Phonophoresis Versus Topical Application of Ketoprofen: Comparison Between Tissue and Plasma Levels

Background and Purpose. Over the last few decades, application of ultrasound has been attempted to enhance transdermal transport of several drugs, a method referred to as “phonophoresis.” The purposes of this study were to examine the influence of ultrasound on the transdermal delivery of ketoprofen in humans and to compare the concentrations found after continuous and pulsed application. Subjects and Methods. Twenty-six patients with knee disorders requiring arthroscopy were randomly assigned to 1 of 3 groups. Just before surgery, phonophoresis of a ketoprofen gel (Fastum gel) was given to group A using continuous ultrasound (1 MHz, 1.5 W/cm², for 5 minutes). Group B received the same treatment but with pulsed ultrasound (100 Hz, 20% duty cycle). Group C received 5 minutes of sham ultrasound with the ketoprofen gel. The ultrasound head was moved over a 10-cm² area using small, continuous, circular movements. Biopsies of adipose tissue and synovial tissue were taken during surgery to evaluate the local penetration of the drug. Blood samples also were collected to determine whether ketoprofen entered the systemic circulation. Results. The concentration of ketoprofen in plasma was negligible in all 3 groups. The concentration of ketoprofen in synovial tissue differed from that in fat tissue. A difference in concentration of ketoprofen in synovial tissue was found between group C and groups A and B. The concentration of ketoprofen in fat tissue and synovial tissue was consistently higher in group B than in group A. Discussion and Conclusion. This study confirms that phonophoresis of ketoprofen allows the attainment of higher local concentrations, whereas systemic exposure is lower. The results indicate that, in contrast to sham phonophoresis, ultrasound can increase the transdermal delivery of ketoprofen. [Cagnie B, Vinck E, Rimbaut S, Vanderstraeten G. Phonophoresis versus topical application of ketoprofen: comparison between tissue and plasma levels. Phys Ther. 2003;83:701–712.]

Key Words: Ketoprofen, Phonophoresis, Plasma, Synovial tissue, Transdermal drug delivery.

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Since the pioneering work of Fellinger and Schmid, who first added ultrasound to the management of digital polyarthritis with hydrocortisone, phonophoresis has been used to enhance transdermal drug delivery in sports medicine and orthopedic rehabilitation. Phonophoresis is believed to accelerate functional recovery by decreasing pain and promoting healing.

Phonophoresis has been used to administer various drugs, including local anesthetics and antibiotics. This technique also has been used successfully to deliver anti-inflammatory medication to inflamed subcutaneous tissues. The possibility of delivering nonsteroidal anti-inflammatory drugs (NSAIDs) through the skin for either local or systemic effects is being investigated increasingly. Conflicting reports have been published regarding the depth and quantity of these drugs delivered to subcutaneous structures with the assistance of phonophoresis. However, many of these studies, whether conducted in a clinical setting or using animal models, have been difficult to apply to practice. Intensities and durations that are not commonly used in a clinical setting have been used. Another important factor is that some of the products used in these studies do not transmit ultrasound energy.

Fastum gel* (ketoprofen 2.5%, ethyl alcohol, carbomer, diethanolamine, essence of lavender, methyl para-hydroxybenzoate, and propyl para-hydroxybenzoate) is a medication used to decrease inflammation and pain and has been shown to be of benefit in clinical practice when delivered transcutaneously. It contains a nonsteroidal anti-inflammatory agent, ketoprofen. Ketoprofen (2-[3-benzoylphenyl] propionic acid) is used for a variety of rheumatic and musculoskeletal conditions. Several investigations have demonstrated beneficial outcomes when ketoprofen was delivered transcutaneously, such as a faster improvement in pain, stiffness, and edema. Whether the benefits observed with passive transcutaneous permeation of ketoprofen, and potentially with iontophoretic permeation of ketoprofen, are due to local tissue effects or an effect following systemic distribution, however, remains open to discussion.

Therefore, the purpose of our study was to examine the influence of ultrasound on the transdermal delivery of ketoprofen (Fastum gel) in humans using clinically relevant settings and media. The primary objective of our study was to assess local absorption and distribution of ketoprofen after phonophoresis in relation to plasma level. The secondary objective was to compare the concentrations found after continuous, pulsed, and sham ultrasound application.

Materials and Methods

Subjects

Twenty-nine patients (20 men and 9 women) with knee disorders requiring arthroscopy participated in the study. The mean age of the subjects was 36 years (SD=14.7, range=21–68). They had to complete a questionnaire regarding demographic data and contraindications to the use of Fastum gel (as specified by the manufacturer) and ultrasound. A list of these contraindications is given in Table 1. Patients having any contraindication were excluded from the study. Participants who had used Fastum gel within 30 days prior to the test also were excluded. After the protocol for the investigation had been explained, the subjects signed an informed consent form before undergoing any test.

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Ms Cagnie, Dr Rimbaut, and Dr Vanderstraeten provided concept/research design. Ms Cagnie provided writing. Ms Cagnie and Ms Vinck provided data collection and analysis. Dr Rimbaut and Dr Vanderstraeten provided project management, subjects, facilities/equipment, and institutional liaisons. Ms Vinck provided clerical support. Ms Vinck, Dr Rimbaut, and Dr Vanderstraeten provided consultation.

The research protocol for this study was approved by the Ethics Committee of Ghent University Hospital.

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Table 1.
Contraindications to the Use of Ultrasound or Fastum Gel

<table>
<thead>
<tr>
<th>Contraindications to the Use of Ultrasound*</th>
<th>Contraindications to the Use of Fastum Gel (as Specified by Manufacturer)</th>
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<tbody>
<tr>
<td>Cancer</td>
<td>Open wounds</td>
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<td>Diabetes</td>
<td>Infected wounds</td>
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<td>Tuberculosis</td>
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<td>Deep vein thrombosis</td>
<td>Stomach ulcer</td>
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<td>Abscesses</td>
<td>Ketoprofen allergy</td>
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<tr>
<td>Prosthesis/implanted medical devices</td>
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<td>Sensory disturbances</td>
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</table>

Procedure

Before starting phonophoresis, the treatment areas were marked using a circular stencil (10 cm²). The treatment sites corresponded with the location of the biopsies. Previously, the biopsy sites had been thoroughly discussed with the 3 orthopedic surgeons from the same department who performed the arthroscopy. One 10-cm² template was placed laterocranially from the patella. From this area, synovial tissue was taken during the biopsy. Mediocaudally from the patella at the joint line of the knee just medial to the patellar tendon, the other template was fixed in order to biopsy the adipose tissue.

The subjects were assigned to 1 of 3 groups using a blocked design, in which the 29 volunteers for the study were divided into blocks of 3 each. Subjects in groups A (n=10) and B (n=10) received phonophoresis with Fastum gel, using a 1-MHz Sonopuls 590† with a 5-cm² sound head at an intensity of 1.5 W/cm². Group A was given continuous ultrasound, and group B was given pulsed ultrasound (100 Hz, 20% duty cycle). The subjects in group C (n=9) received sham phonophoresis with Fastum gel (topical application of Fastum gel with no ultrasound). Each participant received phonophoresis at both sites while in a supine position with the knee extended. A 5-cm-long strip of Fastum gel was applied locally. For 5 minutes, the ultrasound head was moved over the cream using small, continuous, circular movements. After the ultrasound treatment, the cream was removed from the knee.

To evaluate the local penetration of ketoprofen, 2 tissue biopsies (adipose tissue and synovial tissue) were taken during the knee arthroscopy at the described biopsy sites. The time interval between application of Fastum gel and biopsy ranged between 47 and 77 minutes, with a mean of 58 minutes. The samples were frozen at –20°C and stored until analyzed by a chromatography procedure to determine the ketoprofen concentration. To determine the systemic effect of phonophoresis, a blood sample was collected 120 minutes after topical application of Fastum gel. The data of 3 subjects could not be used due to analysis problems in the laboratory. One sample could not be analyzed due to insufficient tissue, and 2 samples could not be used due to extraction problems.

Data Analysis

Statistical analysis was performed with the SPSS 10.05 program. The Kolmogorov-Smirnov test was applied to determine whether the values followed a normal distribution pattern, with the level of significance set at P <.05. Because the data were not normally distributed, we present the outcome measurements in terms of median and interquartile range. We used a Kruskal-Wallis analysis of variance for comparisons among the 3 groups, followed by the Mann-Whitney U test for subsequent pair-wise comparisons. Two related sample analyses were done to examine the difference in concentration between fat tissue and synovial tissue in the 3 groups.

Results

Plasma Levels

The detection threshold for ketoprofen in plasma is 0.002 µg/mL. No plasma ketoprofen was detected in either the sham ultrasound group or the continuous ultrasound group. In the pulsed ultrasound group, however, the plasma concentration was 0.004 µg/mL (interquartile range=0.002).

Tissue Levels

Only minimal levels of ketoprofen were found in fat tissue regardless of method of delivery (sham, pulsed, or continuous ultrasound) (Tab. 2). Conversely, both pulsed and continuous ultrasound produced higher concentrations of ketoprofen in synovial tissue than in

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† Enraf-Nonius BV, AV Delft, the Netherlands.
‡ SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.

[^1]: Enraf-Nonius BV, AV Delft, the Netherlands.
[^2]: SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.
Although the ketoprofen concentration in synovial tissue was not different between the pulsed and continuous ultrasound groups, the concentration was consistently higher in the pulsed ultrasound group (Figure).

**Discussion**

Topically applied drugs can induce local and systemic effects that can be distinguished by examining local tissue drug concentrations (under the site of application) and blood or urine level. For years it was thought that all topically applied drugs entered the capillary network, became systemic, and then returned to the local area through the bloodstream. Research has shown that local delivery is separate from systemic delivery. Although these studies were carried out using topically applied drugs without ultrasound, we believe the findings are of value for understanding the distribution patterns for topically applied drugs enhanced with ultrasound. According to systemic effects, diffusion through the epidermis to the dermis is a possibility, and drugs with local targets diffuse into the area immediately below the administration site, such as subcutaneous tissue, muscle, synovium, ligaments, tendons, and joints.

Our study confirms that topical applications of ketoprofen with ultrasound attain high local concentrations, even though plasma levels and systemic exposure are low. We found the concentration of ketoprofen in plasma to be negligible. This finding is consistent with the results of previous studies. Conner-Kerr et al attributed the low concentration of dexamethasone in blood plasma to the rate-limiting function of the stratum corneum, because retention of medications in the stratum corneum has been thought to delay systemic drug delivery of corticosteroids for up to 72 hours post-administration. Ballerini et al analyzed blood samples drawn 2, 6, and 12 hours after the administration of ketoprofen and found that ketoprofen concentration in plasma reached a peak at the 6th hour after topical application and remained constant until the 12th hour. Because we investigated only a relatively short time course (120 minutes), the peak times for ketoprofen penetration into the venous blood may be outside the time limits we used. Considering a possible latent release of ketoprofen into the plasma, we urge caution in interpreting our results.

The ketoprofen concentration in synovial tissue differed from the concentration in fat tissue in the pulsed ultrasound group as well as in the continuous ultrasound group. Synovial tissue, in contrast to adipose tissue, is highly vascularized and therefore receives ketoprofen both directly and through the general circulation. In our study, however, this could not be determined because the concentration of ketoprofen in plasma is negligible. Ketoprofen is highly protein bound. The fact that ketoprofen is more bound to proteins in synovial tissue than in fat could account for this finding.

No difference was found between the continuous and pulsed ultrasound groups regarding plasma, fat tissue, and synovial tissue. However, the ketoprofen concentration was consistently higher in the pulsed ultrasound group than in the continuous ultrasound group (Tab. 2). The mechanisms by which ultrasound acts as an enhancer of drug delivery are poorly understood. Thermal effects as well as nonthermal properties of ultrasound have been considered, and both can enhance the diffusion of topically applied drugs. Heating from ultrasound increases the kinetic energy of the molecules in the drug and in the cell membrane, dilates points of entry such as the hair follicles and the sweat glands, and increases the circulation to the area sonicated. These physiological changes can enhance the opportunity for drug molecules to diffuse through the stratum corneum and be collected by the capillary network in the dermis.

The nonthermal mechanical characteristics of ultrasound also can enhance drug diffusion by oscillating the cells at high speed, changing the resting potential of the cell membrane and potentially disrupting the cell membrane of some of the cells in the area. There may be some pushing and pulling of the cells with the propagation of the sound wave through heterogeneous tissues, but it is unlikely that radiation or streaming forces are sufficiently strong or consistent enough to push drug molecules into the tissue. The effect of ultrasound on a biological system also may be associated with cavitation, that is, the formation of small gaseous bubbles. Cavitation may cause mechanical stress, temperature elevation,
or enhanced chemical reactivity, thus affecting drug transport.5,18

Pulsed-wave ultrasound possesses several potential benefits over continuous-wave ultrasound. The latter has a tissue-heating effect that pulsed-wave ultrasound does not have.15 This heating effect may have a deleterious effect on phonophoresis. Tissue heating can become very painful, necessitating continuous motion of the ultrasound head, which diffuses the ultrasonic energy over a larger area. With pulsed-wave ultrasound, patients can tolerate a virtually stationary sound head, ensuring a more concentrated ultrasound dosage at the treatment site.10

Benson et al19 found that pulsed-output ultrasound provided the most effective conditions in the technique of phonophoresis of lignocaine and prilocaine from EMLA cream.8 Among all the possible mechanisms of phonophoresis, cavitation may play the dominant role.5,20,21 Nevertheless, conflicting results have been reported concerning its occurrence during pulsed ultrasound versus continuous ultrasound. Nussbaum15 reported that the scale of cavitation depends on the ultrasound characteristics; bubble growth is limited by low-intensity, high-frequency, and pulsed ultrasound. Mitragotri et al20 confirmed this statement. They found that the cavitation threshold increases as the mode of ultrasound application changes from continuous to pulsed. Sun and Liu,22 however, suggested that cavitation is more likely to occur when pulsed ultrasound is used, provided that the ultrasound intensity during the pulses exceeds the threshold of cavitation occurrence and the duration of the pulses is long enough for the cavitation to develop.

Although ultrasound has been used for phonophoresis with a variety of techniques and settings, the most commonly used ultrasound method, corresponds to therapeutic ultrasound (frequency in the range of 1–3 MHz and intensity in the range of 1–2 W/cm2).21 In our study, a frequency of 1 MHz was used. Mitragotri et al20 reported that the phonophoretic enhancement in the therapeutic frequency range varies inversely with ultrasound frequency. They found that 1-MHz ultrasound enhances transdermal transport of estradiol across human cadaver skin in vitro by 1.5-fold, but that 3-MHz ultrasound at the same intensity induces an enhancement of only 1.5-fold. They further hypothesized that the observed inverse dependence of sonophoretic enhancement on ultrasound frequency occurs because cavitational effects, which are primarily responsible for phonophoresis, vary inversely with ultrasound frequency.20

The size of the treated area may play an important role in the outcome of ultrasound treatments. Some experts15 contend that the treatment area should not be larger than twice the effective radiating area (ERA) of the ultrasound head. Data to support this approach, however, are not yet available. Because the ERA of the ultrasound head we used was 5 cm2, we treated a surface of 10 cm2. Sites with a surface of much more than twice the ERA have frequently been treated, but exact data about the treated area are usually missing in written reports.10,23 The treated area in relation to the ultrasound head used may influence the results of any study. We believe it is important to keep this in mind when interpreting the results of our study.

Recently, authors4,10,15,24 have argued that many of the commonly used cream-based preparations used for ultrasound do not allow for adequate transmission of the acoustic wave. Gel-based preparations appear to us to be superior with respect to transmissivity of ultrasound. The rate of diffusion of drugs depends on a number of physicochemical and pharmacologic factors, among which lipid solubility and protein binding play a determining role.6 Beetge et al13 concluded that the most reliable variable for predicting transdermal absorption is the log P value. The log P value is a measure of how well a substance partitions between a lipid (oil) and water. Drugs with a balanced lipophilic/hydrophilic character and drugs with a log P value of <2 are considered to be potential candidates for transdermal delivery.21 Ketoprofen, with a log P value of 0.97, tends to be closest to the optimum value indicated for NSAIDs13; therefore, we conclude that Fastum gel allows an adequate transmission.

Our results should be viewed with consideration the limitations of our study. The biopsies were taken by different orthopedic surgeons. Nevertheless, the biopsy sites had been thoroughly discussed in advance. In addition, the time from treatment to biopsy varied a lot (47–77 minutes) due to unexpected changes in the schedule of the arthroscopies. Both factors may explain the high inter-individual variability in ketoprofen concentration and may have influenced our results.

Changes in tissue levels of drugs used in phonophoresis do not necessarily indicate that a particular drug concentration will have a therapeutic effect. Our data indicate, however, that phonophoresis of ketoprofen appears to be superior to topical application. Synovial tissue is the major site of inflammation. Therefore, increasing the concentration of ketoprofen in synovial tissue, rather than in fat tissue, through phonophoresis seems to be of potential clinical importance.

8 AstraZeneca LP, Wilmington, DE 19850-5437.
Conclusion

Our results confirm that phonophoresis of topically applied ketoprofen (Fastum gel) can result in high local tissue concentrations, even though plasma levels and systemic exposure are low. Although a statistical difference was not found, it would appear from our results that pulsed ultrasound provided the most effective conditions for delivering ketoprofen to certain subcutaneous tissues.

References