Ionto

- Science of Iontophoresis
- Calculating Dosage and Delivery
- Alternative compounds
- Competition
- Product Discussion
History of Iontophoresis

1745  First claims of medication transfer with electrical current

1879  First demonstration of charged compounds passing through the skin when strychnine was delivered into a rabbit using electrical current

1985  Lidocaine was first introduced as a buffering agent, making iontophoresis more comfortable for patients and allowing the modality to gain wider acceptance

1992  Empi® launches the first buffered electrode that does not require the use of external buffers. Empi also launches Dupel® iontophoresis system

1998  IOMED® launches IOGEL® electrodes utilizing Silver-Silver Chloride technology to stabilize pH

2002  The first electrode that does not require an external phoresor is introduced

2003  Empi launches Action Patch®

2004  IOMED launches Companion 80™ patch

2007  Empi launches Hybresis,™ “Accelerating Drug Delivery through Iontophoresis Technology”
Definition of Iontophoresis

A site-specific drug delivery system used by clinicians to deliver a water-soluble drug with either a negative or positive charge through the skin using low-level electric current

- Why it works:
  - Like charges repel
  - Current opens pathways in the skin
Benefits of Iontophoresis

vs. INJECTIONS
- Virtually painless
- Non-invasive
- Less risk of infection
- Less drug required
- Less risk of tissue necrosis and tendon rupture

vs. ORAL MEDICATIONS
- Localized
- Minimal risk of systemic side effects
- Avoids GI tract
Like Charges Repel

- Like charges repel
- Electric current makes skin permeable
- Pathways through the skin open up
- Like charge ions are repelled and delivered through the skin
Effects of Direct Current

- On skin
  - Decreases skin resistance
  - Increases permeability through skin pathways

- On compounds
  - Hydrolysis of water
  - pH changes
Skin Response to Iontophoresis

- A normal iontophoresis response may include
  - Redness (erythema)
  - Warmth

- Primarily seen with patients having:
  - Red hair
  - Freckles
  - Fair skin
  - Sensitive skin
  - Heat/Cold sensitivity?
When an electrical current flows through water, a process called **hydrolysis** can take place. 

\[ \text{H}_2\text{O} \rightarrow \text{H}^+ \text{ and OH}^- \]

Some of the water molecules are split into 2 ions, a positive hydrogen ion (H+) at the anode (+), and a negative ion, hydroxide (OH-) at the cathode (-).

When these ions change the pH of water, it can cause discomfort during treatment, and extreme pH changes can cause a chemical burn.
Managing pH and Hydrolysis

1. Buffering:
Buffering is a process that adjusts the pH of the solution to safe levels for the skin.

2. Stabilizing:
Silver-Silver Chloride (Ag/AgCl) prevents hydrolysis from occurring, therefore no pH changes occur.
Factors Affecting Drug Delivery

- Skin impedance
- Direct current:
  • Reduces skin impedance (resistance) and increases permeability
- Molecular weight:
  • Less than 8000 Daltons is optimal molecular size for iontophoresis
- Dosage: Increasing dose will increase drug delivery
- Concentration of the drug/compound in the solution (2% - 5%)
- Tissue Hydration

**Figure 2. In Vitro Passive and Iontophoretic Delivery of Dexamethasone Phosphate as a Function of Applied Dosage.**

Note: At all evaluated dosages (P < 0.001, by means of 2-way ANOVA), measurements indicated that the delivery was significantly greater under conditions of iontophoretic current flow when compared with passive delivery.
Transdermal Delivery

- Epidermis $\rightarrow$ 0.075-0.15mm
- Dermis $\rightarrow$ 1-4mm
Transdermal Delivery

Negative Charge

Key Point

1 to 16 mm
Ion Transport

- The cathode (BLACK) will only repel negative ions.
- The anode (red) will only repel positive ions.

Iontophoresis is limited to medications/ionic solutions with the following profile:

- The ions must be charged.
  - Dexamethasone and acetic acid are both negative.

- Relatively small ions
  - They must have a molecular weight less than 8000 daltons.

- Must be in a solution- no creams or suspensions.
Dosage

- Iontophoretic dosage is simply a product of the current amplitude and time

\[
\text{Dosage (mA*min)} = \text{Current (mA)} \times \text{Time (min)}
\]

- Typical treatment consists of a 40 to 80 mA*min dose
- Important:
  - Electrical dosage and drug dosage are different
  - Drug Delivery is proportional to the electrical dosage
    - This allows us to discuss/infer drug delivery from mA*min data
## Iontophoretic Dosages Used In Successful Studies

<table>
<thead>
<tr>
<th>Author / Date</th>
<th>Number of Subjects</th>
<th>Current Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertolucci, 1982</td>
<td>$n = 30$</td>
<td>65 mA * min</td>
</tr>
<tr>
<td>Delacerda, 1982</td>
<td>$n = 8$</td>
<td>85 mA * min</td>
</tr>
<tr>
<td>Harris, 1982</td>
<td>$n = 50$</td>
<td>100 mA * min</td>
</tr>
<tr>
<td>Braun, 1987</td>
<td>$n = 1$</td>
<td>76 mA * min</td>
</tr>
<tr>
<td>Hasson, 1992</td>
<td>$n = 1$</td>
<td>65 mA * min</td>
</tr>
</tbody>
</table>

$X = 78$ mA * min
Calculating Dosage

\[ \text{current (mA)} \times \text{treatment time (min)} = \text{Dose (mA*min)} \]

4.0mA (current) X for 10 minutes (time) = 40mA*min

2.0mA (current) X for 20 minutes (time) = 40mA*min

4.0mA (current) X for 20 minutes (time) = 80mA*min

4.0mA (current) X for 15 minutes (time) = 60mA*min
Indications
Indications

- The FDA cleared indication for iontophoresis is the delivery of ionic substances.
  - This is essentially similar to saying the FDA cleared indication for a hypodermic needle is the delivery of liquids
  - While this allows for a very large number of potential uses, it limits the allowable promotional activities
- A physician’s prescription is needed for Iontophoresis and for the use of prescription ions.
Contraindications

The contraindications are essentially the same throughout all electrical stimulation applications

- **Cardiac Pacemakers**: Do not use on patients with pacemakers or other implanted electrically sensitive devices
- **Drug sensitivity**: Do not use on patients with known sensitivity to the drug being administered
- **Compromised skin**: Do not use on broken skin, sunburn, acne, or other irritated or compromised skin
- **Skin sensitivity**: Do not use with known sensitivity to electrical current or to the solution being administered
- **Head treatment**: Do not treat across either the temporal region or the orbital region
Common Uses

The most common uses for iontophoresis are the delivery of drugs for the treatment of inflammation (-itis)

- Corticosteroids such as dexamethasone
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Other common uses are:

- Pain
- Scarring
- Calcification (-osis)
- Muscle spasm
Common Treatment Sites

- Lateral Epicondylitis
- Carpal Tunnel Syndrome
- Plantar Fasciitis
- Subcutaneous Bursitis
- Achilles Tendinitis
- De Quervain's Tenosynovitis
- Patellar Tendinitis
- Calcaneal Bursitis
- Biceps Brachii Tendinitis
- Patellar Band Friction Syndrome
- Rotator Cuff Syndrome
- Popliteal Tendinitis
Inflammation

Inflammation is the natural response of vascular tissues to harmful stimuli (including trauma, infection, or irritants). It is a tightly regulated process that is critical for overall health.

The purpose of inflammation is three fold:

- Prevent the spread of cellular debris
- Clean up infection or wound sites
- Set the stage for repair process
### Acute vs. Chronic Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Acute Inflammation</th>
<th>Chronic Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causes</strong></td>
<td>Injury, infection</td>
<td>Repeated injury, inflammation, microtrauma, tissue disease or degeneration</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Days to weeks</td>
<td>Weeks to Years</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Healing, Abscess formation, Chronic inflammation</td>
<td>Tissue destruction, Fibrosis</td>
</tr>
</tbody>
</table>

**Note:** Chronic inflammation is also typically devoid of noticeable swelling, although it may come and go with repeated activity as may pain and ROM
Alternative Compounds & Stages of Healing

- **Corticosteroids**
  - Acute Inflammation
    - Approximately 1–3 weeks

- **NSAIDS, Calcification Management**
  - Chronic Inflammation
    - Approximately 4–6+ weeks

- **Scar Tissue Management**
  - Repair Regeneration
    - Approximately 4+ weeks
Example:
Inflammation Treatment Guideline – Tendonitis

- Beneficial effects should be seen within 3 to 4 treatments sometimes as early as the second. Duration of therapy is usually 4-10 treatments (as long as objective outcomes are present continue treatment until resolved)

- Frequency: Alternating days (Monday, Wednesday, and Friday)

- Dose is 40 mA*min increasing to 80 mA*min PRN (as needed)

- Dexamethasone used
Example:
Treatment Guideline – Scar Tissue or Calcification

- For scar tissue use directly over the problem scar – some providers will follow with scar massage. Expect to get satisfactory results with treatment 3 times a week for 3-4 weeks.

- Frequency: Alternating days (Monday, Wednesday, and Friday)

- Dose is 40 mA*min increasing to 80 mA*min PRN (as needed)

- Acetic Acid used
Device Parameters

- Dose: FDA cleared up to 160 mA*min - Empi
  - Typical treatment is 40-80 mA*min
- Amplitude- .1-4 mA
- Time: completely dependent on the dose and amplitude.
- Current Density: If the current amplitude remains the same, a larger electrode will have a lower current density than a smaller electrode.
  - As a result, the smaller electrodes may cause discomfort at an amplitude that is comfortable with a larger electrode.
Competing Ions at the Negative Electrode

- Corticosteroid ion
- Cl⁻ (competing ion)
### Common Compounds

- Lidocaine
- Dexamethasone
- Ketoprofen
- Acetic Acid
- Sodium Chloride
- Potassium Iodide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Principle Indication(s)</th>
<th>Treatment Rationale</th>
<th>Iontophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>Calcific tendonitis; myositis ossificans</td>
<td>Acetate is believed to increase solubility of calcium deposits in tendons and other soft tissues</td>
<td>2-5% aqueous solution from negative pole</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>Skeletal muscle spasms</td>
<td>Calcium stabilizes excitable membranes; appears to decrease excitability threshold in peripheral nerves and skeletal muscle</td>
<td>2% aqueous solution from positive pole</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Inflammation</td>
<td>Synthetic steroid antiinflammatory agent</td>
<td>4 mg/ml in aqueous solution from negative pole</td>
</tr>
<tr>
<td>Iodine</td>
<td>Adhesive capsulitis and other soft-tissue adhesions; microbial infections</td>
<td>Iodine is a broad spectrum antibiotic, hence its use in infections and so on; the sclerolytic actions of iodine are not fully understood</td>
<td>5-10% solution or ointment from negative pole</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Soft-tissue pain and inflammation (e.g. bursitis, tendovaginitis)</td>
<td>Local anesthetic effects produce transient analgesia</td>
<td>4-5% solution or ointment from positive pole</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Skeletal muscle spasms; myositis</td>
<td>Muscle relaxant effect may be due to decreased excitability of the skeletal muscle membrane and decreased transmission at the neuromuscular junction</td>
<td>2% aqueous solution or ointment from positive pole</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Local edema (subacute and chronic stage)</td>
<td>Appears to increase permeability in connective tissue by hydrolyzing hyaluronic acid, thus decreasing encapsulation and allowing dispersion local edema</td>
<td>Reconstitute with 0.9% sodium chloride to provide a 150 ug/ml solution from positive pole</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Muscle and joint pain in acute and chronic conditions (e.g., over-use injuries, rheumatoid arthritis)</td>
<td>Aspirinlike drugs with analgesic and antiinflammatory effects</td>
<td>10% trolamine salicylate ointment or 2-3% sodium salicylate solution from negative pole</td>
</tr>
<tr>
<td>Zinc Oxide</td>
<td>Skin ulcers, other dermatologic disorders</td>
<td>Zinc acts as a general antiseptic; may increase tissue healing</td>
<td>20% ointment from positive pole</td>
</tr>
</tbody>
</table>
Current Drug Delivery Portfolio

- **Empi**
  - Hybresis®
  - Dupel®
    - Dupel B.L.U.E (Optimized)
    - Dupel White
  - ActionPatch®

- **IoMED**
  - IOGEL®
  - Optima®
  - TransQE, TransQFlex
  - Companion 80

- **Performa Ve**
Proposed Drug Delivery Portfolio

Drug Delivery

Traditional
- Dupel B.L.U.E (Premium pH Balanced)
- Iogel (Premium pH Stabilized)
- Dupel White (Low-Cost)

Patch
- Hybresis (Ultra-Premium, Power to Deliver)
- Action Patch (Buffered Patch)
- Companion 80 (Low Cost Patch)
Product Discussion—Dupel B.L.U.E.

- Bi-Layer Ultra Electrode
- High efficiency design for optimal delivery
- Karaya return pad
Product Description—Dupel White

- 80 mA-min
- Cost-effective
- Available in various sizes
- Karaya return pad
Product Description—ActionPatch

- Same Buffer as Dupel BLUE
- 6-hour treatment time
- Pull tab to begin treatment
- LED indicates treatment status
- Karaya return pad
Product Discussion—Hybresis

- Delivers both + and – charged water soluble drugs/compounds
- Predictable dosage time due to Skin Conductivity Enhancement
- Decreases in-clinic setup and treatment time
- Shorter patch wear times
- Even current distribution
Hybresis Patch

Silver (+)

- Silver-Silver Chloride components serve two purposes:
  - Maintain safe pH for patient
  - Creates electrochemical cut-off switch when treatment is completed
Compound Application

- Positive Pad—it is critical to use only compounds with a chloride ion on the Positive Electrode (ie, provided saline, Lidocaine)

- Compounds without a chloride ion used on the Positive side WILL result in skin staining or “tattooing” (ie, Dexamethasone, Magnesium Sulfate)
Dose Controller

Buttons
- STANDARD MODE
- START/PAUSE
- ON/OFF

LEDs
- Hybresis Mode LED

Alarm Conditions
- ▶️ = Low Battery
- ❌ = Current Interrupt
  (Could be a dry pad or Controller not attached properly)
Three Treatment Modes

- **Standard**
  - Provides controlled drug delivery with the wireless Dose Controller that can be mounted directly on the Patch

- **Patch-Only**
  - Provides convenience and short wear times, which can improve treatment compliance and reduce the likelihood of skin irritation

- **Hybresis Mode**
  - Offers precise dose control and reduces wear times with a 3-minute Skin Conductivity Enhancement, allowing patient to leave the clinic
Hybresis Application

1. Clean the treatment site
2. Do not shave skin—hair may be trimmed to improve adhesion
3. Attach Dose Controller to patch and place on a flat surface with absorbent pads facing up
4. Saturate the drug pads of the correct polarity thoroughly with a water-soluble drug/compound on one pad and supplied saline on the other
5. Make sure the treatment site has intact skin
6. Remove the adhesive liner from the hydrated patch, and apply over the treatment site
   - Avoid pressing directly on the drug pads
7. Begin treatment by activating the dose controller
Hybresis Mode

1. Push START on the Dose Controller
   - The light will flash while the current is increasing
   - When appropriate current is reached, light becomes steady green
   - After 3 minutes, SCE treatment is complete and alarm will sound. Light begins flashing as current decreases.

2. Remove the Dose Controller from the Patch

3. Return the Dose Controller to the Charging Station

4. Patch remains on the patient depending on the dose
   - 1 hour for 40 mA-min. dose
   - 1.5 hours for 60 mA-min dose
   - 2 hours for 80 mA-min dose
Clearly Communicate Value
PT Value Proposition

- Hybresis is the only product that offers the accuracy of traditional iontophoresis and the convenience of a patch

Hybresis offers:

- Accurate Dose Delivery
- Ease of Use
- Reduced in-clinic treatment time
MD Value Proposition

- Needle-free, localized drug delivery can help your patients and your practice

Hybresis offers:

- Another billable opportunity
- Ability to control patient care
- Added value for your patients
Good MD Practice Targets

- Pain Practice
- Primary Care
- Podiatry
How to start the conversation

- How many of your patients will refuse an injection?
- How many patients would benefit from an “extended release” inflammation treatment following an injection?
- How many of your patients are not an option for PT?
Thank You