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# Electromotive administration of topical medications in clinical physiotherapy practice: A review

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## To cite this article:

Odeyemi Emmanuel, Oyedemi Jeremiah, Okonji Adaobi. Electromotive Administration of Topical Medications in Clinical Physiotherapy Practice: A Review. *American Journal of Health Research*. Special Issue: Supplementary Prescribing in Nigeria: A Needy Concept to Promote Clinical Physiotherapy Practice. Vol. 2, No. 5-1, 2014, pp. 34-39. doi: 10.11648/j.ajhr.s.2014020501.17

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**Abstract:** Oral and injection routes of drug administration has adverse effect in the body system, hence, there is paradigm shift in route of drug administration to the use of electromotive force via the skin where applicable; and this by passes the first pass effect metabolism. Both iontophoresis and ultra-sonophoresis are examples of procedures for the electromotive administration of drugs. Potential serious side-effects are eliminated because transdermal routes of drug administration are known to possess little or no side effects. Iontophoresis is the introduction of medicinal ions into the body using Direct Current. It is a painless, sterile and non invasive technique with minimal adverse reactions in the gastro-intestinal system. The dose depends on current and time of treatment and a typical dosage is 40 mA-min. This review revealed that Iontophoresis is being used to subdue inflammation using topical Non-steroidal anti-inflammatory drugs, administer antibiotics to combat infection, manage bicep brachii spasticity of stroke survivors, promote wound healing, reduce bacteria colonization, combat fungal infection; and has produced analgesic effects in several studies. Also, the reviewed showed that ultrasonophoresis is relevant in clinical physiotherapy practice.

**Keywords:** Iontophoresis, Clinical Practice, Electromotive Drug Administration, Ionic Charge

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## 1. Introduction

### 1.1. Iontophoresis

There are emerging roles for physiotherapists in drugs prescription and administration with evidence based guidelines being established towards the establishment of requisite trainings and legislations to support practice [1, 2]. Drug therapy is usually required for orthopaedic/musculoskeletal disorders and it is primary used to reduce pain and inflammation. Physiotherapists are currently re- focusing on alternate route of drug therapy such as transdermal administration [3]. This scope of practice is increasingly expanding, as physiotherapists continue to identify with new roles. However, a primary concern would be employing the most effective route of drug administration within the scope of physiotherapy practice and disease condition

The bioavailability of drugs is an essential concept in drug administration. It is the measurement of the rate and extent to which an unchanged fraction of an administration dose

reaches the systemic circulation [4]. Bioavailability of certain drugs is adversely affected by certain factors such as pre-systemic metabolism [4]. Oral routes of drug administration are known to be significantly affected by the first pass effect metabolism, with the intravenous route known to have a 100% bioavailability [4]. However, with the limitations involved in the IV routes and injection routes, other routes less affected by first pass and known for other adverse effects are being explored for their obvious advantages [5, 6]

In order to increase the efficacy of certain drugs, more especially those needed for local actions as common with many 'physiotherapeutic' drugs are currently been emphasized [7]. The transdermal route of drug administration has been an age long means of delivery therapeutic substances to the body especially for local effects [8]. It involves the use of direct manual and transdermal patch applications, and more recently Electromotive Drug Administration [3,9,10]. In pharmacotherapy, increasing study are being focused on the use of therapeutic medications randomly as adjuncts within the domains of physiotherapy treatments [[11, 12, 13, 14]. Iontophoresis is regarded as a

form of Electromotive Drug Administration (EMDA), and it is a technique that uses a small electric charge to deliver drugs and bioactive agents via the skin [3, 9, 11,13,15]. It was simply defined as the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties [16]. There are enhanced strategies to deliver medications through the skin especially drugs of differing lipophilicity and molecular weight [9,17]. Potential serious side-effects are eliminated because transdermal routes of drug administration is known to possess little or no side effects [12,18, 19]. The most challenging for physiotherapist is understanding the knowledge of active ingredient in topical medications [3,20]. Marowino provided a cross reference for charges on some drugs [21], (Table 1).

## 1.2. Historical Background

The history of iontophoresis is reported in literature as far back as the mid 1700s [22]. The method of iontophoresis was described by Pivati in 1447; and Gavani and Vota. The two scientists in the 18<sup>th</sup> century used the knowledge of electricity that it can move different metal ions, and that the movement of the ions produce electricity [22]. According to Helmstadter, increasing progress was made in the 19<sup>th</sup> century notably by William James Morton (1846-1920), Stephen Leduc (1853-1939) and Fritz Frankenhauser (1868) on electromotive administration of metal ions and alkaloids [23]. At 20<sup>th</sup> century, the method of administering pharmacological agents by iontophoresis became popular due to the work of Leduc (1900) who introduced the term 'iontotherapy' and formulated the laws for this process [24]. Until the early 20<sup>th</sup> century, current medicated drug delivery was known as "cataphoresis". Frankenhauser introduced the term "iontophoresis" before 1908 [22]. Iontophoresis is the introduction of ionic molecules into the skin by means of electricity [25]. However, it has been noted that due to improvement in understanding its mechanism, many non-ionic materials such as polypeptides are been speculated to be delivered into the body by iontophoresis.

**Table 1.** Ionic charges of selected drugs and relevant conditions [21]

Drugs	Charges	Conditions
Acetic acid	Negative	Calcium deposits
Chloride	Negative	Scar tissue
Dexamethasone	Negative	Inflammation- tendonitis/ bursitis
Calcium	Positive	Muscle spasm/muscle dysfunction
Hydrocortisone	Positive	Anti- inflammatory steroid/myositis
Zinc oxide	Positive	Antiseptic/wound healing
Salicylates	Negative	Arthralgia/myalgia
Lidocaine	Positive	Tenosynovitis
Atropine sulphate	Positive	Hyperhydrosis
Magnesium	Positive	Muscle relaxant
Zinc oxide	Positive	Wound healing/antiseptic

The following have been identified as the benefits of iontophoretic techniques of both ionized and un-ionized drugs:

- Depending on the current applied, it enables continuous or pulsatile delivery of drug.

- Permits easier termination of drug delivery.
- Offers better control over the amount of drug delivered since the amount of compound delivered depends on applied current, duration of applied current, and area of skin exposed to the current.
- Restoration of the skin barrier functions without producing severe skin irritation.
- Improving the delivery of polar molecules as well as high molecular weight compounds.
- Ability to be used for systemic delivery or local (topical) delivery of drugs.
- Reducing considerably inter and or intra subject variability in view of the fact that the rate of drug delivery is more dependent on applied current than on stratum corneum characteristics.
- Improved drug delivery over passive transdermal delivery method
- It avoids GIT side effect, inactivation of drug by GIT enzymes, interaction of drug with food and first-pass metabolism of drugs in GIT.
- It provides controlled and sustained release of the medicament.
- It improves the bioavailability of drug.
- It provides uniform drug plasma concentration.
- It improves the patient's compliance.
- It can be administered to non- responsive, unconscious and nauseating patient.
- It also provides easy termination of drug in case of toxicity by removal of the formulation from the skin [26, 27, 28, 29 ].

## 1.3. Mechanism, Dosage and Application

The mechanism of iontophoresis is based on the general principle that like charges repel. Thus, during iontophoresis, if delivery of a positively charged drug (DC) is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode. On application of an electromotive force the drug is repelled and moved across the stratum corneum towards the cathode, which is placed elsewhere on the body [30]. According to Glikfeld, the movement of the drug ions between the electrodes occurs through the skin and not on the surface. Thus communication between the electrodes along the surface of the skin has been shown to be negligible [26].

Although, Direct or Galvanic current is the most suitable for iontophoretic delivery of drugs but there are newer evidences supporting alternate and faradic currents. The dose period depends on the current and time of treatment. It is expressed as milliampere minutes (mA-min) with the recommended milliampere-minute dose depending on the electrode used. [21]) a typical dosage is 40 mA- (e.g., 4 mA x 10 minutes or 2 mA x 20 minutes, etc). The current setting is chosen based on patient comfort and when using mobile patches, a microampere current is used for much longer periods of time. [21].

Medical device manufacturers now provide automated and portable devices which are being developed to reduce the

time burden of iontophoresis treatment for patients. There is the introduction of a more mobile solution to iontophoresis treatment—sold under the brand name of IontoPatch®—that may be worn by the patient for a 24-hour period. The clinical time component of treatment is eliminated altogether and the patient gets a more sustained 24 hour effect [31].

Iontophoresis is effective in many clinical conditions, while it is been considered investigational in certain areas. [9, 11, 23, 32]. The use of the application in physical therapy had been well documented by Costello and Jeskey [11]. Most of these reports are, however, poorly substantiated or are reports of clinical trials that lacked controls. Further studies with larger sample sizes have also been recommended [3].

Drugs such as analgesics, muscle relaxants and anti-arthritis are in the domain of drugs with differing lipophilicity and molecular weight [17]. In an attempt to minimize and or avoid the side effects; mild, moderate or adverse, of these drugs in the systemic circulation; there is increasing focus on local drug delivery directly to site of action. There are other global issues such as non-compliance with the use of oral medications as a result of certain factors such as taste, bulk etc that are being put into consideration. [4, 33]. Iontophoresis has been reported to be effective in the treatment of hyperhidrosis and several musculoskeletal conditions using appropriate medications. [3,9,14, 34].

#### **1.4. Non-Steroidal Antiinflammatory Drugs (NSAIDs)**

Iontophoresis has also been documented to subdue inflammation [21]. The oral administration of Non-steroidal anti-inflammatory drugs provokes adverse effects most especially in the gastrointestinal tract [4]. NSAIDs are well known pharmacologic agents that produce analgesic, antipyretic and anti-inflammatory effects [4, 35]. Hence, increasing interest has been shown in studies establishing the efficacy of NSAIDs administration via other routes [12, 14]. Diclofenac, Ibuprofen, piroxicam, Pirprofen, Lys-aspirina, Ketorolac, salicylic acid have all been reportedly used for investigational studies for their therapeutic effects most especially in musculoskeletal conditions and sport related injuries [14, 36]. Diclofenac and Ibuprofen were reportedly used to provide topical analgesia using iontophoresis [28, 37].

#### **1.5. Magnesium and Gentamicin Sulphate**

Onigbinde et al showed that magnesium sulphate iontophoresis was able to reduce bicep brachii spasticity among stroke survivors. Gentamicin sulphate iontophoresis was also reported by Onigbinde et al to promote wound healing and reduce bacteria colonization [3]. Iontophoresis of antibiotics has been shown to be more effective for treating superficial infections than systemically administered antibiotics.

#### **1.6. Corticosteroids**

Corticosteroids such as dexamethasone sodium phosphate (or dexamethasone in a sodium phosphate solution) and methylprednisolone sodium succinate have been widely

reported for the treatment of pain and inflammatory conditions such as tendinopathies and arthritis [14, 38].

#### **1.7. Lidocaine**

Lidocaine iontophoresis has also been explored and increasingly considered for pain management in soft tissue injuries [38, 39, 40]. Prospective studies such as the iontophoresis of lidocaine for the pain management of acute soft tissue injuries in the emergency had been found to be more effective than the oral administration of non-steroidal anti-inflammatory medication [38]. Similarly, patients with ‘tennis elbow’, showed clinical improvement when iontophoresis of lidocaine was administered [39]. Other studies have likewise established these prospects while further studies are being suggested to substantiate the use of lidocaine iontophoresis [12, 14].

#### **1.8. Glucosamine**

Glucosamine Sulphate iontophoresis has been documented in several studies to be effective in alleviating pain and improving functions among subjects with knee OA [13].

#### **1.9. Copper**

A 0.2% solution of copper sulphate iontophoresis has been used to treat chronic fungal infections of the feet following an average of six to seven treatments [42].

#### **1.10. Lithium**

Lithium iontophoresis was reportedly used to obtain therapeutic effect in the treatment of gout [43].

#### **1.11. Acetic Acid**

Acetic acid iontophoresis combined with taping, gave considerable relief from pain and stiffness symptoms in the management of Plantar Fascitis [44]. Acetic acid iontophoresis has been described in case reports for the treatment of patients with calcium deposits around the shoulder and for myositis ossificans affecting the quadriceps femoris muscle. There were reported resolution of the calcium deposition, with reduction in symptoms and improved function in the two cases. Iontophoresis has also been indicated for the following purpose; useful in treating scars or adhesions, to treat inflammatory conditions of the skin and joints, spasm relief, analgesia, to treat edema, and for treating open skin lesion [45].

Iontophoresis has also been documented for dermatological conditions such as psoriasis, inflammatory skin conditions, decubitus ulcer and burns. There is likewise a similar increasing interest in the other health field such as dentistry, surgery etc [11]. According to Costello and Jeske, the interests of the pharmaceutical and physical therapy professions in iontophoresis are often different [11]. Many medical practitioners are interested primarily in the delivery of medication to achieve a systemic concentration sufficient for a desired effect whereas physical therapists are interested

in directing larger quantities of a medication into a localized treatment region and minimizing systemic levels of the medication [11].

### 1.12. Contraindications and Adverse Effect

Typical of drug therapies, there are possible contraindications and adverse effects. Amongst are electric and chemical burns, pain arising from high current density, ionic competition and cardiac arrest.

## 2. Ultrasonophoresis

The stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability of drugs [46]. Transdermal drug delivery has gained prominence over other forms of drug delivery due to its potential advantages, including minimal trauma induction, noninvasiveness, increased patient compliance and potential for continuous, controlled delivery [47]. Drug of high molecular weight, ionic and polar which can only be deliver into the deeper layer of the skin by various skin penetration that requires chemical enhancers, drug formulation enhancer and physical enhancer which includes iontophoresis, sonophoresis (phonophoresis) and electroporation to overcome this formidable barrier [48].

There are several methods of delivering medication transcutaneously but the most common is through intramuscular injection which is generally considered to be invasive [49]. The recent advances in non-invasive penetration enhancer can be categorized into three generations of development. Archana described the first-generation transdermal delivery systems or enhancer in clinical use for delivery of small, lipophilic, low-dose drugs which are drugs that can cross the skin at therapeutic rates with little or no enhancement. [50]. This delivery systems is limited primarily by the barrier posed by skin's outermost layer called stratum corneum [51]. Second-generation delivery systems use chemical enhancers, iontophoresis and non-cavitation ultrasound that involve mechanical force that is referred to as phonophoresis. They yielded additional advances for small molecule delivery by increasing skin permeability and driving forces for transdermal transport [49]. Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitation ultrasound [51].

Ultrasound (US), a form of acoustic energy, is often used in physical therapy because of its non-thermal mechanisms which play a primary role in producing a therapeutically significant increase in the rate of cell membrane permeability and molecular diffusion [52]. Use of ultrasound in therapeutics and drug delivery has gained importance in recent years, evident by the increase in patents filed and new commercial devices launched [53]. Therapeutic ultrasound is a commonly used modality that utilizes high-frequency sound waves (usually 1 to 3 MHz) that pass through the skin to underlying structures. The tissue temperature is raised with

increased blood flow to skin, it decreases pain secondarily by decreasing muscle spasm, and promote healing of various tissue. Other claims, however, such as the utility of ultrasound as anti-inflammatory modality, remain controversial [54]. Phonophoresis also known as ultrasonophoresis is an example of these ultrasound-enhanced therapies described as the migration of drug molecules through the skin under the US transducer. The technique uses therapeutic ultrasound to introduce pharmacologic agents, usually anti-inflammatory or analgesic drugs, through intact skin into the subcutaneous tissues [55]. Furthermore, phonophoresis has been shown to increase skin permeability to various low and high molecular weight drugs, including insulin and heparin [53].

In physical therapy, phonophoresis of nonsteroidal anti-inflammatory drugs (NSAIDs) is commonly used to treat inflamed tissues, and in addition phonophoresis of ketoprofen allows the attainment of higher local concentration; whereas systemic exposure was lower [52]. Most authors have shown that, when compared with placebo treatments or ultrasound alone, phonophoresis provides clinical improvement by decreasing pain and increasing function [55]. In a randomized controlled study by Gurney et al to describe if phonophoresis will facilitate the transmission of HA in human connective tissue among 21 patients undergoing anterior cruciate ligament reconstruction surgery. They found that phonophoresis does not appear to facilitate the absorption of HA in connective tissue when compared with simple absorption (sham), [54]. Also, Giovana et al studied the effect of diclofenac phonophoresis on human subject among 14 volunteers. They found that previously applied therapeutic ultrasound irradiation enhances the percutaneous penetration of the topical diclofenac gel [56]. Similarly, Saliba et al determined the effect of ultrasound on the transcutaneous absorption of dexamethasone using 2 grams of 0.33% dexamethasone cream with an intensity of 1.0 W/cm<sup>2</sup> (50% pulsed) at an output frequency of 3 MHz for 5 minutes and compared with sham ultrasound treatments that were delivered at an intensity of 0.0 W/cm<sup>2</sup> (50% pulsed) at an output frequency of 3 MHz for 5 minutes [55]. They observed that the rate of appearance and the total concentration of dexamethasone in the serum were greater in subjects after phonophoresis than after sham ultrasound. The sham group had only trace amounts of dexamethasone in the serum, indicating that drug absorption was negligible without the ultrasound energy [55].

## 3. Conclusion

This review revealed that iontophoresis and ultrasonophoresis are effective and well tolerated methods for delivering ionized medications, bio-active agents and drug molecules through the dermis using minimal electric current and ultrasound. Also, the review showed the spotential prospect of iontophoresis and phonophoresis as electromotive means of administering drugs.

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