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The effect of ultrasound on the percutaneous absorption of lignocaine

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The influence of ultrasound on the percutaneous absorption of lignocaine from a cream base was investigated in a double-blind cross-over trial in healthy volunteers. Mean data indicated that there was a slightly faster onset time for local anaesthesia when ultrasound was administered when compared with control values (no ultrasound). However, the differences were not statistically significant. Further controlled clinical studies are required into the effect of ultrasound on percutaneous absorption since the technique (phonophoresis) has been alleged to enhance percutaneous penetration of a number of drugs.

Keywords lignocaine ultrasound percutaneous absorption

Introduction

The technique of using ultrasound to enhance the percutaneous absorption of drugs (phonophoresis) was first reported by Fellinger & Schmid in 1954. The technique involves placing the topical preparation on the skin over the area to be treated and massaging the area with an ultrasound source. The ultrasonic energy is said to enhance percutaneous absorption and tissue penetration of the active ingredients from the topical product. The initial investigators (Fellinger & Schmid, 1954) reported successfully treating polyarthritis of the digital joints of the hand by using hydrocortisone ointment driven into the inflamed area using ultrasound.

The major problem with this study and further studies carried out to date is the absence of adequate controls. A typical example of a further study involved a double-blind clinical trial with three groups of patients receiving either lignocaine/dexamethasone with ultrasound, a placebo with ultrasound or a placebo with no ultrasound (Moll, 1979). No information was given as to the effects of lignocaine/dexamethasone without ultrasound.

Quillen (1982) stated that phonophoresis offers a safe, painless alternative to injection for inflammatory conditions. He stressed that tendinitis, bursitis and painful trigger points have been successfully treated with this technique. The report, however, did not include the results of any treatments and since ultrasound alone is often used in sports medicine to treat inflammatory conditions it is difficult to say whether combined drug-ultrasound treatments offer advantage over either treatment given alone or the two treatments used at different times. Further uncontrolled or anecdotal clinical reports have been published concerning the following drugs: lignocaine (Novak, 1964), carbocaine (Cameroy, 1966) and hydrocortisone (Griffen, 1966; Griffen *et al.*, 1967; Kleinkort & Wood, 1975; Wing, 1982) while in a short review on phonophoresis Antich (1982) reported that the major medications used today with this technique

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included the anti-inflammatories (cortisol, dexamethasone and salicylates) and local anaesthetics. A more comprehensive review covering both animal and clinical data has recently been published (Skauen & Zentner, 1984).

It is clear therefore that the technique which supposedly is capable of driving medication across the skin barrier and into the underlying structures merits further study in a controlled manner. The aim of the present study was to examine the effect of ultrasound on the percutaneous absorption of lignocaine from a cream base in healthy volunteer subjects in a double-blind controlled clinical trial.

Methods

The study was carried out on ten healthy volunteer subjects (males and females) who each gave written informed consent. The study was approved by the University Ethics Committee.

Initial experimentation was carried out to develop a suitable experimental protocol, in particular to standardise the ultrasonic intensities to be used, the time of application of the ultrasound and the contact time of the local anaesthetic product with the skin. To evaluate when percutaneous absorption has taken place, the loss of sensation of the skin to pricking using a hypodermic needle was tested. Based on initial results the protocol shown below was drawn up. The trial, which consisted of two treatment periods, was carried out on two separate occasions 7 days apart in a double-blind cross-over fashion. A cream, prepared in our own laboratories containing 25% lignocaine, was utilised.

Treatment periods

The two treatment periods were as follows:

(a) *Day 1:* A site on each forearm of each subject was marked using a circular stencil (diameter 6.5 cm) and an indelible marker. A time schedule for the 10 volunteers was prepared to allow the following procedures to be carried out:- To each site was applied 1.5 g of the anaesthetic cream and the area covered with Micropore® surgical tape. After 6 min the tape was removed and the ultrasound head used to rub the area with a circular motion for 5 min. Treatment with the ultrasound head was randomised, the ultrasonic generator (Sonostat Model 633, Siemens) being set to either 2.0 W/cm^2 or 0.0 W/cm^2 for the left and right arms respectively. The instrument gave a pulsed output at a frequency of 870 kHz. The head used for the ultrasonic massage had a nominal radiating area of 4 cm^2 and a maximum power output of 12 W. During the treatment periods neither the administrator nor the volunteer subjects knew at which intensity the generator had been set. After each ultrasound treatment the remaining cream was removed and the site tested for loss of sensation by pricking the test area three times with a hypodermic needle. This test was carried out immediately and at 5 min intervals thereafter. Two end-points were recorded:

(i) time post-treatment taken for dulling or partial loss of sensation

(ii) time post-treatment taken for complete loss of sensation.

(b) *Day 2:* The procedure was exactly as for day 1; however, the ultrasound intensities used on each arm of each subject were crossed over so that each application site received each of the two ultrasound intensities. The volunteers and the administrator of the ultrasound were again unaware of the intensity being used or that it had been changed from day 1.

Analysis of variance was used, to assess differences in the effect onset times between right and left arms and differences due to ultrasound administration.

Results

The procedures were well tolerated by all volunteers and informal questioning indicated that the volunteers and the operating physician were indeed unaware as to whether the ultrasound instrument had been switched on or off during treatment periods. Initial experimentation indicated that a 6 min contact period with the cream prior to ultrasound treatment was required for reproducible local anaesthesia.

For analysis of variance two groups of subjects were distinguished by which treatment was applied to the left (or right) arm on day 1. In all cases below the P value for partial loss of sensation data is given first followed by that for total loss of sensation. the analysis of variance showed that no significant difference was found:

(i) between group means taken over days and treatments ($P = 0.1141$; 0.1790),

(ii) between day means taken over groups and treatments ($P = 0.5108$; 0.5912),

(iii) between treatment means over groups and days ($P = 0.1505$; 0.6894).

The absence of significant interactions between treatments and groups ($P = 0.8420$; 0.8036),

days ($P = 0.2596; 0.3069$), and groups by days ($P = 0.7362; 0.8017$) indicates that the non-significant overall treatment effect was not influenced by either the arm to which ultrasound had been applied or the day on which the assessments were made (Table 1).

The time (combined results of the two treatment days) taken to partially lose sensation varied from 20–75 min while the time taken to totally lose sensation ranged from 25–85 min. Although statistically insignificant it is interesting to note that in both cases the mean data indicated a more rapid onset of effect after ultrasound was applied when compared with massage using the ultrasound head with the energy supply turned off.

Discussion

The experimental protocol was devised specifically for this investigation with the local anaesthetic cream. The aim of the 6 min contact time of the cream prior to the application of the ultrasound was to saturate the outer layers of the skin (stratum corneum). It was envisaged that the ultrasound source would then be more successful at driving the drug through this layer to underlying structures. Although there was a trend in the results towards an increased absorption rate in the presence of ultrasound the results were marginal and not statistically significant.

A number of hypotheses could be used to explain the present data. These include:-

(a) Ultrasound energy does not influence absorption i.e. phonophoresis does not work.
(b) Lignocaine has physical and chemical properties which make it unsuitable for this method of administration.
(c) The testing method presently used was not sensitive enough to distinguish changed absorption rates.
(d) The coupling capacity of the particular formulation used did not allow optimal transmission of ultrasonic energy from the unit to the volunteer, therefore decreasing the phonophoretic effect.
(e) An increase in local blood flow caused by ultrasound may have negated the increased pharmacological effects of an enhanced lignocaine absorption by increasing drug clearance from the tissue.

Obviously these and other questions concerning phonophoresis must be answered if progress within the field is to be achieved. It is the wish of the authors that this initial study will encourage the clinical pharmacologists to come together with their pharmacy, physiotherapy and medical physics colleagues to examine this method of administration more fully, in well designed clinical trials. The times involved in the various absorption stages must be known so that an optimal formulation for a particular drug can be achieved. It would be futile, for example, to administer cream and ultrasound simultaneously without a 'pre-soak' period if this resulted in poor transfer characteristics. The ability of the cream, gel or ointment to transmit ultrasonic energy between the head and the skin (coupling efficiency) is also an important formulation consideration. It appears wasteful of time and resources if hospitals and clinics continue to use ultrasound together with expensive steroidal and non-steroidal preparations if indeed the same clinical outcome could be achieved using either treatment alone or if the treatment schedule is poorly designed so that an optimal penetration of the drug by the phonophoretic process is not achieved.

Table 1 Comparison of the times (min, mean ± s.d.) taken for the subjects to partially lose and totally lose the sensation to pain when both arms were treated with the same intensity of ultrasound.

	Ultrasound intensity			
	2 W/cm²		*0 W/cm²*	
	Arm		*Arm*	
	Left	*Right*	*Left*	*Right*
Partial loss of sensation ($n = 10$)	36.50 ± 16.34	33.50 ± 7.47	36.50 ± 9.44	41.50 ± 8.18
Total loss of sensation ($n = 10$)	47.00 ± 16.02	47.50 ± 10.87	48.00 ± 10.59	49.50 ± 9.56

No significant differences were found between results for the same treatments on different treatment days or between the combined data for ultrasound treatment versus no ultrasound treatment ($P > 0.05$; analysis of variance).

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