Iontophoresis and Phonophoresis as a Transdermal Technique for Drug Delivery

Policy Number: 8.03.14  Last Review: 3/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for iontophoresis when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Iontophoresis may be considered medically necessary to administer local anesthesia prior to a venipuncture or dermatologic procedure.

Iontophoresis of fentanyl may be considered medically necessary for the short-term (i.e., less than 24 hours) management of acute postoperative pain in adult patients requiring opioid analgesia in a monitored facility (e.g., inpatient hospital, outpatient hospital, ambulatory surgical center).

When Policy Topic is not covered
Iontophoresis as a transdermal drug delivery technique for other medical indications is considered investigational.

Phonophoresis alone or in combination with iontophoresis as a transdermal drug delivery technique, is considered investigational for any medical indication.

Considerations
When iontophoresis is used in the treatment of musculoskeletal disorders, the procedure is often performed by physical therapists.

Description of Procedure or Service
Iontophoresis is a method of transdermal local drug delivery using electrical current. A charged, ionic drug is placed on the skin with an electrode of the same charge, allowing direct current to drive the drug into the skin. Ultrasound transdermal delivery involves the use of ultrasonic energy to enhance delivery of
solutes either simultaneously or via pre-treatment, and is referred to as sonopheresis or phonophoresis.

**Background**

Iontophoresis may take advantage of sweat ducts, sebaceous glands, hair follicles, and imperfections in the skin to achieve penetration. Alternatively, electrical potential across the skin could alter its permeability, possible creating potential-dependent pores in lipid bilayer membranes. It has been proposed for numerous uses, including delivering local anesthetic before skin puncture or other painful dermal procedure, local drug delivery for agents such as nonsteroidal anti-inflammatory drugs, or corticosteroids for musculoskeletal inflammatory disorders. In the treatment of musculoskeletal disorders, iontophoresis is often offered in the physical medicine and rehabilitation setting. The proposed mechanism for phonophoresis is to increase skin permeability by the formation of gaseous cavities within the intracellular lipids on exposure to ultrasound.

**Regulatory Status**

A number of iontophoresis devices have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA) to “introduce ions of soluble salts or other drugs into the body.” The FDA prohibits labeling or promoting their use with specific drugs prior to the FDA having specifically approved the drugs for iontophoretic administration. Two iontophoretic transdermal devices are being developed for patient-activated delivery of fentanyl for postoperative pain. The IONSYS™ fentanyl iontophoretic transdermal system is manufactured by ALZA and marketed by Ortho-McNeil. Transdermal iontophoretic fentanyl (IONSYS) received FDA approval in May 2006. Janssen-Cilag EMEA is also investigating a patient-controlled fentanyl iontophoretic transdermal delivery system in Europe. These patch systems are intended for 24-hour use in hospitals, and allow patients to control the number of doses of fentanyl (40 mcg delivered over 10 minutes), with a maximum delivery of 6 doses per hour.

The SonoPrep® (Echo Therapeutics, Inc) phonophoresis device is cleared by the FDA as class 2 electromedical equipment. SonoPrep® uses low frequency ultrasound (55kHz) to enhance skin permeability.

**Rationale**

This policy was based on an updated 2003 TEC Assessment on iontophoresis (an original TEC Assessment on iontophoresis was conducted in 2000), which re-evaluated 3 indications. (1,2) The 2003 TEC Assessment (1) offers the following conclusions and observations:

In general, for most indications, placebo-controlled studies demonstrated that iontophoretic delivery of a drug exceeded the effects of an iontophoretic delivery of a placebo. While these studies are an important first step, they are considered insufficient to validate the efficacy of iontophoretic drug delivery compared to other methods, such as no drugs, topical applications of drug, oral, subcutaneous, intradermal injection, etc. The crucial issue is whether iontophoretic drug delivery
is at least as beneficial as other treatments and other routes of drug administration. The benefit of iontophoresis for local drug delivery could be the avoidance of adverse effects of systemic administration of higher doses of drugs and possibly equivalent or greater therapeutic effects.

1. Administering local anesthetic before skin puncture or dermal procedures.
   The 2000 TEC Assessment identified 12 controlled studies, and the 2003 TEC Assessment identified an additional controlled 15 studies, which demonstrated that the effects of iontophoretic administration of local anesthetics exceed placebo. Published and unpublished (studies submitted to the U.S. Food and Drug Administration [FDA]) showed improved self-reported visual analogue scale pain ratings, higher proportions of patients reporting pain-free dermatological procedures; and fewer rescue injections of local anesthetics.

   The comparison of iontophoresis to alternate interventions focused on the comparative effects of a topical anesthetic preparation called EMLA (eutectic mixture of local anesthetics; lidocaine and prilocaine). Studies showed that iontophoretic administration of local anesthesia is at least as beneficial as EMLA for reducing pain before venipuncture or dermatologic procedures. Iontophoresis can cause minor skin irritation, but it acts more quickly than EMLA: 15 minutes versus 45 minutes or more.

2. Treatment of musculoskeletal inflammatory disorders with nonsteroidal anti-inflammatory drugs (NSAIDs).
   The 2000 TEC Assessment identified 4 placebo studies that suggested that iontophoretic delivery of NSAIDs exceed placebo effects. No additional comparison to placebo trials were noted in 2003. No studies compared the relative effects of iontophoretic delivery to other routes of NSAID administration.

3. Treatment of musculoskeletal inflammatory disorders with corticosteroids.
   The 2000 TEC Assessment identified 5 placebo studies with mixed results, and the 2003 TEC Assessment identified 4 additional placebo studies. Placebo studies did not consistently report significantly better outcomes for groups receiving corticosteroids compared to those receiving placebo. No studies compared the relative effects of iontophoretic delivery of corticosteroids to other routes of corticosteroid delivery.

A search of the MEDLINE database for articles published from 2003 through July 2007 identified five industry-sponsored randomized controlled trials on the use of the patient-controlled fentanyl transdermal system. Two ALZA-sponsored placebo-controlled trials with the IONSYS system have been published. (3, 4) The most recent was a multicenter, randomized, double-blind, parallel-group study from 20 U.S. hospitals. (4) Subjects admitted to the post-anesthesia care unit after major abdominal, orthopedic, or thoracic surgery were randomized to fentanyl iontophoresis (n=244) or a placebo system (n=240). Bolus doses of IV fentanyl were allowed during the first 3 hours upon patient request; no analgesics were allowed for the rest of the 24-hour study. Twice as many placebo patients (60% versus 29%) withdrew from the study because of inadequate pain relief during the
24-hour monitoring period. Secondary outcome measures, including pain intensity scores, were improved with the active treatment (3.5 versus 5.4 on a 10-point scale). Three patients in the active group withdrew due to adverse effects of treatment (nausea, pruritis). The most common adverse effect was mild-to-moderate erythema after system removal, occurring in 25% of patients treated with iontophoretic transdermal fentanyl.

Fentanyl iontophoresis was compared with patient-controlled IV morphine for postoperative pain in 3 industry-sponsored multicenter studies. (5-7) The studies were conducted at a total of 136 hospitals in the U.S. and Europe, with a combined enrollment of 2,100 patients. The 3 studies used similar protocols, with bolus doses of IV fentanyl or morphine allowed during the first 3 hours postoperatively, and patients randomized to self-activated dosing with the iontophoretic fentanyl patch (40 micrograms over 10 minutes) or IV morphine (up to 10 mg per hour) for 24 hours. Due to the different delivery methods (skin patch versus IV line), these studies were open-label. The primary efficacy measure, patient global assessment of pain control, and the secondary measure of pain-intensity scores, were similar for the 2 groups (e.g., “excellent” or “good” ratings of 83% versus 82%, respectively and pain ratings of 3.0 versus 3.0, respectively). (5) Common adverse events during treatment were similar in the two groups; no cases of respiratory depression were reported with transdermal iontophoresis. (5-7) Mild to moderate skin irritation was common with the fentanyl patch systems. In one study, over 50% of patients in the iontophoresis group were found to have erythema 24 hours after system removal. (6) Results from these 5 studies, which show greater pain relief than placebo and similar pain relief to morphine in the acute postoperative period, support the clinical efficacy of the patient-controlled iontophoretic fentanyl system.

Iontophoretic administration of ketamine was not more effective than placebo in 33 patients with intractable central pain. (8) Other randomized double-blind controlled studies examined iontophoretic application of acetic acid or dexamethasone for a variety of soft tissue pain syndromes. A study of iontophoretic dexamethasone (up to 6 treatments within 15 days) in 199 patients with acute lateral epicondylitis found a significant 23-mm improvement on the 100-mm patient visual analog scale ratings, compared with 14 mm for placebo at 2 days after completing treatment and 24 mm compared with 19 mm at 1 month. (9) No difference was observed in the percentage of patients from each group who rated their global improvement as moderate or better (48% dexamethasone versus 41% saline). Another small study (n=25) compared iontophoresis of dexamethasone with saline in patients with acute Achilles tendon pain. (10) No differences were observed for a toe-raise test or range of motion test. The authors reported that some pain measures were decreased with iontophoretic dexamethasone at some time points. However, only one of 4 dichotomous (yes/no) pain measures showed consistent improvement over the 4 assessments (2 weeks to 6 months), and there was no adjustment for missing data or for the multiple comparisons. A third study with only 31 patients found that iontophoretic dexamethasone was not effective for plantar fasciitis. (11) The same study reported that iontophoresis of acetic acid was better than dexamethasone for
plantar fasciitis. However, since only one of the 14 outcome measures was shown to be better than placebo, the clinical relevance of this finding is unclear. Another study (36 patients) found that acetic acid iontophoresis added no clinical benefit to physiotherapy for the treatment of calcifying tendonitis of the shoulder. (12) Overall, the results from these studies do not provide support for the iontophoretic application of acetic acid or dexamethasone for pain, tendonitis, or fasciitis.

2008 Update
A search of the MEDLINE database for the period of August 2007 through August 2008 indicates continued interest in the development of iontophoresis as a drug delivery method. The literature search, which focused on iontophoresis of therapeutic agents other than fentanyl or local anesthetics, did not identify any additional controlled trials. Therefore, the policy statements are unchanged.

2009 Update
A search of the MEDLINE database was performed for the period September 2008 through September 2009. The literature search identified no new high quality evidence that would alter previous conclusions.

Amirjani et al (13) conducted a study in Canada (n=17) comparing six sessions of iontophoresis with 0.4% dexamethasone sodium phosphate with distilled water to determine the effectiveness of corticosteroid iontophoresis in relieving carpal tunnel syndrome manifestations in mild to moderate cases. The results showed iontophoretic delivery of dexamethasone to be well-tolerated; however, it was not shown to be an effective treatment. Given the small size of the study and variability of drug delivery to the targeted tissue, these data are inconclusive.

Gurney et al (14) conducted a study (n=29) to compare the concentrations of dexamethasone in tendon tissues of humans using iontophoresis versus sham. The authors concluded that “Iontophoresis facilitates the transmission of dexamethasone to connective tissues in humans.” However, given the small size of this study, author-reported issues with electrode placement, lack of clinical outcomes, and conflicting results with other clinical trials that examined the effectiveness of iontophoresis on inflammatory conditions, there is lack of evidence demonstrating the clinical efficacy of iontophoretic delivery of dexamethasone for the treatment of inflammatory conditions.

A review article by Turner et al (15) discussed the use of laser Doppler flowmetry/imaging to measure cutaneous perfusion accompanied by iontophoresis of acetylcholine and sodium nitroprusside for determining patients at risk of development and progression of cardiovascular disease. The authors concluded that “It is clear from previous studies that this technique provides an easy, validated, and reproducible method for investigators to assess and monitor endothelial function in patients with a variety of pathologic conditions, but it may also be used to examine disease progression over time and responsiveness to treatment, thereby facilitating clinical trials. However, a standardization of protocols would help reduce the apparent controversy seen in the literature.”
These data are inconclusive to draw conclusions regarding the clinical use of iontophoresis to monitor endothelial function.

A review article by Rao et al (16) discussed the transdermal drug delivery technologies with a focus on phonophoresis used alone as a sole transdermal technique or in combination with other transdermal delivery techniques. The authors stated that “Sonophoresis (phonophoresis) has been shown to increase skin permeability to various low and high molecular weight drugs, including insulin and heparin. However, its therapeutic value is still being evaluated.”

Phase III clinical trials are underway for an iontophoretic sumatriptan patch (Zelrix™, NuPathe, Inc.). (17)

As of October 2009, this transdermal formulation for migraines has not been approved by the U.S. Food and Drug Administration (FDA).

Summary
The available evidence for the use of iontophoresis to administer local anesthesia prior to a venipuncture or dermatologic procedure, and fentanyl for the short-term (i.e., less than 24 hours) management of acute postoperative pain in adult patients is sufficient to show improvement in net health outcome. Therefore, the policy statements for their use as medically necessary remain unchanged.

Given the lack of evidence to show improvement in net health outcome, the policy has been modified with the addition of a policy statement on the use of phonophoresis as a transdermal delivery technique, alone or in combination with iontophoresis, which is investigational.

Medicare National Coverage
No national coverage determination.

References:
1. 2003 TEC Assessment: Iontophoresis for Medical Indications.
2. 2000 TEC Assessment: Iontophoresis for Medical Indications.

Billing Coding/Physician Documentation Information

97033 Application of a modality to 1 or more areas; iontophoresis, each 15 minutes
97035 Application of a modality to 1 or more areas; ultrasound, each 15 minutes
97039 Unlisted modality (specify type and time if constant attendance)
E1399 Durable medical equipment, miscellaneous

When iontophoresis is used to apply local anesthetic prior to a venipuncture or prior to a dermatologic procedure, iontophoresis is an integral component to the venipuncture or dermatologic procedure.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

10/1/06 New policy.
3/1/07 No policy statement changes.
9/1/07 No policy statement changes.
3/1/08 Policy statement revised to indicate postoperative fentanyl iontophoresis may be considered medically necessary.
3/1/09 No policy statement changes.
3/1/10 A policy statement was added to reflect iontophoresis in combination with sonophoresis (phonophoresis) as investigational. The other policy statements are unchanged.
3/1/11 No policy statement changes.
3/1/12 No policy statement changes.
3/1/13  No policy statement changes.
3/1/14  No policy statement changes.
3/1/15  No policy statement changes.
3/1/16  No policy statement changes.
3/1/17  No policy statement changes.
3/1/18  No policy statement changes.

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