# Topical Anesthetics

## *Anestésicos tópicos*


### ABSTRACT

**Introduction:** The use of topical anesthetics, has increased in recent years. While they are undoubtedly useful when recommended appropriately by a dermatologist, the improper use of topical anesthetics may result in complications, mainly due to inadequately applying them to wounded or inflamed skin; use on large areas of the body or mucus membranes; or use by high-risk patients. Adverse reactions can include transient local effects, allergic and/or irritative reactions, or more severe (though rare) effects, such as methemoglobinemia, arrhythmias, and cardiorespiratory failure. This paper discusses the commercial formulations of topical anesthetics currently available, their history, pharmacology, clinical use, and potential side effects.



**Keywords:** anesthetics; analgesia; lidocaine; prilocaína; tetracaine.



### *RESUMO*

***Introdução:*** *Os anestésicos tópicos, de indiscutível utilidade na rotina do dermatologista, têm sido cada vez mais utilizados pela população, nem sempre com prescrição e supervisão médica. Seu uso pode envolver complicações ligadas, principalmente, à aplicação inadequada, seja em pele lesada ou inflamada, em grandes áreas corporais, em mucosas ou em pacientes de risco. As reações adversas podem variar desde efeitos locais transitórios, reações alérgicas e/ou irritativas, até quadros mais graves, embora raros, como metemoglobinemia, arritmias e insuficiência cardiorrespiratória. Este artigo visa discutir as preparações comerciais de anestésicos tópicos hoje disponíveis, seu histórico, farmacologia, aplicação clínica e complicações.*



***Palavras-chave:*** *anestésicos; analgesia; lidocaína; prilocaína; tetracaína.*


## INTRODUÇÃO

The recent growth in the demand for cosmetic and surgical procedures has resulted in the increased use of topical anesthetics, which are necessary to control pain in order to ensure patients' comfort and better treatment results. Unfortunately, topical anesthetics are being indiscriminately used without a prescription – which raises questions about their safety. Nevertheless, in spite of the controversy, they have been used for a long time, with considerable security. The first reference to the use of topical anesthetics is from South America: the native inhabitants of Peru noticed perioral numbness when chewing coca leaves (Erythroxylon coca). The active alkaloid (cocaine) was isolated by Niemann in 1890 and used to anesthetize conjunctival mucous membranes by Koller in 1884. The development of esters similar to benzoic acid continued up until 1943, when Loefgren synthesized lidocaine, the first anesthetic amides. Since then, several combinations of amides, esters and adrenaline have been used for small surgeries and cutaneous procedures.[1]

## Continued Medical education


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We are still far from obtaining the ideal topical anesthetic, which would swiftly and effectively reduce pain over a prolonged period of time with minimum side effects. It would also be easy to apply and remove, with an agreeable cosmetic impact when applied.[2] The appropriate selection of topical anesthetics will depend, therefore, on the characteristics of the drug compound the vehicle used, and where it will be applied.

This article's objective is to review the commercial preparations currently available in Brazil, their mechanism of action clinical use, and adverse reactions.

## CUTANEOUS ANATOMY AND ANESTHETICS ABSORPTION

The epidermis serves as a barrier to the penetration of topical medicines, including anesthetics. The epidermis is an avascular layer of skin, with a thickness of between 0.12 and 0.7 mm. The stratum corneum – constituted of water and lipids that hamper the diffusion of the anesthetic towards the dermis – is the least penetrable layer, and is relatively impermeable to ionized molecules. Compounds with a higher concentration of neutral bases achieve better penetration in the stratum corneum.[1]

The anesthetic's capacity to penetrate the stratum corneum depends on the agent's pKa, a chemical parameter that indicates at which pH the ionized (salt) and non-ionized (base) forms of a drug exist in similar amounts.[3] The closer the agent's pK is to the skin's pH, the larger the amount of base formed and, therefore, the better the penetration.[2,3]

The removal of the stratum corneum results in a larger concentration of anesthetic in the dermis. The intentional removal can be accomplished using microdermabrasion or an ablative laser in low flow rates.4 Degreasing the skin with alcohol or acetone (and hydrating it) also increases the anesthetic's penetration. Due to the absence of stratum corneum in mucous surfaces, topical products take effect almost immediately, but their systemic absorption is also higher. Conversely, due to the stratum corneum thickness in the palmar-plantar areas, topical anesthesia is ineffective in those sites.[1,4]

## MECHANISM OF ACTION

The sensation of pain depends on the ability to transmit nerve impulses, which in turn depends on the propagation of the stimulus along the nerve fiber. That transmission is only possible due to the difference in concentrations of sodium and potassium in the intra and extracellular fluids, which establishes an ionic gradient between the means. That gradient is sustained by the Na+/K+ ATPase pump. When in resting state, the extracellular element is positive in relation to the intracellular element. When nerve excitation takes place, the membrane's permeability to sodium increases, causing a temporary depolarization called "action potential."5 The return to the original state (initial gradient) is made by decreasing the permeability to sodium and the activity of the Na+/K+ ATPase. Topical anesthetics inhibit the depolarization of the fiber, thus blocking the transmission of the pulse. The exact mechanism that causes this process is not yet well established.[5,6,7]

The painful stimuli are transmitted by small unmyelinated nerve fibers – which are more sensitive to anesthetics than myelinated fibers that transmit other types of sensations. Consequently, patients may feel pressure and vibration yet be insensitive to pain.[5]

Topical anesthetics are biochemically classified into two functional groups: esters and amides. Their basic structure consists of a lipophilic aromatic ring and a hydrophilic amine group connected by an intermediate chain. This chain is the basis for classifying the anesthetics into esters or amides. [1,3,5] (Figure 1)

The main difference between the two groups is their chemical stability. Esters are relatively unstable in solution, and easily metabolized in the plasma by pseudo-cholinesterase. One of their metabolites is para-aminobenzoic acid (PABA), which has considerable allergenic potential. Amides are more stable, have a smaller sensitization capacity, and are metabolized in the liver.[3,5]

Other pharmacologic factors – such as liposolubility, ability to form protein linking , pKa, and local vasodilatation – determine the agent's penetration and efficacy. Lipophilic molecules are swiftly diffused through the epidermis and inside nerve terminals. Once in the dermis, the molecules that have a higher capacity to from links with proteins are more stable, leading to a more prolonged analgesia. The anesthetic formulation's components that cause vasoconstriction can prolong the duration of the anesthesia and reduce its serum concentration. The effects of local heat can increase or possibly reduce the penetration of some anesthetics. Heat can cause vasodilatation and, consequently, enhance systemic absorption, increasing toxicity and reducing duration. Occlusion is an additional factor that increases the permeability of anesthetics by increasing the temperature and hydration of the stratum corneum.[1,2,5]

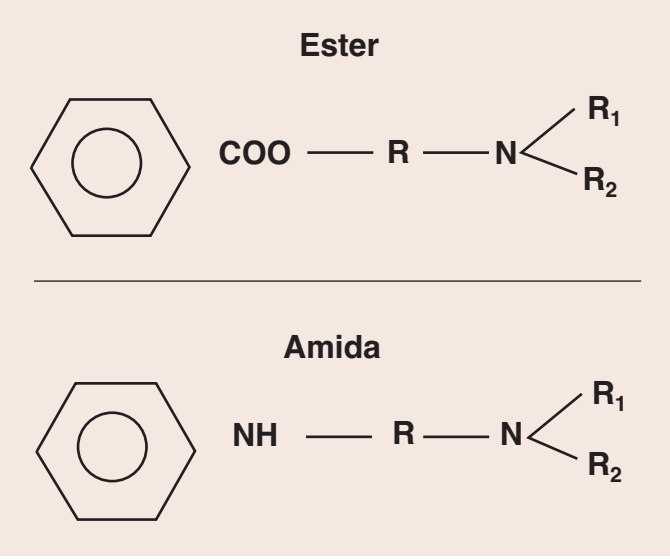


**Figure 1:** structural differences between anesthetics of the ester and amides groups.[5]

## EMLA® (EUTETIC MIXTURE OF LOCAL ANESTHETICS)

EMLA® is a topical anesthetic used worldwide, with proven safety and efficacy.[9,10,11,12] EMLA® is an emulsion; the oily phase is an eutectic blend of 2.5% lidocaine and 2.5% prilocaine, that, at room temperature are crystals that are nor absorbed by the skin. The eutectic blend is a compound with a melting point lower than that of its separate components. At room temperature, the compound is predominantly in a liquid state.[2,8,9,10]

It is recommended that EMLA® be applied on intact skin, under occlusion, for at least one hour. The duration of the application is directly correlated to the depth of the analgesia, which reaches 3 mm after 60 minutes and 5 mm after 120 minutes. It has a biphasic action on the vasculature, causing vasoconstriction up to 90 minutes and vasodilatation 2 to 3 hours after the application.[2,10] Its adverse effects are mainly local. On rare occasions it can cause an itching or burning sensation and purpura.[1,12] The cream's alkaline pH can cause lesions to the conjunctival mucous membrane.[1]

Lidocaine is an amide-type anesthetic that may (as with the other amides) cause serious allergic reactions on rare occasions. Any allergic contact dermatitis caused by EMLA® is usually caused by the prilocaine.[11,13] The systemic absorption of lidocaine causes dose-dependent adverse effects. The first phase of the symptoms of such toxicity includes buzzing, perioral paresthesia, and a metallic taste. Patients may first become somnolent, and later agitated, apprehensive and talkative due to the impact on the central nervous system. If such reactions occur, the topical medication must be removed completely and cardiovascular resuscitation procedures should be considered.[14] The second phase of the adverse reaction is a generalized tonic-clonic seizure. The third phase is characterized by cardiovascular and respiratory depression in addition to arrhythmias.[1]

Prilocaine is also an amid-type anesthetic. Methemoglobinemia is its most serious adverse effect. It develops with the oxidation of the ferrous (+2) to the ferric (+3) form of the iron, which makes the hemoglobin molecule unable to transport oxygen. This phenomenon normally takes place inside the erythrocytes, however methemoglobin is constantly reduced to hemoglobin by the NADH-methemoglobin-reductase. Ortho-toluidine, prilocaine's metabolite, prevents the reduction of the ferric ion into ferrous iron. Increased methemoglobin levels (5 to 15%) result in cyanosis; respiratory insufficiency – and possibly death – may occur at levels above 15%. Infants, especially premature ones, are more susceptible to this complication due to the immaturity of their methemoglobin-reductase enzyme. Other high-risk patients are those with glucose 6-phosphate dehydrogenase deficiency or using medicines that induce methemoglobinemia (Table 1). The treatment for methemoglobinemia is based on the use of oxygen and methylene blue.[1,2,12,15,16] While potentially serious, the development of methemoglobinemia is rare, even in infants.[17,18]

The maximum dose of EMLA® depends on the patient's age and weight, the treated surface, the duration of application, and the integrity of the cutaneous barrier, as well as on liver and kidney functions. The maximum

dose in children is calculated based on body weight (Figure 2). In adults, as an approximate parameter, application on wounded or inflamed skin (or on surfaces larger than 2,000 cm2) may cause systemic effects.[2]

## ELA-MAX®

ELA-max® is a topical anesthetic composed of 4 or 5% lidocaine, presenting a liposomal distribution system that uses multilamellar vesicles comprised of several lipidic layers dispersed in aqueous element. The 4% concentration is marketed in Brazil under the name Dermomax®. The liposomes allow the anesthetic's penetration in the skin by carrying the encapsulated drug to the dermis and promoting its gradual liberation; the liposomes also protect the anesthetic from metabolic degradation, increasing the duration of the effect.[9,19,20,21] The recommended duration for application is 15 to 45 minutes, without the need for occlusion. Its use in mucous membranes is not recommended, for there are no studies demonstrating a safe dose in such areas.[2]

The adverse effects of ELA-max® are the same as those described for the lidocaine component of EMLA®. After an application of 60 g ELA-max® on a 400 cm2 skin surface for a period of 3 hours, the serial levels of lidocaine vary from 0.05 to 0.16 mcg/ml. Toxic levels occur in concentrations higher than 5 mcg/ml. A single application in children weighing less than 10 kg must not cover an area larger than 100 cm2, and in children weighing 10-20 kg it must not cover an area larger than 200 cm[2.1,2,19]

## TETRACAINE

Tetracaine is an ester-type anesthetic that is not found in industrialized formulations in Brazil – it is only available for dispensing in that country. In Europe it is marketed under the commercial name of Amethocaine®.1 Tetracaine gel is not approved by the FDA, and in Brazil, is only available for dispensing. .[9]

It is more lipophilic than lidocaine or prilocaine, and can permeate the stratum corneum more easily and form deposits

**Chart 1 - Main substances associated with methemoglobinemia [2]**

| Main substances associated with methemoglobinemia | |
|---|---|
| Acetaminophen | Naphthalene |
| Anilines | Nitrites/Nitrates |
| Benzocaine | Nitrofurantoin |
| Chloroquine | Nitro-glycerine |
| Dapsone | Nitroprusside |
| Phenacetin | Paraquat/monolinuron |
| Phenobarbital | Primaquine |
| Phenoperidine | Quinine |
| Flutamide | Sulfamethoxazole |
| Metoclopramide | Sulphonamides |

| Chart 2 - Maximum doses and areas of application for EMLA in children [2] | | | |
|---|---|---|---|
| **Age** | **Weight** | **Total maximum dose and duration of application** | **Maximum area of application (cm2)** |
| 1-3 months | < 5kg | 1g (1hour) | 10 |
| 4-12 months | > 5kg | 2g | 20 |
| 1-6 years | > 10kg | 10g | 100 |
| 7-12 years | > 20kg | 20g | 200 |

there. These deposits are gradually liberated, reducing systemic absorption and prolonging the duration of the anesthetic effect.[1]

The most common side effects are local pruritus, edema and erythema. In the dermis, tetracaine is hydrolysed by unspecific tissular esterases into PABA, which is responsible for the allergic reactions. Its use is not recommended in mucous membranes, due to the absence of studies about its safety.

S-Caine Peel® is a eutectic blend of 7% lidocaine and 7% tetracaine that has been recently approved by the FDA. The product is applied on the skin using a creamy vehicle, and should remain in contact for 60 minutes. After drying, it turns into a flexible and easy-to-remove membrane.[16]

## ANESTHETICS IN MUCOUS MEMBRANES

### OROPHARYNX

There are numerous topical preparations of lidocaine available for analgesia of the oropharynx: 2% and 5% solutions, and 5% ointments. They are indicated for decreasing the pain in surgical procedures, and for symptomatic control of mucositis and stomatitis aphthosa. The anesthetic effect is practically immediate, and the plasmatic levels are similar to those associated with intravenous injection. The maximum dose should not exceed 4.5 mg/kg or 300 mg for a 70 kg adult, and 100 mg for a 50 kg child.[2]

Benzocaine 20% in liquid, gel or spray is used for relieving the pain in mucositis, gingivitis, and pharyngitis; for facilitating the placement of orotracheal and nasotracheal probes; and as an adjuvant for local anesthesia. Food ingestion should be avoided for one hour after application due to difficulties in swallowing and possible aspiration. Since it is in the ester group, allergic reactions are possible. Its application to large and inflamed areas is contraindicated because of the increased absorption. Although rare, there is a risk of toxicity, including methemoglobinemia.[2]

### OPHTHALMIC MEMBRANES

There are several proparacaine- and tetracaine-based formulations for ophthalmologic use. Risks are minimal when used in the recommended concentrations and doses; however, repeated or prolonged use can delay epithelial healing and cause cornea ulcerations.[2,1]

## DISCUSSION

The use of topical anesthetics (with and without medical supervision) has grown significantly over the last few years, causing concerns about the risks of improper use. In the United States, the FDA published a public health alert in 2008 that described the deaths of two women (22 and 25 years old) who used topical anesthetics on the legs, under occlusion, before laser-based epilation. In both cases, the anesthetics were creams that contained high concentrations of lidocaine and tetracaine, which had been dispensed at pharmacies.[22] In January 2009, the FDA issued another public health alert on the subject, in addition to a letter addressed to physicians that warned about the potential risks of the incorrect use of those substances.[23,24] In particular the letter highlighted a recent study by Lambertz et al that compared the efficacy of the topical application of 4% lidocaine gel to oral acetaminophen or ibuprofen to reduce pain and discomfort during mammographies. The study concluded that the use of topical lidocaine significantly reduced

discomfort during the examination.[25] Although no serious adverse reactions were described, the FDA fears that using such medication without medical supervision may lead to an increase in adverse effects.

Several studies demonstrate that using the recommended doses of commercially available topical anesthetics is safe. Physicians should be aware, however, of the risks that can occur if they are inappropriately used: application to large areas, on wounded or inflamed skin, in mucous membranes, in high-risk patients, and when associated with injectable anesthetics. Physicians should also be careful that dispensed preparations do not to exceed the maximum dose, taking into account that the absorption may not be of the same as that of the industrialized products. ●

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# QUESTIONS FOR CONTINUING MEDICAL EDUCATION (CME)

**1. All of the following are conditions that allow a better penetration of topical anesthetics in the skin except for:**

a) Higher hydro solubility of the medicine
b) Degreasing with acetone
c) Agent's pKa close to the skin's pH
d) Previous use of ablative laser
e) Occlusion

**2. The following alternative is correct regarding topical anesthetics:**

a) Amides group substances are more easily metabolized in the plasma by the enzyme pseudocholinesterase than those in the esters group
b) The amides are more stable in solution than the esters
c) The metabolite generated by the degradation of amides anesthetics is para-aminobenzoic acid (PABA), meaning that this anesthetics group has a greater sensitization potential
d) Esters-type anesthetics are metabolized in the liver
e) The amides have greater sensitization potential

**3. All of the factors below are linked to higher risks of systemic adverse effects except for:**

a) Renal or hepatic insufficiency
b) Occlusion
c) Application on palms and soles
d) Application to mucous membranes
e) Application on inflamed skin

**4. Methemoglobinemia is a side effect mainly caused by which anesthetic substance?**

a) Tetracaine
b) Xylocaine
c) Lidocaine
d) Prilocaine
e) Cocaine

**5. Signs and symptoms of the first phase of intoxication by lidocaine are:**

a) Cyanosis and dyspnea
b) Pruritus, erythema and edema
c) Buzzing, metallic taste, perioral paresthesia
d) Angioedema
e) Seizures and cardiorespiratory failure

**Key**
Prophylaxis in dermatologic surgery. 2010; 2(1): 47-53.

1c | 2e | 3d | 4a | 5c | 6c | 7d | 8b | 9a | 10b

**Answers must be submitted at www.surgicalcosmetic.org.br. The deadline for answering the questionnaire will be in the e-mail containing the direct link to access the Journal.**

**6. Anesthetic substances belonging in the amides functional group are:**

a) Lidocaine and tetracaine
b) Prilocaine and lidocaine
c) Prilocaine and tetracaine
d) Benzocaine and tetracaine
e) Tetracaine and cocaine

**7. All of the below alternatives regarding adverse reactions of topical anesthetics are correct except for:**

a) Allergic contact dermatitis is more commonly caused by lidocaine than prilocaine
b) Edema, erythema and pruritus at the application site are the most common side effects of tetracaine
c) Unintentional contact with topical anesthetics in cream may lead to a lesion in the conjunctival mucus caused by the formulation's alkaline pH
d) Serious allergic reactions to topical anesthetics are very rare
e) Even in infants, methemoglobinemia is a rare event

**8. The treatment of methemoglobinemia caused by the use of topical anesthetics is made using:**

a) Activated coal
b) Oxygen and dialysis
c) Sodium bicarbonate
d) Oxygen and Prussian blue
e) Oxygen and methylene blue

**9. The following are risk factors for methemoglobinemia caused by topical anesthetics, except for:**

a) A deficiency of glucose-6-phosphate dehydrogenase enzyme
b) Concomitant use of paracetamol
c) Prematurity
d) Concomitant use ofdapsone
e) Concomitant use ofmetoclopramide

**10. Regarding topical anesthetics, it is correct to assert that:**

a) The use of topical anesthetics is not associated with a risk of death
b) Topical anesthetics can never be applied to children less than 2 years old due to the high risk of methemoglobinemia
c) The absorption of anesthetics in dispensed preparations is not always equal to that of commercial products, even when in similar concentrations
d) The association of topical anesthetics with injectable anesthetics does not pose an additional risk
e) In adults, the application of EMLA in areas greater than 200 cm2 can cause systemic side effects