Evaluation of Liposomal Delivery System for Topical Anesthesia

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Local anesthesia is an integral aspect of cutaneous surgery. Its effects provide a reversible loss of sensation in a limited area of skin, allowing dermatologists to perform diagnostic and therapeutic procedures safely, with minimal discomfort and risk to the patient. Moreover, the skin acts as a major target as well as principle barrier for topical/transdermal (TT) drug delivery. The stratum corneum (SC) plays a crucial role in barrier function for TT drug delivery. Despite the major research and development efforts in TT systems and their implementation for use of topical anesthetics, low SC permeability limits the usefulness of topical delivery, which has led to other delivery system developments, including vesicular systems such as liposomes, niosomes, and proniosomes, with effectiveness relying on their physiochemical properties. This review gives in-depth coverage of liposomes and their use as a delivery route for topical anesthetics.

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Topical anesthetics were developed in the latter half of the 19th century, beginning with topical use of cocaine. However, it has taken nearly a century for effective and safe topical anesthetics to become readily available. Currently, pain can be effectively alleviated for procedures such as cryotherapy, shave biopsy, and curettage of molluscum contagiosum. Procedures such as laceration repair, which at one time required the use of painful infiltrative anesthetics, now can be accomplished safely and comfortably with the use of topical anesthetics.[1] Topical anesthetics originated in South America; native Peruvians noted perioral numbness when chewing the leaf of the cocoa plant (*Erythroxylon coca*). The active alkaloid, cocaine, was isolated by Niemann in 1860 and applied to conjunctival mucosa for topical anesthesia by Koller in 1884. The development of similar benzoic acid esters continued until 1943 when Loefgren synthesized lidocaine hydrochloride, the first amide anesthetic.[2]

We review the administration of local anesthetics, specifically the liposomal delivery system for topical anesthesia, based on a review of the literature and clinical experience.

Anatomy

The epidermis and dermis each play a distinct role in the pharmacology of topical anesthetics. The epidermis, an avascular layer measuring 0.12 to 0.70 mm in thickness, functions as a barrier to the diffusion of topical anesthetics. Within the epidermis, the lower compact portion of the stratum corneum (SC) is the most effective barrier.[3] The ability of an anesthetic to penetrate the SC depends on its negative logarithm of the ionization constant (pK_a). The time of onset of local anesthesia, therefore, is predicated on the proportion of molecules that convert to the tertiary lipid-soluble form when exposed to physiologic pH (pH 7.4). The ionization constant (pK_a) for the anesthetic predicts the proportion of molecules that exists in each of these states.[4]

By definition, the pK_a of a molecule represents the pH at which 50% of the molecules exist in the tertiary lipid-soluble form and 50% exist in the quaternary water-soluble form. The pK_a of all local anesthetics is greater than 7.4 (physiologic pH); therefore, a greater proportion of the molecules exists in the quaternary water-soluble form when injected into tissue that has a normal pH of 7.4.[5]

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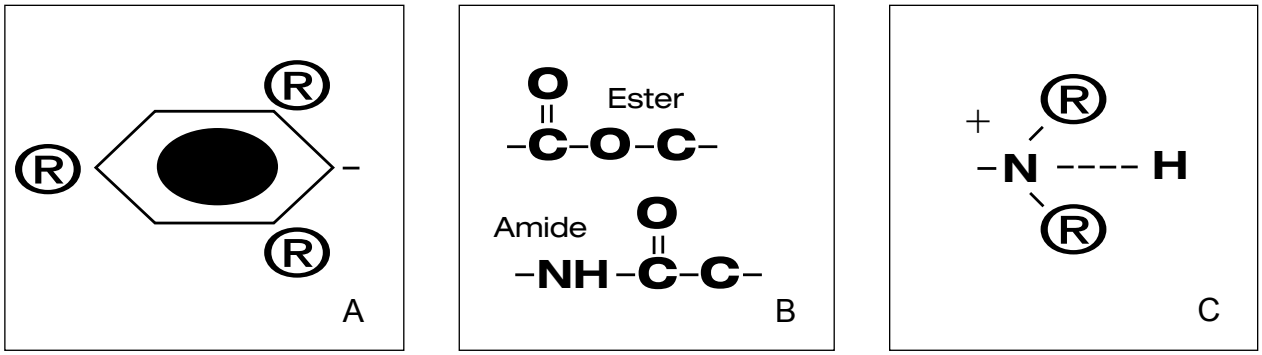

Figure 1. Structure of local anesthesia. Composed of a lipophilic aromatic ring (A); an intermediate chain of either an ester or amide (B), which defines the anesthesia as an ester anesthesia or amide anesthesia; and a hydrophilic terminal amine (C).

In simple words, local anesthetics require a higher pH than the normal physiologic pH of the body (pH ≥7.4) to have more permeability, which explains why the acidic environment associated with inflamed tissues favors the quaternary water-soluble configuration of anesthetics and renders them less permeable.

Absorption of anesthetics is further enhanced by numerous fingerlike protrusions of mucosal cells, which interdigitate with cells of dermal tissue. Chemically, mucous membranes absorb the salts of local anesthetics as readily as the bases and produce a similar blockade.[6] When anesthetics are applied to mucous membrane surfaces, the blood levels of the mucous membrane are similar to intravenous injection and the mucosa vasculature is very rich, depending on the area exposed, the anatomic site, the concentration, and the total quantity applied.[7] Furthermore, in comparison of the effects on mucosa versus skin after anesthetic removal, anesthesia persists longer in the mucosa.[3]

Structure of Local Anesthetics

The local anesthetic molecule consists of 3 components: lipophilic aromatic ring, intermediate ester or amide chain, and hydrophilic terminal amine. Each of these components contributes distinct properties to the molecule (Figure 1).[4,8,9]

For local anesthetics to diffuse through neural membranes, lipophilic properties are required, while protein binding requires hydrophilic properties.[10] The clinical properties of local anesthetics and their characteristics are summarized in Table 1.

Pharmacologic Factors Affecting Topical Anesthesia Penetration and Efficacy

Integrity of the epidermis, heat, occlusion, lipid solubility, type of anesthetic, and other factors that influence local anesthetic distribution and plasma concentrations affect the penetration of the anesthetic. Moreover, a patient's age, liver function, and cardiovascular status, as well as the degree of protein binding and the drug delivery system, all affect the anesthetic's penetration.[11]

Table 1.

Characteristics and Clinical Correlations of the Properties of Local Anesthetics

Characteristic	Clinical Correlation	Explanation
Lipid solubility	Potency	Enhances diffusion through neural membrane
Dissociation constant	Time of onset	Determines the proportion of anesthetic in lipid-soluble form
Chemical linkage	Metabolism	Esters hyrolyzed in plasma by cholinesterases, amides biotransformed in the liver
Protein binding	Duration	Affinity to plasma protein determines longevity

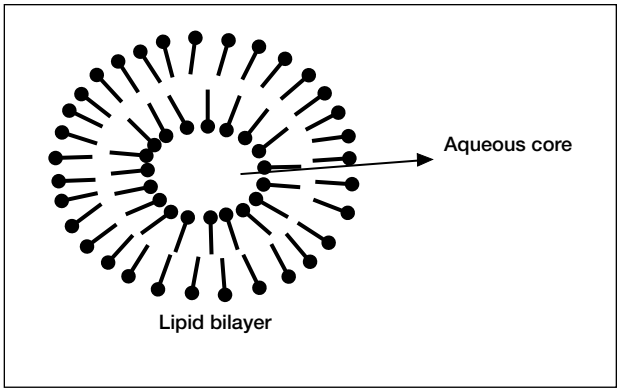

Figure 2. Basic vesicular delivery system structure. The lipid bilayers are separated by water or aqueous buffer compartments.

Delivery Systems

The skin is a major target for topical/transdermal (TT) drug delivery. The SC provides a main barrier against drug transport, and SC intercellular lipids help to regulate penetration. This lipid matrix, which is composed of ceramides, free fatty acids, cholesterol sulphate, and minor lipids, plays a major role in barrier function.[12,13] Despite the advantages of TT drug delivery, low SC permeability may limit its usefulness. To increase permeability, chemical and physical approaches, including tape stripping[14-17]; iontophoresis[18-20]; electroporation[18,19,21-24]; and vesicular delivery systems, such as liposomes and niosomes,[25-28] have been examined to lower SC barrier properties.

Vesicular Delivery Systems

Various vesicular delivery systems have been developed and have attracted considerable attention in TT drug delivery for many reasons. These penetration enhancers are biodegradable, nontoxic, amphiphilic, and effective in the modulation of drug-release properties. Their effectiveness is largely dependent on their physiologic properties, such as composition and size, and on the application conditions.

Most drugs permeate via the intercellular lipid matrix, such as the intercellular and transcellular routes. However, vesicular delivery systems use the following 3 potential pathways of drug permeation into the viable tissue: (1) through hair follicles with associated sebaceous glands; (2) via eccrine sweat ducts; or (3) across continuous SC, between appendages. Follicular pathway is important for small or macromolecule delivery with vesicular systems. The pilosebaceous unit (hair shaft, hair follicle, and sebaceous gland) provides a route that bypasses the intact SC, which makes it more permeable.[29]

Liposomes

Liposomes are microscopic vesicles composed of one or more concentric lipid bilayers that are separated by water or aqueous buffer compartments (Figure 2); the diameter of liposomes ranges from 80 nm to 10,000 nm. Liposomes (also called phospholipid vesicles) were first described by Bangham.[30,31] These vesicles, which are composed of one or more phospholipid bilayer membranes, can entrap both hydrophilic and hydrophobic drugs, depending on the nature of the drug. Hence, it is possible to apply water-insoluble drugs in liquid form. Based on their size, liposomes are known as either small or large unilamellar vesicles (10–100 or 100–3000 nm, respectively). If more than one bilayer is present, the liposomes are referred to as multilamellar vesicles. The effectiveness of liposomes in ocular drug delivery depends on a number of factors, including drug encapsulation efficiency and the size and surface charge of the liposomes.[32]

Liposomes may permeate follicles via a lipid-rich channel that coats the follicular duct, with subsequent entry into the follicular cells. It has been suggested that liposome-entrapped molecules could be incorporated into hair shafts by delivery of the molecules into the follicle matrix cells and by differentiation of matrix cells into hair shafts through the process of follicular maturation.[33] Small and large molecules can be conveyed to the skin through the follicular pathway using the vesicular systems. The liposomal delivery system is the first vesicular system reported to facilitate a 3- to 5-fold accumulation increase within the epidermis and dermis.[21,22] Liposomes have several functions in TT delivery, including a retention effect into the SC and an enhancing effect. In the case of anesthetics, liposome formulations penetrate more than control formulations and have a higher retention in the SC.[29]

Liposomal Delivery Systems in Topical Anesthetics

Two creams containing lidocaine 4% and 5% are available and are supplied in a patented liposomal delivery system. A patented liposomal delivery system containing lidocaine 4% in a liposomal matrix is available over-the-counter. The product is US Food and Drug Administration–approved for the temporary relief of pain from minor cuts and abrasions of the skin, minor burns, minor skin irritation, and insect bites. The cream is applied to intact skin for 15 to 40 minutes without occlusion.[30,32] The product is free of both ester and prilocaine hydrochloride and does not require occlusion or a prescription. Onset of anesthesia on the lip occurs within 15 minutes of application; anesthesia occurs within 30 minutes on keratinized skin. Anesthesia equivalent to lidocaine 2.5% plus prilocaine 2.5% under occlusion is predicted to occur faster than lidocaine 4% alone.[32] It also has been proven to be

Table 2.

Common Topical Anesthetics and Their Delivery Systems

Product	Active Agent(s)	Rx	Pregnancy Category[a]	Vehicle
EMLA® Cream	Lidocaine 2.5% plus prilocaine 2.5%	Rx required	B	Eutectic cream
ELA-Max® Cream	Lidocaine 4%	OTC	B	Liposomal
L.M.X.4™/L.M.X.5™	Lidocaine 4%/5%	OTC	B	Liposomal
Betacaine®	Lidocaine 5%	OTC	B	Ointment
Lidocaine (for laser therapy)	Lidocaine 30%	Compounded	B	Ointment
Topicaine® 4%/5%	Lidocaine 4%/5%	OTC	B	Gel
Tetracaine	Tetracaine 4%	Compounded	C	Lecithin gel

Abbreviations: Rx, prescription; OTC, over-the-counter.

[a]Pregnancy category B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Pregnancy category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

effective in providing dermal analgesia before chemical peeling.[33] The safety of the product's application to mucous membranes has not been evaluated.[34] Despite a paucity of data and lack of a US Food and Drug Administration indication, clinicians are beginning to use lidocaine cream 4% for topical anesthesia before performing dermatologic procedures. Table 2 describes common topical anesthetics and their delivery systems.

Conclusion

Despite the major research and development efforts in TT systems and their implementation for topical anesthetic use, low SC permeability limits the usefulness of topical delivery. Liposomes represent a favorable form of transdermal delivery for anesthetics; however, several factors affect their permeability across the skin barrier. The efficacy and safety of a delivery system remain as the guidelines for further development of more reliable and efficient transdermal delivery systems.

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