DRUG INFORMATION NOTE

Review of a New Topical Anesthetic, Liposomal Lidocaine, for Procedural Pain in Children

Amelia Yip, Herpreet Soin, and Anna Taddio

The introduction of the topical local anesthetic cream EMLA (a eutectic mixture of the local anesthetics lidocaine and prilocaine) revolutionized the management of procedural pain in children. Since lidocaine–prilocaine was first launched over 10 years ago, several other topical anesthetics have become commercially available for use in children, including liposomal lidocaine, the subject of this article. The pharmacologic profile of liposomal lidocaine offers several advantages over lidocaine–prilocaine, including faster onset of action and fewer adverse effects. This drug is currently available in Canada and the United States under the trade names Maxilene 4 (RGR Pharma, Windsor, Ontario) and LMX (formerly ELA-Max; Ferndale Laboratories, Ferndale, Michigan), respectively.

Maxilene 4 is a liposomal encapsulated formula containing 4% lidocaine. Liposomal encapsulation involves the use of lipid bilayers to rapidly deliver the lidocaine into the dermis of the skin. The liposome protects the lidocaine molecule from metabolic processes and from removal by blood circulation and acts as a depot in the epidermis for prolonged release of the drug.[1] The rate at which lidocaine is released into the dermis depends on the stability and permeability of the lipid bilayer in the skin environment. After release, the lidocaine accumulates in the vicinity of pain receptors and nerve endings, where it exerts its local anesthetic action. It stabilizes neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The onset, depth, and duration of dermal analgesia depend primarily on the duration of application.[1]

Effective analgesia is achieved within 30 min of application of liposomal lidocaine and persists beyond 30 min after removal of the cream.[1] The usual dose for adults and children is about 2.5 g, applied to the skin as a small mound, with or without an occlusive dressing.[2] For a child of less than 10 kg the cream should not be applied to an area greater than 100 cm^2 (maximum dose area) (roughly the size of a child's abdomen).[3] The manufacturer states that use in children under the age of 2 years should be carefully monitored[2]; however, liposomal lidocaine can potentially be used in neonates with a maximum dosage similar to lidocaine–prilocaine (1 g per day for infants from 37 weeks gestational age to 3 months).[4] Liposomal lidocaine can be stored at room temperature for up to 3 years.[2]

The documented adverse effects of liposomal lidocaine are localized skin reactions, which may occur during or immediately after treatment. These include erythema, edema, and mild irritation. Allergic reactions due to liposomal lidocaine cream may include urticaria, angioedema, bronchospasm, and shock. In pediatric studies, the incidence of local skin reactions was 12.1%[5] and 43%[6] for skin blanching in 2 separate studies and 1.7% for erythema.[5] Systemic reactions after topical use of liposomal lidocaine have not been reported. However, if a sufficient quantity were absorbed into the systemic circulation, systemic reactions might include central nervous system excitation and/or depression, as well as cardiovascular manifestations including bradycardia, hypotension, and cardiovascular collapse and arrest.[7,8]

A key advantage of liposomal lidocaine over lidocaine–prilocaine is the absence of prilocaine. Lidocaine–prilocaine consists of 2.5% lidocaine and 2.5% prilocaine,[5] and it is the latter that is primarily responsible for increased methemoglobin concentrations in infants, a systemic toxic effect that can occur with overdose or in susceptible populations.[9,10] Increased methemoglobin

concentrations have not been observed with liposomal lidocaine.[11] In addition, products such as lidocaine–prilocaine cause vasoconstriction, which may lead to increased difficulty in performing procedures such as IV cannulation. Lidocaine has fewer vasoconstrictive effects[12] and may prove to diminish some of the difficulties associated with use of topical anesthetics during routine procedures. In addition, the flexibility associated with not having to use an occlusive dressing for liposomal lidocaine may prove beneficial, in that other studies have shown pain and irritation on removal of the occlusive dressing.[3,4]

Liposomal lidocaine is preferable to tetracaine 4% gel (Ametop), another commercially available topical anesthetic that was launched several years after lidocaine–prilocaine. Liposomal lidocaine and tetracaine both have an onset of action of 30 min and lack the systemic adverse effect of methemoglobinemia[8]; however, tetracaine requires refrigeration and is more likely to cause hypersensitivity reactions following repeated use.[13]

The efficacy of liposomal lidocaine in adults has been well established,[14-17] but to date only a handful of studies have been performed in children.[4-6,18,19] In 4 of the 5 studies, liposomal lidocaine was compared with lidocaine–prilocaine. In the first of these, Eichenfield and others[5] used a blinded crossover trial to compare the 2 anesthetics during venipuncture. A total of 120 children 5 to 17 years of age were recruited from the community for double randomization (treatment regimen [application of study medication for either 30 or 60 min] and order of application of the topical anesthetics [lidocaine–prilocaine first or liposomal lidocaine first]) for 2 separate venipunctures. In all groups, mean scores on a visual analogue scale ranging from 0 mm (no pain) to 100 mm (worst possible pain) were 10 mm or less, and there were no significant differences between groups. The investigators concluded that for venipuncture, application of liposomal lidocaine for 30 min without occlusion was equivalent to application of lidocaine–prilocaine for 60 min with occlusion.[5] Side effects that occurred in the group that received liposomal lidocaine included pallor (12.1%), erythema (1.7%), skin discomfort (1.7%), and pruritis (1.7%).

Two other studies compared lidocaine–prilocaine with liposomal lidocaine, both applied with an occlusive dressing, in children undergoing IV cannulation. Kleiber and others[4] conducted a randomized crossover trial with 30 pediatric volunteers (7 to 13 years old) who received both anesthetic treatments, and Koh and others[6] conducted a single-treatment design study with 60 children 1 to 10 years of age who were randomly assigned to receive lidocaine–prilocaine or liposomal lidocaine. In both studies there was no difference in pain scores between the 2 treatment groups. Kleiber and others[4] reported mean pain scores of 20.5 (standard deviation [SD] 22.7) for lidocaine–prilocaine and 24.0 (SD 17.6) for liposomal lidocaine on the validated Oucher pain scale, which ranges from 0 (no pain) to 100 (worst pain). Koh and others[6] reported mean pain scores of 26.8 (SD 27.5) for lidocaine–prilocaine and 25.7 (SD 25.3) for liposomal lidocaine on a visual analogue scale ranging from 0 (no pain) to 100 (worst pain). Koh and others[6] also found significantly more blanching in the group treated with lidocaine–prilocaine (67% of the subjects treated with lidocaine–prilocaine but only 43% of those treated with liposomal lidocaine had blanching; $p = 0.04$), but this difference did not make the procedure more difficult for the technician.

Luhmann and others[18] compared application of liposomal lidocaine with SC injection of lidocaine buffered with sodium bicarbonate in 69 children 4 to 17 years old who were undergoing IV cannulation. There was no difference in pain scores (visual analogue scale) between the 2 groups. Average pain scores were 3.4 (SD 2.9) for SC lidocaine and 2.6 (SD 2.5) for liposomal lidocaine ($p = 0.19$) on a scale ranging from 1 (no pain) to 10 (most painful). No side effects were documented. The findings of this study indicate that liposomal lidocaine, a less invasive method of pain control, is comparable in effect to buffered lidocaine administered subcutaneously.

Smith and others[19] investigated pain during office meatotomy in children pretreated with liposomal lidocaine or lidocaine–prilocaine for 30 min or 45 min. With the 30-min application time, liposomal lidocaine was more effective in decreasing pain than lidocaine–prilocaine. Mean pain scores were 1.1 (SD 2.9) for liposomal lidocaine and 1.8 (SD 2.6) for lidocaine–prilocaine ($p < 0.05$) on the Wong-Baker Face pain scale, which ranges from 0 (no pain) to 10 (worst pain). With the 45-min application time, the mean pain scores were 0.3 (SD 0.8) for liposomal lidocaine and 0 for lidocaine–prilocaine ($p > 0.05$). No side effects were documented.

Cost comparisons indicate that of the 3 commercially available topical local anesthetics — lidocaine–prilocaine, tetracaine gel, and liposomal lidocaine — lidocaine–prilocaine is the least expensive, with a list price of $1.00 per gram. Tetracaine costs $2.29 per gram, and liposomal lidocaine costs $1.16 per gram (all cost data according to the Hospital for Sick Children Hospital contract for 2005). Lidocaine–prilocaine is available in

5-g and 30-g tubes or as a 1-g patch. Tetracaine is available only in a single-dose tube (1.5 g), and liposomal lidocaine is available in a 5-g or a 30-g tube. For both lidocaine–prilocaine and tetracaine, a Tegaderm dressing (3M, St Paul, Minnesota) is distributed with the cream by the manufacturer;, however, no dressing is provided with liposomal lidocaine, and the total cost of administration must be adjusted to account for the extra cost of the dressing (if occlusion is used).

In summary, liposomal lidocaine is a new topical anesthetic that offers advantages over previously available products, including short onset of action, lack of systemic adverse effects, infrequent local reactions, and the option of application without a dressing. Liposomal lidocaine is therefore a good candidate for routine use in children undergoing painful cutaneous procedures.

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Amelia Yip, BSc, MSc, is a Clinical Research Assistant, Department of Pharmacy, The Hospital for Sick Children, and Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

Herpreet Soin, BScPhm, is a Pharmacist with the Department of Pharmacy, The Hospital for Sick Children, Toronto, Ontario. She is also a Master of Science candidate in the Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

Anna Taddio, BScPhm, MSc, PhD, is a Scientist with the Department of Pharmacy and Population Health Sciences, Research Institute, The Hospital for Sick Children, and Graduate Faculty of Pharmaceutical Sciences, University of Toronto, Toronto, Ontario.

Address correspondence to:
Dr Anna Taddio
Department of Pharmacy
The Hospital for Sick Children
555 University Avenue
Toronto ON
M5G 1X8

e-mail: anna.taddio@sickkids.ca