Transdermal Administration of Anti-inflammatory Medications in Sports Injuries: Use of Iontophoresis and Phonophoresis to Enhance Delivery

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The delivery system itself occasionally proves to be the ultimate determinant of transdermal drug flow.
—Jeffrey J. Berti and James J. Lipsky

Abstract
Transdermal delivery of anti-inflammatory medications, both nonsteroidal and corticosteroids, has enjoyed at least a decade of success in Canada and the US. Iontophoresis and phonophoresis offer substantial benefits for the transdermal delivery of these medications and can be valuable additions to existing treatment modalities for minor sports-related injuries. Included with this article is historical and explanatory information about iontophoresis and phonophoresis, as well as formulations and case reports related to the treatment of sports-related injuries. The article emphasizes the importance of a compounding pharmacist’s involvement in developing a successful treatment plan.

Iontophoresis and Phonophoresis
Iontophoresis is based on the principle that ions repel like ions. The use of iontophoresis as a drug-delivery method dates from the work of LeDuc, who in 1908 demonstrated that ions could be driven across the skin by means of an electrical current. Harris concluded that iontophoresis is a clinically effective, painless, and safe mode of delivering ionized anti-inflammatory drugs to inflamed tissues. DeLacerda demonstrated that iontophoresis is effective in the administration of anti-inflammatory drugs to treat shoulder girdle myofascial syndrome. Allen identified dexamethasone sodium phosphate for the treatment of tendonitis, bursitis, and arthritis, and lidocaine hydrochloride as a dermal anesthetic and in trigeminal neuralgia. Nowicki et al compared delivery of dexamethasone via iontophoresis with that via injection in the rabbit patellar tendon and concluded that both offered anti-inflammatory efficacy.

Phonophoresis is the use of ultrasound to drive molecules of a topically applied medication to produce therapeutic concentrations at selected sites through the skin. A drug preparation is usually applied to the skin and allowed to absorb for a period of time, after which ultrasound is applied. Drugs widely administered via phonophoresis include the corticosteroids dexamethasone sodium phosphate and hydrocortisone and the nonsteroidal anti-inflammatory drugs (NSAIDs) ketoprofen and naproxen. We have varied from this format by administering diclofenac sodium in a vanishing penetrating base (VanPen; Professional Compounding Centers of America [PCCA], Houston, Texas).

Applications of Iontophoresis and Phonophoresis in Sports Medicine
The availability of diclofenac sodium, ketoprofen, and piroxicam in powder form, coupled with increased understanding and skill in the use of chemical absorption enhancers, has brought the skills of
I first connected with Pat Clayton, the athletic therapist for the Calgary Stampeders of the Canadian Football League, in the Spring of 1994. I had recently completed the PCCA Basic Compounding Course, and I recognized the potential value of Pluronic lecithin organogel (PLO) as a base vehicle for topical preparations. At that time, diclofenac sodium was the most widely prescribed oral NSAID in Alberta. Pat and I decided to try a transdermal preparation of the drug as a treatment for minor but painful soft-tissue injuries in team members. We began with diclofenac 2% in PLO gel and over 10 years eventually settled on a concentration of diclofenac 8%. We also changed the base over time, concluding that VanPen base more effectively accepted this concentration of the drug. This preparation is prescribed mostly for musculoskeletal inflammatory conditions; a variation that includes bupivacaine 1% with the diclofenac is used for management of acute minor trauma. The preparation is put through an Exacta Ointment Mill to reduce particle size, and is administered transdermally or via phonophoresis. (In some cases, we recommend that the patient apply the cream every 12 hours between phonophoresis sessions.) Chemical enhancers are key to an effective transdermal preparation, and VanPen base, PLO (soya lecithin, isopropyl palmitate), isopropyl myristate, and urea are all appropriate choices for specific applications.

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**Diclofenac Preparations Used for Phonophoretic Transdermal Delivery**

**Diclofenac 8% Cream**

<table>
<thead>
<tr>
<th>Rx</th>
<th>For 100 g</th>
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<tbody>
<tr>
<td>Diclofenac sodium</td>
<td>8.0 g</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>qs</td>
</tr>
<tr>
<td>VanPen base</td>
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</tr>
</tbody>
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**Diclofenac 8%/Bupivacaine 1% Cream**

<table>
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<tbody>
<tr>
<td>Diclofenac sodium</td>
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</tr>
<tr>
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**Diclofenac Preparations Used for Iontophoretic Transdermal Delivery**

**Diclofenac 0.4% (4-mg/mL) Sterile Solution**

<table>
<thead>
<tr>
<th>Rx</th>
<th>Dexamethasone sodium phosphate 52.0 mg</th>
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<tbody>
<tr>
<td></td>
<td>(1.3 mg equals 1 mg dexamethasone base)</td>
</tr>
<tr>
<td></td>
<td>Sterile water for injection qs 10 mL</td>
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</tbody>
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**Diclofenac 0.4% (4-mg/mL)/Lidocaine 4% (40-mg/mL) 1:2 Ratio**

<table>
<thead>
<tr>
<th>Rx</th>
<th>Dexamethasone sodium phosphate 15.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lidocaine hydrochloride 240 mg</td>
</tr>
<tr>
<td></td>
<td>Sterile water for injection qs</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared. Note: Calculate for at least 5% excess.
2. Accurately weigh and/or measure each ingredient.
3. Add sufficient sterile water for injection to bring the total dexamethasone sodium phosphate to 3 mL.
4. Add sufficient sterile water for injection to bring the lidocaine hydrochloride to 6 mL.
5. Combine and filter through an appropriate sterile 0.2-µm filter into a sterile empty vial.

**Stability**

A beyond-use date of 14 days stored in a refrigerator can be used for this preparation.

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**Dexamethasone Preparations Used for Iontophoretic Transdermal Delivery**

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**WARNING**: Diclofenac sodium powder is hazardous if inhaled. Wear a face mask and/or work within a safety hood.

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The compounding pharmacist to the attention of innovative medical prescribers in the field of sports medicine.
Pat and the Stampeders football team have used transdermal NSAID preparations for 10 years with great success. The true excitement and value for me as a compounding pharmacist working with the team is recognizing that I have the key ingredient—knowledge—that adds to the success of their medical treatment plans.

Case Reports

**Patient 1:** 57-year-old man  
**Diagnosis:** First-degree acromioclavicular sprain of the left shoulder  
**Treatment:** Two phonophoresis treatments (diclofenac 8% in VanPen base; continuous 1 w/cm² for 5 minutes), followed by four iontophoresis treatments (dexamethasone 1 mL/application [see iontophoresis protocol in accompanying box; current used was 2.0 mA] and two Iontopatch treatments) (dexamethasone 1 mL applied over a 24-hour period while the patch was on). Note: The parameters for Iontopatch treatment are the same as for iontophoresis. These treatments often are given in conjunction with other modalities such as heat, ice, manual therapy, and exercise.  
**Treatment Results:** The patient reported significant improvement at his last visit, and an examination revealed substantial objective improvement.  
**Side Effects:** None reported.

**Patient 2:** 51-year-old woman  
**Diagnosis:** Bursitis of the left hip (iliopectal bursa)  
**Treatment:** Both phonophoretic and iontophoretic treatments (four) with the same doses as Patient 1  
**Treatment Results:** The patient’s symptoms improved but did not resolve completely.  
**Side Effects:** None reported.
Patient 3: 48-year-old woman  
Diagnosis: Postoperative bursitis of the right greater trochanter after undergoing bilateral Birmingham hip surgery  
Treatment: Six iontophoresis treatments and six Iontopatch treatments on the right hip and six phonophoresis treatments on both hips  
Treatment Results: The patient’s bursitis resolved completely.  
Side Effects: None reported.

Patient 4: 47-year-old man  
Diagnosis: Postoperative bursitis and lateral knee pain on the left side after undergoing Birmingham surgery on the left hip  
Treatment: Two phonophoresis treatments and eight iontophoresis and Iontopatch treatments to the hip  
Treatment Results: The patient’s pain resolved completely.  
Side Effects: None reported.

Patient 5: 48-year-old polo player  
Diagnosis: Partial thickness tears in the right rotator cuff (supraspinatus and infraspinatus)  
Treatment: One iontophoresis and four Iontopatch treatments.  
Note: The patient is currently receiving treatment, attending once per week during the polo season.  
Treatment Results: The treatment has helped significantly, allowing the patient to continue playing polo.  
Side Effects: None reported.

Patient 6: 50-year-old woman  
Diagnosis: Overuse injury to the tensor fascia latae  
Treatment: Three phonophoresis treatments (pulsed 1.0 w/cm² for 5 minutes at 80%), and three Iontopatch treatments with 2 days between each treatment  
Treatment Results: The patient’s pain decreased by 90%, and function increased to 100%.  
Side Effect: Slight skin reaction to the glue in the patch.

Patient 7: 56-year-old woman  
Diagnosis: Tennis elbow (lateral epicondylitis)  
Treatment: Four iontophoresis treatments administered every second day  
Treatment Results: The patient’s symptoms were 100% resolved.  
Side Effects: None reported.

Patient 8: 15-year-old soccer player  
Diagnosis: Left groin strain  
Treatment: Six iontophoresis treatments  
Treatment Results: 80% to 90% resolution of the patient’s symptoms  
Side Effects: None reported.

Patient 9: 17-year-old downhill ski racer  
Diagnosis: Bilateral Achilles tendonitis  
Treatment: Eight phonophoresis treatments (dose-pulsed 1 w/cm² for 5 minutes at 80%/leg)  
Treatment Results: The patient’s symptoms resolved completely.  
Side Effects: None reported.

Patient 10: 26-year-old quarterback  
Diagnosis: Second-degree sprain to his clavicular ligament  
Treatment: Six Iontopatch treatments with dexamethasone and lidocaine on consecutive days  
Treatment Results: Pain and inflammation resolved within 2 weeks. The patient was able to return to full play in the third week.  
Side Effects: None reported.

Patient 11: 46-year-old woman  
Diagnosis: Postoperative bursitis of the trochanter following Birmingham surgery  
Treatment: Iontophoresis on one day followed by two Iontopatch treatments  
Treatment Results: The bursitis resolved completely in 3 days.  
Side Effects: None reported.

Discussion  
Iontophoretic and phonophoretic treatments with anti-inflammatory drugs are most commonly used in soft-tissue injuries, including muscle pulls and tears, ligament sprains, and tendinitis (Pat Clayton, oral communication, September 4, 2005). We have had the greatest success in bicipital tendonitis, Achilles tendonitis, hamstring and quadriceps strains and, to a lesser extent, or lumbar sacral strain.  
Iontophoresis is of great benefit in treating bursitis, in particular trochanteric bursitis, in patients who have undergone hip surgery. Iontophoresis in these cases is about 80% successful, although figures vary somewhat depending on the condition being treated.  
Use of the diclofenac gel between treatments helps relieve inflammation, reducing symptoms (Mary Ann Dunlop, personal communication, September 4, 2005). Iontophoresis and phonophoresis enhance the activity of anti-inflammatory medications, and their topical application is appealing to patients because it avoids gastrointestinal and other systemic effects. These treatments also allow potent anti-inflammatory drugs to be used on younger athletes, in whom systemic administration of these drugs is usually avoided. Moreover, the dosing schedule is convenient, brief, and easily remembered, increasing compliance.  
The most common side effect is a rash from the diclofenac gel; this occurs in a small percentage of patients, about 2% to 5%, usually after prolonged use outside the clinic. The rash is not itchy and it resolves quickly; patients don’t seem too concerned with it.  
It is important to note that any or all of these treatments may be part of combined modality therapy, as indicated in the note to case report #1.  
The cost of these treatments, like any medical treatment, is a consideration. The compounding pharmacist can check with third-party payers to see if the treatment is covered for a patient. Not all clinics can afford the equipment required to administer iontophoretic and phonophoretic therapy. The pharmacist should be prepared to refer patients to a facility that can provide this service.

Conclusion  
Both iontophoresis and phonophoresis can be valuable additions to existing treatment modalities for minor sports-related injuries.
The knowledge and skills of a compounding pharmacist can be a valuable addition to the development of a successful treatment plan. Physicians and other prescribers, pharmacists, physical therapists, and athletic trainers need to be educated on the value of iontophoresis and phonophoresis so that these modalities can be better utilized. Teamwork within these professions and improved utilization of iontophoretic and phonophoretic modalities could have a substantial positive effect on treatment of these disorders.

One of the great values of the teamwork approach to pain therapy is the trust that develops in the preparations that the pharmacist makes. Knowledge is the key ingredient in properly made preparations. If pharmacists are to provide the solutions they must be the right solutions.

Acknowledgment
The author thanks Pat Clayton, BA, CAT, Athletic Therapist for the Calgary Stampeders Football Club, and the therapists at the Glencoe Club Physiotherapists group: Mary Anne Dunlop, BScPT, BScPED; Yvonne Anderson, BScPT; and Judy Morey, BScPT, for their contributions; and Jim Thorne, MD, Sports Medicine specialist, for his review of the article.

Suggested Reading

References
11. Diclofenac sodium [material safety data sheet]. Houston, TX: Professional Compounding Centers of America; New York, NY: Medisca.

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