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Phonophoresis

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Summary

A literature review of some of the important aspects of phonophoresis of interest to research scientists and institutional pharmacists is presented. Topics covered are drug phonophoresis in vivo, in vitro phonophoresis, effects of ultrasound on living tissue, and the direct effects of ultrasound on the drug substances. While drug phonophoresis has been used in only a limited way in the past, it appears to have a potential in the future as a drug delivery method/system for specialized purposes.

Introduction

Phonophoresis (sonophoresis, ultrasonophoresis) is defined as the movement of drugs through living, intact skin and into soft tissue under the influence of an ultrasonic perturbation. It has been used rather widely in physical medicine in this country and especially in Eastern Europe for many years. Although phonophoresis is often applied coincidentally with drug compounds, there has been little discussion of the subject in the American pharmaceutical literature. For this reason this literature survey was compiled to acquaint pharmaceutical technologists with some of the possible uses of ultrasound.

Drug phonophoresis in vivo

In 1954 ultrasound was used in conjunction with hydrocortisone ointment to treat inflamed digital joints (Fellinger and Schmid, 1954). Since then hydrocortisone has

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been the most widely studied drug in the ultrasono-phonophoresis field. Injections of hydrocortisone combined with ultrasonic 'massage' have shown improved results over simple hydrocortisone injections in the therapy of bursitis and post-traumatic lesions (Newman et al., 1958; Coodley, 1960; Mune, 1963). Studies of cortisol penetration into swine muscle and nerve tissues after exposing a topically applied ointment layer to ultrasound of varying frequencies have been reported (Griffen and Touchstone, 1963, 1965, 1972). Although the highest penetration was observed at 250 kHz, 3600 kHz was preferred because of less skin damage at the higher frequency. The standard 1 MHz frequency was considered to be a poor choice especially for deep-lying nerves. When cortisol was driven into nerve tissue in situ, the quantity penetrating the nerve was greater than the quantity retained by overlying muscle. The response appeared stronger and more consistent when 90 kHz energy was the driving force as compared to a 1 MHz force when the intensity and duration of treatment were equal. When ultrasonically driven hydrocortisone was compared with a placebo in 102 patients (Griffen et al., 1967), 68% of those receiving drug in conjunction with ultrasound had a marked decrease in pain and significant increase in range of motion; 28% of those receiving the placebo and ultrasound had a marked decrease in pain and increase in range of motion. A retrospective study of 285 patients treated phonophoretically with hydrocortisone applied as either a 1% cream or 10% ointment was conducted (Kleinkort and Wood, 1975). The authors concluded that the 10% 'phonophoretic injection' offered a safe, effective alternative for the delivery of locally concentrated anti-inflammatory agents without the attendant risks and discomfort of percutaneous injections.

Rats with dermatitis were treated with a steroid ointment with and without ultrasound (Kozin, 1976). Ultraphoretic administration of the steroid enhanced the antiproliferative effect of the drug by activating regenerative processes. Ultrasonic therapy (0.2 W/cm^2) of rat dermatitis with steroid ointment was used for both treatment and prevention. Ultraphonophoresis aided in normalization of the biochemical and structural processes of the skin (Chirkin and Kozin, 1976).

The passage of hydrocortisone through isolated frog skin was studied (Gatev, 1972). Under the influence of ultrasound, higher concentrations of hydrocortisone migrated than with controls. The effect was proportional to the duration of exposure and the intensity of the ultrasound only when high concentrations of hydrocortisone and high ultrasonic intensities were employed. With low concentrations of drug and low ultrasonic intensity there were no differences noted from the controls. In another study (Griffen and Touchstone, 1963) animals treated with comparatively high intensity ultrasound (3 W/cm^2) in conjunction with low drug concentrations in an ointment base and those treated with low intensity ultrasound (1 W/cm^2) in conjunction with a high drug concentration in an ointment base yielded the highest drug recovery from muscle tissue. Thus, it seemed that ultrasound had an important influence on hydrocortisone penetration especially at high intensity. There appears to be some difference of opinion as to whether low intensity ultrasound and low concentrations of hydrocortisone are effective.

Arthritis has been experimentally induced in rabbits (Tsitlanadze, 1971a, 1973) with observed changes that were similar to those of rheumatoid arthritis in the

structure of the knee-joint and in the chemistry of tissue samples. Hydrocortisone phonophoresis and ultrasonic therapy reversed these changes. It was found that the phonophoresis inhibited the pathogenic process manifested by a decreased number of circulating leukocytes and a decreased concentration of sialic acids in the blood. Elevated copper and aluminum and depressed zinc levels were normalized through cortisone phonophoresis.

Transcorneal phonophoresis of hydrocortisone has been studied (Zobina and Proskurova, 1970; Kleiman, 1972). Larger amounts of steroid were taken up into the anterior chamber than by simple diffusion alone. The highest concentrations of hydrocortisone in the anterior chamber of the eye were found after bath phonophoresis on the open eye. The extent of penetration was related to the ultrasonic intensity, time of exposure, and initial drug concentration. The bath phonophoretic method with 1% hydrocortisone and 0.2 W/cm^2 intensity for 5 min was considered effective and resulted in a doubling of the drug concentration in the anterior chamber as compared to studies performed without ultrasound. Hydrocortisone phonophoresis has also been used for the treatment of corneal opacity (Kleiman, 1972).

A variety of skin conditions have been treated with hydrocortisone phonophoresis (Braginskii, 1975). Phonophoresis/hydrocortisone combinations have been used to treat chronic psoriasis (Bel'ts and Bondarenko, 1971), kraurosis vulvae, lichen sclerotrophicus vulvae and pruritis vulvae essentiallis (Burgudzheiva, 1971a, 1971b, 1971c, 1972, 1974). Hydrocortisone and cuprenil were used in the therapy of scleroderma (Dozhanskaia, 1980). Hydrocortisone phonophoresis was studied in the treatment of facial nerve neuritis (Grinshte et al., 1971; Antropova, 1974), vasomotor rhinitis (Nikalaevskaia, 1969, 1970), allergic rhinitis (Kornienko, 1974), nonspecific polyarthritis (Tsitlanadze, 1971b), and a variety of musculo-skeletal diseases (Artamonova and Nikitina, 1977; Blinova and Ishenenko, 1972; Bioarintseva and Grushlavski, 1972; Bratslavskaia and Vitushikina, 1975; Kamrash et al., 1974; Kharitonov et al., 1975; Nagovitsyn and Vakhatova, 1971; Safiulina, 1967).

A treatment for oral and genital herpes simplex virus, type 2, using phonophoresis has been proposed (Fahim, 1978, 1980a, 1980b). A lotion containing urea, tannic acid, zinc oxide, and menthol was micromassaged ultrasonically into the affected area with positive results. Phonophoresis of interferon for the treatment of herpetic keratitis in rabbits has been studied (Shpak, 1978, 1979). Phonophoretically applied interferon was the most effective treatment observed for the experimental keratitis. Another study (Marmur and Shpak, 1980) was conducted in rabbits with induced herpetic keratitis treated with either instillations of interferon, ultrasonic phonophoresis of interferon, or ultrasonics alone. The effectiveness of phonophoretically applied interferon was markedly better than ultrasonics or interferon alone. Histochemical investigations revealed a normalizing action of interferon phonophoresis on the RNA, proteins, and carbohydrates of the cornea, the content of which was disturbed in herpetic keratitis.

Phonophoresis of hypotensive agents and papain have been used in the treatment of eye diseases (Cherkasov et al., 1974; Korkhov, 1979a, 1979b). In rabbits with experimental purulent ulcers of the cornea, penicillin phonophoresis (Goral'chuk,

1976) was shown to be effective therapy. Various other drugs have been administered phonophoretically for diseases of the eye (Tosk, 1979; Gmyria, 1979).

Several antibiotics including tetracycline, biomycin and penicillin have been phonophoretically administered for therapy of skin diseases (Parikov, 1966; Indkevich, 1971, 1972; Dynnik, 1977).

Phenylbutazone, alpha-chymotrypsin and other non-steroidal anti-inflammatory drugs have been used phonophoretically (Brondolo, 1960; Famaey, 1975; Wanet and Dehon, 1976).

Phonophoresis has been used in the treatment of tubular sterility (Suvorova, 1978) and as a method for perfusion of ovaries in vivo (Wortmann et al., 1973).

Patients with chronic tonsillitis (Babich, 1974), chronic pharyngitis (Tsyganov, 1979), and vocal fold nodules (Vasilenko and Nikolaevskaia, 1975; Trinos, 1979) have been treated by drug phonophoresis.

Absorption of thiamin and ascorbic acid from 0.5–2% solutions applied to the skin of young adults was increased by 50% after exposure to ultrasound at 880 kHz and intensities of 0.3–1.0 W/cm^2 (Glushchenko, 1977).

A wide variety of drug/ultrasound combinations in addition to those mentioned above have been recorded in the literature (Mironova, 1977; Novak, 1964; Grishutova, 1979; Va:Inshte:IN et al., 1975; Glushchenka, 1976; Didenko, 1978; Dohnalek, 1965; Chatterjee, 1977; Romaniuk, 1974; Razvozova, 1974; Lazaretnik, 1969; Klare and Kury, 1960).

In vitro phonophoresis

The transfer of deuterium oxide into a 2% albumin solution in a glass dialyzing cell fitted with a cellulose membrane using an ultrasonic bath at an intensity of 0.18 W/cm^2 was measured (Mendez et al., 1976). Statistical analysis showed a significant increase in deuterated water transfer attributed to the ultrasound.

Ultrasonic energies (0.2–0.6 W/cm^2) applied either continuously or pulsed at 4 ms intervals increased the penetration of Trilon-B through a cellophane membrane and through frog skin (Grinshtein et al., 1972).

The passage of hydrocortisone phonophoretically through cellophane membranes and frog skin has been demonstrated (Safiulina and Proskurova, 1970). When the ultrasonic exposure time was doubled diffusion was increased by 5–10%.

Phonophoretically enhanced diffusion of sodium and potassium chloride through cellophane membranes has been reported (Lenart and Auslander, 1980). It was suggested that the effect was mainly due to acoustic-induced microcurrents. Because the intensity of ultrasound in a field is not uniform, the anticipated heterogeneous distribution of energy in the solutions would create currents similar to those obtained by mechanical stirring. This would lead to a decrease in the thickness of the diffusion layer, thus increasing the observed diffusion process. However, mechanical stirring resulted in smaller diffusion increases than ultrasound. Either ultrasound provided more effective stirring or other factors such as radiation pressure, gravitation, cavitation and acoustic pressure were important.

Ultrasonically induced release of boric acid from 5 dermatologic bases was

greatest with emulsifying bases containing spermaceti and lanolin (Murav'ev et al., 1973). Less boric acid was released from bases containing stearic acid soaps or the emulsifier T_2, and no boric acid was released from a petroleum base. The rate of release was measured by noting a change in pH of a receptor medium from alkaline to acid.

Effects of ultrasound on tissue

Numerous reports have appeared regarding effects of ultrasound on tissue, organs and body systems. A few illustrative cases which may be appropriate to phonophoresis are included here.

It has been postulated (Fry and Dunn, 1972) that ultrasound may produce structural and functional changes by way of thermal, cavitational, or other mechanical mechanisms not yet well understood. There is evidence for a small cumulative effect over a very short time base (less than 5 min) but there is no evidence for cumulative effects on any longer scale. Short-term cumulative effects may be attributed to transient temperature rises inherent in all ultrasonic irradiation procedures in tissue.

It has been suggested (Hill, 1972) that a major factor influencing the interaction of ultrasound with living cells under experimental conditions was the occurrence of 'stable' or 'resonant' bubble type cavitation in the media in which cells were irradiated. The mechanical shear resulting from this cavitation leads to cell membrane disruption and disruption of other large structural cell components. Chemical changes due to free radicals appear to play a minor role in ultrasonically induced biological changes.

Microstreaming, stable and transient cavitation, and temperature have been listed as important parameters in cell interactions with ultrasound (Hughes, 1972). Even slight rises of temperature (2–3°C) in certain areas of a cell may be sufficient to cause cell death. This is particularly true in the case of membrane systems such as cell interfaces, mitochondria, lysosome or Golgi bodies where loss of function would have widespread deleterious effects at the level of cellular control mechanisms.

Thresholds for cellular changes during phonophoresis were studied (Griffin and Touchstone, 1972) for ultrasonic energies less than 1 W/cm^2 to greater than 1000 W/cm^2. In the 1 MHz range at energies of 1–3 W/cm^2, changes in liver and peritoneal tissue were noted. At 10 W/cm^2 of continuous ultrasonic irradiation, changes in the ultrastructure of striated muscle appeared. Abnormal mitosis occurred at energies up to 100 W/cm^2 while lesions in the brain were evident at energies of 10^2–10^4 W/cm^2. The lowest energy thresholds for disruptive tissue effects occurred in suspensions of low viscosity (e.g. water) or high dissolved gas content where cavitation, either stable or transient, took place. When focused ultrasound was used the threshold tended to be higher.

Ultrasound of varying intensity has been shown to result in changes in reactivity to tissue antigens in white rats (Mgaloblishvili and Khirsel, 1975). The intensity of positive reactions was directly related to the intensity and duration of the ultrasonic waves.

No correlation was found between a given ultrasonic dose to the skin and changes in skin temperature or changes in blood flow (Paaske et al., 1973). They stated that any beneficial effects of ultrasound cannot be ascribed to increased blood flow in cutaneous, subcutaneous and muscle tissue.

The burning of mouse skin exposed to ultrasonic energy at a frequency of 1 MHz has been reported (Kirsten et al., 1963). Ten to 20% of the animals were burned after 5 min treatments of 10 kW/m^2 at 7 days old and 40 kW/m^2 at 4 days old.

The epidermis of white mice was damaged following exposure to ultrasound of 1 MHz and 3–6 MW/m^2 for 30 s. Differences were noted in the degree of damage depending upon the time of irradiation with respect to the hair growth cycle (Argyris and Bell, 1959). Skin lesions were discovered in rats treated with 10 kW/m^2 for 1 min at 1 MHz. As the intensity or duration of insonation was increased greater damage was noted. Blisters, edema, congestion and even hemorrhage were described (Cowden and Abell, 1963).

Alcohol dehydrogenase, lysozyme, and catalase have been analyzed after exposure to cavitating 20 kHz ultrasound for varying times (Coakley et al., 1973). Catalase activity was the least affected; however, alcohol dehydrogenase and lysozyme were both inactivated at an exponential rate. The rate of inactivation decreased with increasing protein concentration. The authors suggested that the mechanism of inactivation was chemical rather than mechanical.

Protein breakdown in the presence of ultrasound has been shown to decrease with decreases in the intensity of transient cavitation, yet still occur to a small extent under conditions of stable cavitation (O'Shea and Bradbury, 1973). There was no evidence of a limiting molecular weight below which degradation did not occur. There was clear evidence of non-random fission near the center of the molecule.

The local application of pulsed 3 MHz ultrasound at 1 W/cm^2 once every 10 s for up to 10 min stimulated healing of chronic varicose ulcers (Dyson et al., 1976). Even though insonated ulcers were significantly improved compared with controls, there were variations in response to the treatment. Other workers (Aktov and Khodakov, 1974) found that continuous ultrasonic treatment of cow mammary glands at 1 W/cm^2 resulted in increased leukocytes, proteins and nitrogen-containing substances in the milk. At 0.8 W/cm^2 ultrasound did not affect the mammary glands of healthy cows, but had a beneficial effect on the mammary glands of cows with mastitis since it increased milk leukocytes, total protein, nitrogenous substances, pH, serum albumin, the activities of catalase and alkaline phosphatase, and increased lactose and immunoglobulin levels.

Plantar warts have been treated with ultrasound at a frequency of 1 MHz and intensities of 0.1–3 W/cm^2 (Kent, 1950). In 90% of the cases pain almost immediately disappeared followed by necrosis of the wart. Furthermore, the normal surrounding skin was described as 'unharmed'.

When used improperly there is ample evidence that ultrasound can be harmful. However, when used at a proper frequency, power level and duration, ultrasound appears to be a safe technique for enhancing drug administration and effectiveness in humans.

Effect of ultrasound on drugs

While numerous references can be found to the physical and chemical effects of ultrasound on various substances, few direct studies are available to show the effect of ultrasound, at clinical dosages, on drugs used phonophoretically.

Therapeutic levels of ultrasound have been shown to have no effect on the pH or R_f values of hydrocortisone solutions (Gatev, 1973a). At 0.6–2 W/cm^2 for 5–10 min, no changes in structure and other physicochemical properties were noted using chemical and fluorimetric methods. The results indicated that phonophoresis did not alter hydrocortisone and the method was suitable for therapeutic treatment (Gatev, 1973b). Hydrocortisone solutions exposed to ultrasonic intensities of 2 W/cm^2 for 10 min did not exhibit detectable decomposition (Popov et al., 1970).

Sodium dodecylbenzene sulfonate was decomposed more rapidly than sodium dodecyl sulfate by ultrasonic treatment at 304 kHz in 0.01–0.1 mmol/l aqueous solution with both the benzene ring and the alkyl group decomposing (Hagiwara, 1972). The decomposition rate increased with increasing ultrasonic intensity and treatment time, but no pH effect was observed.

Conclusions

It has been proposed that ultrasound moves a particle in an oscillatory fashion about a rest position, but this is not sufficient to explain movement through tissue (Griffen, 1966). Current thinking suggests that radiation pressure may be responsible for the successful administration of drugs percutaneously via ultrasound. The depth of ultrasonic penetration and, hence, the extent of change in drug efficacy patterns, is related to frequency, with the lower frequencies leading to greater penetration. However, the literature currently available is sketchy and does not allow one to assess the adequacy of the controls used, the sensitivity of the analytical methods or the suitability of the procedures used for clinical evaluation. Certainly, carefully designed studies are needed to clarify and define the effects of ultrasound on drug absorption. Nevertheless, the data available indicate that phonophoretic procedures may be useful in the enhancement of both localized and systemic drug therapies.

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