Report

The Effect of Ultrasound on the in Vitro Penetration of Ibuprofen Through Human Epidermis

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Received December 5, 1988; accepted February 24, 1989

The objective of this study was to develop an in vitro method to investigate the effect of ultrasound on the in vitro absorption of ibuprofen from a propylene glycol/water vehicle through human epidermis. A diffusion cell was modified so ultrasound could be applied to the vehicle and skin. Since ultrasound can increase the temperature underneath the area of application, control representing temperature effects ran concurrently to the ultrasound experiment. The results demonstrate that ultrasound can increase the penetration of ibuprofen through human skin. This increase in diffusion was greater than for controls where an equivalent increase in temperature was utilized. The results also indicate that evaporation of vehicle components may alter the skin/vehicle partition coefficient, decreasing the effects of ultrasound on the penetration of ibuprofen through the skin.

KEY WORDS: ultrasound; phonophoresis; temperature; ibuprofen; human skin; in vitro percutaneous absorption.

INTRODUCTION

Ultrasonic energy is a form of mechanical energy generated by using a piezoelectric crystal which is made to vibrate by passing an alternating current through the material (1). This form of energy has been used in physical medicine for the treatment of a variety of localized inflammatory conditions of nerves, muscle, ligaments, and skin. Both thermal and nonthermal effects are considered to be responsible for the clinical benefit of ultrasound (2).

One reported property of ultrasonic energy is its ability to increase the percutaneous penetration of drug molecules through the skin; this effect is known as phonophoresis (3). Phonophoresis with topical antiinflammatory or local anesthetics is currently utilized by physical therapists as part of their treatment plans. Early experiments in pigs have concluded that ultrasonic energy is capable of driving hydrocortisone into underlying tissues (4–8). Recently, however when phonophoresis was administered with a variety of drugs in double blind crossover clinical trials using human volunteers, a significant increase in the absorption of the drug was reported (fluocinolone acetonide gel, lidocaine/prilocaine cream) (9,10). The effect of ultrasound on the skin penetration of mannitol, inulin, and physostigmine in rats and guinea pigs was studied. These results indicated that ultrasound eliminated the lag time for transdermal penetration of these drugs and significantly increased the amount absorbed (11). In other clinical trials there was not a significant increase in percutaneous absorption (lidocaine cream, benzylamine gel) (12,13).

Clinically the ultrasonic dose can range from 0.001 to 2 W/cm² and is chosen on the basis of what gives the patient a sensation of warmth during treatment which is tolerable (2). The transducer can be applied either in a stationary position or with a moving technique; either method requires a medium to transmit sound waves which is called a coupling medium. In clinical practice the moving technique is more frequently used. The physical therapist moves the transducer in a gentle motion in direct contact with the areas to be treated. The pattern of movement and the dose of ultrasound are determined by the physical therapist depending on the condition, area of treatment, type of patient, and type of machine output used. Intensities up to 2 W/cm² can be achieved with the moving technique but very few individuals can tolerate up to 0.2 W/cm² for more than 2 min using the stationary technique (2).

Another consideration is the length of ultrasound treatment. From the literature cited in this article the most common treatment time is 5 min, up to about 20 min.

Ultrasound treatments may also be administered either on a continuous or on a pulsed mode. As the name implies, with the pulsed mode there is a time interval between ultrasonic outputs. When conducting a study using pulsed output, the pulse period and pulse duration should be recorded. With pulsed output it is possible to use higher intensities of ultrasound with a lesser chance of tissue damage (2).

The main objectives of this study were to develop an in vitro method and to investigate the effect ultrasound has on
the *in vitro* percutaneous penetration of ibuprofen through human epidermis from a propylene glycol/water vehicle. Another objective was to differentiate the effect of ultrasound from the effect of an equivalent temperature increase, on the penetration of ibuprofen from the same vehicle.

**MATERIALS AND METHODS**

**Materials and Equipment**

Materials and equipment were as follows: glass scintillation vials, Kimble Glass Company (Toledo, Ohio); nine-cell Franz diffusion apparatus (1.5-cm diameter), Crown Glass Company (Somerville, N.J.); constant temperature circulator, Exacal EX-100B, Neslab Instrument Inc. (Newington, N.H.); ultrasound generator Dynasound 601 and ultrasound transducer (15-mm diameter), lead zirconate titanate, Dynawave Corporation (Geneva, Ill.); digital thermocouple thermometer, Digi-Sense, and type K thermocouples (0.029-in. diameter) with miniconnector Kapton-insulated, Cole Parmer (Chicago); Fisher pump Model A-1, Fisher Scientific Company (Itasca, Ill.); constant-temperature circulator, Thermomix II, B. Braun (Melsungen, West Germany); and liquid scintillation counter, Packard Tri-Carb 4640, Packard Instrument Company (Downers Grove, Ill.).

**Chemicals**

Chemicals were as follows: ibuprofen USP (98% purity), Upjohn Company (Kalamazoo, Mich.); \(^{14}C\)-ibuprofen (20 µCi/mg, 98% purity), The Boots Company (England); propylene glycol USP, American Drug Industries (Chicago); sodium phosphate monobasic and sodium phosphate dibasic anhydrous, Mallinckrodt Chemical Works (St. Louis, Mo.); sodium chloride, Aldrich Chemical Company Inc. (Milwaukee, Wis.); and scintillation cocktail, Ready-Solv MP, Beckman Instruments Inc. (Fullerton, Calif.).

**Diffusion Cell**

The diffusion-cell apparatus used in these experiments is shown in Fig. 1. Instead of the glass caps provided by the

Fig. 1. Illustration of the diffusion chamber, similar to the one described by Franz (14), modified for the application of ultrasound.