Evaluation of the Penetration Depth of Transdermally Applied 3% GA MHPh 2Na-10% Lidocaine Gel in Man

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In order to estimate the penetration depth of transdermal 3% GA MHPh 2Na-10% lidocaine gel mixture, the following physiological functions of the skin were examined before and after a 60 min occulusive application of the gel in 16 adult volunteers.

Thermal sweat expulsins ceased completely on the gel-treated ventral surface of one forearm in all the first 5 subjects, though it continued on the untreated contrast area of the other forearm. Sympathetic skin response (SSR) was also no longer induced on the gel-treated middle finger in 1 of another 3 subjects and was severely depressed in the other 2 subjects, while the SSR on the untreated index finger appeared constantly.

Vasomotion of the skin circulation on another 3 subjects, remained unaffected on both the gel-treated and the untreated fingers. Extraction of a leg-hair in the treated area did not induce pain sensation in all the last 5 subjects.

In addition to the transcellular main roots, some of the transcutaneously applied gel seems to penetrate deeply into the skin through the appendageal roots such as the eccrine sweat glands and the pilosebaceous glands. (Key words: dermal patch anesthesia, lidocaine gel, sudomotion, vasomotion)

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We have developed a 10% lidocaine gel mixture containing 3% glycyrrhetinic acid monohemiphthalate disodium (GA MHPh 2Na) as an absorption promoter after preliminary studies[1,2]. Our double-blind human study confirmed that 10% lidocaine gel with 3% GA MHPh 2Na was more effective in alleviating the pain of pinpricks and venous cannulation than the lidocaine gel without it [3]. Venous cannulation was carried out without pain in 65.5% of adult patients and 82.4% of child patients who received the occlusive lidocaine gel patch for about 60 min[4]. A stripping pretreatment with gum tape or a cleaning pretreatment with benzin was useful in shortening

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the latency time of the dermal patch anesthesia[5].

In the present study, several physiological functions of the skin are investigated as indicators to estimate the penetration depth of transdermally applied 3% GA MHPh 2Na-10% lidocaine gel.

Materials and Methods

With the approval from the Institutional Ethics Committee on Human Research, we studied 16 healthy adult volunteers with a mean age of 33.3 ± 7.5 yrs. Thermal or mental sweating, vasomotion of skin circulation, and pain sensation at hair extraction were examined before and after a 60 minute application of the 3% GA MHPh 2Na-10% lidocaine gel. Approximately 0.3g of the gel, soaked in a round sponge with a diameter of 15 mm and a thickness of 1 mm, was applied and was covered with an adhesive plastic film (Tegaderm®, 3 M Corp., USA). Composition of the lidocaine gel mixture is shown elsewhere[2,3].

Regional thermal sweating was observed in a continuous and quantitative mode by using a 2-channel AMU-3 Hidrograph® (Forshon Corp., Japan) on 5 of the subjects. A couple of open-ended plastic capsules, 1 cm in diameter, were fixed with a weak negative pressure on the ventral sides of both forearms. Each capsule was ventilated with a fresh dry gas. The increase of humidity in each outflow gas was detected as a change of electric resistance. The increases of humidity, reflecting sweat expulsions, were taken in digital readings ($mg \cdot cm^{-2} \cdot min^{-1}$) and also recorded on a 2 channel recorder. The measurement of humidity was interrupted for 60 minutes with a transdermal application of the lidocaine gel on one forearm, while it was continued throughout the experiment on the other forearm.

Mental sweating was observed as a sympathetic skin response (SSR) with a Neuropac 8® (Nihon Kohden Corp., Japan) on another 3 of the subjects. SSR was evoked by a random electric stimulation (pulse width 0.3 msec, intensity 7 mA) applied to the unilateral forearm and recorded from the palmar sides of the contralateral index and middle finger tips. The stimulation and the recording were performed through disposable surface electrodes for ECG monitoring. SSR was observed before and after the application of the lidocaine gel on the middle finger, while it was observed without interruption by the gel patch on the index finger.

Vasomotion of the skin circulation was observed by using two ALF 2100 laser Doppler flowmeters® (Advance Corp., Japan) on another 3 subjects. The instruments utilizes an infrared He-Ne laser (wavelength 780 nm, 2 mW output at the tip). The output signal is expressed as ml/100g tissue/min conventionally, although the quantification presents many problems to be solved. Plate type probes, which consist of parallel exciting and receiving optic fibers separated by a distance of 0.5 mm, were attached by a double-sided adhesive disk to the palmar sides of the index and the middle finger tips and the output signals were recoreded on a heat pen recorder at a time constant of 1.0 sec. The laser Doppler flowmetry was interrupted for 60 min with a transdermal application of the lidocaine gel on the middle finger, while it was continued on the index finger.

In another 5 subjects, the lidocaine gel was applied to the ventral hairy part of the leg for 60 min and pain sensation by hair extraction was examined.

The above studies were conducted in the operating room, where room lights were dimmed and ambient noise was kept low. Room temperature was maintained in the range of 25 to 26°C.

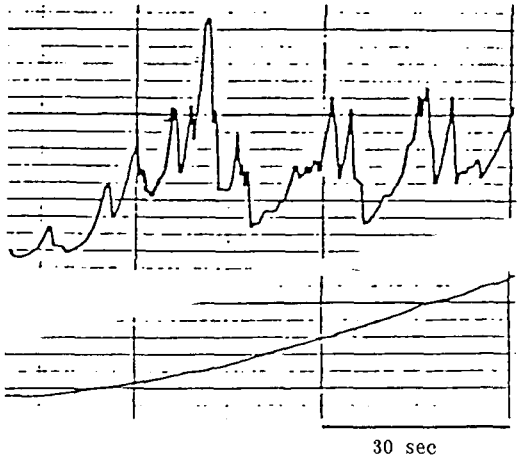

Fig. 1. Typical thermal sweat expulsions recorded from the ventral side of the forearm by Hidrograph® in an individual subject (30 yr, male).

upper trace: before application of the lidocaine gel.

lower trace: 5 min after 60 min application of the gel.

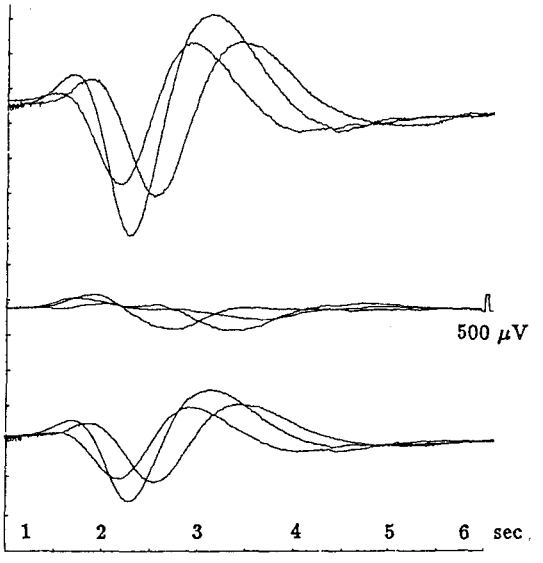

Fig. 2. Typical sympathetic skin responces recorded from the palmar side of the middle finger tip in an individual subject (33 yr, male).

upper traces: before application of the lidocaine gel.

middle traces: 5 to 8 min after 60 min application of the gel.

lower traces: 90 to 95 min after 60 min application of the gel.

Before starting each study, the subjects were allowed to adjust to the environment in a supine position for at least 10 min.

Results

The Hidrograph® study revealed that thermal sweating ceased completely on the gel-treated forearm in all 5 subjects, though it continued on the untreated opposite forearm (fig. 1). The SSR on the gel-treated middle finger was also no longer induced in 1 of 3 subjects and was severely depressed in the other 2 subjects, while the SSR on the untreated index finger appeared constantly. The SSR tended to recover with time after removal of the dressing and the gel (fig. 2).

The laser Doppler flowmetry showed a tendency of increasing skin blood flow to some extent, not only on the treated finger, but also on the untreated finger. Vasomotor waves of the skin circulation, such as the basic wave and the reflex wave[6], remained unaffected on both fingers of the 3 subjects. A good synchronization was also maintained in the cutaneous vasomotor flow waves between the gel-treated and the untreated fingers, as shown in figure 3.

All 5 subjects did not complain of pain sensation at extraction of a leghair.

Discussion

The inactivation of thermal and mental sweating indicates that the transdermally applied lidocaine reached the postganglionic cholinergic fibers around the eccrine sweat glands at the dermis or the subcutaneous tissue. In the finger-tip where mental sweating was studied, the epi-

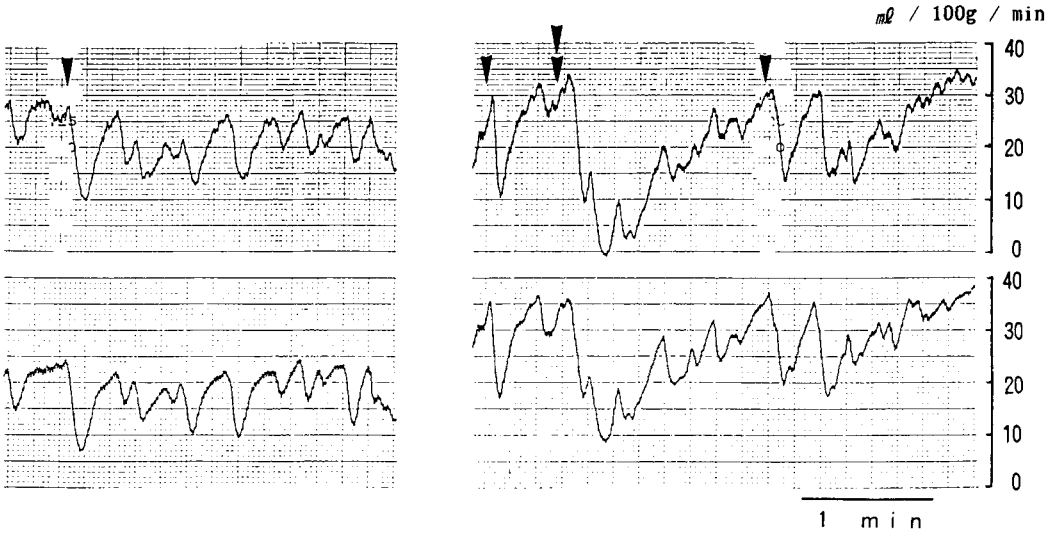

Fig. 3. Typical cutaneous vasomotor flow waves recorded from the palmar sides of the untrated index finger (upper trace) and the ajacent gel-treated middle finger (lower trace) in an individual subject (27 yr, male).

left column: before application of the lidocaine gel.

right column: 5 min after 60 min application of the gel.

▼ : deep inspiration.

▼▼ : nociceptive stimuli added to the contralateral forearm.

dermis is often as thick as 0.2–0.4 mm. In such areas, skin analgesia to pin-pricks (needle insertion less than 0.5 mm) is hardly obtained by the 60 min application of 3% GA MHPh 2Na-10% lidocaine gel. Nevertheless mental sweating on the finger-tip was severely depressed. It can be assumed that some of the transdermally applied lidocaine penetrated into the skin deeply through the eccrine sweat glands, besides the transcellular roots.

Painless extraction of a leg-hair supports the penetration through the appendageal roots. The hair follicles are surrounded with the palisade nerve endings and are located in the subcutaneous tissue deeper than the eccrine sweat glands. It is likely that some of the transdermal lidocaine penetrated into the skin deeply through the pilo-sebaceous glands and anesthetized the nerve endings, in addition to that through the transcellular roots.

The epidermis, especially the stratum corneum, is thought to be the main barrier for transdermally applied drugs and also to be the reservoir for them. Bjerring et al.[7] reported that the maximal depth of analgesia was obtained 30 min after a 90 min application of EMLA cream and explained the delayed increase of analgesia as attributable to a deposit of the anesthesia cream in the upper skin layers. In the present study, numbing sensation on the finger-tip remained until the next day, while complete analgesia was not obtained on that area by a 60 min application of the lidocaine gel.

Laser Doppler flowmetry is a non-invasive method of monitoring blood perfusion through the cutaneous circulation. It has been used to follow the transdermal absorption of topically applied vasodilators, such as nicotinic acid esters[8]. Many local anesthetics, including lidocaine, are known

vasodilators. Vasodilation is a suitable process for venous cannulation. The present study has demonstrated that the blood flow in the cutaneous circulation is slightly increased by the dermal patch anesthesia. But it was observed on the untreated finger, as well. Therefore the increase in blood flow is not always indicative of the transdermal absorption of the lidocaine. Some of the subjects exhibited a slight, transient errythema following removal of the preparation. Woolfson et al.[9] insisted that such occasional errythema should be regarded as a pharmacological effect rather than a side effect of the formulation.

A laser Doppler probe with fiber separation at 0.5 mm was used in the present study, indicating that the penetration depth of the laser light was approximately 1 mm[10]. In the dermis of the finger-tip, arteriovenous anastomoses (AVAs), which play an important role in peripheral thermoregulation, are abundant[11]. The AVAs arise from arteries and arterioles up to 0.1 mm in diameter and situate in the deeper layers of the skin at about the same depth as the sweat glands[12]. Laser Doppler flowmetry, with the ALF 2100, measures blood flow through both superficial vessels, presumably capillaries, and deeper vessels including AVAs of the finger. Reflex waves, which followed a deep inspiration or nociceptive stimuli, as shown in figure 3, are attributed exclusively to the constriction of the vessels located deeper in the skin, possibly of AVAs. Vasomotor waves of the cutaneous circulation, such as the basic wave and the reflex wave[6], were not depressed at all by the dermal patch of the lidocaine gel. It means that sympathetic vasomotor nerves were not anesthetized and were still functioning. Namely, absorption of the transdermal lidocaine through transcellular roots is not remarkable, compared with that through the above mentioned appendageal roots.

The present findings suggest that some of the transcutaneously applied gel seems to penetrate into the skin deeply through the appendageal roots, such as the eccrine sweat glands and the pilo-sebaceous glands, in addition to the transcellular roots.

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