

Contact urticaria from Emla[®] cream

J. WATON¹, A. BOULANGER¹, P. H. TRECHOT², J. L. SCHMUTZ¹ AND A. BARBAUD¹

¹Dermatology Department, Fournier Hospital, Nancy, France, and ²Pharmacology Department, Central Hospital, University Hospital of Nancy, France

We report the first case of immediate-type hypersensitivity caused by Emla[®] cream. A 55-year-old woman, after using Emla[®] cream, went on to develop urticaria. An open test was positive to Emla[®] cream. Patch tests and prick tests were performed with Emla[®] cream, the components of Emla[®] cream (lidocaine, prilocaine and castor oil) and other local anaesthetics. The patch test with lidocaine and the prick test with Emla[®] cream were both positive. An intradermal test and subcutaneous administration of 3 anaesthetics that had negative patch tests and prick tests were performed and well tolerated, allowing their use. In the literature, anaphylactic reactions to lidocaine injections, delayed-type hypersensitivity after lidocaine subcutaneous injections and contact dermatitis from Emla[®] cream have all been described. This first case of contact urticaria from Emla[®] cream was due to lidocaine and did not show any cross-reaction with other local anaesthetics.

Key words: contact urticaria; lack of cross-reaction; lidocaine; local anaesthetic; medicaments.
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We report the first case of contact urticaria due to Emla[®] cream (Astra Zeneca, Rueil Malmaison, France). From our case and a review of literature, we tried to determine the existence of cross-reactions between lidocaine and other local anaesthetics (LA) to find an alternative treatment.

Patient and Methods

A 55-year-old woman applied Emla[®] cream under a dressing (Tegaderm[™], 3M, Health Care, Borken, Germany) 2 hr before the removal of a naevus. The removal of the lesion was impossible because at the site of application of Emla[®] cream, she developed itchy erythematous papules and pseudo-vesicles. Topical corticosteroids relieved the reaction in a few hours.

She had previously developed a rash while taking an antibiotic, but the name of the antibiotic remained unknown. Her medical history showed many injections and applications of LA without her ever having had any adverse reaction. She had had local anaesthesia for a skin cyst's excision, peridural anaesthesia during childbirth, anaesthesia for dental care and topical application of oxybuprocaine for ophthalmologic examination that were all well tolerated.

1 year before, for the removal of another naevus, she had applied Emla[®] cream (lidocaine

2.5%, prilocaine 2.5%, hydrogenated castor oil, carboxypolymethylene and sodium hydroxide) followed by an injection of Xylocaine[®] (lidocaine) and did not develop any adverse reaction.

An open test was performed with Tegaderm[®] on one forearm and Emla[®] cream on the other.

Patch tests were done with the European standard series (Chemotechnique, Malmö, Sweden), lidocaine hydrochloride 5% petrolatum (pet.), prilocaine 5% pet., Emla[®] cream and castor oil pure. To study potential cross-reactions between LA, we also tested other substances, as listed in Table 1. Tests were read at 20 min, day (D) 2 and D4.

Prick tests were done with Emla[®] cream, prilocaine, articaine, mepivacaine, bupivacaine, dibucaine, procaine, tetracaine and polidocanol. Tests were read at 20 min, 40 min, D2 and D4 (Table 2).

Intradermal tests were performed with bupivacaine, mepivacaine and articaine, according to published guidelines for drug skin testing (1). Subcutaneous administrations of mepivacaine, bupivacaine and articaine, with progressively increasing dosages (0.01 ml, 20 min later: 0.5 ml, 1 hr later: 1 ml), were carried out.

Results

The skin test results are reported in Tables 1, 2 and 3. The initial open test with Emla[®] cream

Table 1. Patch test results

		20 min	D2	D4
Benzocaine	3% pet.	—	—	—
Polidocanol (Trolab)	5% pet.	—	—	—
Tetracaine hydrochloride	5% pet.	—	—	—
Procaine	1% pet.	—	—	—
Dibucaine (Trolab)	5% pet.	—	—	—
Bupivacaine	pure	—	—	—
Caine mix III		—	—	—
Benzocaine	5% pet.			
Dibucaine	2.5% pet.			
Tetracaine	2.5% pet.			
Caine mix IV		+	NT	NT
Amylocaine	2.5% pet.			
Lidocaine	5% pet.			
Prilocaine	2.5% pet.			
Lidocaine hydrochloride	5% pet.	+	—	—
Prilocaine	5% pet.	—	—	—
Emla [®] cream	pure	—	NT	NT
Castor oil	pure	—	—	—

NT = non-tested; pet. = petrolatum; D2 = day 2; D4 = day 4.

was positive, the skin immediately displaying contact urticaria with itchy papular erythema. The corresponding open test with Tegaderm[™] was negative.

Patch tests with lidocaine hydrochloride (Table 1) and caine mix III (containing lidocaine) were positive at 20 min, with a pseudo-vesicular reaction (Table 2). Therefore, the patch test with Emla[®] cream was removed.

Patch tests and prick tests with prilocaine were negative, confirming an isolated sensitization to lidocaine. The prick test with Emla[®] cream was positive, confirming an immediate-type hypersensitivity (Table 3).

As patch tests and prick tests with bupivacaine, mepivacaine and articaine were negative, subcutaneous administrations of articaine 5 mg/ml, mepivacaine 10 mg/ml and bupivacaine 40 mg/ml, with progressively increasing dosages (0.01 ml, 0.5 ml and 1 ml), were carried out and were well tolerated.

Table 2. Prick test results

		20 min	40 min	D2
Polidocanol	Pure	—	—	—
Tetracaine	Pure	—	—	—
Procaine	Pure	—	—	—
Dibucaine	Pure	—	—	—
Bupivacaine 5 mg/ml	Pure	—	—	—
Mepivacaine 10 mg/ml	10 ⁻¹ , pure	—	—	—
Articaine 40 mg/ml	10 ⁻¹ , pure	—	—	—
Prilocaine	Pure	—	—	—
Emla [®] cream	Pure	P2	P7	—
Codeine	P6			

P = papule; D2 = day 2.

Table 3. Intradermal test results: performed from 10 to 4, then 10–3, 10–2, 10–1 to the reported concentration

	30 min	D1
Bupivacaine 5 mg/ml	—	—
Mepivacaine 10 mg/ml	—	—
Articaine 40 mg/ml	—	—

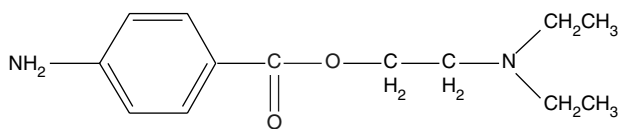
D1 = day 1.

Discussion

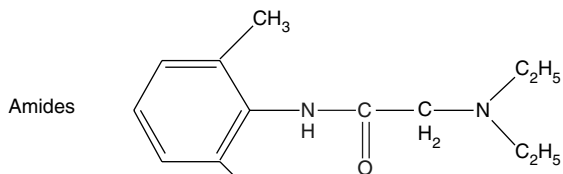
Local anaesthetics are divided into 2 main classes based on their chemical structure. The ester group includes procaine, benzocaine, oxybuprocaine, chlorprocaine, tetracaine and butoform. The amide group includes lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine and dibucaine (Fig. 1). The amide group is divided into 2 subgroups with or without a thiophene ring (Fig. 2).

The first local anaesthetic was cocaine, highlighted by Niemann in 1860: when he tasted it, his tongue became numb. Later, in 1890 the first ester LA was developed, and in 1943, the first amide

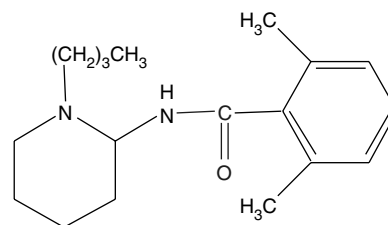
Esters



Procaine



Lidocaine



Bupivacaine

Fig. 1. The 2 main classes of local anaesthetics.

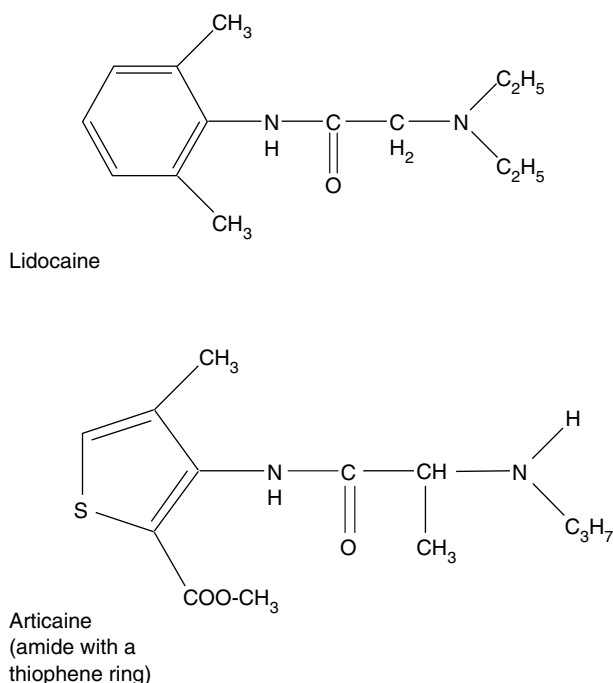


Fig. 2. Amide local anaesthetics (LA) and amide LA with a thiophene ring.

LA, lidocaine, the most commonly used LA for cutaneous surgery. The LA are made up of an

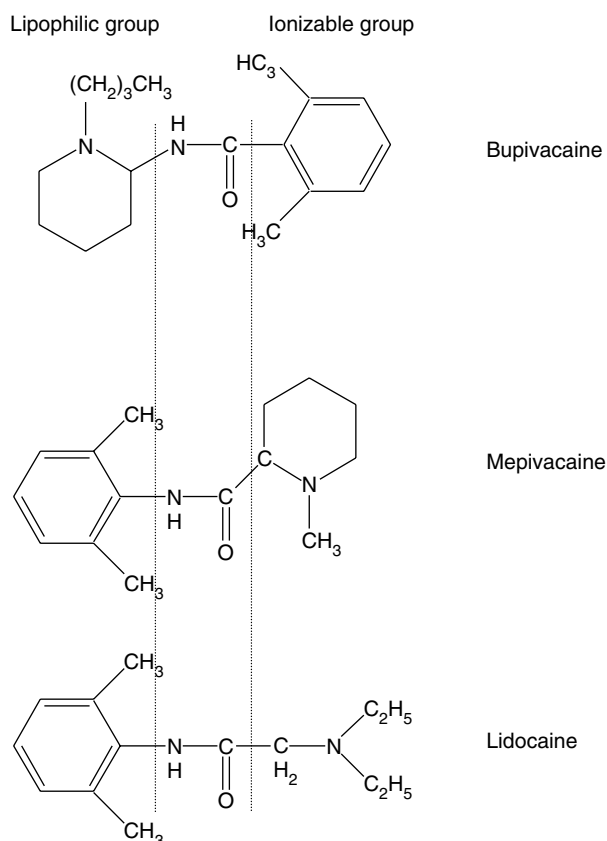


Fig. 3. Chemical structure of local anaesthetics.

intermediate chain, ester or amide, between a lipophilic group and an ionizable group (Fig. 3). The amide LA, which have a thiophene ring contained in the lipophilic group, can have an increased concentration in tissue.

Different types of allergy to lidocaine have been described. Anaphylactic reaction to lidocaine injection is rare. Bonnet et al. (2) described 1 case of anaphylactic reaction and analysed 47 other cases published since 1961. Most patients with a history of allergy to LA are not truly allergic. Retrospectively, Chandler et al. (3) analysed the files of 59 patients with 70 reactions due to LA; there were no positive skin tests nor positive drug provocation challenges in any of the patients. Therefore, an immediate-type hypersensitivity reaction must be differentiated from non-allergic adverse reactions [e.g. vagal malaise, Hoigné's syndrome (4)] or immediate-type hypersensitivity to excipients (e.g. parabens, sodium metabisulfite in epinephrined anaesthetics).

On the other hand, Breit et al. (5) described 1 case of delayed-type hypersensitivity, after an intra-articular injection of lidocaine, associated with a cross-reaction with mepivacaine. This delayed reaction is very uncommon as there is only 1 other case with such a reaction (6) in the literature.

Emla[®] cream is a topical anaesthetic, a 5% eutectic mixture of lidocaine and prilocaine. Cutaneous side effects are usually very mild and transient, including itching, burning, pain, pallor or blanching, erythema, oedema and purpura (7). Dong et al. (8) published 1 case of irritant contact dermatitis induced by Emla[®] cream, with necrosis of keratinocytes on histopathological examination.

Moreover, Emla[®] cream has previously been reported to induce contact dermatitis with delayed-type hypersensitivity (9, 10), due to lidocaine or prilocaine, with frequent cross-reactions or co-sensitization between prilocaine and lidocaine.

In conclusion, we report the first case of immediate-type hypersensitivity to Emla[®] cream, due to immediate sensitization to lidocaine without any cross-reactions with other LA. Cross-reactions between LA may occur between the amide LA but probably not between the structurally unrelated classes such as ester LA. In the literature, only 9 cases of cross-reactions with amide LA have been described.

Breit et al. (5) described 1 case of cross-reaction between lidocaine and mepivacaine. Suhonen and Kanerva (11) reported 1 patient who reacted to prilocaine, lidocaine and articaine. Curley et al. (12) had a patient allergic to lidocaine who also

reacted to prilocaine, mepivacaine and dibucaine. Hardwick and King (13) had a patient sensitized to lidocaine and bupivacaine. Redfern and Waterloo (14) had 1 case of allergy to lidocaine, mepivacaine and ropivacaine. Van Ketel (15) reported 1 case of a reaction to lidocaine, prilocaine and mepivacaine. Fregert et al. (10) had a patient sensitized to bupivacaine, mepivacaine and prilocaine. Black et al. (16) had a patient allergic to lidocaine who also reacted to prilocaine. Bircher et al. (17) had a lidocaine-allergic patient with a cross reactivity to bupivacaine, mepivacaine and prilocaine.

We were surprised to find that Weightman and Turner (18) described 2 patients with positive patch tests to lidocaine and benzocaine, an ester LA. Was this co-sensitization or 2 isolated cases of cross-reactions between amide LA and ester LA? We note that cross-reactions between amide LA with cycle on ionizable group (mepivacaine and bupivacaine) and amide without cycle on ionizable group have been observed (5, 12–15, 17). Consequently, the structure of the ionizable group cannot predict a cross-reaction. In the same way, cross-reactions are described between amide LA and amide LA with a thiophene ring, differentiated by the lipophilic group. Also, cross-reactions might be due to product residue of LA, but nothing has been proven.

Because allergy to amide LA is rare, the cross-reaction groupings among amide LA are not well known. Consequently, hypersensitivities to all LA must be tested in order to advise our patients and their physicians.

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Address:

Pr Annick Barbaud
Service de Dermatologie Vénéréologie
Hôpital Maringer Villemin Fournier
C.H.U. Nancy
36 Quai de la Bataille-54000-Nancy
France
Tel: +33 3 83 85 24 65
Fax: +33 3 83 85 24 12
e-mail: a.barbaud@chu-nancy.fr