are cheaper.

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