J. Pharm. Pharmacol. 1991, 43: 115–116
Communicated August 8, 1990

COMMUNICATIONS

External control of drug release and penetration: enhancement of the transdermal absorption of indomethacin by ultrasound irradiation

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Abstract—The effect of ultrasound (1 MHz) on transdermal absorption of indomethacin from an ointment has been studied in rats. Ultrasound energy was supplied for 10 min at a range of intensities (0·25, 0·5 and 0·75 W cm^{-2}), energy levels commonly used for therapeutic purposes. The pronounced effect of ultrasound on transdermal absorption of indomethacin was observed for all three intensities studied. The mean AUC value (33·22 $\mu g\ h\ mL^{-1}$) after irradiation at 0·75 W cm^{-2} was 3·4 times the control value (9·70 $\mu g\ h\ mL^{-1}$).

Recently, much research has focused on the discovery of methods for improving the transdermal absorption of drugs. Many reports have described efforts to change skin permeability using chemical enhancers, because the stratum corneum is recognized to be the barrier for transdermal drug delivery. In addition to the use of chemical enhancers, it is possible to increase the transdermal absorption by physical methods (Rolf 1988) such as iontophoresis(electric field) or phonophoresis (ultrasound). Ultrasound has previously been explored for treating localized skin conditions, and for delivering drugs to inflamed joints (Skauen & Zentner 1984; Tyle & Agrawala 1989). However, there are few investigations of the effect of ultrasound on transdermal delivery systems (Brucks et al 1989; Levy et al 1989) and no pharmacokinetic data are available quantifying the efficacy of ultrasound.

We have previously shown (Miyazaki et al 1985, 1988) the feasibility of pulsed drug delivery from implantable devices controlled by external ultrasound. In this paper, we report the effect of ultrasound on the transdermal absorption of a model drug, indomethacin, from an ointment in rats. Transdermal delivery of indomethacin is desirable in order to reduce the frequency of dosing and the gastric irritation associated with oral administration.

Materials and methods

Male Wistar rats, 250-350 g, were used. The day before the experiment the hair of the abdominal parts was carefully removed with an electric clipper and a razor. On each study day the rats were anaesthetized by intraperitoneal injection of sodium pentobarbitone and indomethacin ointment (1 g, 1% w/w; Sumitomo Pharmaceutical Co., Osaka) was applied to a 3 cm diameter circular site on the abdominal skin. The area around the application site was covered with Saran Wrap film (Asahi-Dow, Tokyo) followed by the ultrasonic gel. Ultrasonication was produced by a commercially available 1 MHz ultrasound system (Model AU-1, Asahi Denshi Kogyo Co., Osaka) approved for human use. The treated area was irradiated for 10 min at therapeutic intensities (0·25, 0·5 and 0·75 W cm^{-2}) being employed as continuous irradiation. Skin temperature was recorded after ultrasound application by placing a temperature coupler (TAKARA SZL-64) on the surface of the treated skin.

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Control animals were treated by the procedure described above, except that the probe was not applied.

For evaluating the effect of ultrasound on the transdermal delivery of indomethacin, blood samples were taken by cardiac puncture at hourly intervals after drug administration, and assayed for indomethacin using HPLC (Miyazaki et al 1986).

Results and discussion

Fig. 1 shows the mean plasma level profiles of indomethacin and Table 1 summarizes the area under the plasma concentration curve (AUC) up to 4 h post-administration, calculated by moment analysis (Yamaoka et al 1981).

There was a distinct difference in plasma concentration responses with and without ultrasound treatment. The pronounced effect of ultrasound on transdermal absorption was observed for all three intensities studied; the 0·75 W cm^{-2} appeared to be the most effective intensity in improving the transdermal absorption of indomethacin. As shown in Table 1, the mean AUC value (33·22 $\mu g\ h\ mL^{-1}$) after irradiation at this intensity was 3·4 times the control value (9·70 $\mu g\ h\ mL^{-1}$).

In the field of cancer chemotherapy, ultrasound has been used to produce local hyperthermia (42–43°C, Hahn et al 1975). Care must be taken to avoid excessive exposure which might sometimes cause skin burning. The temperature of the skin is one indicator of overexposure. Fig. 2 shows the change of skin surface temperature while exposed to ultrasound for 10 min. Application of ultrasound irradiation increased the temperature

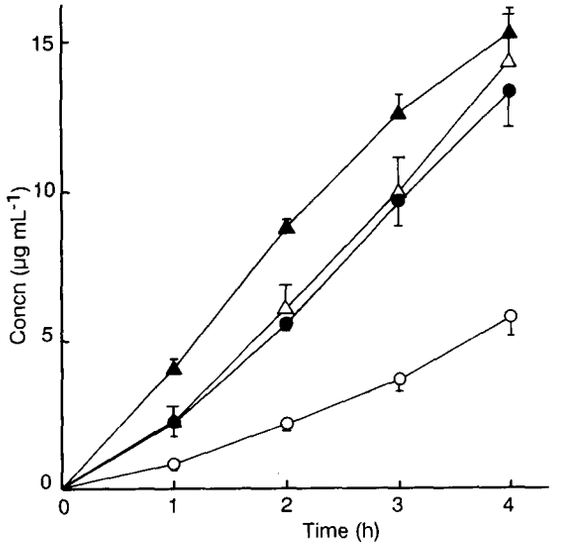

FIG. 1. Effect of an ultrasound irradiation on the plasma levels of indomethacin from an ointment in rats. Each rat was irradiated with 1 MHz ultrasound for 10 min at the intensity levels of 0 (-○-), 0·25 (-●-), 0·5 (-△-), and 0·75 (-▲-) W cm^{-2}. Each value is the mean ± s.e.m. of 4–9 experiments.

Table 1. Comparison of AUC values with and without ultrasound.

Intensity (W cm^{-2})	n	AUC[a] (μg h mL^{-1})
0	9	9·70 ± 1·07
0·25	5	24·20 ± 1·58*
0·5	6	25·85 ± 2·77*
0·75	6	33·22 ± 1·49*

[a] Up to 4 h post-administration. Each value is the mean ± s.e.m.
* Significantly different from the control ($P < 0·001$, Student's t-test).

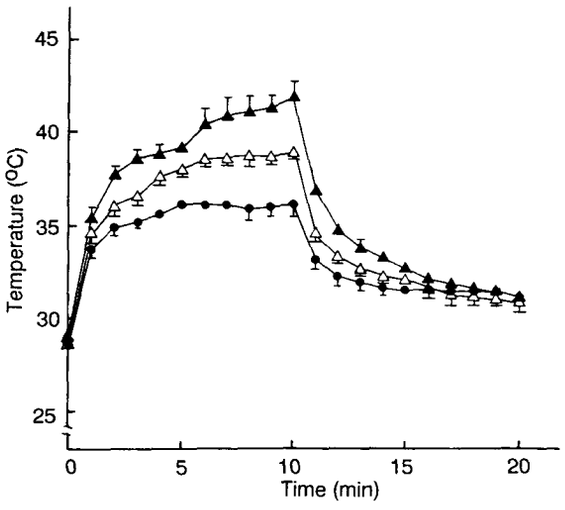

FIG. 2. Effect of an ultrasound irradiation on the surface skin temperature of rats. Each rat was irradiated with 1 MHz ultrasound for 10 min at the intensity levels of 0·25 (-●-), 0·5 (-△-), and 0·75 (-▲-) W cm^{-2}. Each value is the mean ± s.e.m. of 3 experiments.

of the skin proportionally to the ultrasound intensity; the temperature decreased rapidly when the ultrasound irradiation was discontinued. High intensity (0·75 W cm^{-2}) of the ultrasound is feasible because surface skin temperatures after the ultrasound application did not exceed the maximum acceptable temperature of 42–43°C.

The mechanism by which the ultrasound irradiation increases absorption is not well understood. The rate-limiting step in the percutanous absorption of drugs is passage across the stratum corneum. We suggest that a mechanism for enhanced transdermal absorption is via conformational changes of the lipid and protein structures in the stratum corneum, facilitating drug permeation (Nanavaty et al 1989). Some localized heat is also produced by ultrasonic irradiation. This may also have played a role in enhanced drug absorption noted in the present study (Sasaki et al 1987).

In general, the frequency range of the ultrasound used for diagnostic and therapeutic purposes is between 0·5 and 5 MHz and the range of intensity is between 0·5 and 5 W cm^{-2}, with application for between 1 and 10 min.

The present study has demonstrated that therapeutic ultrasound enhanced the transdermal absorption of indomethacin from an ointment to a statistically significant extent. Thus when used at a proper frequency, intensity, and time of application, ultrasound could be a safe technique for enhancing the passage of various drug molecules through skin.

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