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Use of Ultrasound to Enhance the Local Anesthetic Effect of Topically Applied Aqueous Lidocaine

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Background: **Currently available local anesthetics, such as EMLA (eutectic mixture of local anesthetics), have poor skin penetration when administrated topically. As 60 min is needed for EMLA to be fully effective, attempts to accelerate transdermal delivery of a local anesthetic, such as lidocaine, by use of "electrical" and "physical" energy has previously been reported. The current experiment was undertaken to determine whether ultrasonic energy can increase the local anesthetic effect of lidocaine in the skin of mice.**

Methods: **Hairless mice were immersed in a beaker containing 2% aqueous lidocaine. Ultrasound (48kHz, 0.17 W/cm^2) was applied to the beaker by an ultrasound-generating water tank for 5 min. To examine anesthetic effects, the skin of the legs was stimulated using various voltages ranging from 0 to 50 V before and after treatment. The number of times the hairless mouse reacted out of six stimulations was counted.**

Results: **Stimulation by 15 V at 30 min after lidocaine and ultrasound exposure resulted in positive reaction of 1.3 ± 1.6 (mean ± SD) compared with 5.2 ± 2.0 before treatment. Significant anesthetic effects continued for 2 h. Immersion to lidocaine alone without ultrasound showed no evidence of analgesia after treatment. Ultrasound alone to the legs also caused no anesthetic effects.**

Conclusions: **It was concluded that ultrasound exposure to the legs of hairless mice along with topical 2% lidocaine solution rapidly induced an anesthetic effect. (Key words: Anesthetics, local: lidocaine. Anesthetic techniques: transdermal; ultrasound.)**

EVEN with the use of fine needles, making a skin wheal with a local anesthetic is painful. A eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA), which can penetrate the intact skin, is currently available. However, 60 min is needed for EMLA to be fully effective.[1] Rapid transdermal delivery of a local anesthetic, such as lidocaine, by the use of "electrical" or "physical" energy has previously been reported. Application of electric fields delivers ionic drugs through the skin in the case of iontophoresis.[2] Although enhanced transdermal delivery of lidocaine by means of iontophoresis in pig skin has been proven by measuring increased serum concentration and radiolabeled lidocaine deposits within the skin,[3–5] anesthetic effects induced by the drug have not been investigated, probably because of the minute amount of lidocaine that penetrates the skin.

Ultrasound applied to the skin along with lidocaine also increases the concentration of the drug in rabbit skin tissue compared with controls.[6] However, McElnay *et al.* could not obtain significant differences in anesthetic effects between ultrasound-treated and untreated skin in combination with lidocaine applied as a cream in human volunteers.[7] It was concluded that ultrasound had no enhancing effect on transdermal penetration of lidocaine or, alternatively, that the ultrasound method may have been inappropriate. Recently, a new method of applying an aqueous drug instead of cream or gel in combination with ultrasound was introduced.[8,9] Transdermal delivery of insulin was clearly enhanced in these experiments. In the current study, anesthetic effects induced by transdermal delivery of aqueous or gel lidocaine in combination with ultrasound exposure was investigated in hairless mice.

Materials and Methods

All studies were approved by the institutional animal care committee. Male hairless mice (8–12 weeks, 25–35 g) were obtained from a local supplier. The mice were isolated for at least a week in separate plastic cages before the experiment to prevent skin damage. To standardize ultrasound-exposing conditions, the body and legs of the mice were washed with warm tap

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water and wiped dry before treatment. The mice were used only once. Two percent aqueous lidocaine solution (Xylocaine, *p*H 5.0–7.0) and lidocaine gel (Xylocaine Jelly, *p*H 6.2–6.6) were obtained from Fujisawa Pharmaceutical Co. (Osaka, Japan). The *p*H of saline used was 5.0–7.0. An ultrasound-generating water tank (Branson 1200, Branson Ultrasonics, Danbury, CN) was filled with 2.0 L of degassed water. A silver electrode 15 cm in length (25 G) coated with black rubber except at the tip was specially made. The tip of the electrode was in the shape of a small ball (2 mm in diameter) to avoid scratching or irritating the skin. An electric stimulator (Model SEN-1101, Nihon Kohden, Tokyo, Japan) was used for all stimulations.

Electric Stimulation

Anesthetic effect was determined by electrical stimulation of the extensor portion of the leg using the electrode previously described. The voltage of stimulation by the monopolar electrode was variable, from 0 to 50 V. Pulse frequency was fixed at 100 Hz with a duration of 1 msec. The tail was loosely attached to a wire for the indifferent ground polarity. Thirty minutes before the experiment was carried out, the mouse was stimulated five times with the maximum 50 V to each leg. This resulted in a conditioned response to mere contact of the electrode at 0 V.

Experiment Protocol

Fifty milliliters of 2% lidocaine solution was added to a 500 ml beaker (Pyrex, Iwata Glass, Tokyo, Japan). The beaker was immersed and positioned in the ultrasound-generating water tank so that the liquid level in the beaker and the degassed water in the tank were the same. A mouse was placed inside the beaker. The mouse was free to move within the beaker. The depth of the aqueous lidocaine solution was just enough to soak the hind legs of the mouse when standing against the glass wall of the beaker during the treatment. Ultrasound was then activated for 5 min. The frequency of the ultrasound was 48 KHz, and the intensity was 0.17 W/cm^2. Temperature increase of the solution in the beaker was less than 1° C. Immediately after exposure to ultrasound, the legs of the mice were gently rinsed with water and dried. The mouse was transferred to a transparent plastic cage for behavior observations.

Immediately before and after treatment, stimulation with the electrode was carried out three times for each leg by a single observer who had no knowledge of the treatment method or the electric voltage being used. Contact duration of the electrode to the leg was no more than 2 s. Response to the stimulation was considered positive when the leg stimulated was completely lifted off the floor of the cage immediately after contact with the electrode. The voltage was varied randomly from 0 to 50 V in 5 V increments by another person. One round of stimulation required approximately 2 min. This procedure was repeated at 0, 15, 30, 45, 60, 75, 90, 120, and 180 min after treatment. The number of positive responses and voltage of the stimulation were recorded at each testing time.

To compare the effects of ultrasound in aqueous and gel lidocaine, the same ultrasound exposure and stimulation test procedures were carried out using 2% lidocaine gel (30 g) instead of lidocaine solution in the beaker.

Control Experiments

For the control experiments, the above procedure was carried out without activating the ultrasound generator to evaluate the effects of lidocaine alone to the skin. Furthermore, the effects of ultrasound alone to the legs were determined by exposure of ultrasound to the hairless mouse in 50 ml of saline instead of the lidocaine. Electric stimulation and behavior scoring were identical to the main experiment. All legs of the mice were later inspected for possible burns or scratches caused by the electrode.

Statistic Methods

Values were expressed as mean ± SD of four to six different animals for each experiment. Groups were compared with baseline using a one-way analysis of variance (ANOVA) for repeated measures. Difference between groups was assessed by two-way ANOVA for repeated measures. All statistics were computed using the Statview II statistic package (Abacus Concepts Inc., Berkeley, CA) on the Apple Macintosh II computer (Cupertino, CA). A P value < 0.05 was considered to be statistically significant.

Results

Local Anesthesia: Control Data

Table 1 shows the mean score at various voltages and time periods of mice immersed in 2% lidocaine alone. Note that the score at 0 V before treatment is greater than 5. The mice responded to touch sensation of the

Table 1. Mean Score of Mice Treated with Lidocaine Alone

Voltage (V)	Minutes after Exposure to Aqueous Lidocaine									
	−5	0	15	30	45	60	75	90	120	180
0	5.0 ± 1.7	5.0 ± 1.0	6.0 ± 0	5.0 ± 1.0	5.6 ± 0.6	4.6 ± 1.5	4.6 ± 1.5	5.3 ± 0.5	5.6 ± 0.6	3.7 ± 2.0
5	4.3 ± 0.6	4.0 ± 1	4.7 ± 1.7	4.0 ± 1.7	5.3 ± 0.6	5.3 ± 1.2	5.0 ± 1.0	5.3 ± 0.6	4.7 ± 0.6	3.7 ± 2.5
10	5.0 ± 1.7	4.7 ± 1.2	5.0 ± 1.7	4.7 ± 2.3	5.7 ± 0.6	4.3 ± 2.0	5.3 ± 0.6	5.3 ± 1.2	6.0 ± 0	4.7 ± 1.5
15	4.7 ± 1.2	6.0 ± 0	5.3 ± 1.2	5.7 ± 0.6	6.0 ± 0	5.3 ± 0.6	5.7 ± 0.6	4.3 ± 1.5	6.0 ± 0	5.0 ± 1
20	6.0 ± 0	6.0 ± 0	5.0 ± 1.7	5.3 ± 1.2	6.0 ± 0	6.0 ± 0	5.0 ± 1.0	5.3 ± 0.6	6.0 ± 0	6.0 ± 0
25	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	5.6 ± 0.6	6.0 ± 0	6.0 ± 0	6.0 ± 0
30	5.3 ± 1.2	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
35	5.6 ± 0.6	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
40	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
45	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
50	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0

Values are mean ± SD. Values after treatment did not differ ($P < 0.05$) from those values obtained before treatment.

electrodes because of learning from the multiple preexperiment stimulation by high-voltage electricity. Significant differences ($P < 0.05$) of touch sensation were not observed between pre- and posttreatment scores. Five- to fifty-volt stimulation also showed no significant differences from initial scores. Stimulation over 35 V revealed no analgesia at all time points.

Results of mice exposed to ultrasound alone showed similar findings (table 2). Scores at all time points and voltages were greater than 4. Response to 0 V stimulation also did not differ from pretreatment scores at all time points. No edema or erythema of the legs was observed after the experiments.

Local Anesthesia: Drug Effects

Response of the mice to stimulation decreased immediately after exposure to ultrasound with lidocaine (fig. 1, table 3). Response scores to touch sensation (0 V) and stimulation by low-level voltage (5–35 V) significantly decreased compared with initial data before treatment ($P < 0.05$). Touch sensation diminished for at least 2 h after ultrasound exposure with lidocaine treatment. The peak of anesthetic effects to touch (0 V) was at 30 min. The response to stimulation greater than 5 V later recovered to baseline at 180 min after ultrasound exposure. There was no reduction in response to stimulation by 40–50 V throughout the experiment.

Table 4 shows the scores of mice treated with 2% lidocaine gel base and ultrasound. Statistically significant differences between groups ($P < 0.05$) was obtained compared with aqueous lidocaine with stimulations under 35 V. Minimum score after ultrasound exposure was 3.5 ± 2.3 points at 15 min (0 V). Statis-

Table 2. Mean Score of Mice Treated with Ultrasound Alone

Voltage (V)	Minutes after Ultrasound Exposure									
	−5	0	15	30	45	60	75	90	120	180
0	5.0 ± 1.7	5.0 ± 1.0	5.6 ± 0.6	4.3 ± 2.1	5.0 ± 1.7	5.3 ± 1.2	6.0 ± 0	5.6 ± 0.6	5.6 ± 0.6	4.3 ± 2.0
5	5.3 ± 0.6	6.0 ± 0	6.0 ± 0	5.3 ± 0.6	4.6 ± 0.6	5.0 ± 1.7	5.0 ± 1.0	5.6 ± 0.6	5.6 ± 0.6	5.3 ± 1.2
10	4.0 ± 2.6	4.7 ± 1.5	5.6 ± 0.6	5.3 ± 1.2	4.3 ± 2.9	5.6 ± 0.6	4.6 ± 1.2	6.0 ± 0	5.0 ± 1.7	6.0 ± 0
15	5.3 ± 0.9	6.0 ± 0	5.6 ± 0.5	5.3 ± 0.5	5.0 ± 1.4	5.3 ± 0.5	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
20	5.6 ± 0.5	6.0 ± 0	6.0 ± 0	5.6 ± 0.5	5.3 ± 0.9	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
25	5.0 ± 0.8	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
30	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
35	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
40	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
45	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
50	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0

Values are mean ± SD. Values after treatment did not differ ($P < 0.05$) from those values obtained before treatment.

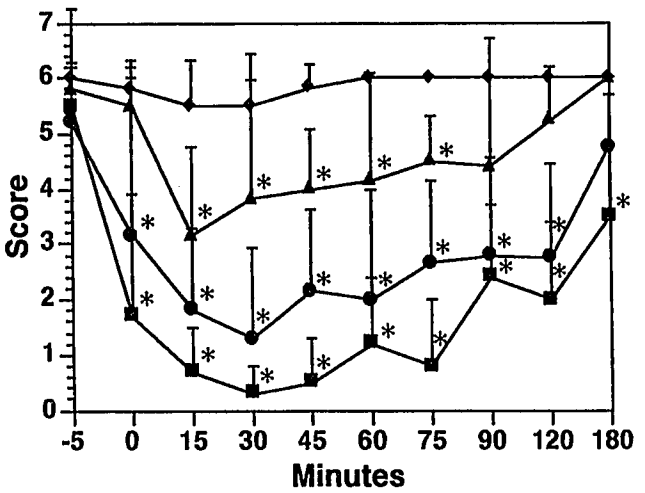

Fig. 1. Change in score after exposure to aqueous lidocaine and ultrasound. Symbols indicate stimulation voltages as follows: 0 V (■); 15 V (●); 30 V (▲); and 45 V (♦). Each point represents the mean ± SD of six animals. *$P < 0.05$ *versus* baseline.

tical differences ($P < 0.05$) from scores before and after treatment were not obtained with stimulation at all time points. Examination of the skin of the legs after these experiments revealed no burns, edema, erythema, or abrasion caused by ultrasound exposure or electric stimulation.

Discussion

All currently available local anesthetics have poor skin penetration when applied topically. A cream containing a eutectic mixture of local anesthetics (EMLA) requires considerable application time for sufficient effect, because of the drug rate-limiting barrier of the stratum corneum of the skin. The experiment reported here investigated the use of ultrasound to accelerate transdermal delivery of lidocaine. The aqueous solution of lidocaine with ultrasound exposure resulted in greater local anesthetic effects compared with lidocaine alone. As anesthetic effects were not solely induced by ultrasound exposure, it is likely that lidocaine within the skin was responsible for the analgesia.

Data from the current study indicate that the touch sensation of the legs almost disappeared from 15 to 75 min after ultrasound exposure in the presence of aqueous lidocaine. Response to low-voltage stimulation was also decreased over approximately the same period. However, mice immersed in lidocaine alone showed neither decrease of sensation or less response to electric stimulation during the time the experiment was performed.

Almost all previous investigations dealing with ultrasound exposure to the skin have used a gel or cream, because these formulations were thought to couple the ultrasonic transducer with the skin more easily and allow transmission of ultrasonic energy from the apparatus to the skin of the volunteer or animal.[10–14] However, lidocaine gel showed significant difference ($P < 0.05$) of anesthetic effects compared with aqueous lidocaine in the current study. Although the mechanism by which ultrasound enhances analgesia is unclear, recent findings by Brucks *et al.*[15] have suggested the nonthermal effects of ultrasound in addition to a temper-

Table 3. Mean Score of Mice Treated with Aqueous Lidocaine and Ultrasound

Voltage (V)	Minutes after Ultrasound Exposure									
	−5	0	15	30	45	60	75	90	120	180
0	5.5 ± 0.8	1.7 ± 2.2*	0.7 ± 0.8*	0.3 ± 0.5*	0.5 ± 0.8*	1.2 ± 1.2*	0.8 ± 1.2*	2.4 ± 1.3*	2.0 ± 1.4*	3.5 ± 1.3*
5	4.7 ± 1.8	2.2 ± 2.3*	0.5 ± 0.6*	1.0 ± 1.0*	1.0 ± 1.7*	1.3 ± 1.5*	1.5 ± 1.3*	2.6 ± 1.7*	1.8 ± 1.0*	3.7 ± 0.5*
10	4.3 ± 1.6	2.5 ± 2.6*	0.8 ± 1.1*	0.7 ± 1.0*	1.2 ± 1.5*	2.0 ± 1.5*	1.8 ± 1.3*	2.2 ± 2.4*	2.0 ± 1.2*	3.2 ± 2.7
15	5.2 ± 2.0	3.2 ± 2.9*	1.8 ± 1.5*	1.3 ± 1.6*	2.1 ± 1.5*	2.0 ± 2.0*	2.7 ± 1.5*	2.8 ± 1.8*	2.8 ± 1.7*	4.8 ± 1.0
20	5.3 ± 1.2	4.3 ± 2.0	1.5 ± 1.0*	2.2 ± 1.7*	2.8 ± 1.5*	2.5 ± 1.2*	2.0 ± 1.9*	3.4 ± 1.9*	3.5 ± 2.1	4.0 ± 2.2
25	5.0 ± 1.3	4.7 ± 1.5	2.3 ± 2.4*	1.7 ± 1.5*	2.5 ± 2.1*	3.2 ± 1.9*	3.8 ± 1.5*	3.8 ± 2.4	4.5 ± 1.3	4.8 ± 1.9
30	5.8 ± 0.4	5.5 ± 0.8	3.2 ± 1.6*	3.8 ± 2.1*	4.0 ± 1.0*	4.1 ± 1.9*	4.5 ± 0.8*	4.4 ± 2.3	5.3 ± 1.0	6.0 ± 0
35	5.8 ± 0.4	5.7 ± 0.8	4.3 ± 1.6*	3.5 ± 2.2*	4.8 ± 1.2*	4.7 ± 2.0	5.5 ± 0.5	4.6 ± 1.1*	6.0 ± 0	6.0 ± 0
40	5.8 ± 0.4	6.0 ± 0	4.8 ± 1.5	5.2 ± 1.0	5.3 ± 1.0	5.6 ± 0.5	5.6 ± 0.8	6.0 ± 0	6.0 ± 0	5.5 ± 1.0
45	6.0 ± 0	5.8 ± 0.4	5.5 ± 0.8	5.5 ± 0.8	5.8 ± 0.4	5.8 ± 0.4	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
50	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	5.6 ± 0.5	5.8 ± 0.4	6.0 ± 0	6.0 ± 0	6.0 ± 0

Values are mean ± SD.

* $P < 0.05$ *versus* values before treatment.

Table 4. Mean Score of Mice Treated with Gel Lidocaine and Ultrasound

Voltage (V)	Minutes after Ultrasound Exposure									
	−5	0	15	30	45	60	75	90	120	180
0	5.0 ± 1.4	5.0 ± 2.0	3.5 ± 2.3	3.8 ± 1.7	4.5 ± 1.3	4.0 ± 1.8	4.0 ± 2.5	4.8 ± 1.0	5.0 ± 1.2	5.2 ± 1.5
5	5.5 ± 1.0	4.5 ± 1.3	4.2 ± 1.3	3.8 ± 2.0	5.0 ± 1.4	4.5 ± 1.0	4.8 ± 1.0	5.5 ± 0.6	5.3 ± 0.5	5.8 ± 0.5
10	6.0 ± 0	5.7 ± 0.5	4.5 ± 1.7	4.3 ± 1.3	4.5 ± 1.3	5.7 ± 0.5	4.7 ± 1.5	5.2 ± 0.9	5.7 ± 0.5	6.0 ± 0
15	5.5 ± 1.0	6.0 ± 0	5.0 ± 1.4	4.8 ± 1.2	5.3 ± 0	5.0 ± 0.8	5.5 ± 0.6	5.5 ± 0.6	6.0 ± 0	5.5 ± 1.0
20	6.0 ± 0	6.0 ± 0	5.2 ± 1.3	5.0 ± 0.7	5.0 ± 1.0	5.3 ± 0.8	6.0 ± 0	6.0 ± 0	6.0 ± 0	5.8 ± 0.4
25	6.0 ± 0	6.0 ± 0	6.0 ± 0	5.5 ± 0.5	5.5 ± 0.8	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
30	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	5.8 ± 0.4	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
35	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
40	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
45	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0
50	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0	6.0 ± 0

Values are mean ± SD. Values after treatment did not differ ($P < 0.05$) from those values obtained before treatment.

ature increase may alter skin permeability. Ultrasound produces countless microscopic bubbles that oscillate in size. When these bubbles collapse, microscopic liquid jets are expelled that reach 400 km/h.[16] The vibrating gas bubbles cause radiation streaming (a steady twisting action on a particle near the bubble) or acoustic streaming (circulatory motion in the liquid near the bubbles).[17] These phenomena occur especially near rough solid surfaces (the skin, in this experiment). The bioavailability of lidocaine was probably enhanced at the surface of the skin with this ultrasound. As viscosity of the liquid greatly affects production of the microbubbles, such materials as cream or gels are unfit for rapid microstreams to occur compared with aqueous solutions. Thus, the difference of anesthetic effects between lidocaine solution *versus* gels effected can be explained. The modest enhancing of transdermal drug delivery by ultrasound in previous reports[10–14] with cream or gel may also have been caused by this mechanism.

The safety and reversibility of the analgesia caused by ultrasound is yet to be investigated. However, microscopic examination of rabbit skin tissue exposed at similar ultrasound intensity for longer periods has shown no inflammation or cell damage.[9] The recovery to touch sensation is evidence that the peripheral nerve was not permanently damaged. Furthermore, taking into account that the ultrasound intensity of the present experiment is one-fifth the energy of therapeutic ultrasound used in clinical situations, damage to the skin and underlying tissues (*e.g.*, muscles and blood vessels) is presumed to be minimal.

In conclusion, ultrasound exposure to the legs of hairless mice along with topical 2% lidocaine solution rapidly induced an anesthetic effect, whereas lidocaine alone showed no significant anesthetic effects. Furthermore, compared with aqueous lidocaine, the drug in the gel form with ultrasound resulted in less anesthetic effect. Ultrasound exposure to the skin with aqueous lidocaine may be a useful means for rapidly inducing local anesthesia noninvasively.

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