VOLUME 10 NUMBER 4

Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

COMPOUNDING FOR IONTOPHORESIS

GOALS AND OBJECTIVES

Goal: To provide pharmacists, pharmacy students and pharmacy technicians supportive information on the basics of compounding solutions for iontophoretic administration.

Objectives: After reading and studying this article, the reader will be able to:

1. Discuss the development of iontophoresis in contemporary pharmacy.
2. List the basic equipment requirements for iontophoresis.
3. Describe the variables that affect iontophoresis.
4. Explain the methods of extemporaneously preparing solutions for iontophoretic administration.
5. Discuss the desired characteristics of a potential iontophoretic patch.

PREFACE

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. Iontophoresis is becoming more widespread today with many pharmacists compounding solutions for this mode of administration. Iontophoresis has been called by some as a method of making "needle-less injections". There are many factors involved in compounding solutions for iontophoresis that must be considered, as discussed in this issue. Pharmacists involved in this mode of administration will generally work with physical therapists as well as physicians. The future of iontophoresis is very promising as newer, microprocessor-controlled devices are introduced into the marketplace.

INTRODUCTION

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. 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. Oftentimes 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 electrical 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

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 inter-patient variability, (4) avoiding the risks of infection, inflammation, and fibrosis associated with continuous injection or infusion since it is noninvasive, and (5) enhancing patient compliance with a convenient and non-invasive

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therapeutic regimen.

DISADVANTAGES

Some disadvantages also need to be mentioned for this mode of administration. For example, in the past there existed the possibility of burns if the electrodes were improperly used. This problem is now minimized as the newer units use battery packs with very low current instead of household current. Compliance with a current-time recommendation according to the method used essentially avoids iontophoretic burns. The formation of undesirable vesicles and bullae in skin being treated can be avoided by periodically interrupting a unidirectional treatment current with a relatively short pulse of current in the opposite direction. There is also the minor inconvenience of using an electrical device that, although small, may be a bother to some patients. It is anticipated that the size of these units will continue to decrease to obviate this problem.

HISTORY OF IONTOPHORESIS

Iontophoresis (cataphoresis, ionic treatment, electrolytic treatment, ion transfer, electrophoresis) was first conceived early this century when in 1908, Le Duc demonstrated that ions could be driven across the skin by means of an electric current.[1,2] From that time until 1924, numerous studies were undertaken utilizing ophthalmological iontophoresis. However, many difficulties were encountered including corneal scarring, tissue burning and some electrical shocking of patients. In 1911, Albrecht studied the use of cocaine and epinephrine iontophoresis for anesthesia of the tympanic membrane and demonstrated good results.[1] However, only limited anesthesia to the external auditory meatus was obtained using this same technique. Because of these and other major technical problems encountered, iontophoresis was virtually discarded until the early 1940's when it was again used experimentally for the transfer of penicillin and sulfadiazine into the infected eyes of animals with results that were reported as successful.[1,2]

Historically, there have been several different medications administered iontophoretically for widely varying disorders, e.g., melodinine for the treatment of vitiligo, glycopyrronium bromide for the treatment of hyperhidrosis, sodium salicylate for palmar and plantar warts, steroids for Peyronie's disease, acetic acid for calcium deposits in muscle and joint disorders and alpha-chymotrypsin in inflammatory reactions involving joints and soft tissues. Some studies have included the administration of local anesthetics combined with steroids for muscular and tendonous injuries.[1] In attempts to decrease the chance of severe infection in burn cases, iontophoresis of penicillin into burn eschars has been utilized. Histamine iontophoresis has been used to induce local capillary dilatation in order to obtain accurate determinations of blood gases and it has also been suggested as an aid in the healing of chronic sclerotic ulcers. In dental work, iontophoresis of local anesthetic agents has been used for tooth extraction, treatment of infected tooth root canals, and for deposition of fluoride into the dentin of teeth.

For some years, many have been attracted with the prospect of administering insulin to patients with diabetes using iontophoresis. Such an approach would possess several advantages: (1) with suitable patient-adjusted current control, it is theoretically feasible to administer insulin in both baseline and bolus dosages as is done with continuous subcutaneous insulin infusion, (2) there is no transcutaneous penetration by a needle and therefore problems of localized infection, inflammation, and localized fibrosis do not arise and (3) insulin does not traverse narrow tubing, therefore the possibility of crystallization is absent.

The actual list of drugs used iontophoretically is quite long. For example, drugs that have been studied in the past 60 years for iontophoretic administration include acetic acid, N-acetylcysteine, adenosine salts (var.), bleomycin, bupivicaine HCl, butazolidin, citrate, catecholamines, cefazolin sodium, cefoxitin sodium, cocaine HCl, copper, cortisone, cyclophosphamide, doxorubicin, dexamethasone sodium phosphate, diphenhydramine HCl, epinephrine bitartrate, fluorescein, gentamicin sulfate, glucocorticoids, histamine, hyaluronidase, hydrocortisone phosphate, hydrocortisone sodium succinate, idoxuridine, 6-hydroxydopamine, iodine, levarterenol bitartrate, lidocaine (HCl and with epinephrine HCl), mepivacaine HCl, methylcholine chloride, methotrexate, methylene blue, methylprednisolone sodium succinate, metoprolol, nicotinic acid, optidase, papaverine, oxycodone, penicillin, phenylephrine HCl, phosphorus, pilocarpine, potassium iodide, procaine HCl, prilocaine HCl, ragweed pollen extract, sodium benzoate, sodium fluoride, sodium iodide, sulfacetamide, sulfadiazine, sulfapyridine, sulfathiazole, thymidine salts, thymine arabinoside, thyrotropin releasing hormone, ticarcillin, triamcinolone, uridine salts (var.), vasopressin, vidarabine monophosphate, zinc sulfate and zinc oxide.

IONTOPHORESIS MECHANISM AND DEVICES

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. 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/cm^2 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.

THEORETICAL

Topically applied, ionized drugs or chemicals do not ordinarily penetrate into surface tissues sufficiently to achieve a therapeutic level. Surface tissues of the skin consist of membrane barriers which are rich in lipids or fats. Drugs which are lipid-soluble are more readily absorbed by membranes than water-soluble, ionized

substances. When salts of drugs are dissolved in aqueous solutions, ionized or electrically charged particles are formed. This process of ion formation is called dissociation or ionization. Many, if not most, drug substances today are available in salt form as that is the form in which they are generally water-soluble. The problem of membrane penetration of ionic drugs can be overcome by providing an energy source which increases the rate of penetration. Electrical energy, in the form of a small direct current, will assist the movement of ions. According to electrical principles, like charges repel each other and opposite charges attract. Thus positive drug ions are repelled from the positive electrode and negative drug ions are repelled from the negative electrode.

When iontophoresis is performed, the active electrode (with the same charge as the drug) is placed over the tissues which require medication. The indifferent or return electrode (with the opposite charge as the drug) containing an indifferent electrolyte is placed at a convenient location elsewhere on the body. The electrodes are connected to the direct current source (iontophoresis device). The current is then gradually increased to the proper level for the time duration required.

There are a few relationships that are important in iontophoresis.

Ohm's Law states that:

$$V = I R$$

where V is electromotive force in volts, I is current in amps and R is resistance in ohms. The importance of this relationship is that at constant voltage, any change in resistance results in a change in current level. Very often, the resistance decreases during a procedure; as a result the current, in milliamps, will increase. This may require some adjustment during the procedure unless the device is microprocessor controlled to compensate, as most are today.

Coulomb's Law states that:

$$Q = I T$$

where Q is the quantity of electricity, I is current in amps and T is time in minutes. Thus, it is stated "mA-min" as the "current dosage", and procedures state a recommended mA-min dosage and/or maximum. When stated as a maximum, mA-min (or maximum mA) must be observed to prevent damage to the tissues.

Faraday's Law states:

$$D = (IT)/(ZF)$$

where D is the amount of drug delivered (in gm-equivalents), I is the current in amps, T is time, Z is valence and F is Faraday's Constant. From this relationship, the more electricity delivered, the more drug delivered. Thus we speak of electrical dosage and drug dosage in terms of mA-min.

The rate of migration (M) of ions in the presence of electrolytes in an electric field is directly proportional to the field strength (H) and the effective charge (e) of a particle and inversely proportional to the radius of the particle (r, which includes the hydrate and ion shell in the calculation) and to the viscosity (η) of the medium in which the particles are moving. The rate of migration is given by:

$$M = \frac{H e}{6 \pi r \eta}$$

The iontophoretic procedure involves a number of variables that must be controlled in the interest of patient safety and optimal drug delivery. Faraday's Law has been used by some to provide information concerning the rate of deposition of the drug at the skin surface. However, due to the complexity of the factors involved during the process of iontophoresis, theoretical predictions based on it are difficult. Abramson[3] used Coulomb's Law for predicting an electrophoretic treatment unit, independent of the area of the electrode.

Abramson and Gorin[4] defined an equation relating the iontophoretic dosage to the various components contributing to it. These included contributions due to electrical mobility, electroosmosis, and simple diffusion. Another equation, defining the iontophoretic current, I, passing through an electrode tip, having a resistance RE, and surrounding tissues release energy, P, in the form of heat is given by[5]

$$P = I^2(RE + Re)$$

where Re is the resistance of the tissues. This relationship is used in in vitro experiments.

Burnette and Marerro[6], using predictions based on the Nernst-Planck flux equations, found agreement with their predictions when measuring the iontophoretic transport of thyrotropin releasing hormone on hairless mouse skin. The relationship they discussed is:

$$J_i = [h(qe_i + qc_i)(dR_i / dx) + k']C_i IDA$$

where J_i is the flux of the i-th species, h and k' are proportionality constants, qe is a constant resulting from direct, electrically induced, ion motion, qc is a constant pertaining to electrically induced convective flow, C is the solute concentration in the pore, R is the resistance of the solute, ID is the total applied current density, and A is the surface area of the skin. This equation shows that the flux of the drug is directly proportional to the total applied current density.

ELECTROENDOOSMOSIS TRANSPORT

Drugs can also be transported via electroendoosmosis. When a current is applied, there is also a flow of water from the electrode reservoir into the skin. Any drug in solution, ionized or nonionized, can follow the water flow into the skin. In this manner, some drugs that are not ionized can also be given iontophoretically. If only the nonionized drug is to be given, it may be necessary to add a small quantity of sodium chloride to the solution for conductivity and to establish electroendoosmotic flow.

VARIABLES INVOLVED

As can be seen or derived from the above relationships, there are a number of variables that will control or affect the process of iontophoresis. These include the drug concentration, drug salt form, pH of the drug microenvironment, the electrical source type, the current intensity and duration, current type, the electrolyte in the donor and receptor cells, the conductance of the drug solution and the mobility of the drug moiety, the ionic strength of the drug solution, viscosity and dielectric constant of the medium, stability of the drug during the iontophoresis process, the type of matrix containing the drug, i.e., solution vs. gel and size, charge and nature of the electrode.

Drug Concentration: An increased drug uptake by the skin after iontophoresis with an increase in drug concentration has been reported.[7,8]

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 iontophoresis.[9] 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.

pH of the Drug Microenvironment: Changes in the pH of the fluid at the driving electrode has produced only minor changes in the uptake of radioactive phosphorus by various tissues in rats in one study.[7] Release of histamine from aqueous media during iontophoresis also produced a similar behavior.[8] Harpuder has, however, demonstrated a significant dependence on pH during electrophoretic therapy.[10] The change in flux for lidocaine HCl during iontophoresis has been related to the degree of ionization.[11] The results obtained with iontophoresis of sulfonamides were also shown to parallel the degree of ionization.[12] The pH is the determining factor governing the amount of drug present in the ionized state, according to the Henderson-Hasselbalch equation. For optimum iontophoresis, it is desired to have a relatively large proportion of the drug in the ionized state.

Electrical Source Type: Some iontophoretic devices have been designed to be of the constant voltage type. The difficulty with this is that as the resistance changes, so does the voltage and current. Therefore, constant current devices have been developed providing a constant current even though the resistance might change during the iontophoresis process.

Current Intensity and Duration: From Faraday's Law we know that in an electrolytic solution the transported quantity of electricity depends on the strength of the current and the duration of its passage.[13] The same number of ions will be transported at different strengths of current if the time for current flow is inversely related to their strengths. The rate at which the ions are introduced into the body with various current strengths can play an important role. When the current is stronger, more ions penetrate at one time, and their accumulation produces the desired local effect and may even build up a reserve of ions that will later be diffused more deeply into the tissues, perhaps resulting in a prolonged drug effect. The strength of the current used also depends on the sensitivity of the patient.[14]

Current Type: Most iontophoretic devices use a "constant" current. The current is initiated at a low level and slowly increased to some operating level, then lowered again to zero. Some devices have also used a "pulsed" current for delivering the drug.

Electrolyte in the Donor and Receptor Cells: Electrical current is carried by positive and negative ions in solution. There is no major distinction between ions of the same charge even though they are composed of different chemical elements. Therefore, solutions for iontophoresis should be as pure as practical and generally contain as few extraneous substances as possible. Drug solutions should be prepared with ultrapure water. It has been shown that the presence of excipients in dosage forms, i.e. preservatives in injections, will reduce the conductivity of solutions by as much as 5 to 10%. The total current supplied by the amperometer will be carried by drug ions along with the same charge as drug ions in the donor cell plus the counter ions present in the receptor cell. Therefore, the competing ions in the donor cell and the counterions in the receptor cell will be affecting the actual current carried by the drug moiety. Iontophoretic rate of drug transfer can therefore be adjusted by concentrations of electrolyte in the donor and receptor cells.

Conductance of the Drug Solution and the Mobility of the Drug Moiety: The conductance and mobility of the same drug solution differs by a factor of the charge on the drug; therefore, these two parameters need to be studied together.

Ionic Strength of the Drug Solution: Few papers are available concerning ionic strength of the drug solution during iontophoresis. A report on a decrease in the uptake of phosphorous by tissue has been published(5).

Viscosity of the Medium: The migration of a drug molecule is usually inversely related to the viscosity of the medium in which it is contained.

Stability of the Drug During the Iontophoresis Process: The drug undergoing iontophoresis must be stable in the solution environment up to the time of iontophoresis and also during the iontophoretic process. Not much information is available, however, concerning drug stability during the iontophoresis process. Drugs which are easily oxidized or reduced must be appropriately formulated. This is important because oxidation or reduction of a drug not only decreases the total drug available but the degradation compounds, if they possess the same charge as the drug ion, will compete with the drug ion and reduce the overall transmembrane rate of the drug.

Type of Matrix Containing the Drug-Gel vs. Solution: The migration of the drug under the influence of the electrical current will be different when the matrices are different. This can be related to differences in viscosities, material electrical charge and porosities. A limited amount of work has been accomplished in this area. Bannon and coworkers report in the literature using hydrogels with cellulose membranes that the passive release of salbutamol from the hydrogel across the membrane was matrix-controlled and the transfer of drug under the influence of the electrical current was found to increase linearly with current strength.[15-16]

Size, Charge and Nature of the Electrodes: Electrode material used should be harmless to the body and sufficiently flexible to be applied close to the body surface. The distribution of the active drug species within the skin depends on the size and position of the electrodes. The literature indicates that greater amounts of drugs are usually, but not always, introduced by larger electrodes. Often desirable features would be a disposable, nonconductive material containing the electrode attachment with a skin adhesive coating on one side.

FUTURE OF IONTOPHORESIS

As the variables concerning iontophoresis are characterized and methods of controlling the variables are developed, it is important to look at the clinical applications of iontophoresis. Currently, the devices used are small but ultimately it is envisioned that the iontophoresis patch dosage form will become commonplace. These self-contained units will have either single or multiple doses of drugs whose delivery rates can be altered. Ideally, the new iontophoretic patch will have the following characteristics:

(1) It will contain sufficient drug for administration of up to 7 days.
(2) It is easily applied and will not easily wash off the skin.
(3) It will deliver the drug at a predetermined rate over the selected time period.
(4) The actual quantity of drug delivered over the time period can be analyzed by the drug remaining in the patch after the time period of administration.
(5) Compliance will be easily monitored and assured and administration of the patch can be done by weekly visits.
(6) Visual examination of the patch will detect tampering and the patch can be devised such that if removed, the electrodes are disconnected and the delivery of the drug will cease.

COMPOUNDING SOLUTIONS FOR IONTOPHORESIS

As can be seen in the theoretical discussion, any ionized substance in solution can compete for the current in the iontophretic process. Consequently, for efficient iontophoretic transfer, it is best to only have the drug in solution, unless there is justification to have other ingredients present, such as acid or base for pH adjustment to increase the ratio of ionized:unionized drug present. Also, the drug solutions should be sterile as there is the possibility of moving bacterial components or pyrogens into the skin during the iontophoresis process. Other considerations are the following:

Packaging: As the solutions do not contain preservatives, they should be packaged in individual unit of use containers.

Labeling: For professional use only. For use by iontophoresis. Not for injection.

Quality Control: Theoretical yield compared with actual yield, physical observation, pH, sterility tests.

EXAMPLE SOLUTIONS

Drugs and their concentrations that are currently used in iontophoresis include acetic acid (2-5%), atropine sulfate

(0.001-0.01%), calcium chloride (2%), sodium chloride (2%), potassium citrate, copper sulfate (2%), dexamethasone sodium phosphate (0.4%), estriol (0.3%), fentanyl citrate, fluoride sodium (2%), gentamicin sulfate (0.8%), glycopyrrolate (0.05%), hyaluronidase (150 units/mL), idoxuridine (0.1%), lidocaine hydrochloride (4%:with or without epinephrine), lithium chloride (2%), magnesium sulfate (2%), metholoyl chloride (0.25%), morphine sulfate (0.2-0.4%), pilocarpine hydrochloride, potassium iodide (10%), sodium salicylate (2%), tretinoin, and water. Only a few representative formulas will be given here as they are all somewhat similar.

Rx Dexamethasone 4 mg/mL Solution for Iontophoresis

Dexamethasone Sodium Phosphate (Equivalent to 400 mg Dexamethasone)	527 mg
Sterile water for injection qs	100 mL

Method of Preparation

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Dissolve the dexamethasone sodium phosphate in the sterile water for injection.
4. Filter through a sterile 0.2µm filter into a sterile container.
5. Package into individual dose containers and label.

Stability

A beyond-use date of 6 months can be used for this formulation.[17]

Rx Lidocaine Hydrochloride 4% Solution for Iontophoresis

Lidocaine hydrochloride	4 g
Sterile water for injection qs	100 mL

Method of Preparation

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Dissolve the lidocaine hydrochloride in the sterile water for injection.
4. Filter through a sterile 0.2µm filter into a sterile container.
5. Package into individual dose containers and label.

Stability

A beyond-use date of 6 months can be used for this formuation.[17]

Rx Acetic Acid 2% Solution for Iontophoresis

Glacial Acetic Acid	2 mL
Sterile water for injection qs	100 mL

Method of Preparation

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Mix the glacial acetic acid with the sterile water for injection.
4. Filter through a sterile 0.2µm filter into a sterile container.
5. Package into individual dose containers and label.

Stability

A beyond-use date of 6 months can be used for this formulation.[17]

Rx Ketorolac 6 mg/mL Solution for Iontophoresis

Ketorolac tromethamine	600 mg
Sterile water for injection qs	100 mL

Method of Preparation

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Obtain the required number of ketorolac tromethamine tablets and thoroughly pulverize.
3. To the powder, add sufficient sterile water for injection to volume.
4. Filter through a paper filter to remove the insoluble tablet excipients.
5. Then, filter through a sterile 0.2µm filter into a sterile container.
6. Package into individual dose containers, replace the head space with nitrogen and label. An alternative would be to package in syringes and remove any air in the syringe by displacement with the plunger.

Stability

A beyond-use date of 6 months can be used for this formulation.[17]

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