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Review

Drug Delivery by Phonophoresis

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Phonophoresis is defined as the migration of drug molecules, contained in a contact agent, through the skin under the influence of ultrasound. Several drugs have been introduced into the body by this technique. The design of a phonophoretic drug delivery system is in developmental stages in various research laboratories. Parameters affecting the delivery of drugs by this technique and devices available for drug delivery purposes are discussed in this review.

KEY WORDS: phonophoresis; drug delivery; transdermal drug delivery; ultrasound; ultrasonic drug delivery; phonophoretic drug delivery.

INTRODUCTION

Topical application of drugs has focused attention on their skin permeability and on chemical permeability enhancers which decrease the barrier function of the stratum corneum (1). External control of drug release and penetration can also be achieved by iontophoresis (2), i.e., by electric field, and phonophoresis (3), i.e., by ultrasound. The transfollicular and transappendageal (skin pores) routes constitute the major penetration pathways for these techniques even though the surface area occupied by these pathways is relatively small (Fig. 1). Iontophoresis has been the subject of recent reviews (2,4). This review details the technique of phonophoresis and its application to drug delivery.

Phonophoresis is defined as the migration of drug molecules, contained in a coupling/contact agent, through the skin under the influence of ultrasound. Enhanced drug penetration is thought to result from the thermal, mechanical, and chemical alterations of biological tissues by ultrasonic waves (5). Phonophoresis and iontophoresis have common features but also distinct differences. (a) There is little hazard of skin damage with proper application, but periosteal burns can result if either technique is applied improperly. (b) During iontophoresis the drug must be ionized in order to be electrically transported. (c) Ultrasonic waves penetrate up to 5 cm below the skin, whereas iontophoresis penetrates only to an approximate depth of 1 cm. (d) The usual treatment time for phonophoresis is 10 min, as compared to 20 or 30 min suggested for iontophoresis (6,7). Thus phonophoresis may offer an alternative to injection with minimal trauma and damage to the site, although minor skin discoloration may develop following prolonged use. The length of the treatment, output frequency, and power level required for phonophoretic drug delivery vary with the drug, site, and individual person.

MECHANISM OF ACTION AND THEORY

Ultrasound causes mechanical disturbance in an absorbing medium and mechanical energy associated with the sound field is continually converted into heat (9). This thermal change is thought to mediate phonophoretic drug delivery. However, control experiments are lacking that show whether heat alone can have similar effects.

The effect of ultrasound on a biological system may also be associated with cavitation, the formation of small gaseous inclusions (9). Cavitation may cause mechanical stress, temperature elevation, or enhanced chemical reactivity causing drug transport. Kremkau (10) reported that cavitation in suspensions of a chemotherapeutic agent plays a role in its cytotoxic enhancement. Ultrasound appears to cause rapidly reversible cell damage which persists in the presence of cytotoxic drugs (10). One theory suggests that ultrasound affects the permeation of the stratum corneum lipid structure as the limiting step in permeating through the skin (11,12). Kost *et al.* showed steady penetration rates of the experimental and control groups after the ultrasound was turned off (11). This is evidence for the reversible effect of ultrasound. However, for most situations in phonophoretic drug delivery, the exact physical mechanisms are not known. Due to the complexity of the factors involved during the process of phonophoresis, theoretical predictions and their correlation with experimental data have not been attempted in the literature.

THERAPEUTIC APPLICATIONS

As early as 1954, Fellinger and Schmid showed that ultrasound could carry hydrocortisone across an avascular membrane to treat polyarthritis of the digital points of the hand (13). In 1958, Newman *et al.* found hydrocortisone delivered by injection and phonophoresis superior to injection alone (14). In 1963, Griffin and Touchstone reported *in*

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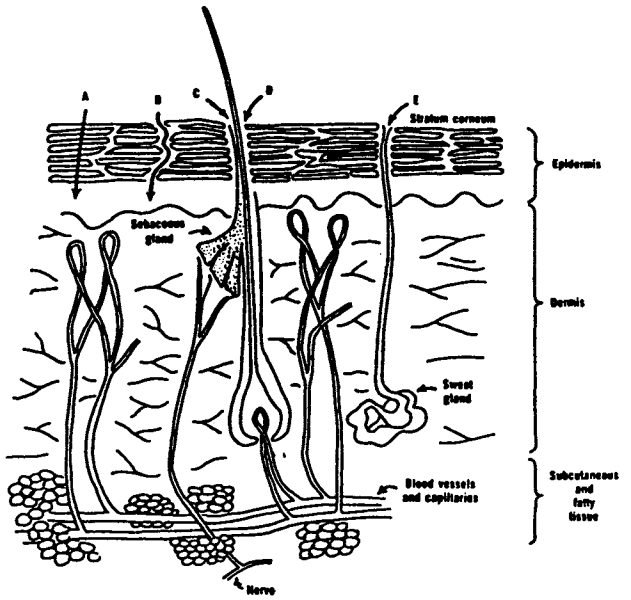

Fig. 1. Schematic presentation of probable routes of penetration: A, transcellular; B, diffusion through channels between cells; C, through sebaceous gland; D, transfollicular; E, through sweat ducts. (Reproduced with permission from Ref. 60.)

vitro research on pig tissue demonstrating that ultrasound could drive cortisol into skeletal muscle and paravertebral nerve (15).

A double-blind study comparing hydrocortisone versus a placebo was reported by Griffin *et al.* (16) (Table I). In their study, 68% receiving hydrocortisone plus ultrasound had significant decrease in pain and increase in range of motion, compared to 28% of those receiving a placebo plus ultrasound (16). In 1975, Kleinkort and Wood found a 10% hydrocortisone preparation plus ultrasound more effective in reducing pain than a 1% preparation plus ultrasound in a variety of inflammatory conditions (17). The results support the empirical choice of 10% concentration in clinics by other investigators (16). Wing reported a case study describing the use of phonophoretically driven hydrocortisone for a patient with temporomandibular joint dysfunction (18). Goddard *et al.* reported complete absence of any antiinflammatory action under the influence of ultrasound on acute inflammation in the rat (19). A well-designed study reported by Pratzel *et al.* measured the amount of indomethacin in the urine of pigs and human volunteers after cutaneous application of the drug with and without phonophoresis (62). The results showed that ultrasound did not increase the absorption of indomethacin over controls, but iontophoresis was effective in increasing maximum indomethacin levels and urinary excretion. Famaey (63,64) and Wanet and Dehon (65) reviewed the scientific basis of phonophoresis of nonsteroidal antiinflammatory agents and emphasized the necessity of objective studies to prove the therapeutic efficacy of phonophoresis.

Tendinitis, bursitis, and painful "trigger points" have been successfully treated with this technique (6). The clinician must, however, acknowledge the limitations imposed by the systemic introduction of specific medications and their potential side effects. An important consideration is that prolonged application of steroids to load-bearing structures such as tendons and ligaments may lead to their failure under stress (20). Novak, in an uncontrolled clinical case study, has reported an increase in the concentration of lignocaine in tissues under the influence of ultrasound for a topically applied solution of lignocaine base on the quadricep muscles of rabbits (21). This was in contrast to the double-blind crossover trials in healthy volunteers studies reported by McElnay *et al.* which showed that ultrasound did not significantly increase the percutaneous absorption of lignocaine (22). A number of factors may account for these results, including physical and chemical properties unsuitable for phonophoresis, a testing method of pricking not sensitive enough to distinguish changed absorption rates, and an increase in local blood flow caused by ultrasound negating the increased pharmacological effects of an enhanced lignocaine absorption by increasing drug clearance from the tissue (22). In contrast, McElnay *et al.* reported an increase in percutaneous absorption of fluocinolone acetonide using ultrasound to a small but statistically significant extent over controls in a double-blind crossover trial (35). Benson *et al.* recently reported the effect of ultrasound on the percutaneous absorption of lignocaine and prilocaine from Emla cream in healthy volunteer subjects, in a double-blind placebo controlled crossover trial (23). The results showed that ultrasound treatment led to a significant increase in the rate and extent of absorption of lignocaine and/or prilocaine as determined by the duration of anesthesia; however, the rate and extent of absorption of lignocaine as determined by the onset of action were not significant at the 95% level.

Kremkau extensively studied the effects of ultrasound and chemotherapeutic drugs in mouse leukemia (10). The treatment was applied *in vitro* with cells in suspension. The cells were inoculated into host mice and survival was monitored. Ultrasound enhanced the cytotoxic action of arabinosyl cytosine, BCNU, cyclophosphamide's active metabolite, nitrogen mustard, and melphalan. The experimental protocol is shown in Fig. 2. The author concluded that ultrasound appeared to cause rapid reversible cell damage which persisted in the presence of cytotoxic drugs resulting in a significant loss of lethal potential of the malignant cells to the host (10). These studies demonstrate the usefulness of phonophoresis in chemotherapy since the ultrasound localizes the drug delivery to the desired area, thus increasing the effectiveness without increasing systemic toxicity.

In addition to drug delivery applications, ultrasound by itself has long been used in physical medicine for virtually every region of the body in clinical conditions including the treatment of injury, treatment of superficial human cancerous nodules (24,25) and hyperthermia (25), orthopedic diagnosis (7), noninvasive determination of material properties of biologic tissues including healing cutaneous wounds (26) and edema formation (27), treatment of subdeltoid bursitis (28), treatment of chronic leg ulceration (29) and determination of the mechanism of phagocytic activity of reticuloendothelial system (30).

EXPERIMENTAL VARIABLES

Many studies reported in the literature lack adequate controls needed for satisfactory evaluation of data. For ex-

Table I. Drugs Used in Various Disease Conditions for Therapy by Phonophoresis

Drug(s)	Condition/disease	Reference (No.)
1. Dexamethasone	Inflammatory conditions	Quillin (6)[a]
2. Arabinosyl cytosine	Anticancer drug (leukemia)	Kremkau (10)[b]
3. BCNU	Anticancer drug (leukemia)	Kremkau (10)[b]
4. Cyclophosphamide's active metabolite	Anticancer drug (leukemia)	Kremkau (10)[b]
5. Nitrogen mustard	Anticancer drug (leukemia)	Kremkau (10)[b]
6. Melphalan	Anticancer drug (leukemia)	Kremkau (10)[b]
7. Mannitol	Diuretic	Kost *et al.* (11)[b,c]
8. Zinc oxide and tannic acid	Herpes simplex	Fahim (20)[c]
9. Urea and dimethyl sulfoxide	Demidox mites	Fahim (20)[d]
10. Lignocaine/lidocaine	Local anesthesia	Novak (21),[a] McElnay *et al.* (22)[d]
11. Lignocaine and prilocaine	Local anesthesia	Benson *et al.* (23)[d]
12. Lignocaine and dexamethasone	Pain	Moll (31)[a]
13. Benzydamine	Sports injuries	Benson *et al.* (34)[d]
14. Fluocinolone acetonide	Inflamed conditions	McElnay *et al.* (35)[d]
15. Ibuprofen	Antiinflammatory	Nanavaty & Brucks (36)[b]
16. Benzoic acid	Antifungal agent	Julian & Zentner (38)[b]
17. Potassium chloride Sodium chloride Calcium chloride	Electrolyte replenishers	Lenart & Auslander (39)[b]
18. Hydrocortisone	Inflamed digital joints/subdeltoid bursitis	Fellinger & Schmid (13)[a] Newman *et al.* (14)[c] Griffin & Touchstone (15)[b] Griffin *et al.* (16)[d] Kleinkort & Wood (17)[c] Wing (18)[a] Julian & Zentner (38)[b] Shamatava *et al.* (42)[c] Tsitlanadze (43)[c] Gatev (44)[a]
19. Paraaminohippuric acid	Diagnostic aid	Kost *et al.* (45)[c]
20. Silver nitrate	Edema	Fyfe & Chahl (46)[c]
21. Phenylbutazone	Arthrosynovitis	Brondolo (47)[a]
22. Carbocaine	Local anesthesia	Cameroy (48)[a]
23. Tetracycline	Low udders infections (cows)	Parikov (49)[a] Ragelis (50,51)[c]
24. Streptomycin	Antibiotic	Ragelis (50)[c]
25. Fluorafur	Allergy	Smalyukh (52)[c]
26. Physostigmine	Cholinesterase inhibitor	Kost *et al.* (53)[c]
27. Penicillin	Antibiotic Purulent ulcer	Ragelis (50)[c] Goral'chuk (54)[c]
28. Thiodine	Vertebral osteochondrasis	Chilingaryan *et al.* (55)[c]
29. Papain	—	Korkhov (56)[c]
30. Interferon	Herpetic keratitis	Shpak (57)[c]
31. Penicillin Streptomycin Tetracycline	Antibiotics	Ragelis (58)[c]
32. Thiamin	Vitamin deficiency	Glushchenko (59)[c]
33. Ascorbic acid	Vitamin deficiency	Glushchenko (59)[c]

[a] Based on clinical impressions (qualitative).
[b] Based on *in vitro* experiments.
[c] Based on controlled comparative study (quantitative but not double-blind).
[d] Based on double-blind study (well-conducted study).

ample, Moll (31) reported a double-blind clinical trial comparing three groups of treatments: (a) lignocaine/dexamethasone with ultrasound, (b) placebo with ultrasound, and (c) placebo without ultrasound. The paper lacked the data on the effects of lignocaine/dexamethasone without ultrasound.

It is not clear if drug–ultrasound treatment used to treat inflammatory conditions resulting from sports offer any advantages over ultrasound treatment alone or the two treatments used independently (6,35). Both pulsed- and continuous-wave ultrasound have been used in the literature. The technique of phonophoresis depends on several variables, the origin of which may be physical or physiological. An understanding of these factors for the optimization of the phonophoretic drug delivery process is very important.

Frequency. This is a physical (acoustical) factor related

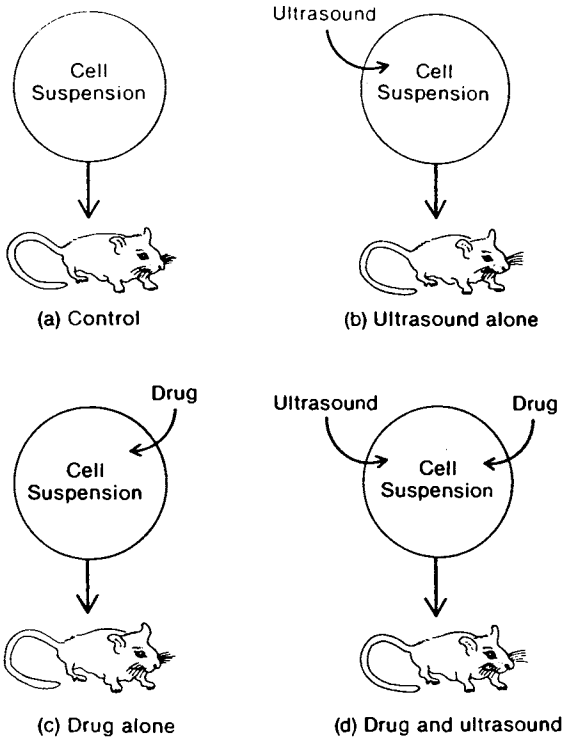

Fig. 2. L1210 mouse leukemia drug and ultrasound treatment experimental setup. (Reproduced with permission from Ref. 61.)

to the physiological effects of ultrasonic energy. The depth of penetration of ultrasonic energy into living tissue is inversely proportional to the frequency (7). Lower frequencies give deeper penetration and greater spread of energy per unit volume of tissue (32). The frequency used for phonophoresis is typically from 20 kHz to 10 MHz. The most used frequency in the literature is 870 kHz. Kost and Langer (33) have reported that the preferred range of frequency for phonophoresis is from 0.5 to 1.5 MHz. Benson *et al.* (23) have shown 1.5 MHz (1:1 pulsed output) and 3.0 MHz (continuous output) to be most effective for improving the rate of percutaneous absorption, and 1.5- and 3.0-MHz (1:1 pulsed-output) treatments for improving the extent of drug absorption. However, Benson *et al.* (34) did not find any statistical difference in percutaneous absorption of benzydamine between controls (no ultrasound) and those using ultrasound at differing frequencies.

Intensity. Another physical factor related to the absorption of ultrasonic energy is the rate of energy flux per unit area. The intensity of ultrasound should be high enough to obtain the desired measurement without masking by humoral or nervous system compensation the variable under study (32) and should be low enough not to cause any significant elevation in skin temperature (33). The energy can be of a high intensity for a short duration, or vice versa. However, the results must be evaluated cautiously since the physiological effects might be different for the two extremes even though the total energy added is the same. The intensity of ultrasound for phonophoresis varies from 0 to 3 W/cm^2 (33) and is dependent upon the patient tolerance and area under treatment. It should rarely exceed the accepted therapeutic maximum of 2.5 W/cm^2 (5).

Exposure Time. The time of irradiation of skin with ultrasound can affect phonophoresis. A 5-min exposure is commonly reported in the literature (5,22,34,35) but Kost *et al.* (11) were able to get a significant response with a 2-min exposure. The maximum limit of exposure should be determined by measuring the skin temperature. The time should be decreased or the treatment stopped when the temperature of the skin rises 1 to 2°C (33). A separate criterion should be established to ensure adequate exposure when larger times and areas are required for the treatment (5).

The frequency, intensity, and time of exposure are interdependent as well as the function of the molecule being diffused and nature (i.e., thickness and resistance to permeation) of the skin at the site of exposure (33). Dunn *et al.* (8) proposed that the relationship between intensity, I, and exposure time, t, is (8)

$$It^{1/2} = c(f,T)$$

where c is a weak function of frequency, f, and T is the temperature of the tissue.

Coupling/Contact Agent. A coupling or contact agent is needed to transfer ultrasonic energy between the ultrasound source and the skin. A good coupling agent should have an absorption coefficient similar to that of water and be nonstaining, nonirritating, and slow drying. The coupling agent should retain a paste or gel consistency at body temperature in order to maintain contact between the ultrasound source and the skin (33). Ideally, the coupling agent should have a low capacity for dissolved gases (32).

Examples of coupling agents are mixtures of mineral oil and glycerin, water and propylene glycol (36), cream (23), and an aquasonic gel (33). The coupling agent may also serve as a drug carrier (33). Drug-containing ointments can also serve as coupling agents (23,35). The amount of coupling agent to be applied should be optimized. McElnay *et al.* (35) reported that the minimum weight needed to produce an easily measurable response within a given time period should be used. This is particularly important with gels containing steroids, since too much gel can mask ultrasound effects. Loss of contact gel during ultrasonic application due to adhesion to the transducer head should be accounted for in the interpretation of data as well as coupling efficiency (22).

Contact Time. The length of contact time of drug containing coupling agent with the skin before the application of ultrasound and the total contact time of the drugs with the skin must be standardized. The purpose of the initial contact time is to saturate the stratum corneum prior to the application of the ultrasonic driving force (35). A 5- to 6-min contact time has often been reported (34,35). McElnay and coworkers (22) found that a 6-min contact period with drug containing cream prior to ultrasound treatment was required for reproducible local anesthesia.

Skin Site. The thickness and permeability of skin at the site of exposure of ultrasound govern the treatment conditions, i.e. frequency, intensity, and time of exposure. No difference in responses between left and right forearms were found in skin equidistant from the elbow and wrist on the flexor surface of the forearm during phonophoresis of steroids in a skin blanching test (35).

Cavitation/Bubble Formation. Ultrasound causes bubble formation in water and on the radiating surface of the transducer, because of expulsion of the dissolved gases, mostly O_2 and CO_2, out of solution. The bubble formation decreases the efficiency of energy transfer from the transducer to the skin application site. Cavitation requires the formation, expansion, and collapse of bubbles. At low frequencies, there is not enough time between the periods of condensation and rarefaction to allow for a full buildup of charge on the bubble surface. The fluctuation of electrical charge on the bubble surface causes the collapse. Although both intra- and extracellular fluids are known to contain many dissolved gases, exposure of tissues to clinically used ultrasound energy at intensities of less than 3 W/cm^2 does not give rise to cavitation (32). An effective way of dealing with the bubble formation is to substitute nonaqueous solvents such as mineral oil for water as the coupling agent. Because gases dissolve less in these solvents, there is less likelihood of bubble formation.

The experimental protocol should be designed specifically to test the hypothesis that ultrasound energy does not influence absorption of drugs through skin, i.e., phonophoresis does not work (22). Other questions which need to be addressed are as follows:

(1) How does the physicochemical properties of the drug molecule influence this method of administration? Not all drugs can be administered through all routes.
(2) Does ultrasound cause chemical changes in the drug molecule? Julian and Zentner (38) did not find any ultrasound-induced degradation of benzoic acid and hydrocortisone, but this might not be true for all drugs, especially proteins and peptides.
(3) Is the method measuring the response adequately sensitive to distinguish changes in the absorption of drugs?
(4) Is the position of the ultrasound generator in relation to the desired site of action suitable? The effect of ultrasound depends on diffusion direction and is greatest when the ultrasonic wave is normal to the membrane with the same direction of propagation on the diffusion flow (39).
(5) Should continuous or pulsed ultrasound be used? Continuous ultrasound provides combined mechanical and heating effects and pulsed ultrasound provides an equivalent mechanical affect. A recent study (23) indicates that pulsed-output ultrasound provided the most effective conditions for maximum increase in rate and extent of drug absorption through phonophoresis.
(6) What is the effect of ultrasound on the equilibrium partition coefficient between the skin and the drug in coupling agent? Julian and Zentner (38) found no significant effect of ultrasonic irradiation on the partition coefficients of benzoic acid in polydimethylsiloxane and hydrocortisone-cellulose model membranes but did not test the drugs with biological tissues, specifically skin.

EQUIPMENT AND DEVICES

A number of ultrasound devices are available commercially for use in diagnostics and physical therapy. The working principle of these devices is rather simple. The ultrasonic power supply generator converts 50/60-Hz voltage to high-frequency 20-kHz electrical energy. This electrical energy is transmitted to the transducer within the converter, where it is changed to mechanical vibrations. Nearly all transducers use piezoelectric material, either a quartz or a ceramic such as lead zirconate titanate. In the future, special polymers such as polyvinylidene fluoride may be utilized (33).

A simple type of unit is a disk (or rectangle or ring) of piezoelectric material with electrodes (e.g., gold or other electrical conductors) on both faces, to which electrical connections are made (9). The unit with electrical leads is embedded in epoxy or other similar material and placed in a housing to provide mechanical protection. This assembly forms a small compact device which is called the transducer probe or commonly referred to as the transducer, probe, soundhead, or applicator. A transducer probe can be held in the operator's hand and applied to the desired portion of the patient's body. The hand-held transducers are usually 2–4 cm in diameter. Typical spatial-average, temporal-average intensities used for treatment range from 0.1 to 3.0 W/cm^2 (9). Treatment consists of moving the applicator over the area to be treated, which is covered with a coupling agent consisting of a gel or oil in order to provide good acoustic coupling. The length of the treatment is 5–15 min. Figure 3 shows a hand-held soundhead being used for driving a water-soluble ointment containing the antiinflammatory drugs dexamethasone and lidocaine (6). Pulse and continuous mode may be used. The pulse mode (typically with 2–3 msec on time and 10–20 msec off) allows a higher intensity to be used during the pulse without increasing the skin temperature (9). A small ultrasonic instrument enables the patient to administer the treatment (12).

DynaWave Corp. (Geneva, Ill.) markets DynaWave Model 12, DynaSound Model 801, and DynaLator Model 811 ultrasonically controlled devices, which are designed to deliver physiologically acceptable continuous or pulsed ultrasonic energy for short duration. The transducer head in these devices can be a point probe or pads which can conform to body contours. The DynaLator Model 811 can be programmed.

Another suitable ultrasonic generator available which could be used for drug delivery is manufactured by White Water Electronics Inc. and has a frequency of 1100 ± 10 kHz, a continuous power output of 0 to 32 W, and an effective power level at the applicator head of 3.0 W/cm^2.

For *in vitro* studies, ultrasonic cell disrupters have often been used with modification of transducer probes (38). The point probes are made of titanium alloy and are available in various sizes. One particular type which has found use in phonophoresis is Vibracell ultrasonic processor made by Sonics and Materials, Danbury, Conn. (33).

The FDA has classified ultrasonic devices for specialized use (diathermy) into Class II (performance standards) and for all other uses into Class III (premarket approval) (40). The primary intended use of these devices is not drug delivery, although they can be used for that purpose.

FUTURE DIRECTIONS

Many laboratories are investigating transdermal drug

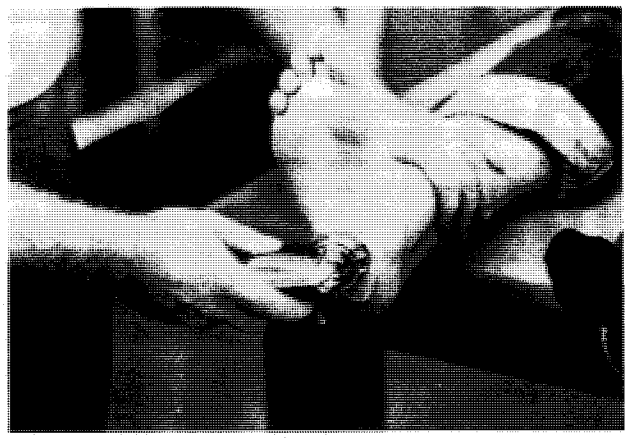

Fig. 3. Phonophoretic application of a water-soluble ointment containing dexamethasone and lidocaine for inflammatory condition. The ultrasound soundhead drives medication percutaneously into inflamed structures. (Reproduced with permission from Ref. 6.)

delivery enhancement by ultrasound. The available data indicate that phonophoresis may enhance both localized and systemic drug delivery. Cygnus Research (Redwood City, Calif.) and MIT (Cambridge, Mass.) currently focus their research on delivery through ultrasound pulsing of three compounds—D-mannitol, inulin, and physostigmine—previously considered unsuitable for transdermal delivery because of their molecular structures (12,41). Carefully designed experimental studies are needed to define the mechanism of ultrasound on drug absorption.

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REFERENCES

1. H. A. Abramson and M. H. Gorin. *J. Phys. Chem.* 44:1094–1102 (1940).
2. P. Tyle and B. Kari. In P. Tyle (ed.), *Drug Delivery Devices: Fundamentals and Applications,* Marcel Dekker, New York, 1988, pp. 421–454.
3. D. M. Skauen and G. M. Zentner. *Int. J. Pharm.* 20:235–245 (1984).
4. A. K. Banga and Y. W. Chien. *J. Control. Rel.* 7:1–24 (1988).
5. W. S. Quillin. *Athletic Train.* Summer:109–110 (1980).
6. W. S. Quillin. *Phys. Sportsmed.* 10(6):211 (1982).
7. T. J. Antich. *J. Orthopaed. Sports Phys. Ther.* 4(2):99–102 (1982).
8. F. Dunn, J. E. Lohnes, and F. J. Fry. *J. Acoust. Soc. Am.* 58:512 (1975).
9. National Council on Radiation Protection and Measurements. Biological Effects of Ultrasound: Mechanism and Clinical Implications, NCRP Report No. 74, NCRP, Bethesda, Md., 1983.
10. F. W. Kremkau. *Br. J. Cancer* 45 (Suppl V):226–232 (1982).
11. J. Kost, D. Levy, and R. Langer. *Proc. Int. Symp. Control Rel. Bioact. Mater. 13,* Controlled Release Society, 1986, pp. 177–178.
12. C. Starr. *Drug Topics* July 18:36–44 (1988).
13. K. Fellinger and J. Schmid. Klinik and Therapie des Chronischen, Gelenkreumatismus, Maudrich, Vienna, Austria, 1954, pp. 549–554.
14. M. Newman, M. Kill, and G. Frompton. *Am. J. Phys. Med.* 37:206–209 (1958).
15. J. E. Griffin, J. C. Touchstone, and A. C. Liu. *Am. J. Phys. Med.* 44(1):20–25 (1965).
16. J. E. Griffin, J. L. Echternach, R. E. Price, and J. C. Touchstone. *Phys. Ther.* 47(7):594–601 (1967).
17. J. A. Kleinkort and F. Wood. *Phys. Ther.* 55(12):1320–1324 (1975).
18. M. Wing. *Phys. Ther.* 62(1):32–33 (1982).
19. D. H. Goddard, P. A. Revell, J. Cason, S. Gallagher, and H. L. F. Currey. *Ann. Rheum. Dis.* 42:582–584 (1983).
20. M. S. Fahim, U.S. Patent No. 4,309,989 (1982).
21. E. J. Novak. *Arch. Phys. Med. Rehab.* 64:331–332 (1964).
22. J. C. McElnay, M. P. Matthews, R. Harland, and D. F. McCafferty. *Br. J. Clin. Pharmacol.* 20:421–424 (1985).
23. H. A. E. Benson, J. C. McElnay, and R. Harland. *Int. J. Pharm.* 44:65–69 (1988).
24. A. A. Poltera, O. Reyna, G. Z. Flores, A. M. Nowell De Arevalo, and F. Beltranena. *Lancet* 1:505 (1987).
25. C. Marchal, P. Bey, R. Metz, M. L. Gaulard, and J. Robert. *Br. J. Cancer* 45:Suppl. V (1980).
26. J. E. Olerud, W. O'Brien, Jr., M. A. Riederer-Henderson, D. Steiger, F. K. Foster, C. Daly, D. J. Ketterer, and G. F. Odland. *J. Invest. Dermatol.* 88(5):615–623 (1987).
27. J. Serup and B. Stanberg. *Contact Derm.* 17:80–84 (1987).
28. J. H. Aldes, W. J. Jadeson, and S. Grabinski. *Am. J. Phys. Med.* 33:79–88 (1954).
29. P. G. Wiles, M. Boothby, M. Griffiths, B. Scatchard, and H. J. Bodansky. *Lancet* 2:572 (1987).
30. A. H. Saad and A. R. Williams. *Br. J. Cancer* 45 (Suppl. V):202–205 (1982).
31. M. Moll. *U.S. Armed Forces Med. Serv. Dig.* 30:8–11 (1979).
32. J. E. Griffin. *J. Am. Phys. Ther. Assoc.* 46(1):18–26 (1966).
33. J. Kost and R. Langer. International Patent Application No. PCT/US87/01546 (1988).
34. H. A. E. Benson, J. C. McElnay, J. Whiteman, and R. Harland. *J. Pharm. Pharmacol.* 38S:738 (1986).
35. J. C. McElnay, T. A. Kennedy, and R. Harland, *Int. J. Pharm.* 40:105–110 (1987).
36. M. Nanavaty and R. Brucks. Proceedings of the 20th Annual Pharmaceutics Graduate Student Research Meeting, University of Missouri, Kansas City, June 10–12 (1988).
37. J. F. Kramer. *Arch. Phys. Med. Rehab.* 65:223–227 (1984).
38. T. N. Julian and G. M. Zentner. *J. Pharm. Pharmacol.* 38:871–877 (1986).
39. I. Lenart and D. Auslander. *Ultrasonics* 18:216–218 (1980).
40. J. Stigi. In P. Tyle (ed.), *Drug Delivery Devices: Fundamentals and Applications,* Marcel Dekker, New York, 1988, pp. 81–133.
41. *Chem. Week* Apr. 27:16 (1988).
42. L. A. Shamatava, G. A. Vadachkoriya, and A. D. Tsibadze. *Sb. Tr. Nauchno-Issled. Inst. Kurortol. Fizioter. Tiflis* 35:439–444 (1974).
43. V. G. Tsitlanadze. *Vop. Revm.* 4:19–22 (1973).
44. *St. Gatev. Ekxp. Med. Morfol.* 11(4):231–236 (1972).
45. J. Kost, K. Leong, and R. Langer. *Proc. Int. Symp. Control Rel. Bioact. Mater. 14,* Controlled Release Society, 1987, pp. 186–187.
46. M. C. Fyfe and L. A. Chahl. *Ultrasound Med. Biol.* 6:107–111 (1980).
47. W. Brondolo. *Arch. Ortop.* 73:532–540 (1960).
48. B. M. Cameroy. *Am. J. Orthoped.* 8:47 (1966).
49. V. A. Parikov. *Veterinaria* 43:88–91 (1966).
50. S. Ragelis. *Tsentr. Bol'nitsa.* 22(3):220–225 (1982).
51. S. Ragelis. *Antibiotiki (Moscow)* 26(9):699–703 (1981).
52. N. V. Smalyukh. *Oftal'mol. Zh.* 38(7):397–399 (1983).
53. J. Kost, D. Levy, and R. Langer. In Program and Symposia Abstracts, 3rd Annual AAPS Meeting, Orlando, Fla., 1988, p. 196.
54. M. V. Goral'chuk. *Vestn. Oftal'mol.* 2:50–51 (1976).

55. R. A. Chilingaryan, K. A. Karapetyan, G. G. Manucharyan, R. A. Manucharyan, and T. V. Melikyan. *Zh. Eksp. Klin. Med.* 21(2):152–158 (1981).
56. S. S. Korkhov. *Oftal'mol Zh.* 34(4):241–243 (1979).
57. T. N. Shpak. *Oftal'mol Zh.* 34(2):82–84 (1979).
58. S. Ragelis. *Azerb. Med. Zh.* 59(1):53–60 (1982).
59. L. D. Glushchenko. *Zdravookhr. Beloruss* 11:80–81 (1977).
60. A. Martin, J. Swarbrick, and A. Cammarata, *Physical Pharmacy* Lea & Febiger, Philadelphia, 1983, p. 428.
61. K. W. Kremkau. Ultrasonic Symposium Proceedings, IEEE Cat. No. 77CH 1264-ISU, 142 (1977).
62. H. Pratzel, P. Dittrich, and W. Kukovetz. *J. Rheumatol.* 13(6):1122–1125 (1986).
63. J. P. Famaey. *J. Belge. Med. Phys. Rehab.* 8(3):179–184 (1985).
64. J. P. Famaey. *J. Belge. Rheumatol. Med. Phys.* 30(3):129–141 (1975).
65. G. Wanet and N. Dehon. *J. Belge Rheumatol. Med. Phys.* 31:49–58 (1976).