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LOCAL ANESTHETICS

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ABSTRACT

The agent that interrupt pain impulses in a specific region of the body without the loss of patient consciousness are called are as local anesthetics. Chemically local anesthetics are categorised as benzoic acid derivatives, aminobenzoic acid derivatives, anilide derivatives and miscellaneous agents. Structurally local anesthetics consist of lipophilic entity on one side and hydeophilic secondary amine on other side, joined an alkyl chain through an amide or ester linkage. Alterations in these positions results in altered biological activity. Local anesthetics producess their pharmacological actvity by binding with intracellular voltage dependent sodium channels. Here, we have discussed different local anesthetics used in therapeutics.

KEYWORDS: Local anesthetics, lipophilic and hydrophilic moiety, cocaine, hexylcaine etc.

INTRODUTION

Pain control has not always been as efficacious as it currently is. Throughout our known history, people have attempted to manage pain using many different methods and techniques. One of the first examples of pain control by man was in Egypt over 4,500 years ago around the year 2500 BC. Paintings of apparatuses used to compress peripheral nerves to numb limbs were found on the walls inside the ancient Egyptian tomb of Saqqara. This primitive technique of anesthetizing entire limbs from a proximal site, probably unknowingly at the time, demonstrated the potential capabilities of conduction anesthesia. Compression anesthesia was not the only attempt made to relieve localized pain. Thirteen hundred years later, Homer wrote about the use of bitterroot in The Iliad. Patroclus, a warrior in the Trojan War, was said to have ‘took the pain away and ended all (of Eurypylus’) anguish’ by rubbing

the bitterroot on his wounded leg after being struck by an arrow. Humans have been using herbal remedies for pain control for thousands of years.

Plato and Aristotle documented some of the first cases of using electricity as a method to decrease sensitivity in 350 BC. Aristotle described the numbing effect created by the Torpedo ray's electric shock capabilities. Scribonius Largus, the physician of the Roman emperor Claudius, applied the Torpedo ray's electrical capabilities further by regularly using it to numb the pain from various maladies including headaches and gout. Around the year 1050, another early form of anesthesia was documented; Anglo-Saxon monks wrote about the use of cold water in the medical text called the Leechbook. In the Leechbook, it was recommended that the patient have their limb or area of surgery 'deadened' using cold water prior to performing simple surgeries and removal of cysts. Ice and various 'coolants' are still used today as an inexpensive and rapid form of anesthesia.

Many of the techniques previously discussed slowly evolved over time becoming more efficient and reproducible. This was true for the technique of compressing nerves for numbing limbs. In 1784, the English surgeon James Moore created and utilized adjustable clamps in order to compress the nerves just as the ancient Egyptians. He believed that clamping the limb and thus nerve, blocked pain signals transmitted to the brain. Other surgeons not only used Moore's clamp and method, but also promoted its use for major operations, such as limb amputations during the late eighteenth century. Pressure anesthesia was not the only technique revisited hundreds of years later. In agreement with the Leechbook, Baron Larrey, Napoleon's army doctor, noted the ease and relative patient comfort when amputating limbs that were nearly frozen during Napoleon's invasion of Russia. The use of cold temperature as an anesthetic continued to be used and applied in different manners. Well into the nineteenth century the British physician, Benjamin Ward Richardson, used the technique of spraying ether onto the surgical site, in order to desensitize it. Ward invented an apparatus that he used to spray ether on teeth prior to extracting them.

The agent that interrupt pain impulses in a specific region of the body without the loss of patient consciousness are called are as local anesthetics. These drugs are mainly used for temporary relief of localized pain in dentistry and in minor surgical operations when loss of consciousness is not desired. Local anesthetics produce anesthetsia by inhibiting the excitation of nerve endings or by blocking condution in peripheral nerves. A major breakthrough in modern local anesthesia was made in 1841 when Zophar Jayne, an American

physician, created the framework for the modern hypodermic syringe. Before its invention, physicians had been searching for a method that could deliver adequate amounts of liquid to tissues. Dr Alexander Wood and Dr Francis Rynd, independently, created hypodermic needles and syringes before Jayne, with some controversy as to who created it first. But Jayne's latest creation took the major step forward necessary to progress the field of local anesthesia. Jayne's hypodermic syringe still required an incision to be made before delivering the material, but nonetheless, it was a key first step in the direction of the syringe and needle system. Despite this major breakthrough, traction for its use did not develop immediately. This can partially be attributed to the limited anesthetizing solutions and imprecise delivery system. This is evident by the continued use of alternative methods to numb patients. In London around the year 1858, the dentist Joseph Snape was using electricity to attain anesthesia prior to tooth extractions. Snape reported remarkably good results with patients claiming the experience to be 'delightful'.

Approximately 15 years after the hypodermic syringe was invented, Albert Niemann, a graduate student in pharmacology in Gottingen, Germany, was extracting cocaine from the leaves of the coca plant. At the time, Niemann did not realize its potential as an anesthetic in surgery; however, other researchers noted its effects on Peruvian Indians when they would chew the coca leaves. The Peruvians could work extremely long hours without eating or tiring as long as they chewed the leaves.

Another 20 years later, Sigmund Freud, a graduate student in Vienna at the time, began experimenting with coca leaves on himself to observe its effects. To his surprise, he noted the profound numbing effect it had on his tongue. In 1884, he published the paper 'Uber Cocaine.' In the paper, Freud recommended its use for the treatment of morphine addiction and various other conditions including fatigue and headaches. Freud himself did not utilize the coca extract for surgery; however, he recommended its use for eye surgery to Karl Koller, one of his colleagues. Koller published his first paper on the use of cocaine in eye surgery in 1884.

Surgeons did not quickly adopt the use of cocaine as an anesthetic. However, dentists began using it subcutaneously for tooth extractions. The anesthesia achieved was extremely effective, but the nonstandard dosing caused many unwanted systemic side effects, such as increased pulse, giddiness and exhilaration. Just 6 years later, dentists were already restricting their use of cocaine subcutaneously. Many dentists started solely using cocaine in a diluted

solution as a topical anesthetic. The many reported unwanted side effects initiated the research and development of safer alternative anesthetics.

In 1903, Heinrich Braun, a German surgeon, took one of the first steps toward creating a safer local anesthetic. Knowing that the products of the adrenal glands, such as epinephrine, caused vasoconstriction, Braun added the hormone to a solution of cocaine. He then injected the new solution into his arm and achieved long lasting anesthesia that was confined to his arm. The vasoconstriction caused by the epinephrine kept the anesthetic from diffusing systemically. This formula is an anesthetic solution, i.e., currently used.

Around the same time, William Stewart Halsted and William John Hall formally introduced the concept of conduction anesthesia. This concept of anesthetizing the nerve in a more proximal location to numb structures distal to the injection site, allowed for more efficient and comfortable anesthesia. This reduced the number of injections needed and provided for a more specific and targeted anesthesia method.

Just a year after Braun started experimenting with adding vasoconstrictors to anesthetic solutions, Alfred Einhorn and Alfred von Bayer invented procaine, the first synthetic analog of cocaine. Procaine is commonly referred to by its trade name Novocaine. This analog was much safer and caused fewer side effects than cocaine. It also did not have the addictive properties of cocaine. However, surgeons and dentists soon realized that it caused vasodilation and easily spread systemically. It was then combined with epinephrine to cause vasoconstriction, which allowed the medication to remain locally.

In 1906 Guido Fishcer, the director of the Dental University Institute of Greifswald, Germany, introduced what would become the modern syringe. This model did not have all of the features that are seen today, however, Fischer's version laid the framework for iterations to come. A major breakthrough came toward the end of WWI in 1917, when Harvey S Cook introduced the cartridge system. Cook was a physician for the United States Army in France during the war. Cook envisioned creating a faster and more efficient system that could be used on the battlefield. He modeled his design after observing soldiers load their rifles with ammunition and watching the empty shells being dispensed after firing the gun. He cut glass tubing and filled them with anesthetic solution, so that the prepackaged cartridges of anesthetic were ready to be used on the battlefront or the next day. As astopper for the cartridges, Cook resourcefully used the erasers from the heads of pencils. This system

replaced the old procedure of drawing up the solution into the metal syringe every time anesthesia was needed. More iterations of the carpule system and syringe came in the form of a corkscrew that permitted aspiration in 1947. Later, a harpoon would replace the corkscrew giving us the syringe widely manufactured and used today. Cook patented his carpule system, after the war ended, in 1925 and went on to start Cook Laboratories in Chicago. Eventually, Cook Laboratories would partner with RB Waite, a dentist who created his own improved syringe system, to create the Cook-Waite Company. Cook-Waite would go on to be widely successful manufacturing pre-packaged anesthetic carpules of various solutions.

The most recent major innovation came in 1949 when the Swedish pharmaceutical company Astra introduced Lidocaine to the market. Lidocaine, also known as Xylocaine, was the first non-ester local anesthetic available. Lidocaine proved to have even fewer side effects than procaine while instilling even deeper anesthesia. It is now one of the most widely used local anesthetics. There are three main types of local anesthetics that are clinically used today. Lidocaine 2% with epinephrine 1:100,000 is the most common amide anesthetic used when giving local infiltration anesthesia. It has a rapid onset and a moderate duration of action. Its low pKa and high lipid solubility are both factors that influence the quick onset of action. The average duration of action on soft tissue ranges from 170 to 190 minutes. Bupivacaine 5% with epinephrine 1:200,000 is used for longer procedures. It has an intermediate onset and longer duration of action. It is four times more potent than lidocaine. It is known to be a more painful injection, so it is recommended to anesthetize the surgical area first with a different local anesthetic (topical benzocaine) to lessen to the initial injection. The duration of action in soft tissue ranges from 340 to 440 minutes. Mepivacaine is the most common local anesthetic, if the use of epinephrine is contraindicated. This anesthetic is used for short procedures and when vasoconstriction is less imperative. Its duration of action for soft tissue ranges from 90 to 165 minutes.

Vasopressors are used in conjunction with local anesthetics to increase effectiveness, provide hemostasis, and increase duration. Epinephrine activates the alpha-1 adrenergic receptors, which in turn, constricts the surrounding blood vessels. This prevents systemic toxicity by delaying anesthetic absorption. It is recommended to not use local anesthesia with vasopressors on patients who have diabetes, hypertension, cardiovascular disease, or cerebrovascular disease. The use of epinephrine and other vasopressors increases cardiac

output, heart rate, and stroke volume, so it is recommended to use 3% mepivacaine in patients with cardiac contraindications.

Another novel breakthrough in local anesthesia that has yet to catch on widely came in 2009, when an injectable form of phentolamine mesylate, a vasodilator that reverses local anesthesia, was introduced to the market. The local anesthesia-reversing agent has yet to become popular mainly due to patients choosing to allow the anesthesia to wear off on its own rather than paying for the extra cost of the reversing agent.

Currently, there is ongoing research on how to decrease the pain during the application of local anesthesia. Local anesthesia is an acidic solution that contributes to the burning sensation when receiving an injection. There are current studies analyzing if there are benefits to creating a more neutral solution in order to make the anesthetic injection a more pleasurable experience. Adding sodium bicarbonate to the lidocaine and epinephrine solution is one formula, i.e., under investigation. There are two theoretical advantages that this neutral local anesthetic solution provides: a less painful injection and a faster onset of desensitization. Further research is needed on this topic.

The importance of local anesthesia cannot be overstated. Without local anesthesia, many of today's surgical and dental procedures could not be performed without more invasive methods of achieving patient comfort. With continued research and innovation, the field of local anesthesia will continue to advance the eternal quest for pain control.

Difference between local anesthesia and general anesthesia

Table 1.1: Difference between local anesthesia and general anesthesia.

Parameter	General anesthesia	Local anesthesia
Site of action	Central nervous system (CNS)	Peripheral nervous system (PNS)
Area of body involved	Full body	Restricted area
Consciousness	Lost	Unchanged
Major surgery	Preferably used	Cannot be used

Site of action of local anesthetics or type of local anesthetics or use of local anesthetics.

a. Topical anesthesia: Topical anesthesia is produced by applying an anesthetic agent to the mucous membrane.

- Generally, it is used for relief of pain or itching at the mucous surface, damaged skin surface, wounds, burns etc.

b. Infiltration anesthesia: Infiltration anesthesia is produced by injecting an anesthetic agent subcutaneously.

- It paralizes sensory nerve endings around the area to be rendered or insensitive.

Ex. Tooth extraction.

c. Nerve block anesthesia: Nerve block anesthesia is produced by injecting an anesthetic agent as close as possible to the nerve trunk supplying to the specific area to be anesthetized.

Ex. In minor surgeries.

d. Spinal anaesthesia: Spinal anaesthesia is produced by injecting an anaesthetic agent into subarachnoid space i.e., into the cerebrospinal fluid (CSF) to paralyze the root of the spinal nerves.

- This method is used for inducing anesthesia for abdominal or pelvic surgeries.

e. Epidural anaesthesia: This is a special type of nerve block anaesthesia in which the drug is injected into epidural.

- It is used for surgeries of pelvic viscera.

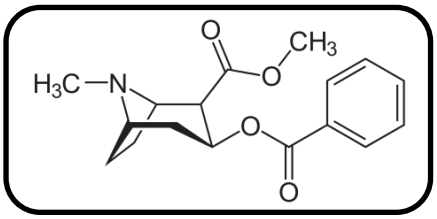
f. Caudal anaesthesia: This type of anaesthesia is produced by injecting an anesthetic agent into caida equina.

- It is used for surgeries of pelvic viscera.

Chemical classification of local anesthetics

1) Benzoic acid derivatives

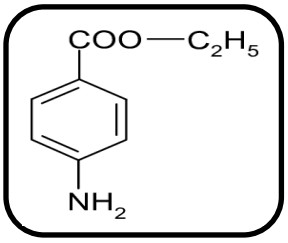
Eg: Cocaine, Hexylcaine, Meprylcaine, Cyclomethycain



Structure: Cocaine

2) Amino benzoic acid derivatives

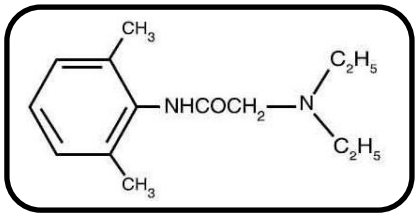
Eg: Benzocaine, Butamben, Procaine, Butacaine, Propoxycaine



Structure: Benzocaine

3) Lidocaine/Anilide derivative

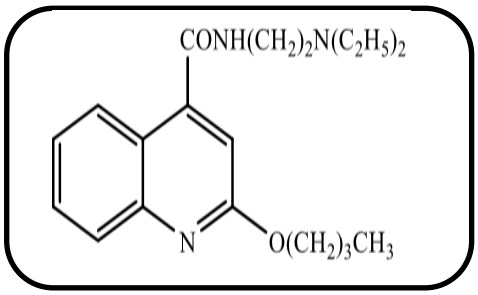
Eg: Lignocaine, Mepivacaine, Prilocaine, Etidocaine



Structure:Lignocaine

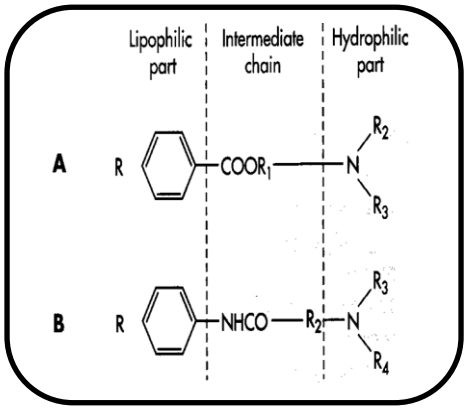
4) Miscellaneous agents

Eg: Phenacaine, Diperodon, Dibucaine.



Structure : Dibucaine

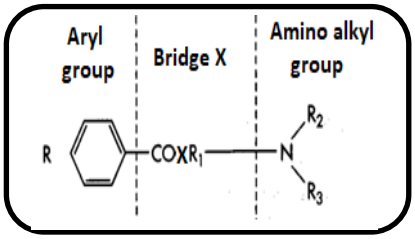
Chemistry of local anesthetics



- Structurally local anesthetics consist of lipophilic entity on one side and hydrophilic secondary amine on other side, joined by an alkyl chain through an amide or ester linkage.
- The clically useful local anesthetics are generally weak bases with amphiphilic property.
- The lipophilic group is usually an aromatic residue.
- The hydrophilic group is secondary or tertiary amine.
- The linkage between aromatic group and alkyl chain is either ester or amide.

SAR OF LOCAL ANESTHETICS

SAR of local anesthetics containing ester linkage



A) SAR of aryl group

- Aryl radical directly attached to the carbonyl group plays an important role in the binding of local anesthetics to the channel receptor protein.
- Hence the attachement of an aryl radical directly to the carbonyl group enhances the local anesthetics activity.
- The substitution of an aryl group which increase the electron density of carbonyl oxygen, increases local anesthetic activity.
- Substitution of electron withdrawing group like chloro or para or both the positions decreases the activity of local anesthetics.

B) SAR of Intermediate Bridge X.

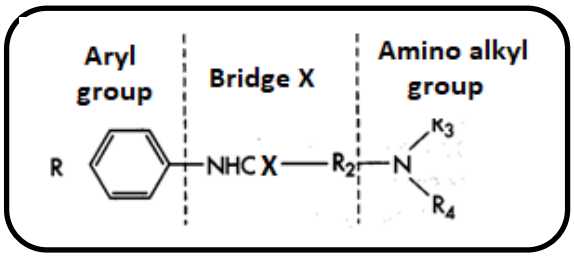
- Here the X may be carbon, oxygen, nitrogen or sulphur.
- The nature of X affects duration of action and relative toxicity.
- In general, amides (X=N) are more resistant to metabolic hydrolysis than esters (X=O), Thioesters (X=S) may cause dermatitis.
- Generally in isosteric procaine, anesthetic protency decreases in the order: sulphur,oxygen,caebon and nitrogen.

C) SAR of Amino alkyl group.

- The local anesthetic activity decreases and irritation property increases in followimg order of amino group.
  $1^0<2^0<3^0$ amine.
- Tertiary amines result in more useful agents. The secondary amines appear to be of longer activity, but they are more irritating; primary amines are not very active and cause irritation.
- In general the amino alkyl group is not necessary for activity of local anesthetics but it is used to from water soluble salts.

- The alkyl group only influences the lipid solubility.
- Local anesthetics like butacaine lacks aminoalkyl chain, they are active but possesses poor water solubility.

SAR of local anesthetics containing amide linkage.



A) SAR of aryl group

- Aryl radical directly attached to the carbonyl group plays an important role in the binding of local anesthetics to the channel receptor protein.
- Hence the attachment of an aryl radical directly to the carbonyl group enhances the local anesthetic activity.
- The substitution of aryl group (Particularly CH_3) at ortho or para position enhance the local anesthetic activity.
- It also enhances steric hindrance and contrinutes to lipid solubility of molecules.

B) SAR of Bridge X.

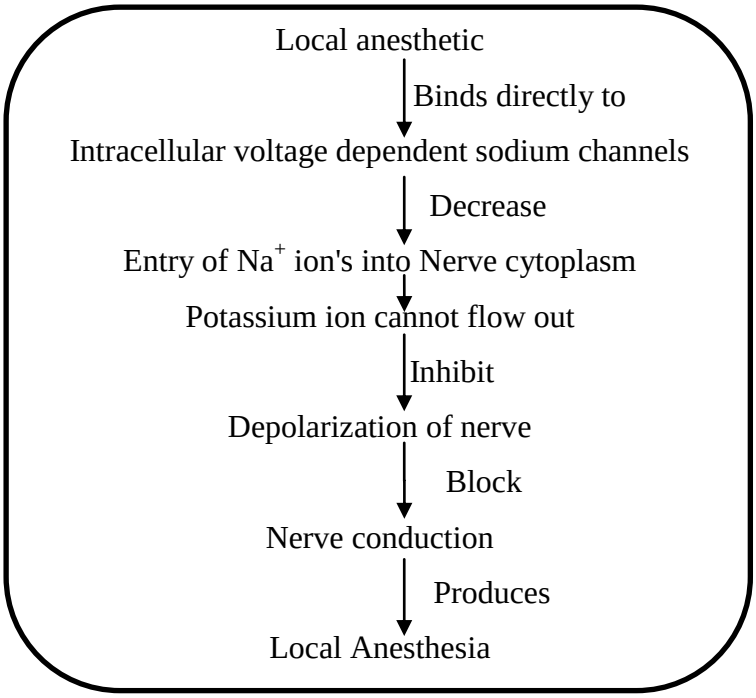
- In general bridge X may be carbon, oxygen or nitrogem.
- The alteration in bridge X alters the duration of action and relative toxicity.

C)SAR of Amino alkyl group

- The local anesthetics activity decreases and irritation property increases in following order of amino group.

  $1^0 < 2^0 < 3^0$ amine
- Tertiary amines result in more useful agents.The secondary amines appear to be of longer activity, but they are more irritating; primary amines are not very active and cause irritation.
- In general the amino alkyl group is not necessary for activity of local anesthetics but it is used to form water soluble salts.
- The alkyl group only influences the lipid solubility.

MOA OF LOCAL ANESTHETICS



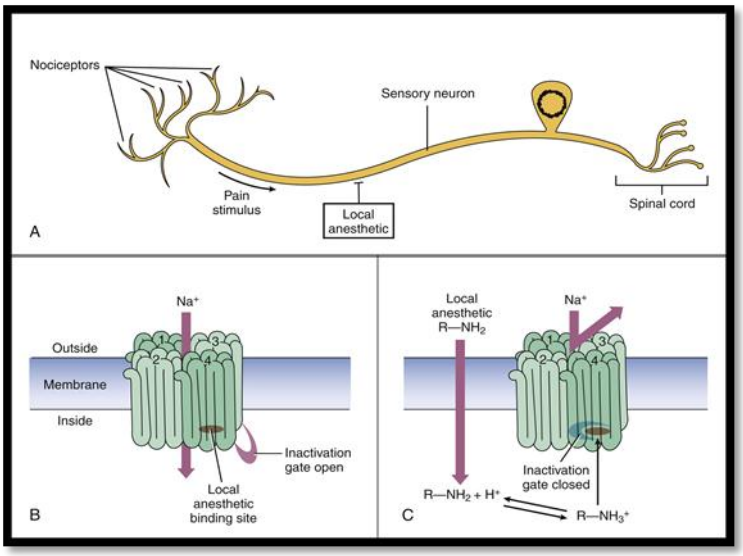
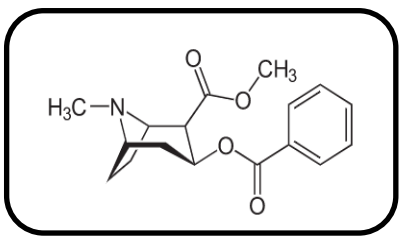


Fig 1.1: Mode of action of local anaesthetics.

BENZOIC ACID DERIVATIVES

Cocaine

Structure

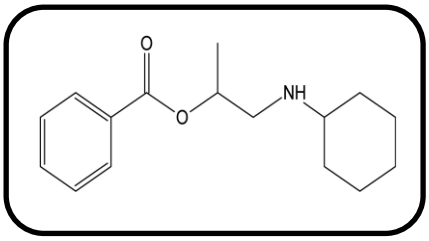


IUPAC NAME: Methyl (1R,2R,3S,5S)-3-benzoyloxy-8-azabicyclo[3.2.1]octane-2-carboxylate.

Therapeutic Use: Cocaine is used as local (topical) anesthetic in the accessible mucous membranes of the nasal oral,and laryngeal cavities.

Hexylcaine

Structure



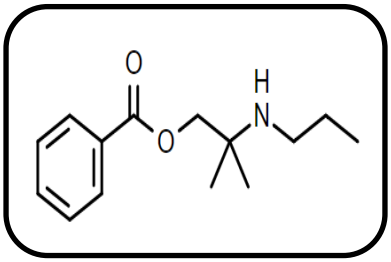
IUPAC Name: 1-cyclohexylaminopropan-2-yl benzoate.

Therapeutic use

It is used as short-acting local anesthetic.

Meprylcaine

Structure



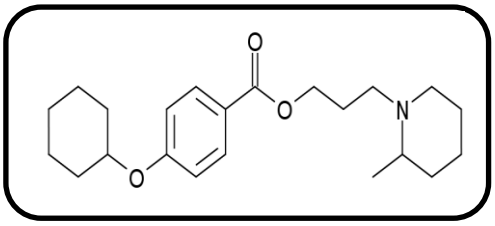
IUPAC Name: Benzoic acid (2-methyl-2-propylaminopropyl) ester.

Therapeutic Use

It is used as a local anesthetic for surface application, infiltration, or nerve block anesthesia.

Cyclomethycaine

Structure



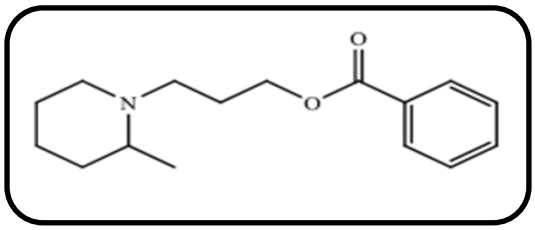
IUPAC Name: 4-(cyclohexoxy)benzoic acid 3-(2-methyl-1-piperidinyl)propyl ester.

Therapeutic Use

It is used as a local anesthetic for surface application, infiltration, or nerve block anesthesia.

Piperocaine

Structure



IUPAC Name: 3-(2-Methylpiperidin-1-yl)propyl benzoate.

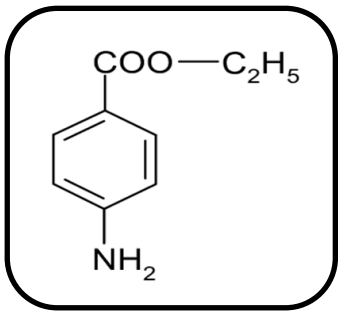
Therapeutic Use

It is used as a local anesthetic for surface application, infiltration, or nerve block anesthesia.

AMINO BENZOIC ACID DERIVATIVES

Benzocaine

Structure



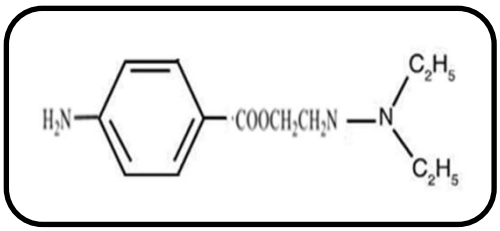
IUPAC Name: ethyl amino benzoate.

Therapeutic Use

It is used as topical anesthetic on oesophagus, mouth, larynx, nasal cavity, rectum, urinary tract, vagina, and respiratory tract or trachea.

Procaine

Structure



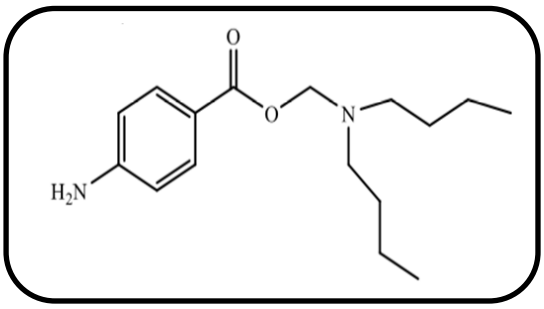
IUPAC Name: 2-(diethylamino)ethyl 4-aminobenzoate.

Therapeutic Use

It is used for penetration anesthesia, spinal block, and peripheral nerve block anesthesia.

Butacaine

Structure



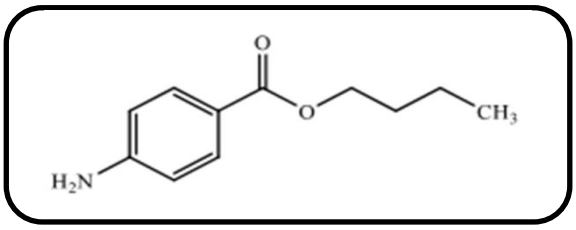
IUPAC Name: 4-aminobenzoic acid 3-(dibutylamino) propyl ester.

Therapeutic Use

It is used as a local anesthetic.

Butamben

Structure



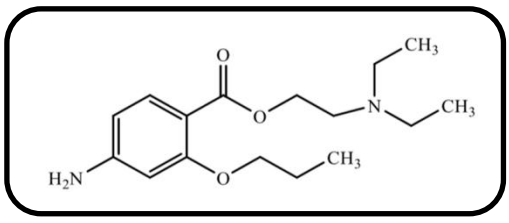
IUPAC Name: Butyl 4-aminobenzoate.

Therapeutic Use

It is used as a surface anesthetic for skin and mucous membrane, for treating chronic pain because of its long duration effect.

Propoxycaine

Structure



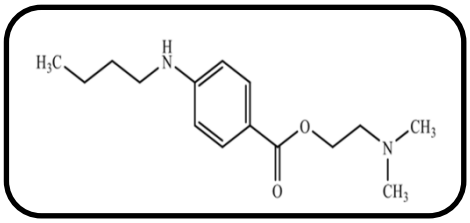
IUPAC Name: 2-(diethylamino)ethyl 4-amino-2-propoxybenzoate.

Therapeutic Use

It is used as a local anesthetic.

Tetracaine

Structure



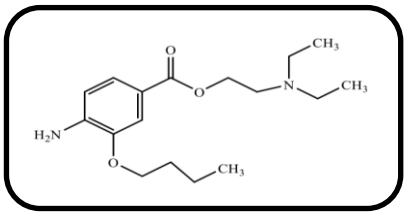
IUPAC Name: 2-(Dimethylamino)ethyl 4-(butylamino)benzoate

Therapeutic Use

In combination with lidocaine, it is used as a local dermal analgesia patch for superficial dermatological procedures and superficial venous access.

Benoxinate

Structure



IUPAC Name: 2-diethylaminoethyl 4-amino-3-butoxy-benzoate.

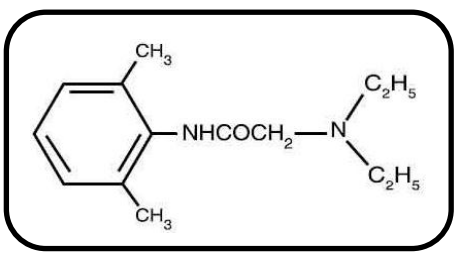
Therapeutic Use

It is used to temporarily numb the front surface of the eye, while measuring the eye pressure or removing a foreign body.

LIDOCAINE/ANILIDE DERIVATIVES

Lignocaine

Structure



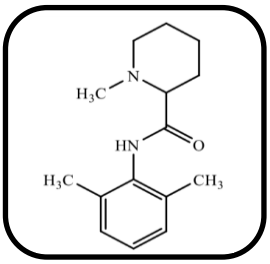
IUPAC Name: 2-(diethylamino)- N-(2,6-dimethylphenyl)acetamide.

Therapeutic Use

It is applied to mucus membranes to relieve pain and to produce infiltration anesthesia.

Mepivacaine

Structure



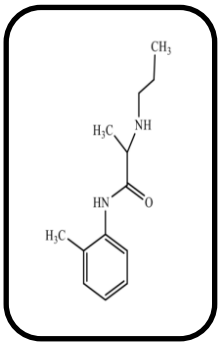
IUPAC Name: (RS)-N-(2,6-dimethylphenyl)- 1-methyl-piperidine-2-carboxamide.

Therapeutic Use

It is used for the production of local or regional analgesia and anaesthesia by local infiltration, peripheral nerves block techniques, and central neural techniques including epidural and caudal blocks.

PRILOCAINE

Structure



IUPAC Name: N-(2-methylphenyl)-N2-propylalaninamide.

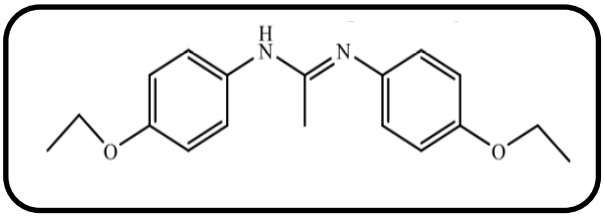
Therapeutic Use

It is used as a local anesthetic in dentistry.

MISCELLANEOUS AGENTS

Phenacaine

Structure



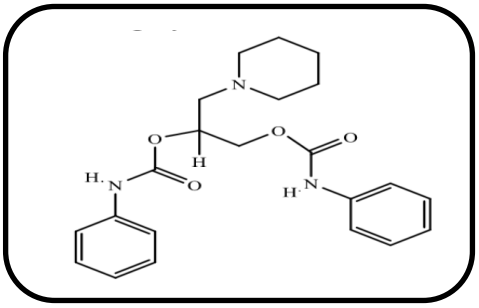
IUPAC Name: (1E)-N,N′-Bis(4-ethoxyphenyl) ethanimidamide.

Therapeutic Use

It is used for producing local anesthesia of the eye.

Diperodon

Structure



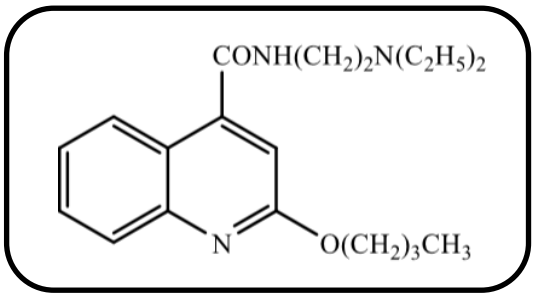
IUPAC Name: [2-(phenylcarbamoyloxy)-3-piperidin-1-ylpropyl] N-phenylcarbamate.

Therapeutic Use

It is used as a local anesthetic for anaesthetising anus.

Dibucaine

Structure



IUPAC Name: 2 - butoxy- N.(2- diethyl amino ethyl) cinchoninamide.

Therapeutic Use

It is used for producing local or regional anaesthesia by infiltration technique.

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