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Phonophoresis of lignocaine and prilocaine from Emla cream *

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Summary

The influence of ultrasound on the percutaneous absorption of lignocaine and prilocaine from Emla cream was investigated in 11 healthy volunteer subjects in a double-blind placebo controlled cross-over clinical trial. Using a specially designed experimental protocol, the effect of both 1 : 1 pulsed output ultrasound (1.5 MHz and 3.0 MHz at intensity 1.0 $W \cdot cm^{-2}$ for 5 min) and continuous output ultrasound at a range of frequencies (0.75 MHz; 1.5 MHz and 3.0 MHz, each at intensity 1.5 $W \cdot cm^{-2}$ for 5 min) were investigated. A placebo control, involving massage without ultrasound for 5 min, was incorporated into each protocol. The pharmacodynamic parameter of loss of sensation caused by lignocaine and prilocaine, was used to monitor the percutaneous absorption of the drugs. A modified skin prick test, which involved pressing the blunt end of a paper clip onto the treatment site, was used. This prevented enhanced drug penetration due to trauma caused by hypodermic needles used in the standard skin prick method. Ultrasound treatment led to an increased rate of absorption of lignocaine and/or prilocaine as determined by onset of anaesthesia; however, this increase was not statistically significant ($P > 0.05$; analysis of variance). Ultrasound increased the extent of absorption of lignocaine and/or prilocaine, as determined by duration of anaesthesia, to a statistically significant degree ($P < 0.05$; analysis of variance).

Introduction

Ultrasound has long been established as a therapeutic agent in physical medicine in the treatment of a wide range of clinical conditions. The technique involves placing an ultrasound coupling agent on the skin over the area to be treated and massaging the area with an ultrasonic source. An ultrasound coupling agent is simply a cream, gel or oil which maintains good contact between the transducer head and the skin. In an attempt to produce a synergistic effect, many physical therapists have replaced the standard coupling agents with topical anti-inflammatory preparations. Thus the technique of phonophoresis, which has been defined as the movement of drugs through intact skin into soft tissue by ultrasonic perturbation (Skauen and Zentner, 1984) has become established as a therapeutic technique in physical medicine.

The use of ultrasound to enhance the percutaneous absorption of drugs was first reported by Fellinger and Schmid in 1954. They successfully treated polyarthritis of the digital joints of the hand by using ultrasound to "drive" hydrocorti-

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sone ointment into the inflamed area. Griffin and co-workers (1963, 1965, 1968, 1972) conducted a series of studies in swine to test the ability of ultrasound to drive hydrocortisone into the deep muscle layers and nervous tissue. They demonstrated that both high and low intensity ultrasound can cause increased penetration of externally applied hydrocortisone. Griffin and coworkers also showed that regardless of the frequency of the ultrasound used, or type of tissue exposed (blood, muscle or nerve) there was more cortisone recovered after phonophoresis than after exposure to drug alone. In addition Griffin et al. (1967) compared ultrasonically driven hydrocortisone with a placebo in 102 patients with diagnoses of elbow epicondylitis, bicipital tendonitis, shoulder osteoarthritis, shoulder bursitis and knee osteoarthritis. In their study, 68% of patients receiving drug in conjunction with ultrasound were rated as 'improved' demonstrating a pain-free normal functional range of motion, while only 28% of patients receiving placebo with ultrasound were rated as "improved". Novak (1964) has investigated the influence of ultrasonic massage on the penetration of a topically applied solution of lignocaine base into the quadricep muscles of rabbits. He reported that the concentration of lignocaine in the tissues was much greater when the tissues had been subjected to ultrasound at the time of application of lignocaine.

Over the past 30 years a number of clinical reports have been published concerning phonophoresis of the following drugs: phenylbutazone (Brondolo, 1960), lignocaine/ dexamethasone (Moll, 1979), carbocaine (Cameroy, 1966), tetracycline (Parikov, 1966) and hydrocortisone (Kleinkort and Wood, 1975; Wing, 1982). In a recent review of phonophoresis, which addressed both animal and clinical data, it was concluded that due to poor study design much of the currently available data does not allow the assessment of the adequacy of the controls used, the sensitivity of the analytical methods or the suitability of the procedures used for clinical evaluation (Skauen and Zentner, 1984). Therefore despite its use for over 30 years, little pharmacokinetic data are available quantifying the efficacy of phonophoresis.

McElnay et al. (1987) recently reported that ultrasound treatment led to enhanced percutaneous absorption of fluocinolone in healthy volunteer subjects in a double-blind placebo controlled cross-over clinical trial. This was in contrast to their earlier studies which showed that ultrasound did not significantly increase the percutaneous absorption of lignocaine alone or benzydamine (McElnay et al., 1985; Benson et al., 1986).

The aim of the present study was to investigate 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 cross-over trial. The pharmacodynamic parameter of loss of sensation caused by lignocaine and prilocaine, was used to monitor the rate and extent of percutaneous absorption of the drugs.

Materials and Methods

The study was carried out on 11 healthy volunteer subjects (both male and female), who each gave written informed consent. The protocol was approved by the University Ethics Committee.

Initial experimentation was carried out to develop a suitable experimental protocol, in particular to standardise the ultrasonic frequency/ intensity combinations to be used, the duration of application of the ultrasound and the contact time of local anaesthetic cream with the skin. Based on initial results in 3 volunteer subjects, the experimental protocol shown below, involving investigation of both continuous and pulsed output ultrasound, was drawn up. The trial, which consisted of 3 separate study days, 7 days apart, was carried out in a double-blind cross-over fashion with each person acting as their own control. The local anaesthetic cream used, was the commercially available Emla cream, which contains 0.5% lignocaine and 0.5% prilocaine as a eutectic mixture in a water-miscible base.

Treatment periods

The three treatment periods were as follows.

(*a*) *Day 1.* Each subject washed their forearms before marking out a 5 cm diameter circular treat-

ment site on each forearm using a ballpoint pen. A portion of Emla cream (2.5 g) was applied to the right forearm and the area covered with Tegaderm adhesive dressing. The preparation was left for a 20 min contact period in an attempt to saturate the stratum corneum. The ultrasound head was then used to massage the areas in turn with a standardised circular motion for a 5 min period. Ultrasound treatments were fully randomised, the ultrasound generator (Sonocel Multiphon Mk II) being set to a frequency of 0, 0.75, 1.5 or 3.0 MHz continuous output ultrasound at an intensity of 1.5 $W \cdot cm^{-2}$ or a frequency of 1.5 or 3.0 MHz 1 : 1 pulsed output ultrasound at an intensity of 1.0 $W \cdot cm^{-2}$. During the treatment period neither the administrator of ultrasound nor the volunteer subjects knew at which frequency/intensity combination the generator had been set. After the ultrasound treatment, the cream was removed from the forearm. The treatment area was tested for loss of sensation immediately and at 5 min intervals thereafter until loss of sensation occurred. The times at which partial and total loss, and recovery, of sensation occurred were recorded.

A modified skin prick test, which involved pressing the blunt end of a paper clip onto the treatment site, was used to monitor sensation loss in this trial. This prevented enhanced drug penetration due to trauma caused by hypodermic needles used in the standard skin prick method.

The complete procedure was repeated with the left forearm using a different frequency/intensity combination.

(*b*) *Day 2.* The procedure was exactly as for Day 1, using different ultrasound frequency/intensity combinations to those administered on Day 1.

(*c*) *Day 3.* The procedure was exactly as for days 1 and 2 using different ultrasound frequency/intensity combinations.

The ultrasound frequency/intensity combinations used were such that each subject received each of the 6 treatments, i.e. 0, 0.75, 1.5 and 3.0 MHz continuous output ultrasound at an intensity of 1.5 $W \cdot cm^{-2}$ and 1.5 and 3.0 MHz 1 : 1 pulsed output ultrasound at an intensity of 1.0 $W \cdot cm^{-2}$ over the 3 treatment days.

Statistical analysis

Analysis of variance was used to compare the times for onset and duration of anaesthesia. Where a statistically significant difference existed, a Newman-Keuls multiple range test was performed on the data in order to determine between which groups differences existed.

Results

Onset of anaesthesia following ultrasound treatment is recorded as time (in min) for the occurrence of both partial and total loss of sensation in Table 1. Although there were considerable decreases in the times required to produce anaesthesia, statistical comparison of the results, using analysis of variance, showed that there were no significant differences in onset times of anaesthesia, between control data and those using ultrasound at differing frequencies. Interestingly these differences reached statistical significance

TABLE 1

Onset of anaesthesia following treatment with differing ultrasound frequencies *

	Ultrasound frequency (MHz)					
	0 (Control)	0.75C	1.5C	3.0C	1.5P	3.0P
Mean partial loss of sensation (min) ± S.E.	20.9 ± 2.9	15.5 ± 6.3	17.7 ± 3.6	12.7 ± 4.9	11.4 ± 3.9	16.8 ± 2.7
Mean total loss of sensation (min) ± S.E.	36.8 ± 6.3	32.3 ± 6.7	33.6 ± 4.6	24.6 ± 5.5	26.8 ± 4.9	28.6 ± 3.1

C = continuous output ultrasound at intensity 1.5 $W \cdot cm^{-2}$; P = 1 : 1 Pulsed output ultrasound at intensity 1.0 $W \cdot cm^{-2}$.

* Analysis of variance indicated that onset times obtained after ultrasound did not differ between treatments or from control values.

TABLE 2

Duration of anaesthesia following treatment with differing ultrasound frequencies

	Ultrasound frequency (MHz)					
	0 (Control)	0.75C	1.5C	3.0C	1.5P	3.0P
Mean duration of anaesthesia to partial recovery of sensation (min) ± S.E.	89.4 ± 13.7	110.7 ± 32.0	125.7 ± 34.4	120.5 ± 22.0	139.5 ± 37.7	179.5 ± 35.6
Mean duration of anaesthesia to total recovery of sensation (min) ± S.E.	169.8 ± 19.9	224.6 ± 34.9	246.6 ± 46.6	221.8 ± 32.4	267.3 ± 47.1	245.9 ± 35.8

C = continuous output ultrasound at intensity 1.5 $W \cdot cm^{-2}$; P = 1 : 1 Pulsed output ultrasound at intensity 1.0 $W \cdot cm^{-2}$.

($P < 0.05$) when analysed using the paired *t*-test for control vs 1.5P (partial loss of sensation) and control vs 3.0C (total loss of sensation).

The duration of anaesthesia, recorded as time (in min), for both partial and total recovery of sensation is shown in Table 2. Statistical comparison, using analysis of variance, showed that ultrasound increased the duration of anaesthesia to both partial and total recovery of sensation, to a statistically significant degree ($P < 0.05$). The Newman-Keuls multiple range test showed that each of the ultrasound treatments significantly enhanced the duration of anaesthesia compared to treatment without ultrasound (Table 3).

TABLE 3

Newman-Keuls multiple range test on data for duration of anaesthesia following treatment with differing ultrasound frequencies

Partial recovery of sensation		Total recovery of sensation	
Treatment	Significance	Treatment	Significance
3.0P vs Control	$P < 0.001$	1.5P vs Control	$P < 0.001$
3.0P vs 0.75C	$P < 0.001$	1.5P vs 3.0C	$P < 0.001$
3.0P vs 3.0C	$P < 0.001$	1.5P vs 0.75C	$P < 0.001$
3.0P vs 1.5C	$P < 0.001$	1.5P vs 3.0P	$P < 0.001$
3.0P vs 1.5P	$P < 0.001$	1.5P vs 1.5C	$P < 0.001$
1.5P vs Control	$P < 0.001$	1.5C vs Control	$P < 0.001$
1.5P vs 0.75C	$P < 0.001$	1.5C vs 3.0C	$P < 0.001$
1.5P vs 3.0C	$P < 0.001$	1.5C vs 0.75C	$P < 0.001$
1.5P vs 1.5C	$P < 0.001$	1.5C vs 3.0P	Not sig.
1.5C vs Control	$P < 0.001$	3.0P vs Control	$P < 0.001$
1.5C vs 0.75C	$P < 0.001$	3.0P vs 3.0C	$P < 0.001$
1.5C vs 3.0C	Not sig.	3.0P vs 0.75C	$P < 0.001$
3.0C vs Control	$P < 0.001$	0.75C vs Control	$P < 0.001$
3.0C vs 0.75C	Not sig.	0.75C vs 3.0C	Not sig.
0.75C vs Control	$P < 0.001$	3.0C vs Control	$P < 0.001$

Treatment C = continuous output ultrasound at intensity 1.5 $W \cdot cm^{-2}$; Treatment P = 1 : 1 Pulsed output ultrasound at intensity 1.0 $W \cdot cm^{-2}$.

Discussion

The experimental protocol was developed specifically for this investigation based on initial experimentation. The pharmacodynamic parameter of loss of sensation caused by lignocaine and prilocaine, was found suitable to monitor the rate of percutaneous penetration of the drugs. During initial experimentation, loss of sensation was determined using the standard skin prick test. It was noted, however, that the hypodermic needle used for testing caused trauma to the treatment site. Since this trauma was likely to cause changed percutaneous penetration the blunt end of a paper clip was used for testing for loss and re-occurrence of sensation in the investigation.

The local anaesthetic cream formulation Emla was chosen because it requires a relatively long contact time with the skin before the application site becomes anaesthetised (the manufacturers recommend a minimum contact time of 60 min). It was envisaged that if ultrasound did enhance the penetration of lignocaine/prilocaine, this effect could be more easily detected using a formulation which did not provide rapid percutaneous penetration of the drugs. Results showed that ultrasound treatment led to an increased rate of absorption of lignocaine and/or prilocaine, as determined by the onset of anaesthesia (11.4–17.7 min vs 20.9 min); however, these increases were

not statistically significant ($P < 0.05$; analysis of variance; Table 1).

Ultrasound increased the extent of absorption of lignocaine and/or prilocaine, as determined by the duration of anaesthesia, to a statistically significant degree (Tables 2 and 3).

The 1.5 MHz (1 : 1 pulsed output) and 3.0 MHz (continuous output) ultrasound appeared to be the most effective frequencies in improving the rate of percutaneous absorption, while the 1.5 MHz and 3.0 MHz (1 : 1 pulsed output) ultrasound treatments were the most effective frequencies in improving the extent of drug absorption.

The results correlate with the observations of Novak (1964), who reported that the concentration of lignocaine in rabbit muscle tissue was greater when the tissues had been subjected to ultrasound at the time of lignocaine application. They also support the work of Moll (1979) who advocated the use of lignocaine and dexamethasone with ultrasound as a new approach to the management of pain.

It would appear from our results that pulsed output ultrasound provided the most effective conditions in the technique of phonophoresis with the currently examined topical formulation. This study indicates that phonophoretic procedures may have some benefit in the enhancement of localised drug therapies.

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References

Benson, H.A.E., McElnay, J.C., Whiteman, J. and Harland, R., Lack of effect of ultrasound on the percutaneous absorption of benzydamine. *J. Pharm. Pharmacol.*, 38 Suppl. (1986) 73P.

Brondolo, W., Phenylbutazone with ultrasonics in some cases or arthrosynovitis of the knee. *Arch. Ortop.*, 73 (1960) 532–540.

Cameroy, B.M., Ultrasound enhanced local anaesthesia. *Am. J. Orthoped.*, 8 (1966) 47.

Fellinger, K. and Schmid, J., *Klinik und Therapie des Chronischen Gelenkheumatismus*, Maudrich, Wein, Austria, 1954, p. 549–552.

Griffin, J.E., Echternach, J.L., Price, R.E. and Touchstone, J.C., Patients treated with ultrasonic driven hydrocortisone and with ultrasound alone. *Phys. Ther.*, 47 (1967) 594–601.

Griffin, J.E. and Touchstone, J.C., Ultrasonic movement of cortisol into pig tissues. 1. Movement into skeletal muscle. *Am. J. Phys. Med.*, 42 (1963) 77–85.

Griffin, J.E., Touchstone, J.C. and Liu, A. C.-Y., Ultrasonic movement of cortisol into pig tissue. II. Movement into paravertebral tissue. *Am. J. Phys. Med.*, 44 (1965) 20–25.

Griffin, J.E. and Touchstone, J.C., Low intensity phonophoresis of cortisol in swine. *Phys. Ther.*, 48 (1968) 1336–1344.

Griffin, J.E. and Touchstone, J.C., Effects of ultrasonic frequency on phonophoresis of cortisol into swine tissues. *Am. J. Phys. Med.*, 51 (1972) 62–78.

Kleinkort, J.A. and Wood, F., Phonophoresis with 1 percent versus 10 percent hydrocortisone. *Phys. Ther.*, 55 (1975) 1320–1324.

McElnay, J.C., Kennedy, T.A. and Harland, R., The influence of ultrasound on the percutaneous absorption of fluocinolone acetonide. *Int. J. Pharm.*, 40 (1987) 105–110.

McElnay, J.C., Matthews, M.P., Harland R. and McCafferty, D.F., The effect of ultrasound on the percutaneous absorption of lignocaine. *Br. J. Clin. Pharmacol.*, 20 (1985) 421–424.

Moll, M., A new approach to pain: lidocaine and decadron with ultrasound. *U.S. Armed Forces Med. Serv. Dig.*, 30 (1979) 8–11.

Novak, E.J., Experimental transmission of lidocaine through intact skin by ultrasound. *Arch. Phys. Med. Rehab.*, 45 (1964) 231–232.

Parikov, V.A., Injection of tetracycline into the tissues of cow udders by ultrasonics. *Veterinaria*, 43 (1966) 88–91.

Skauen, D.M. and Zentner, G.M., Phonophoresis. *Int. J. Pharm.*, 20 (1984) 235–245.

Wing, M., Phonophoresis with hydrocortisone in the treatment of temporomandibular joint dysfunction. *Phys. Ther.*, 62 (1982) 32–33.