Acta Derm Venereol (Stockh) 1989; 69: 18–22

Absorption of Lidocaine and Prilocaine after Application of a Eutectic Mixture of Local Anesthetics (EMLA®) on Normal and Diseased Skin

L. JUHLIN,[1] G. HÄGGLUND[1] and H. EVERS[2]

[1]*Department of Dermatology, University Hospital, Uppsala and* [2]*Department of Clinical Research, Astra Pain Control, Södertälje, Sweden*

Absorption of lidocaine and prilocaine after application of a eutectic mixture of local anesthetics (EMLA®) on normal and diseased skin. Acta Derm Venereol (Stockh) 1989; 69: 18–22.

A eutectic mixture of 5% lidocaine and prilocaine was applied under occlusion for 1 or 2 hours on 25–100 cm^2 areas of normal and diseased skin, and the absorption was followed by measuring the concentrations of the drugs in the draining vein and the general circulation at different time intervals after the application. The analgesic and vascular effects in the skin were also recorded. When the mixture was applied on normal skin the absorption was more rapid from the face than from the forearm. The absorption from diseased skin was faster than that from normal skin, with higher plasma concentrations, and a more rapid but shorter anesthetic effect was noted. With the doses used the plasma levels in the general circulation were 100 times lower than those associated with toxicity. The drug concentrations in the draining vein were highest after treatment of diseased skin and were 2–90 times higher than in the general circulation. The plasma concentrations of lidocaine and prilocaine ran parallel to each other, but the prilocaine level was 10–50% lower than that of lidocaine in the draining vein and 200–300% lower in the general circulation. *Key words: Atopic dermatitis; Psoriasis.* (Accepted September 1, 1988.)

L. Juhlin, Department of Dermatology, University Hospital, S-751 85 Uppsala, Sweden.

Anesthesia for superficial surgical procedures in normal and diseased skin can be achieved by topical application of a eutectic mixture of 5% lidocaine and prilocaine (EMLA®) under occlusion for 60 min (1). The EMLA cream has been found to be of special value when used on donor sites before cutting of split skin grafts (2), for pain-free venepuncture (3–7), for curettage of molluscum contagiosum in children (8), and when removing genital warts (9). The plasma concentrations of both lidocaine and prilocaine were low when the cream was applied on 300 cm^2 areas of the thigh of healthy volunteers or on larger areas of normal skin prior to skin grafting (2, 10).

After one hour's application of EMLA on normal appearing skin, blanching of the skin was often seen, and remained for 30–90 min. The pallor seems to be due to vasoconstriction. When EMLA was applied for 2–4 hours, the blanching was replaced after 30 min to 2 hours by slight to moderate erythema, which persisted for 1–3 hours (11). The reactions were accentuated in dry and eczematous skin of patients with atopic dermatitis. The reactions had a shorter onset than in normal skin, as did the dermal analgesia, indicating more rapid absorption of EMLA (11).

The aim of the present study was to investigate the absorption of the anesthetics from normal facial skin compared with that from normal and diseased skin of the arms by following their concentrations both in the general circulation and in the venous blood draining the treated area of the arm. This absorption is of clinical importance when treating diseased skin. By correlating the plasma levels with the local vascular and anesthetic effects of the drug, such a study might also serve as a pharmacokinetic model for investigations of penetration through the skin.

Volunteers and patients

1. Thirteen healthy volunteers (ages 20–60 years) with normal-appearing skin served as controls. None of them were using any drugs.
2. Eight patients (ages 20–63 years) with chronic plaque-type psoriatic lesions on the hands and/or lower arms. In one of them tests were performed on healed corticosteroid-treated skin.
3. Three women (ages 18–24 years), of whom two had atopic dermatitis and one contact dermatitis affecting the lower arms.

METHODS

Plasma concentrations of lidocaine and prilocaine in the general circulation after topical application of 5% EMLA cream on various sites

Ten healthy volunteers (5 men and 5 women) took part in a cross-over study in which 10 g of EMLA was applied under occlusion (Tegaderm, 3M, USA) on a 100 cm^2 area of the face or forearm. The periphery of the treated area was masked with tape (Dermicel, Johnson & Johnson, USA). When the bandage was removed after 2 h the skin was dried with crepe paper. The colour of the treated skin was noted.

Blood was drawn from an antecubital vein in the arm not used for application of EMLA, into 5 ml heparinized vacuum tubes (Venoject, 75 US PU, Na-Heparin with 20 mg fluoride, Terumo, Belgium), before and at the following times after EMLA application: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h. The plasma was separated and stored at −20°C until analyzed.

Plasma concentrations of lidocaine and prilocaine in the draining vein and the general circulation after application of EMLA on diseased and normal skin

Within an area of 25 cm^2 4–6 g of EMLA 5% cream was applied under occlusion for one hour on one lower arm. In two patients the area was on the dorsal aspect and in the others it was more on the volar aspect. The bandage was then removed and the cream was wiped off with crepe paper. The degree of blanching or reddening (0 to +++) was noted during the following hours. The anesthetic effect was measured by ten pinpricks (10). These measurements were repeated after 30, 60, and 120 min.

Blood was drawn into heparinized Venoject tubes as described above, from both arms at different time intervals for detection of lidocaine and prilocaine. Extreme care was taken to avoid contamination.

Analytical procedure

The lidocaine and prilocaine concentrations in plasma were determined by mass fragmentography (12).

RESULTS

The mean plasma concentrations of lidocaine and prilocaine in the general circulation after application of EMLA to a 100 cm^2 area of the face and forearm in healthy subjects are shown in Figs. 1–2. Maximum plasma levels were reached after 2–2.5 h of application on the face (mean 150 ng/ml of lidocaine and 58 ng/ml of prilocaine). After application on the forearm the maximum level of lidocaine was noted at 5 h (mean 18 ng/ml), whereas the prilocaine levels were below detectable limits.

When EMLA was applied on a 25 cm^2 area in three healthy volunteers for 1 h neither of the substances was detected in the general circulation (<10 ng/ml) within 3 h. In the vein draining the treated area both lidocaine and prilocaine were detected after 2 and 3 h (Fig. 2). The prilocaine level was 10–20% lower than that of lidocaine (Fig. 1). After application on skin lesions of patients with psoriasis and dermatitis, detectable levels of lidocaine (16–450 ng/ml) were found in the general circulation after one hour in all ten patients and of prilocaine in seven of them (Table I). In the draining vein measurable levels of both drugs were found within 60 min and these levels were 2–90 times higher than in the general

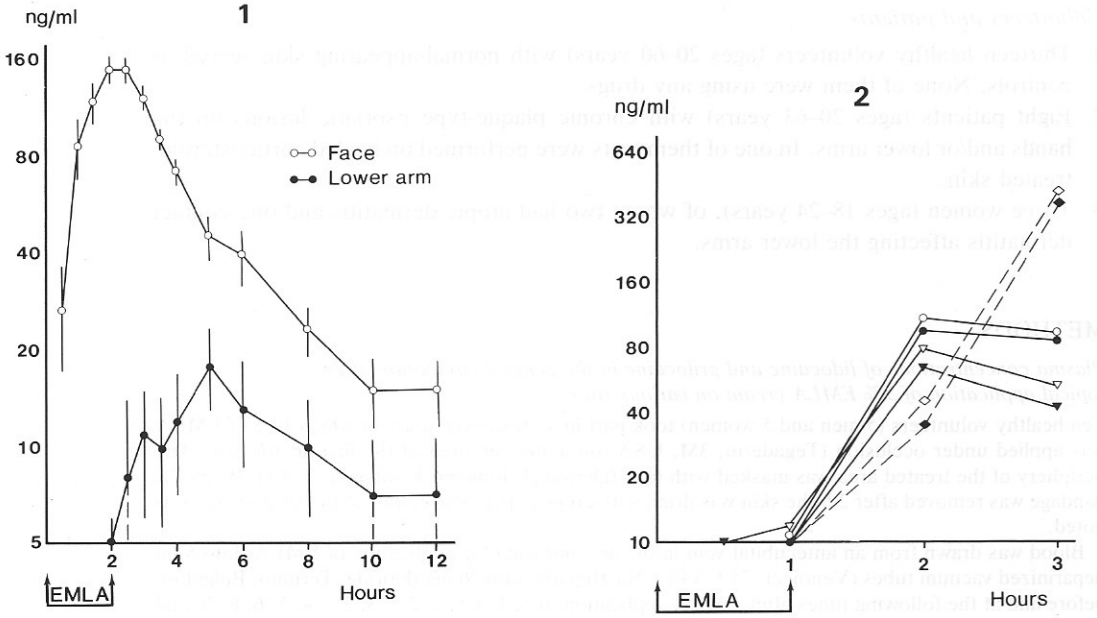

Fig. 1. Lidocaine concentration in plasma of the general circulation after 2 hours of application of EMLA 5% cream on 100 cm^2 of occluded normal skin of the face and forearm. Values are mean ± SEM.

Fig. 2. Plasma lidocaine (○ ▽ ◇) and prilocaine (● ▲ ◆) in the draining vein in three healthy subjects after application of EMLA 5% cream for one hour on a 25 cm^2 area of the forearm.

circulation (Fig. 3). The highest concentrations were found in atopic dermatitis (10000–13000 ng/ml), where they were 1000 times more than in our healthy subjects. In the draining vein from red psoriatic plaques the levels of prilocaine were 10–50% lower than those of lidocaine.

In normal skin analgesia to pin-prick was evident after 60 and 120 min of EMLA under occlusion. Local blanching was often observed after one hour's application and lasted for 10–60 min. Redness was common. When the cream was removed after 2 h of application on the arms, blanching was seen in seven and redness in three of the ten volunteers. The corresponding figures for the facial skin were four with a blanching and six with redness. The psoriatic plaques treated with EMLA for one hour were pale and did not react to pin-pricks when the bandage was removed. The blanching faded away within 20–30 min and pin-pricks were felt at 30 min. Tests to determine the minimal length of time before anesthesia was obtained were later made in similar lesions by applying EMLA under occlusion for 15 and 30 min. In the atopic skin and psoriatic plaques the skin was pale and anesthetic after an application time of 15 min and remained so for 15–30 min. This was in contrast to normal adult skin, where as a rule an application time of 60 min was needed for complete anesthesia.

DISCUSSION

When EMLA was applied on the facial skin the maximal lidocaine levels in the plasma occurred within 2 hours, whereas when the arm was treated the levels were lower and reached a maximum after 5 hours. This indicates more rapid absorption from the face, an observation which has been made for other drugs. After application of EMLA on diseased

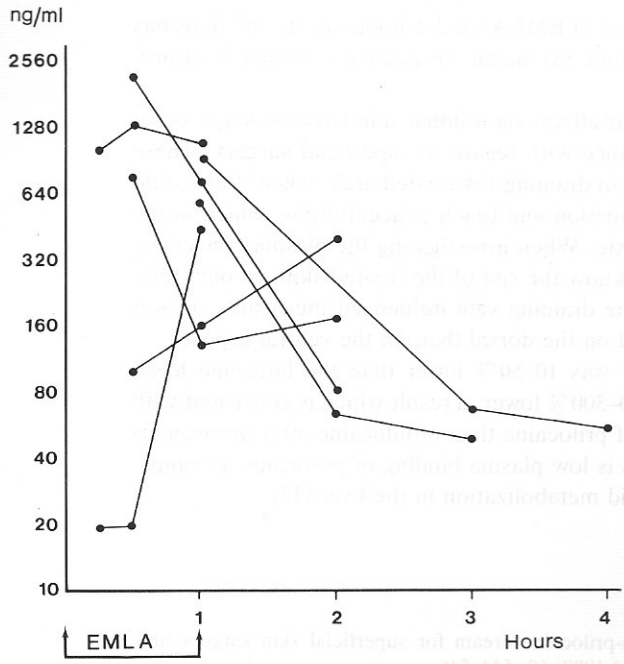

Fig. 3. Plasma lidocaine levels in the draining vein of seven patients with chronic plaque psoriasis after application of EMLA 5% cream for one hour on lesions (25 cm^2) on the forearm.

skin of patients with psoriasis or dermatitis, the plasma concentrations of both drugs increased more rapidly and reached higher levels than were found for normal skin. With the doses used the plasma levels in the general circulation were 100 times lower than those associated with toxicity. However, care must be taken if large areas of diseased skin are

Table I. *Plasma levels of lidocaine and prilocaine (ng/ml) in the draining vein and the general circulation 1 and 2 hours after application of EMLA on a 25 cm^2 area of the forearms of patients with dermatitis or psoriasis and of controls*

	1 hour				2 hours			
	Lidocaine		Prilocaine		Lidocaine		Prilocaine	
Disease	Drain. vein	Gen. circ.	Drain. vein	Gen. circ.	Drain. vein	Gen. circ.	Drain. vein	Gen. circ.
Atopic dermatitis	13 070	450	11 870	190	4 190	360	3 470	240
Atopic dermatitis	11 230	130	9 560	50	2 750	140	2 130	60
Contact dermatitis	200	20	140	<10	310	20	190	<10
Psoriatic lesion	656	16	566	<10	63	16	44	<10
Psoriatic lesion	160	40	140	20	390	–	360	140
Psoriatic lesion	758	162	435	63	82	64	33	30
Psoriatic lesion	132	68	42	20	168	150	62	29
Psoriatic lesion	968	26	824	<10	–	–	–	–
Psoriatic lesion	608	67	796	31	–	–	–	–
Psoriatic lesion	443	45	306	24	–	–	–	–
Psoriatic healed	30	<10	20	<10	37	<10	26	<10
Normal skin	12	<10	<10	<10	80	<10	70	<10
Normal skin	10	<10	<10	<10	45	<10	35	<10
Normal skin	12	<10	<10	<10	108	<10	90	<10

treated. On normal skin of infants, application of EMLA for 2–8 hours on 16 cm^2 areas has resulted in maximal plasma levels of 127 and 131 ng/ml, respectively, which is clearly below the toxic levels (13).

The finding that the analgesic and vascular effects on lesional skin have a quicker onset and disappear faster is of practical importance with regard to superficial surgery. These patients also had the highest levels in the vein draining the treated area, where they could be 90 times higher than in the general circulation and reach concentrations which in the general circulation would be considered toxic. When investigating the plasma concentration in patients it is therefore important to know the site of the treated skin. In our study the site of the treated area in relation to the draining vein influenced the results. Lower levels were noted when EMLA was applied on the dorsal than on the ventral aspect.

In the draining vein the prilocaine level was 10–50% lower than the lidocaine level, whereas in the general circulation it was 200–300% lower, a result which is consistent with the finding of lower blood concentrations of prilocaine than of lidocaine after intravenous injection (14). The probable reason for this is low plasma binding of prilocaine accompanied by a high tissue affinity and more rapid metabolization in the liver (15).

REFERENCES

1. Juhlin L, Evers H, Broberg F. A lidocaine-prilocaine cream for superficial skin surgery and painful lesions. Acta Derm Venereol (Stockh) 1980; 60: 544–546.
2. Ohlsén L, Englesson S, Evers H. An anaesthetic lidocaine/prilocaine cream (EMLA) for epicutaneous application tested for cutting split skin grafts. Scand J Reconstr Surg 1985; 19: 201–209.
3. Ehrenström-Reiz GME, Reiz SLA. EMLA—a eutectic mixture of local anaesthetics for topical anaesthesia. Acta Anaesth Scand 1982; 26: 596–598.
4. Hallén B, Uppfeldt A. Does lidocaine-prilocaine cream permit painfree insertion of IV catheters in children? Anesthesiol 1982; 57: 340–342.
5. Maunuksela E-L, Korpela R. Double-blind evaluation of a lignocaine-prilocaine cream (EMLA) in children. Effect on the pain associated with venous cannulation. Br J Anaesth 1986; 58: 1242–1245.
6. Manner T, Kanto J, Iisalo E, Lindberg R, Viinamäki O, Scheinin M. Reduction of pain at venous cannulation in children with a eutectic mixture of lidocaine and prilocaine (EMLA cream): comparison with placebo cream and no local premedication. Acta Anaesthesiol Scand 1987; 131: 735–739.
7. Hopkins CS, Buckley CJ, Bush GH. Pain-free injection in infants. Use of alignocaine-prilocaine cream to prevent pain at intravenous induction of general anaesthesia in 1–5-year-old children. Anaesthesia 1988; 43: 198–201.
8. Rosdahl I, Edmar B, Gisslén H, Nordin P, Lillieborg S. Curettage of molluscum contagiosum in children: Analgesia by topical application of a lidocaine/prilocaine cream (EMLA). Acta Derm Venereol (Stockh) 1988; 68: 149–153.
9. Hallén A, Ljunghall K, Wallin J. Topical anaesthesia with local anaesthetic (lidocaine and prilocaine, EMLA) cream for cautery of genital warts. Genitourin Med 1987; 63: 316–319.
10. Evers H, von Dardel O, Juhlin L, Ohlsén L, Vinnars E. Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA). Studies in volunteers. Br J Anaesth 1985; 57: 997–1005.
11. Juhlin L, Rollman O. Vascular effects of anesthetic mixture in atopic dermatitis. Acta Derm Venereol (Stockh) 1984; 64: 439–440.
12. Strong JM, Atkinson AJ. Simultaneous measurement of plasma concentrations of lidocaine and its desethylated metabolite by mass fragmentography. Anal Chem 1972; 44: 2287–2290.
13. Engberg G, Danielson K, Henneberg S, Nilsson A. Plasma concentrations of prilocaine and lidocaine and methaemoglobin formation in infants after epicutaneous application of a 5% lidocaine-prilocaine cream (EMLA). Acta Anaesthesiol Scand 1987; 31: 624–628.
14. Lund PC, Covino BG. Distribution of local anesthetics in man following peridural anesthesia. J Clin Pharmacol 1967; 7: 324–329.
15. Tucker GT. Plasma binding and disposition of local anesthetics. In: Dal Santo G, ed. Biotransformation of Anesthetics and adjuvant agents. Internat Anest Clin 1975: 33–59.