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Reviews

Modern iontophoresis for local drug delivery ☆

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Abstract

Iontophoresis, a process that promotes ionic drug penetration using electricity as an energy source, was suggested long ago. Nevertheless, it only achieved some stature after scientific studies conducted during the 1950s and 1960s indicated at least two rational applications: (1) detecting cystic fibrosis by iontophoresis of pilocarpine and (2) myringotomy by iontophoresis of lidocaine/epinephrine. Recently, there has been more interest and further research in the field. Studies from our laboratories on local use of iontophoresis indicated multiple applications in dentistry, dermatology, ophthalmology and physical medicine. In a double-blind evaluation, iontophoresis of fluoride into dentin caused immediate and long-lasting desensitization of thermally sensitive teeth. Studies on fluoride iontophoresis indicated its mechanism of desensitization, safety for use on vital teeth, tooth hardening effect and anticaries effect. Also, we provided extensive evidence that antiviral iontophoresis was effective vs herpes simplex virus type 1 (HSV-1) and HSV-2 lesions in animals. In a double-blind study of human herpes orolabialis, vidarabine monophosphate (Ara-AMP) iontophoresis lowered the HSV titer by more than 4 log units to almost zero at 24 and 48 h. This reduction was statistically different ($P < 0.05$) compared with iontophoresis of a placebo or of acyclovir. In a separate study, idoxuridine iontophoresis resulted in no HSV detected in nine of 11 lesions after 24 h. In active herpes zoster, iontophoresis of Ara-AMP, or of acyclovir, significantly accelerated clinical signs of viral inactivation, compared with placebo. Post-herpetic neuralgia (PHN) was treated by corticosteroid iontophoresis resulting in a marked reduction of pain in 60–70% of more than 1000 patients. In a double-blind trial, absence of pain in areas of skin treated by corticosteroid was noted in six out of six PHN patients, compared with no improvement in a matched placebo-treated area. The research on herpes virus diseases provides scientific evidence that iontophoresis of antivirals should be part of the therapeutic armamentarium for treating surface viral infection. Also, corticosteroid iontophoresis may be useful for therapy of PHN, a painful condition that has no consistently effective therapy at this time.

Keywords: Iontophoresis; Drug delivery; Herpes simplex; Herpes zoster; Post-herpetic neuralgia; Cutaneous penetration; Antiviral

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1. Introduction

Iontophoresis is a method that uses an electrical current to increase the penetration of ionic drugs into the body for therapeutic purposes. Although iontophoresis has the potential of promoting therapy for both local conditions at the body surface and for systemic effects, this paper will be concerned only with local delivery as an aid to penetration of topically applied drugs.

Normally, the penetration of drugs into the skin after topical application is slow because transport depends upon diffusion down a concentration gradient and is driven by thermal energy that causes molecular motion. Not only is diffusion a random process, but also permeability of ions across the skin is further limited by inhibited penetration of charged particles. Sometimes penetration problems can be overcome for lipophilic molecules by using adjuvants that promote diffusion, however, this approach has its limitations. For ionic drugs, penetration can often be optimized by using an applied voltage; the electrical energy increases the degree of penetration of the ions and thereby increasing the concentration of medication at the desired site of action.

Iontophoresis greatly increases ion penetration because like charges repel and opposite charges attract. For example, positive lidocaine ions are repelled from the anode and attracted to the cathode. In an analogous manner, negative idoxuridine ions are repelled from the cathode and attracted to the anode. This principle can be used to produce local anesthesia and antiviral action, respectively.

The process of iontophoresis for local therapy has the following characteristics: (1) a charged (ionic) drug should be used; (2) the drug should be applied at the electrode of the same charge; (3) the condition or disease under treatment must be at or near a body surface; and (4) therapy is enhanced because the drug is concentrated in the tissue of application. As a side benefit, systemic effects are eliminated during short treatments for local therapy because only a minuscule amount of drug reaches the bloodstream.

Iontophoresis is a preferred method for delivery of pilocarpine in a diagnostic test for cystic fibrosis (Gibson and Cooke, 1959). Also, iontophoresis has become a preferred method for obtaining local anesthesia of the tympanic membrane for myringotomy (Comeau et al., 1973). Surface local anesthesia of the skin to a depth of 1–3 cm has been reported in double-blind studies of human volunteers (Gangarosa, 1981). Lidocaine iontophoresis has been used for skin dissection in patients requiring kidney dialysis (Jacobsen and Stephen, 1978), for extraction of loose deciduous teeth (Gangarosa, 1974), and in preinjection topical anesthesia (Gangarosa, 1983). Furthermore, iontophoresis of fluoride was proven, in double-blind controlled, clinical studies, to be effective for the desensitization of hypersensitive dentin (Murthy et al., 1973 Gangarosa et al., 1989; Kern et al., 1989).

Many other uses for iontophoresis have been proposed; these have been reviewed elsewhere (Harris, 1959; Gangarosa, 1983; Sloan and Soltani, 1986; Tyle, 1986). The literature supports the concept that iontophoresis is a method of choice for drug application in the therapy of surface tissues, i.e., whenever an ionic drug is available for an appropriate surface condition, drug delivery can be optimized by electrical assistance.

This review summarizes 19 previous research studies on iontophoresis reported by the authors and their co-workers. These studies have emphasized research and clinical results using iontophoresis for dermatologic, ophthalmologic, and dental conditions. The paper is organized with the following main headings: 2. Methods of procedure for iontophoresis; 3. Treatment of herpes simplex orolabialis; 4. Treatment of herpes zoster (shingles); and 5. Treatment of postherpetic neuralgia.

2. Methods of procedure for iontophoresis

Many of the studies reported in this review utilized the Phoresor 600-PM-2 (Iomed, Salt Lake City, UT) as the power source. In some studies, power sources that delivered equivalent constant direct current were used; these included an earlier generation instrument, the Electromedicator CM-1 (MedTherm Corp, Huntsville, AL) and a

later generation instrument, the Iontophor-PM (Life-Tech, Houston, TX). Also, many of the studies were repeated using two, or sometimes three, of these systems with similar results. Thus, the three power sources are considered interchangeable except for slight modifications. The newer systems have design modifications that provide ease and convenience of operation.

A third generation system designed for application of ionic drugs by iontophoresis is diagrammed in Fig. 1. The operator controls the current (mA), dosage and time through the keypad. The microprocessor uses battery power of 6 V and the voltage is converted to 100 V DC via the step-up circuit. The maximum current output is 4 mA but a 10 mA fuse prevents an unusual surge or output to the patient and protects against a system malfunction. A current direction switch allows the operator to choose (+) or (−) current for the treatment electrode. Also, the microprocessor receives feedback from the current going into or coming out of the switch, and uses the information to keep the iontophoretic current at a constant value, and at the selected milliamperes. Thus, the microprocessor controls the delivered dose (mA min) and the system shuts down when the correct dose is delivered to the patient.

The skin electrodes for all studies were patches modified after the electrode system used for pilocarpine iontophoresis (Gibson and Cooke, 1959). The main component was an oval-shaped piece of absorbent filter paper having an area of 1.37 inch^2. The drug or return solution was soaked into the paper patch, which was placed against the skin and held in place by a strip of 3M Micropore® tape. During manufacture, a stainless-steel clothing snap was penetrated through the tape and its inner surface was covered by a strip of aluminum foil. The tape, snap and patch then served to facilitate the electrical connection, while the attached filter paper held the drug. This small, band-aid like patch could be used alone or could be placed over a piece of cotton padding, thus expanding the area of treatment to the desired size. Later, this electrode design was

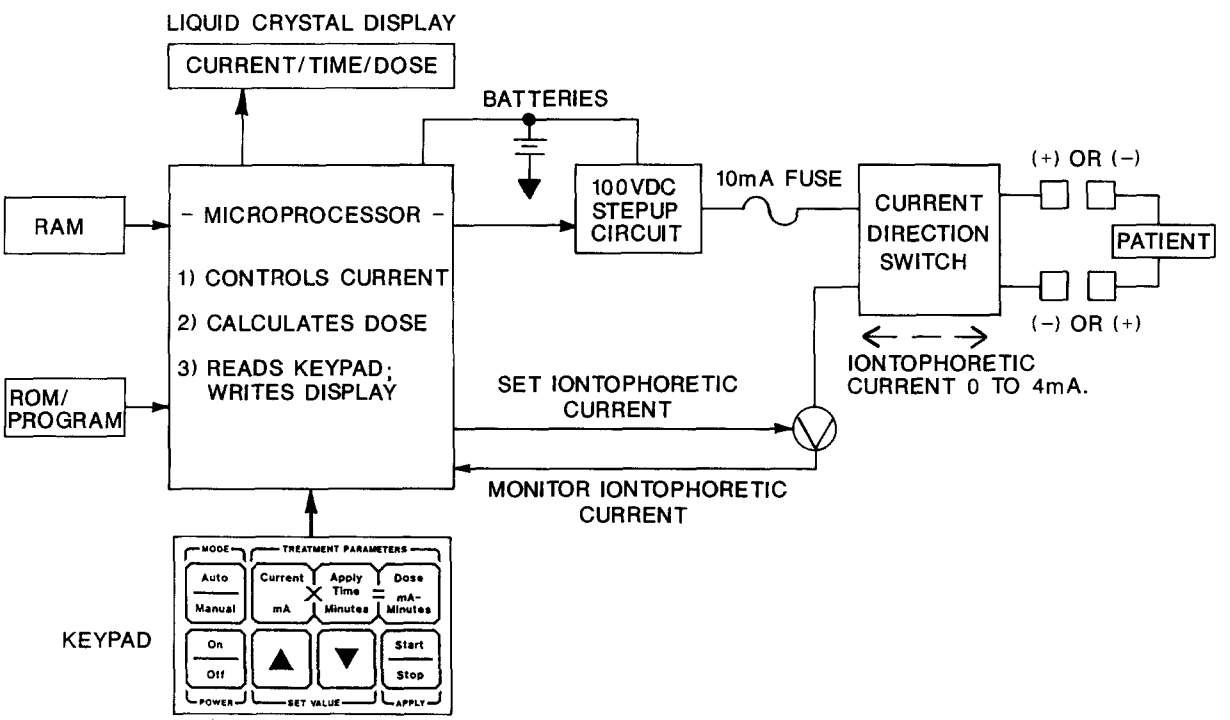

Fig. 1. Diagram of a modern iontophoresis system.

re-engineered to provide the present Life-Tech Meditrode [1] system.

A different device was used as the electrode for the treatment of lip lesions. A piece of plastic (Tygon®) tubing was placed over an insulated connecting device that had a metal rod penetrating through it. Loose cotton was packed to fill the tubing and touch the metal rod, which was connected by a wire to the unit. Solutions of antiviral drugs were soaked into the cotton which allowed engagement of the lesion during the passage of current.

At the return electrode, an indifferent electrolyte or a conductive gel was used. In most of the early research, sodium nitrate was used for the return electrode, but in separate studies performed in the authors' laboratories on rats, phosphate buffers (pH 7) caused the least burning and/or inflammation, sodium nitrate was second best and sodium chloride was worst (Gangarosa and Baker, 1988). In the same study (Gangarosa and Baker, 1988), electrodes with phosphate buffers that had been on patients for 5–20 min at a maximum of 2.0 mA were checked for pH shifts; the change from neutrality was never more than 2 pH units. Such changes in pH are well tolerated by the skin. The phosphate buffers are now used with the Meditrode system as an aid in controlling the pH at the return electrode. Naturally, if one uses higher milliamperes and longer times the phosphate buffer becomes even more important to avoid larger pH shifts.

The above systems and electrodes with minor variations were used for iontophoresis in the 19 studies reported. The system used for animals was almost the same as that used for humans in the clinic with only minor modifications. It would be beyond the scope of this review to repeat all of the methodology, but some essential details related to specific studies of various conditions are included where appropriate.

3. Treatment of herpes simplex orolabialis

The treatment of infections due to herpes simplex virus (HSV) has been the subject of many research studies and anecdotal reports. Most attempts to prove the efficacy of topical treatment of recurrent cutaneous infections due to HSV have failed (Overall, 1982; Corey and Holmes, 1983) Because many nucleoside analogues are effective in vitro and are generally successful in topical therapy for herpes keratitis (corneal infections of the eye), the most probable explanation for treatment failure in cutaneous tissues is lack of penetration.

Lekas (1979) reported that iontophoresis of idoxuridine, an antiviral drug, was successful for treating HSV orolabialis. We presented supporting evidence in limited open clinical trials (Gangarosa et al., 1979). The control was each patient's previous lesion history. These case reports demonstrated rapid relief of discomfort, a rapid appearance of the next stage of the lesion, and a 40–60% reduction in lesion duration. Since these preliminary studies (Gangarosa et al., 1979; Lekas, 1979) indicated that the penetration problem can be overcome by iontophoresis, we started extensive animal and human studies to provide scientific proof that iontophoresis is useful for surface disease caused by HSV.

The long-term goal of our research was to obtain evidence to support the use of the newer and safer nucleoside analogues in controlled human clinical trials. An initial report of the research was presented in 1977 (Hill et al., 1977). During the 1970s, a newer and safer antiviral drug, adenine arabinoside (Ara-A), became the second antiviral agent available for therapy of human HSV. Ara-A was a breakthrough because of lower systemic toxicity compared with idoxuridine. Ara-A was approved for intravenous (i.v.) therapy in herpes encephalitis and in varicella zoster, and also for topical therapy in herpes keratitis (Warner Lambert/Parke Davis Product Insert on Vira-A, 1980). Nevertheless, Ara-A had the disadvantage of low water solubility; this made it desirable to study Ara-AMP, a water-soluble monophosphate derivative that was developed for i.v. use (Whitley et al., 1980).

The highly ionic nature of Ara-AMP made it ideal for electrical delivery (Hill et al., 1977; Park et al., 1977). Iontophoresis of Ara-AMP showed great promise against HSV skin and eye infections in animal studies. We reported (Park et al.,

Table 1
Concentration of Ara-AMP and its metabolites in adult mouse skin acid-soluble fractions after iontophoresis (I) of [^{3}H]Ara-AMP

Time (h) after Tx	Concentration (μg/g of wet skin weight)		
	Ara-AMP	Ara-A	Ara-Hx
0	123.3 ± 4.39	207.3 ± 50.99	3.4 ± 0.68
1	3.9 ± 0.52	23.2 ± 1.08	0.9 ± 0.27
4	1.3 ± 0.14	14.3 ± 1.11	0.8 ± 0.15
24	1.5 ± 0.53	8.7 ± 2.27	0.7 ± 0.11

Each value is the average of four skin samples (38 mm^2). 50 μCi of [^{3}H]Ara-AMP (4 mg) was applied per area. Concentrations were calculated using dpm of administered and detected compounds (Park et al., 1977).

1977) that antiviral concentrations of Ara-AMP and its active metabolites, Ara-A and Ara-Hx, could be maintained in mouse skin for at least 24 h after 10 min of iontophoretic application (Table 1). Actually, the combined activity of Ara-AMP + AraA is about 330-times the antiviral inhibitory concentration (1 μg/g) immediately after administration (0 time) and about 10-times higher after 24 h.

Ocular iontophoresis of Ara-AMP results in concentrations of Ara-AMP and Ara-A in the cornea and aqueous humor that are 6–15-times higher than after topical application of Ara-AMP (Hill et al., 1978). Table 2 shows specific data for the corneal concentrations at 20 and 60 min following drug application.

Ara-AMP applied by iontophoresis to HSV-1 infected mouse skin (Park et al., 1978) effectively prevented lesion development, paralysis, and death. These results may be noted in Table 3; Ara-AMP iontophoresis was superior to any topical antiviral therapy used in the study. Also, excellent therapeutic results in infected rabbit eyes were reported by Kwon et al. (1979), and no corneal damage was apparent after iontophoresis to the eye (Hill et al., 1978).

The mouse experiments showing efficacy against HSV-1 skin lesions (Park et al., 1978) were repeated (Kwon et al., 1980) in a study of both HSV-1 and HSV-2 lesions comparing topical therapy with cathodal iontophoresis of Ara-AMP and with anodal iontophoresis of Ara-T in saline (as we suggested; Gangarosa et al., 1980). The results are shown in Fig. 2. Topical therapy was similar to control for both HSV-1 and HSV-2. Saline iontophoresis alone had no effect. Ara-AMP iontophoresis was effective against both types of virus. These observations verified previous results and extended the demonstration of efficacy to HSV-2. Anodal iontophoresis of Ara-T appeared modestly effective against type-1 virus, but only equal to topical Ara-T against type-2 virus.

A third antiviral agent, acyclovir (ACV), was described by Elion et al. (1977) and was later approved for humans by oral, i.v. and topical use in primary HSV and in immunocompromised pa-

Table 2
Amount of vidarabine monophosphate and its metabolites in acid-soluble fraction of rabbit cornea after topical or iontophoretic administration

Treatment	Time (min)	Concentration (ng/100 mg wet weight ± S.E.)				
		Vidarabine monophosphate	Vidarabine	Ara-Hx	Adenine	Hx and adenosine
Topical application	20	110 ± 29	130 ± 16	150 ± 24	90 ± 11	240 ± 5
	60	50 ± 2	50 ± 15	80 ± 5	50 ± 7	90 ± 2
Cathodal(−) iontophoresis	20	1560 ± 317 [a]	880 ± 275 [a]	1640 ± 317 [a]	1100 ± 166 [a]	1650 ± 292 [a]
	60	400 ± 54 [b]	190 ± 10 [b]	370 ± 68 [b]	480 ± 9 [b]	410 ± 50 [b]

Each value is a mean of four corneas (Hill et al., 1978). The concentrations of vidarabine monophosphate and its metabolites were calculated from the radioactivity determined after chromatography and the specific activity of the tritiated vidarabine monophosphate (5 μCi/100 μg).

[a] Statistically different (S.D.) ($P < 0.01$) from topical application (20 min) (t-test).

[b] S.D. ($P < 0.01$) from topical application (60 min) (t-test).

Table 3
Effects of topical or iontophoretic application of antiviral agents on HSV-1 skin infections in hairless mice

Group [a]	Average lesion score [b]	No. with paralysis	No. dying
Control (infection only)	4.0	9/10	10/10
Iontophoresis (−) of 2% NaCl	4.0	9/10	10/10
Topical application of 10% Ara-AMP	2.8 [c]	7/10 [d]	7/10 [d]
Topical application of 0.5% IUdR	3.0 [c]	6/10 [d]	6/10 [d]
Topical application of 3% Ara-A	2.9 [c]	6/10 [d]	6/10 [d]
Iontophoresis (−) of 2% Ara-AMP	1.2 [c,e]	2/10 [d,f]	2/10 [d,f]

[a] Each group contains data from 10 mice (Park et al., 1978).
[b] Cumulative maximum lesion scores were determined daily for 14 days and scored 0 to 4.
[c] Statistically different (S.D.) from control group ($P < 0.05$, t-test).
[d] S.D. from control group ($P < 0.05$, χ^2 test).
[e] S.D. from any topical application group ($P < 0.05$, t-test).
[f] S.D. from any topical application group ($P < 0.05$, χ^2 test).

tients. Since ACV had a high therapeutic index, it became the drug of choice for therapy of systemic HSV. ACV was the first antiherpes agent available orally for systemic infection and to prevent recurrences.

The approval of ACV for topical therapy of HSV for primary attacks, and later for immunocompromised individuals, appears to have led to widespread use in recurrent HSV, even though the data usually do not support topical efficacy for this use (Spruance et al., 1984 Shaw et al., 1985) or, at best, show only marginal effects (Fiddian et al., 1982 Van Vloten et al., 1983). The following problems in therapy of recurrent HSV led us to include ACV in our animal and human studies of penetration enhancement by ion-

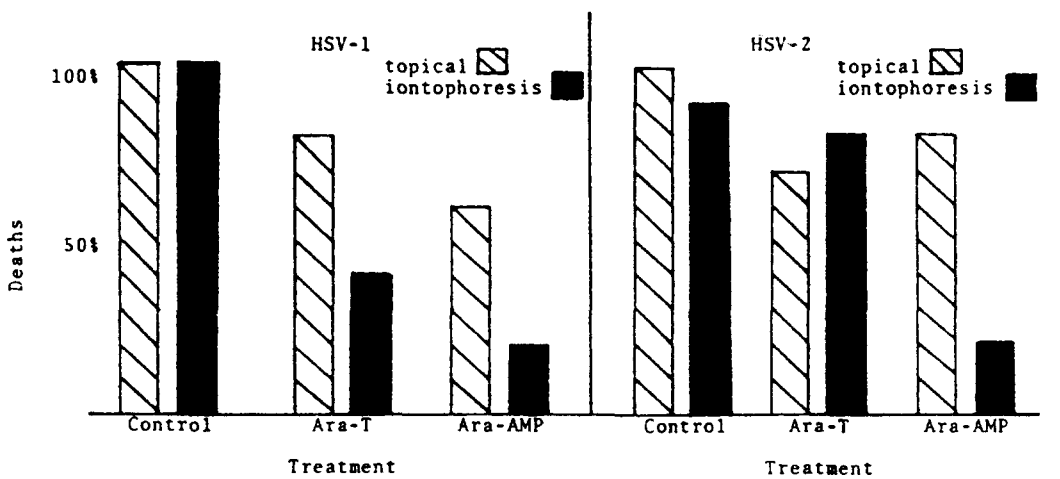

Fig. 2. Comparison of mortality following different applications of antivirals (Kwon et al., 1980). Each bar represents the average for 10 hairless mice. The mouse skin was scratched with a needle and rubbed with a swab containing herpes simplex virus (10^4 PFU/ml). Within 24 h, drug was applied by iontophoresis or topical application. Controls had NaCl applied instead of drug. Ara-AMP iontophoresis was significantly better than Ara-AMP by topical application and controls ($P < 0.05$, t-test). Ara-T iontophoresis was significantly better ($P < 0.05$) than Ara-T topical for HSV-1, but not for HSV-2. None of the topical antiviral treatments were better than controls.

tophoresis: (1) when ACV is given orally to prevent recurrences, the disease tends to recur after drug withdrawal; (2) long-term use of ACV is expensive; (3) resistant viruses and side effects could occur; and (4) topical penetration appears to be limited. ACV was available as a disodium salt which suggested an ionic nature. Our initial animal studies indicated that ACV was more active when applied iontophoretically than when applied topically (Hill et al., 1982).

On the basis of the above-cited animal studies (Hill et al., 1977, 1978, 1982; Park et al., 1978; Kwon et al., 1979, 1980; Gangarosa et al., 1980) and the rapid resolution of recurrent orolabialis lesions in open human trials using iontophoresis of idoxuridine (Gangarosa et al., 1979; Lekas, 1979), we performed a double-blind placebo-controlled clinical trial in human volunteers under an FDA/IND protocol for study of Ara-AMP and ACV (Gangarosa et al., 1986). Although the details are in the original publication, a summary is provided below.

Agents studied were Ara-AMP sodium salt, ACV disodium salt and NaCl as the placebo. 27 volunteer subjects, who had HSV vesicular orolabial lesions within the previous 48 h, were randomly assigned to one of the three agents, forming study groups of nine subjects each. The groups were demographically similar to each other, as indicated by statistical comparison. It was required that each lesion show a positive cytopathic effect (CPE) for infectious HSV by assay on primary rabbit kidney cells (PRK) within the next 48 h or the subject's participation was terminated and the agent was subsequently reassigned to a new volunteer.

Lip lesions were treated using the device described above, with one of the three drugs applied, at physiologic osmolarity, to the lesion on a cotton tip applicator. The drugs were coded and the investigators were masked as to the identity of the drug being used. The iontophoresis module was an adaptation of the Phoresor 600 PM-2 (Gangarosa et al., 1989); it had a 9 V battery that provided up to 60 V DC using a semiconductor, step-up transformer circuit. Current was applied at 0.5–0.7 mA for 6–8 min, resulting in an electrical charge flow of 4.0 mA min or 0.24 C. Additional cotton was used to cover larger lesions and charge flow was increased in proportion to surface area. After treatment, the subject was asked to keep the lesion dry, avoiding application of ointments, coatings, and other preparations.

Table 4
Titers of virus on plaque assay from HSV lesion vesicular fluid

Treatment	Observation interval		
	Baseline	24 h	48 h
Ara-AMP	4.6 ± 0.6	0.8 ± 0.2 [a]	0.2 ± 0.1 [b]
ACV	4.6 ± 0.7	3.0 ± 0.8	2.2 ± 0.9 [c]
NaCl	5.0 ± 0.3	3.0 ± 0.9	1.1 ± 0.6 [d]

Data are mean log PFU ± S.E. values (Gangarosa et al., 1986). Statistically different (S.D.) values were calculated by paired t-test after performing ANOVA.

[a] S.D. ($P < 0.001$) for reduction from baseline, S.D. ($P < 0.05$) compared with ACV, and S.D. ($P < 0.05$) compared with NaCl.

[b] S.D. ($P < 0.001$) for reduction from baseline, S.D. ($P < 0.05$) for reduction from 24 h, and S.D. ($P < 0.05$) compared with ACV.

[c] S.D. ($P < 0.05$) for reduction from baseline.

[d] S.D. ($P < 0.001$) for reduction from baseline, and S.D. ($P < 0.05$) for reduction from 24 h.

The lesion was photographed before and 10 min after treatment. Pre- and post-treatment signs and symptoms were also noted. At 24 and 48 h after treatment and at least seven times within the next 14 days, photographs and lesion evaluation were repeated. Swabbing for virus was attempted at each visit until the dry crust stage.

The results of viral plaque assays on CV-1 cells are shown in Table 4. ANOVA analysis indicated a significant reduction in plaque forming units (PFU) with time ($P < 0.001$). Individual comparisons (within-group t-tests) indicated that Ara-AMP-treated lesions had significantly reduced PFU between 0 and 24 h (-3.80 log, $P < 0.001$), between 0 and 48 h (-4.38 log, $P < 0.001$), and between 24 and 48 h (-0.59 log, $P < 0.05$). In ACV-treated lesions, the reduction of PFU was significant only between pretreatment and 48 h (-2.42 log, $P < 0.05$). Viral titers from NaCl-treated lesions showed a slower reduction, compared with titers from Ara-AMP-treated lesions, with a significant reduction between 0 and 48 h (-3.91 log, $P < 0.001$) and between 24 and 48 h

(−1.91 log, $P < 0.05$), but not between 0 and 24 h. Analysis of PFU comparing different treatments disclosed that (1) all groups started at approximately the same titer, (2) the results of ACV and NaCl treatment were not significantly different, and (3) the log reduction of PFU was significant for Ara-AMP-treated lesions compared with ACV-treated lesions at 24 and 48 h ($P < 0.05$, Student's t-test). The titer of virus at 24 h was also reduced for Ara-AMP treatment compared with NaCl treatment ($P < 0.05$).

The mean change in lesion symptoms for the three groups is given in Table 5. Mean number of days from onset to dry crust was significantly decreased for Ara-AMP treatment (2.4 days; $P < 0.005$) compared with ACV (5.2 days) and NaCl (4.8 days). Also, differences in hours of viral shedding from onset to virus-free lesion, i.e., no cytopathic effect (CPE) on primary rabbit kidney (PRK) monolayers are listed in Table 5. There were statistically significant differences among the groups ($P < 0.05$, Kruskal-Wallis test). Further statistical analysis indicated Ara-AMP-treated lesions had significantly shorter viral shedding time compared with ACV- or NaCl treatment ($P < 0.05$ Mann-Whitney U-test). Ara-AMP-treated lesions had a shorter time to complete healing compared to ACV or NaCl, but this difference was not statistically significant. The rather similar duration of lesions in this study may have been due to repeated viral sampling of all lesions.

Other studies have shown that neither Ara-AMP nor ACV is effective in topical treatment of recurrent cutaneous infections with HSV. Spruance et al. (1979) tested topical 10% Ara-AMP gel in HSV recurrences and found no difference from placebo. Although studies of early, intensive topical application of ACV cream to cutaneous lesions showed a marginal effect (Fiddian et al., 1982; Van Vloten et al., 1983), other investigations could not demonstrate any statistical difference from placebo, irrespective of when therapy was started (Spruance et al., 1984; Shaw et al., 1985). We believe the delivery method used by us, i.e., iontophoresis, accounts for the observed effectiveness of Ara-AMP (Gangarosa et al., 1986), but no difference between ACV and placebo was found after iontophoresis. Lack of effectiveness of ACV iontophoresis may be related to the high solution pH (10.6) attained on dissolving ACV powder. At this high pH, only 5% of the ACV would be ionized and a significant amount of highly mobile hydroxyl ions could compete for the current. This competition could reduce the penetration of ACV.

This study offered scientific evidence that, under the conditions of the experiment, one iontophoretic treatment with Ara-AMP is effective therapy for orolabial HSV. The most important parameters of antiviral effectiveness – reduction in viral titer, elimination of virus and reduced time to dry crust – were significantly better with Ara-AMP treatment than with ACV or placebo. The study, although involving only nine subjects per treatment group, indicated that ARA-AMP iontophoresis could be a useful and significantly

Table 5
Clinical assessment of lesions

Measurement	Ara-AMP	ACV	NaCl
From onset to dry crust (days)	2.4 ± 0.2 [a]	5.2 ± 0.7	4.8 ± 0.3
Virus shedding (h after treatment)	48 ± 6 [b]	85 ± 9	71 ± 9
From onset to complete healing (days)	9.4 ± 1.2 [c]	11.7 ± 1.3	11.6 ± 1.1

Data are mean ± S.E. values (Gangarosa et al., 1986). Statistically different (S.D.) values were calculated using the Mann-Whitney U-test after performing the Kruskal-Wallis test.

[a] S.D. ($P < 0.005$) compared with ACV, and S.D. ($P < 0.001$) compared with NaCl.

[b] S.D. ($P < 0.01$) compared with ACV, and S.D. ($P < 0.05$) compared with NaCl.

[c] Not S.D. from ACV or NaCl.

better than topical antiviral therapy. Even though the study groups were rather small, and the possibility of a β statistical error tends to increase with small sample size, we believe the results support the use of Ara-AMP by iontophoresis for orolabial HSV, and that further clinical trials are indicated.

Unfortunately, Ara-AMP is not available for human use and ACV does not appear to be an improvement for recurrent herpes orolabialis therapy, either in the study above or in clinical use (Gangarosa et al., 1979; Gangarosa, 1983). Therefore, ophthalmic idoxuridine is still used for iontophoresis of HSV orolabialis lesions. After use in several hundred subjects over 20 years, the therapy appears optimal. We also obtained vesicular fluid from 11 successive subjects before treatment with IDU iontophoresis and 24 h later; the fluid was studied for CPE on CV-1 cells. Before treatment all viral samples were positive, but 24 h after treatment there was no detectable HSV in 9/11 samples (Gangarosa, 1993). This observation indicates that idoxuridine iontophoresis displays the same antiviral effectiveness as Ara-AMP.

3.1. Double-blind therapeutic trials of active zoster

Gangarosa et al. (1988) tested the hypothesis that iontophoresis could aid penetration of antivirals for treatment of cutaneous herpes zoster (HZV) and HSV lesions. 'Therapeutic trials' were conducted on cutaneous HZV lesions and large HSV lesions. In 16 volunteers, the therapeutic trial involved outlining three similarly appearing lesion areas for application of either Ara-AMP, acyclovir (ACV) or placebo (NaCl) by cathodal iontophoresis. After 24 h, treated areas were evaluated using a double-blind format. Areas were ranked according to improvement status (reduced inflammation and drying) as follows: 1 = best, 2 = intermediate, 3 = least; averages were used for ties.

In 11 HZV patients, mean ranks were: Ara-AMP 1.71, ACV 1.54 and NaCl 2.75. Results showed significantly better mean rankings ($P < 0.01$) for both Ara-AMP and ACV, compared with NaCl; Ara-AMP and ACV were not significantly different. In five HSV patients the mean ranks were Ara-AMP 1.1, ACV 2.3, and NaCl 2.6; Ara-AMP was first in 4/5 trials and tied for first with ACV once. In all 16 trials an active antiviral rated first. Subsequent treatment by iontophoresis of the most effective agent resulted in extremely rapid healing. This study provides further support for iontophoresis as an aid to dermal penetration of antiviral agents in herpetic infections. The study also indicates a unique method (the therapeutic trial) for choosing the best agent for subsequent use either by systemic administration or by iontophoresis, or by a combination of both methods.

3.2. Treatment of postherpetic neuralgia (PHN)

Postherpetic neuralgia is a painful affliction that often follows cutaneous herpes zoster infection (shingles). As a result of neural malfunction, the patient may experience a long course of suffering with intractable pain in the affected dermatome. Many therapies have been suggested for PHN, but most of them have failed (Murphy, 1976; Stein and Warfield, 1982). Although continuous use of tricyclic antidepressants and carbamazepine may be somewhat useful, there is still no treatment with a high rate of success and patients continue to suffer from prolonged periods of pain.

In 1982, we reported a new treatment for postherpetic pain using methyl prednisolone sodium succinate (SoluMedrol®) iontophoresis combined with pretreatment of the affected dermatome by iontophoresis of lidocaine and epinephrine (Gangarosa et al., 1982). To our surprise, the therapy has been consistently effective and long-lasting in a high percentage of cases. In these reports, patients who had healed herpes zoster lesions in any dermatome were clinically treated. Results were obtained post hoc from their case records. Most of the patients had little evidence of scars and the pain had been present from 1 month to 7 years. The clinical treatment was open, since we were attempting to develop and assess this new method. There was no effort to control for placebo effects, and the evaluation was based upon the patient's perception of pain

relief compared with previous pain in the affected area. The treatment methods, the earlier clinical studies, and a double-blind study of postherpetic neuralgia were reported in 1986 (Gangarosa et al., 1986) and are summarized below.

In a preliminary study (Gangarosa et al., 1982) at three medical centers, a total of 13 patients were treated. The number of treatments performed on each patient varied from one to five except for one patient, who requested frequent retreatments on a biweekly basis. The history of pain was quite variable, ranging from 1 month after active infection to as much as 7 years. Pain was restricted to dermatomes supplied by the affected nerves. Most patients had intradermal pain but a few cases with deeper pain were included; in retrospect, the prognosis was not as good when the pain was deep and perhaps such cases should not have been included. We usually treated two areas of skin (measuring about 10×10 cm), starting with the most painful areas at the first appointment. At later appointments (1-week intervals), adjacent areas often required treatments, but the original area rarely required retreatment.

Pain relief was rated 'good' (100–70% reduction), 'moderate' (40–70%) or 'poor' ($< 40\%$). Ratings were obtained twice: short term (less than 1 month) and long term (greater than 6 months). In the initial evaluation, 2 weeks to 1 month after therapy 10 of 13 subjects had good relief, two had moderate relief and one rated the results as poor. After 6 months, seven of the 10 patients rated good were still at that level, two converted to moderate and one converted to poor. One moderate also converted to poor. None showed increased relief after the first month. The cases that converted from good relief to moderate or poor were retreated with a second course of therapy, after which increased remission of pain occurred. In two of our early cases, relief has lasted over 7 years without return of pain.

Generally, there are no side effects following this method of iontophoretic introduction of drugs since the drugs are confined within the skin area and are slowly released at a rate insufficient to cause systemic effects. In this study, only one patient had a side effect, i.e., a moderately elevated blood pressure after epinephrine iontophoresis, which returned to normal shortly after the procedure was completed.

The new PHN therapy using iontophoresis was later studied at nine medical institutions (eight in Japan and one in the USA) in over 1000 patients (Ozawa et al., 1985, 1992; Shimomura, 1987; Ozawa, 1989). A high percentage relief of pain was observed and verified. Overall, about 70% of patients obtained significant relief that occurred shortly after treatment and was surprisingly long-lasting. There is only a slight possibility of local or systemic side reactions if the iontophoretic therapy is carefully controlled and properly performed.

At the eight Japanese institutions, the main side effect was a small localized burn which occurred in fewer than 10 patients. These burns appeared to be related to defects in the skin and may have been the result of low resistance pathways rather than pH burns, which would occur over the entire patch. Several patients had transient increases in blood pressure which were either clinically insignificant or which quickly returned to normal after the treatment was stopped. Also, three subjects with pacemakers were treated, with no effect on cardiac rhythm. Naturally, one should avoid placement of electrodes directly over a pacemaker, and in any patient susceptible to arrhythmias, avoid introduction of current through the heart pathway (e.g., by avoiding placement of electrodes over the classical EKG lead areas). Our conclusion is that the DC current is innocuous and that the well-known drugs used are extremely safe when used for iontophoresis.

Gangarosa et al. (1986) reported double-blind trials of PHN therapy using a sequential entry design. Each patient had an internal control. Two areas of the skin within the painful dermatome that exhibited a similar pain response to light touch were treated on a double-blind basis; one area was treated with active drugs (anodal iontophoresis of lidocaine + epinephrine, followed by cathodal iontophoresis of SoluMedrol®) and the other with placebo (anodal iontophoresis of epinephrine + sodium nitrate followed by catho-

dal iontophoresis of sodium nitrate). Seven patients were entered into the study, but only six completed the course. After 1 week, pain evaluations were repeated by the same two masked clinicians who had done the original evaluation. All of the six subjects reported that the areas treated with active drugs showed pain relief, but not the placebo-treated area. Further active treatments (not blinded) were then given to the entire affected dermatome. Follow-up examination over 1 year or more indicated that all six patients had continuous pain relief in the full dermatome. The binomial distribution for random occurrence of such a result predicts that it would occur in less than 2% of such trials. This study strongly supports the clinical results described above in numerous patients and substantiates the efficacy of iontophoresis therapy for PHN.

This new therapy for PHN by iontophoresis must be considered in terms of other therapies that have been tried. Most other PHN treatments have failed, some provide only temporary relief, and only one seems hopeful. The latter involves daily use of amitriptiline (Elavil®), either alone or combined with triflupromazine (Murphy, 1976). The antidepressant may modestly reduce pain and perhaps allow some success with biofeedback or other behavorial modification therapy. However, taking antidepressants continuously has disadvantages such as compliance, expense and adverse effects. In our experience, the value of adding the antipsychotic drug to the antidepressant is not clear; this combination has been used with apparent reduction of symptoms in a few of our patients. Amitriptiline alone plus a nonsteroidal anti-inflammatory agent (anaprox, naproxyn) seemed to provide the best results for our 'failures' or 'moderate successes'. Another common treatment is carbamezepine (tegretol). Most of our patients had previously received this therapy with little or no success. Also, most of our recent patients have tried capsaicin and found it not only unsuccessful but also highly irritating. It appears that corticosteroid iontophoresis by our protocol is the treatment that provides a good chance of success with no risk that is apparent.

4. Summary

Iontophoresis of antiviral drugs has been used successfully for treatment of oral and cutaneous herpes simplex, and in active viral infection of herpes zoster. For postherpetic neuralgia, a combination of lidocaine/epinephrine followed by the corticosteroid, methyl prednisolone sodium succinate, provides a high success rate in permanent relief of chronic pain where no other satisfactory therapy is available. With the availability of modern iontophoretic delivery systems and using drugs of choice for specific diseases, iontophoresis deserves a place in the therapeutic armamentarium and consideration for further study.

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