

MODERN ASPECTS REGARDIND THE USE OF LOCAL ANESTHETIC MEDICINES IN DERMATOLOGIC SURGERY

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Abstract

Effective cutaneous anesthesia is an important component of dermatologic surgery. The use of local anesthetics provides anesthesia, necessary for a variety of diagnostic and therapeutic procedures in dermatology while avoiding the potential risks associated with general anesthesia. Modern researches provide new anesthetic formulations that have superior safety and efficacy profiles. Several anesthetic agents are nowadays available, suited for different applications and techniques of administration. The purpose of this review is to summarize the pharmacology and clinical applications of local anesthetics in the expanding field of procedural dermatology.

Rezumat

În chirurgia dermatologică anestezia locală reprezintă o etapă importantă în abordarea cu succes a procedurilor aferente acestei discipline. Anestezia locală este preferată în procedurile cutanate chirurgicale diagnostice și terapeutice, evitând riscurile crescute de morbiditate și mortalitate asociate anesteziei generale. Cercetările în domeniu au dus la apariția de noi substanțe cu efect anestezic local, cu eficacitate și siguranță superioară. Astfel, chirurgia dermatologică actuală beneficiază de numeroase substanțe anestezice și metode variate de administrare ale acestora. Eficacitatea acestora depinde, în mare măsură, de cunoașterea și înțelegerea proprietăților farmacologice, precum și a tehnicilor corecte de administrare. Lucrarea prezintă proprietățile farmacologice și aplicațiile clinice ale substanțelor anestezice locale necesare abordării corecte a intervențiilor în domeniul chirurgiei cutanate.

Keywords: local anesthetics, pharmacology, techniques of administration, dermatologic surgery

Introduction

While pharmacologic therapies are still a vital part of the dermatologist's *armamentarium*, surgery has become an indispensable tool in the diagnosis, treatment and cure of many cutaneous conditions. Effective

cutaneous anesthesia is an important component of dermatologic surgery. Current use of local anesthetics provides anesthesia, necessary for a variety of diagnostic and therapeutic procedures in dermatology while avoiding the potential risks associated with general anesthesia.

In recent years new anesthetic formulations and techniques of administration have evolved in the expanding field of procedural dermatology. Several anesthetic agents with varying pharmacologic properties are available, suited for different applications and techniques of administration.

Pharmacokinetic and pharmacodynamic proprieties of local anesthetics

The molecular structure of local anesthetics allows for the amphipathic properties of individual agents. In this regard, the substances used nowadays as local anesthetics possess three major chemical moieties: an aminic chain (hydrophilic), an aromatic portion (hydrophobic) and an intermediate part which is responsible for the anesthetic effect (fig.1). This intermediate moiety can be either an ester (in this case the drugs are called aminoesters - procaine, chloroprocaine, cocaine, tetracaine) or an amide (in this case the drugs are called aminoamides - bupivacaine, lidocaine, ropivacaine, prilocaine, mepivacaine and etidocaine).

The pharmacologic properties are determined by their solubility in lipid and aqueous environments and their avidity for proteins on sodium ion channels.

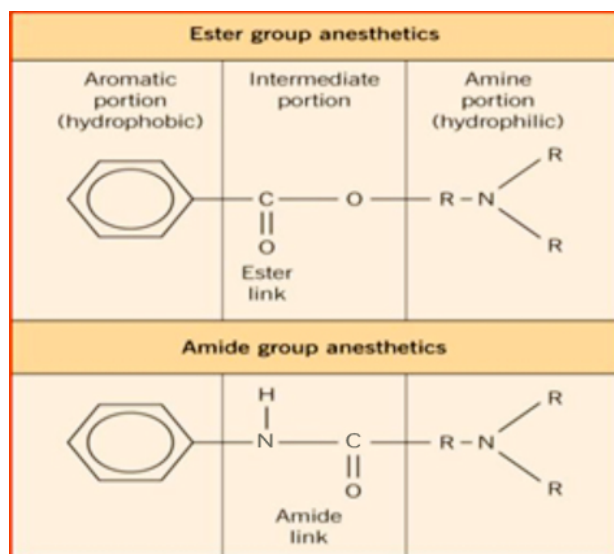


Figure 1.

Basic structure of ester and amide anesthetic molecules

Table I

Substances used as local anesthetics and some of their pharmacokinetic and pharmacodynamic proprieties

Anesthetic medicine	pKa	Onset of anesthetic effect (min)	Duration of anesthetic effect (h)	Maximum dose (mg/kg b.w.)
AMIDES				
LIDOCAINE	7.86	<1	2	4.5
MEPIVACAINE	7.6	3-20	2-2.5	7
PRILOCAINE	7.89	5-6	1-1.5	8
BUPIVACAINE	8.1	4-10	1-3	2
PRIDOCAINE	7.74	3-5	2-4	6
ROPIVAINE	8.07	1-15	2-6	3.5
LEVOBUPIVACAINE	8.1	4-10	2-4	2
ARTICAINE	7.8	1-6	-	7
ESTERS				
PROCAINE	8.9	2-5	0,5-1,5	10
CHLOROPROCAINE	9.1	6-12	-	11
TETRACAINE	8.4	7	-	2

The lipophilic nature of anesthetics is determined by the size of the alkyl substituents on both the tertiary amine and aromatic moieties. Lipid solubility determines the potency of local anesthetics. The avidity for binding proteins on sodium ion channel determines the duration of the anesthetic effect. Both the aromatic and amine moieties participate in protein binding.

The nature of the intermediate moiety decides the metabolic path for each group: aminoesters are metabolized in the blood by plasma cholinesterase enzymes, with the metabolic break down products excreted in the urine. Aminoamides are transported to the liver, where they undergo hepatic enzymatic breakdown *via* microsomal enzymes. Renal diseases don't influence the effect of local anesthetics, as the breakdown products are inactive. Hepatic diseases will prolong the degradation time of the amide anesthetics and dangerously high blood levels may be reached even within the therapeutic dose range.

As pharmacokinetics, local anesthetics can be described in terms of three factors: potency, onset of action and duration of blockade (Table I). Anesthetic potency is correlated with the lipophilicity of the agent - the uncharged state enhances the potency of the anesthetic. Onset of action is

dependent to the dose of the agent administered. The time to onset of blockade with bupivacaine is reduced when the concentration is increased from 0.25% to 0.75% [3]. The duration of action is the factor of greatest importance to the clinician. Short acting agents (procaine, chlorprocaine) are ideal when only a short duration of action is needed (15-30 min). For longer procedures (30-90 min) agents such as lidocaine, mepivacaine and prilocaine are ideal. Long acting agents (bupivacaine, ropivacaine), will give 2-4 h of anesthesia, often providing analgesia in the postoperative period. In all cases, the duration of action is dependent upon protein binding (more binding results in a prolonged action) as well as the degree of vasodilatation induced, which results in a „wash out” of the local anesthetic from the site of the action.

Mechanism of action of the local anesthetics

Local anesthetics are compounds that block the sensory impulse traffic along a nerve. They exhibit their clinical effects on peripheral nerves by temporarily inhibiting the influx of sodium ions required for the generation and propagation of action potentials across the nerve cell membrane, preventing the conduction of nerve impulses. The clinical effects of local anesthetics depend on their ability to diffuse across nerve cell membranes and to bind sodium ion channels blocking sodium influx and nerve depolarization.

Chemically, local anesthetics are weak bases which exist in electrostatic/ionic equilibrium between the uncharged and charged states. In their uncharged, lipophilic state they penetrate easily through the nerve sheath and axonal membranes. The acidic environment within the axoplasm favors their conversion into their charged, hydrophilic form. This entity binds to specific subunits within the transmembrane sodium channels, thereby abolishing the propagation of the action potential. Small unmyelinated nerve fibers (C-fibers) which transport pain sensation are more sensitive than their larger counterparts (A and B fibers); therefore, the patient may lose the ability to feel pain while still maintaining a sense of vibratory and pressure sensations.[2]

The local anesthetics exhibit pKa values from 7.7 (mepivacaine) to 9.1 (chlorprocaine). The pKa is the pH at which half of the compound will exist in a charged hydrophilic form and the other half assumes the uncharged lipophilic state. As pKa rises above physiologic pH, the percentage of the charged form of the local anesthetic also rises. (Fig.2)

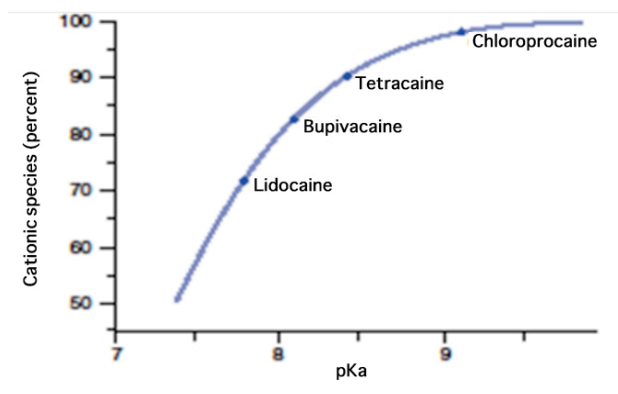


Figure 2

As pKa rises, the percentage of charged molecules increases. The cationic anesthetic penetrates the nerve sheath poorly, resulting in a slower, less dense block.

Therefore, at a normal blood or tissue pH of 7.4, the majority of local anesthetics will exist as protonated bases. Since only the uncharged moiety can penetrate the axon, a higher local tissue pH will enhance this uncharged lipophilic fraction and hasten the onset of the block. Conversely, local anesthetics injected at a site of low pH, such as an abscess, will convert to the charged form, not penetrate the nerve sheath and the block is clinically poor [11].

Administration

Topical anesthetics

The increased frequency of laser surgery and anesthetic procedures has expanded the use of topical anesthesia in procedural dermatology and led to the development of novel formulations that increase the penetration and improve the application of topical anesthetics [13,15]. Various formulations have been developed to improve penetration and efficacy of topical anesthetics (Table II).

EMLA[®] (Astra Zeneca) is an eutectic mixture of 2.5% lidocaine and 2.5% prilocaine and emulsifiers that enhances penetration and concentrate anesthetic agent within the oil component of the emulsion to improve penetration and reduce toxicity. The application for one or two hours under occlusion leads to peak anesthesia that persists for one to two hours. Longer application times under occlusion will result in a more profound anesthesia. 60 min will anesthetize the skin to a level of 2.9 mm, while 120 min provides a 4.5 mm depth of anesthesia [14].

The prilocaine component of EMLA[®] is responsible for the side effects, one of the most serious being the development of methemoglobinemia [7,8].

Other topical agents that lack prilocaine have been introduced in an effort to provide topical anesthesia without the risk of inducing methemoglobinemia.

LMX TM[®] (Ferndale) is a 4% or 5% lidocaine cream formulated in a liposomal delivery system that facilitates cutaneous penetration and increased duration of action. The application for 30 minutes without occlusion leads to effects comparable to EMLA[®] [5][9] (Table II).

The S-Caine peel[®] (ZARS) is an eutectic mixture of 7% lidocaine and 7% tetracaine cream that dries into a film that is easily peeled off. A 20 to 30 minutes application has been found to be effective in several laser procedures (Table II).

Lidocaine 30% hydrophilic mixtures such as Acid Mantle TM[®] (Doak Dermatologics) or Velvachol TM[®] (Novartis) that hydrate the *stratum corneum* for improved penetration have also been useful for laser procedures.

Table II

Modern formulations for topical anesthetics and some of their pharmacodynamic characteristics

Commercial name	Anesthetic composition	Formulation	Application time (min)	Duration of the anesthetic effect (min)
EMLA [®]	Lidocaine 2,5% Prilocaine 2.5%	Eutectic mixture	60-120 (occlusion) 5-10	60-120 15-20
LMX TM 4/5 [®]	Lidocaine 4%, 5%	Liposomal	30	-
Topicaine [®]	Lidocaine 4%,5%	Microemulsion	30-60 (occlusion)	30
Betacaine Enhanced Gel [®]	Lidocaine 5%	Alcohol gel petrolatum emulsion	30	-
Themaderm Betacaine LA [®]	Lidocaine Prilocaine Dibucaine	Petrolatum	30-45	-
Lidocaine Ointment [®]	Lidocaine 30%	Petrolatum	-	-
Photocaine [®]	Lidocaine 6% Tetracaine 6%	Proprietary	-	-
Tetracaine Gel [®]	Tetracaine 4%	Lecithin gel	60 (occlusion)	-
S-Caine peel [®]	Lidocaine 7% Tetracaine 7%	Cream film	60	-

Anesthetic injection techniques

Local infiltration

Local infiltration is the most commonly used technique to achieve cutaneous anesthesia in dermatologic surgery. Anesthetic agents may be injected intradermally or subcutaneously. Intradermal injection leads to immediate onset of action. Subcutaneous injections are less painful, but the onset of action is shorter due to increased absorption.

Lidocaine and bupivacaine are the two agents most widely used for infiltration anesthesia in the practice of dermatologic surgery. Lidocaine 1-2% provides rapid anesthesia, with a duration of 30-60 min. The maximum dose recommended is 5mg/kgbw. The addition of epinephrine 1:200 000 will double the duration of action, as well as it allows an increase in the maximum safe dose to 7mg/kgbw. Bupivacaine (0.25-0.5%) provides a sensory blockade for 1-2 h, but shows little increase in duration with the addition of epinephrine.

The addition of 8.4% sodium bicarbonate solution to the local anesthetic in a 1:10 volume ratio just prior to its use will serve to hasten the block promoting the formation of the uncharged lipophilic moiety, and to reduce the pain of injection [1,6]. Sodium bicarbonate exhibits both antimicrobial and antifungal properties [4]. Warming the anesthetic solution to body temperature appears to have a synergistic effect, along with the addition of bicarbonate, in reducing the pain during injection [12].

Field block anesthesia

Field block anesthesia involves injecting a ring of anesthetic around the proposed surgical site. It's useful for anesthetizing large areas while conserving the amount of anesthetic used or when direct injection into a lesion is avoided. Circumferential anesthesia or ring block, may be used to reduce the amount of anesthesia required for large areas or when direct injection into a lesion is avoided.

Tumescent anesthesia

Tumescent anesthesia involves the subcutaneous infiltration of large amounts of diluted 0.05%-0.1% lidocaine with 1:1 000 000 epinephrine. Infiltration of the deep subcutaneous plane is performed first, followed by the superficial fatty compartment. The solution is injected until firm tumescence of the tissue has been achieved. Anesthesia and epinephrine induced hemostasis develop within about 20 minutes and last for several hours. In the subcutaneous fatty tissue diluted lidocaine is absorbed at a much slower rate than the standard lidocaine concentrations. Doses as high as 35-50 mg/kgbw lidocaine have been found to be safe when used in tumescent anesthesia (Table III).

Table III
Tumescent anesthesia formula

Ingredient	Quantity (mL)
Lidocaine 1%	50-100
Epinephrine (1:1000)	0.5-1
Sodium bicarbonate 8.4%	10
Hyaluronidase 150 U/mL	6 (optional)
Triamcinolone acetonide 40mg/mL	0.25 (optional)
Normal saline 0.9%	900-950

Nerve block techniques

Nerve blocks are an effective and efficient way to anesthetize large areas using the least amount of anesthetic. When injecting in the region of a nerve, care must be taken in order not to inject the accompanying blood vessels. For most nerve blocks, 1% lidocaine with epinephrine and bicarbonate is used. If prolonged anesthesia is desired, 0.25% bupivacaine hydrochloride with epinephrine can be added [10].

Conclusions

Nowadays, the dermatologists are facing an expanding field of dermatologic surgery, engaging in new and exciting surgical therapies.

Local anesthetic agents remain the foundation upon which rests the discipline of dermatologic surgery, allowing punch, incisional and excisional procedures. Local anesthetics provide adequate anesthesia for short superficial procedures, while more complex surgery requires the infiltration of an injectable local anesthetic agent. Although their safety is proven by a 120-year track record, their proper use and the effective management of morbidity rely upon a basic understanding of their pharmacologic properties.

References

1. Adriani J., Regional Anaesthesia: Techniques in Clinical Practice. Springfield; Thomas, 1970
2. Auletta M.J., Grekin R.C., Local Anesthesia for Dermatologic Surgery. New York: Churchill-Livingstone, 1991
3. Auletta M.J., Local anesthesia for dermatologic surgery. *Semin Dermatol* 1994; 13:35-42
4. Bennet RG. Anesthesia. In: Bennet RG, ed. Fundamentals in Cutaneous Surgery. St Louis: Mosby, 1988:194-239
5. Bucalo B.D., Mirikitani E.J., Moy R.L., Comparison of skin anesthetic effect of liposomal lidocaine, nonliposomal lidocaine and EMLA using 30-min application time. *Dermatol Surg*.1998;24(5):537-541
6. Buckley M.M., Benfield P., Eutectic lidocaine/prilocaine cream: a review of the topical anaesthetic/analgesic efficacy of EMLA. *Drugs* 1993; 46:126-51

7. Elsner P., Dummer R.S., Signs of methaemoglobinemia after topical application of EMLA cream in an infant with haemangioma. *Dermatology* 1997;195(2):153-154
8. Frey B., Kehner B., Toxic methaemoglobin concentrations in premature infants after application of a prilocaine –containing cream and peridural prilocaine. *Eur J Pediatr* 1999;158(10):785-788
9. Friedman P.M., Fogelman J.P., Nouri K., Comparative study of the efficacy of four topical anesthetics. *Dermatol Surg* 1999; 25 (12): 950-954.
10. Grekin R.C., Auletta M.J., Local anesthesia in dermatologic surgery. *J Am Acad Dermatol* 1988; Facial nerve blocks 19:599-614
11. Skidmore R.A., Patterson J.D., Tomsick R.S., Local Anesthetics. *Dermatol Surg* 1996; 22:511-22
12. Sylaidis P., Logan A., Digital block with adrenaline: an old dogma refuted. *J Hand Surg* 1998; 23:17-9
13. Moldovan M., Nanu A., Influence of cleansing product type on several skin parameters after single use, *Farmacia* 2010; 58(1):29-37
14. Wahlgren C.F., Quiding H., Depth of cutaneous analgesia after application of a eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA cream), *J Am Acad Dermatol* 2000; 42(4):584-588
15. Dinu Parvu C., Hlevca C., Ortan A., Prisada R., Elastic vesicles as drugs carriers through the skin. *Farmacia* 2010; 58(2):128-135

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