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The Local Anesthetic and Pain Relief Activity of Alkaloids

Havva Sayhan, Serbüent Gökhan Beyaz and
Ahmet Çeliktaş

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Abstract

Alkaloids have been known for several centuries and have been mainly obtained from natural sources that presented important properties with biochemical, pharmacological, and medical effects in living organisms. Alkaloids are derived from amino acids like other important molecules in the functioning of life in our body. Hence, alkaloids are considered as pharmacologically important. Alkaloids are secondary metabolites widely distributed in leaves, stem, root, and fruits of plants which synthesize them. However, administration and consumption of them at right doses are beneficial in terms of health; excess doses will be definitely poisonous and may cause even death. The pharmacological activities of alkaloids are quite diverse. They are important natural products with a wide range of medicinal properties including relief of pain (e.g., morphine), analgesic (e.g., codeine), antiarrhythmic (e.g., quinidine), antibacterial (e.g., chelerythrine), antiasthma (e.g., ephedrine), cholinomimetic (e.g., galantamine), and vasodilatory (e.g., vincamine).

Keywords: alkaloids, local anesthetics, pain relief, analgesia, natural products, mechanism of action, bioorganic chemistry

1. Introduction

MERGEFORMAT plants have been used from ancient times as an excellent source of pharmaceutical compounds in the treatment of diseases and have solid impact on human health. Modern chemistry and material sciences have identified the compounds with pharmacological properties for the development of new drugs. Hence, they have played a major role in drug discovery as natural products and synthetic materials which do not exist in the nature and can only be produced.

The presence of some chemical substances in plant tissues produces a physiological action on the body and regulates the metabolic activity. For example, these chemicals give plants their color or act as defense system based on their toxic effects. Alkaloids have been known for several centuries and have been mainly obtained from natural sources that presented important properties with biochemical, pharmacological, and medical effects in living organisms. Alkaloids are secondary metabolites widely distributed in leaves, stem, root, and fruits of plants which synthesize them. However, administration and consumption of them at right doses are beneficial in terms of health; excess doses will be definitely poisonous and may cause even death. Many alkaloids extracted from plants showed anticholinesterase activity [1, 2] and antioxidant [3], anxiolytic [4], antimicrobial [5], anti-HIV [6], antiparasitic [7], anti-inflammatory [8], and antidepressant [9] properties. After the recognition of vital importance of these nitrogenous secondary metabolites, they are found in animals too [10]. In spite of the investigations on the biological activity of some alkaloids, only a few could be produced commercially due to their complex chemical structures. The synthetic production of some important alkaloid is more common than their isolation from plants. In addition, there are other synthetic compounds that are closely related to the natural alkaloids but lack of some typical properties (e.g., homatropine) [11].

Alkaloids display antimicrobial and antiparasitic properties, act as narcotics, can alter DNA, have an important role in the immune systems, and treat cardiovascular and metabolic disorders, inflammation, infectious diseases, and miscellaneous problems [10, 12–19]. Therefore, modern medicine tends to produce pharmaceuticals on the basis of natural alkaloids and alkaloids with modified structure such as aconitine, ajmaline, berberine, morphine, caffeine, theophylline, ephedrine, atropine, scopolamine, reserpine, and pilocarpine. There are several morphine-containing drugs that are used in cases of surgical operations and postoperative treatments (i.e., Morphalgin, Spasmofen, and Morphin) [20, 21].

2. History

The human race has used alkaloids in the scope of medicinal and pharmaceutical importance even before their discovery as chemical molecules. There are records from the Babylonian, ancient Hebrew, Egyptian, Chinese, Greek, and Assyrian times, such as Sanskrit writings and the works of Hippocrates, showing that they were all familiar with medicinal plants and alkaloids to improve the health in the early 5000 BC. The most prominent examples of medicinal plants based on the earlier beliefs and knowledge were myrrh, opium, cannabis, aloes, casia, and hemlock. For example, native people of America and tribes in the Amazon used the alkaloid quinine in herbal before its official use in the cure of uncomplicated malaria in 1638. The latex of opium poppy (*Papaver*) was already in use in the Middle East and Greece at 1200 BC. The roots of the mandrake plant were used because of sedative properties from the time of Hippocrates (ca. 400 BC). All alkaloids cause a physiological effect on the human body, and different poisonous alkaloids such as the ergot alkaloid, aconitine, and tubocurarine have been used for toxic purposes in ancient time. The poisonous alkaloids were prepared from plants (also from animal sources) and used as poisons for arrows by hunters in different parts

of the world. Literature also refers that some alkaloids including aconitine, atropine, colchicine, coniine, ephedrine, ergotamine, mescaline, morphine, strychnine, psilocin, and psilocybin have been used in executions. Philosopher Socrates was sentenced to death by consuming a cup of hemlock which contains the alkaloid coniine in 399 BC [11, 22–31].

Despite the fact that alkaloids have been in use for ages, actual studies on isolation from plants as relatively pure compounds occurred only in the beginning of the 1800s. In the late 1700s, Lavoisier and others introduced the new developments in chemistry that leads many chemists to try to isolate the active ingredients in plants. The German pharmacist's apprentice Friedrich Sertürner discovered the morphine in opium poppy by dissolving it in acid and neutralizing it with ammonia in 1804 for the first time in history. Morphine is considered for clinical purposes primarily a safe and effective way of pain relief. Although morphine is used clinically, drug addiction began with morphine and related substances. When Sertürner proved that the substance (morphine) he had isolated was indeed responsible for the actions of opium, chemists had isolated several other medically important substances such as quinine, strychnine, and caffeine around that time. While the first use of the name "alkaloids" was in 1819 by a German chemist Carl F.W. Meissner, the term had an extensive usage after the publication of an article in the chemical dictionary of Albert Ladenburg in the 1880s [11, 22–24, 32–37].

3. Properties

An exact and precise definition is somewhat difficult because of differences between the research fields of biology, medicine, and chemistry. The term alkaloid (alkali + oid) means alkali-like substance, and names of alkaloids end in -ine (e.g., atropine, cocaine, and morphine). Many methods have been proposed for the classification of alkaloids such as pharmacological, taxonomic, chemical, and biosynthetic classification. Although chemical classification based on the carbon skeleton is the most accepted way of classification, here we will use the pharmacological one depending on the physiological response. Alkaloids are a class of organic compounds that is made up of carbon, hydrogen, oxygen, and nitrogen. In addition, sulfur and rarely other elements such as chlorine, bromine, and phosphorus are also included in the alkaloids. Primary nitrogenous metabolites including amino acids and polymer of amino acids serve as precursors for alkaloids and are usually largely retained in the structure where the nitrogen in the alkaloid molecule is derived. In particular, alkaloids are synthesized from amino acids mostly derived from four different amino acids: lysine, phenylalanine, tyrosine, and tryptophan. To this respect alkaloids show similar structural features to the originated amino acid (shown in **Figure 1**). Alkaloids usually have one or more heterocyclic ring structure which includes at least one nitrogen atom in the ring. Nevertheless, the nitrogen atom is not within a carbon ring in some alkaloids such as mescaline. They are alkaline in nature due to the nitrogen content that they can absorb acid or hydrogen ions making them a base; however, some do not exhibit alkaline properties. The fact remains that the precise position of the nitrogen atom in the carbon ring or molecule varies with different alkaloids that determines the properties of them [24, 38–40].

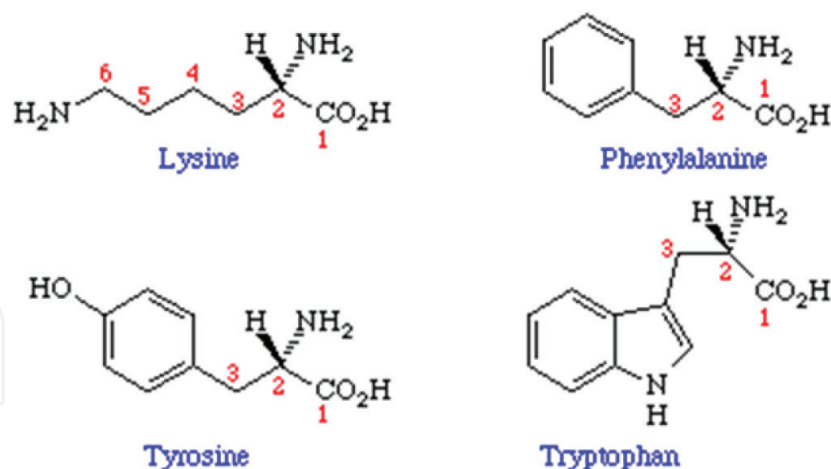


Figure 1. The amino acids used for alkaloid biosynthesis.

From the first impression, the term “secondary metabolite” looks like it is used to describe little importance to plant metabolism or unrelated compounds, although they have broad functional spectrum of specialized metabolism such as defense mechanisms and serve as bioactive compounds for drug discovery, and also other roles have not yet been clearly understood in the plant. It is a matter of controversy among scientists how alkaloids as secondary metabolites make contribution to plants. Some believe that the presence of alkaloids discourages insects and animals from eating plants. Nonetheless, the general properties of alkaloids could be listed as colorless, crystalline solids and nonvolatile, optically active, bitter taste, soluble in organic solvents (i.e., alcohol, ether, chloroform). On the contrary their corresponding salts are highly soluble in water. There are a few liquids such as coniine and nicotine and even a few colored such as berberine is yellow [24, 40, 41].

Alkaloids can form ionic bonds with phenolic hydroxyl groups; hydrogen bonds with hydroxyl groups, carbonyl, or keto groups; and van der Waals and hydrophobic interactions with lipophilic compounds. These interactions will lead a conformational change in the protein structure that is usually associated with a loss or reduction in the bioactivities of proteins (enzymes, receptors, ion channels, hormones, etc.). Apart from other secondary metabolites, alkaloids more specifically interact solely with a single particular target. For example, neurotransmitters and alkaloids both derive from amino acids as a consequence consist of structural similarities and are considered as analogs of each other. Alkaloids can bind to neuroreceptors, either activate (agonists) or inactivate (antagonists) them, and inhibit or activate ion channels such as the Na^+ , K^+ , and Ca^{2+} channels. Alkaloids have shown significant action for the treatment of such dangerous human diseases as cancer, AIDS, and lung diseases [22, 40, 41]. Neurodegenerative diseases (ND) such as Alzheimer’s (AD) disease and dementia primarily affect the neurons in the human (central nerve system) which control many direct body functions and the behavior. The alkaloids show promising pharmacological activities for the treatment of neurodegenerative diseases such as Alzheimer’s disease. Clinical studies of galantamine, which is an alkaloid obtained from daffodil (*Narcissus tazetta*), snowdrop (*Galanthus nivalis*), and snowflake (*Leucojum aestivum*), report the capability of stimulating nicotinic receptors that further enhance cognition and memory [42–49].

4. Plants as a source of alkaloids

There is an enormous range of chemical compounds present in plants where alkaloids take place as a content of secondary metabolites. Alkaloid content is inhomogeneous and usually within a few percent over the plant tissues. Further, most plants produce a few types of closely related alkaloids, whereas some of them may contain several alkaloids in different tissues of the same plants. Therefore, firstly there is a need on the extraction of their mixture and then separation of individual alkaloids. Medicinal bioactive compounds from raw extracts of the plants can be isolated by acid-base extraction. Pure alkaloids are not readily soluble in water, but found to be fairly soluble in organic solvents (ether, chloroform, alcohol, and oils), relatively nonpolar solvents (hexane, benzene, petroleum ether). On the contrary, alkaloids are mostly present in the corresponding salt form in the plant and almost freely soluble in water, mostly insoluble or relatively less soluble in many of organic solvents. As a group, alkaloids are easily extracted in acidic forms because of their basic and lipid properties and separated from other water-soluble materials [32, 33, 38, 49–52].

Usually, the dried and powdered plant source is extracted with lipophilic or nonpolar organic solvents such as 1,2-dichloroethane, chloroform, diethyl ether, benzene, or petroleum ether. Since the alkaloids present in the plant sources as the salt of acids, they are exposed to an alkaline medium to convert the alkaloid salts to the corresponding alkaloid bases. The extraction of the alkaloid bases from the bulk of the crude alkaloid solution is achieved again with a nonpolar solvent. The impurities from the plant in solution are dissolved by dilute aqueous acid and are washed away with water. Alkaloids have different solubilities in certain solvents and different reactivities with certain reagents because of the structural diversity [22, 53, 54].

The alkaloid-based drugs used today are of plant origin, and screening of plant extracts for alkaloids and other pharmacologically active compounds is still in progress for new drug discoveries. Chemists extensively investigated production of alkaloids in plants on a large scale, to make many derivatives of these natural compounds and improve technologies correlated to chemical preparation. The discoveries of high-value chemical compounds in plants serve as model structures for synthetic drugs and allow the large-scale production of them with improved properties. Recently, the deep sea bioenvironment is considered an extremely rich source of novel bioactive alkaloids since marine natural products represent a fascinating example of the large variety of secondary metabolites [22, 40, 55].

5. Fundamentals of alkaloid pharmacology

The most useful portion of the plant (e.g., roots and seeds, stem, leaves, bark, milky exudate, etc.) has gathered as drug which is called as crude drugs and has a long-standing place in medicine. In fact, the comprehensive knowledge on the crude drugs is the basis of pharmaceutical sciences. A number of alkaloids are used as drugs owing to the important pharmacological bioactivity in human bodies. In addition to natural alkaloids, synthetic and semisynthetic

alkaloids are discovered by chemical synthesis and modifications of natural alkaloids. Thus, synthetic and semisynthetic alkaloids are biologically more active with improved properties. For example, morphine potency has been dramatically increased via the addition of a 14-hydroxy group to the morphine alkaloid structure. Moreover, scientific achievements have allowed discrimination of chemical structural differentiations (angle of valence of C, N, H, and moiety) of the alkaloid molecules that can lead into considerable changes in biological activities. Therefore, the interdisciplinary research of bioorganic chemistry, biology, and pharmacology is becoming more important [41, 56–58].

For many years, scientific research has been tried to understand the nature and the function of alkaloids in plant metabolism. The role of alkaloids can be explained based on the functions of these compounds inside and outside the organism producing them. Alkaloids play a protective or chemical defense role in interaction with other organisms. However, it is not entirely clear if this ecologically important role is a basic function of these compounds. New researches suggested this role may be a secondary function of alkaloids in connection with the regulation of metabolism as the result of gene expression. Moreover, alkaloids have a fundamental role inside the organism in which they occur and produced by the activity of the organism's genes, enzymes, and proteins (i.e., quinolizidine alkaloids). Alkaloids are able to self-regulate by changing their structural chemical configurations and biological activity in different cell conditions according to pH changes.

Alkaloids and alkaloid-containing drugs became critical components of the pharmacology for clinical applications due to the tremendous healing capability [30]. Many methods have been proposed for the classification of alkaloids as pharmacological, taxonomic, chemical, and biosynthetic classification. Although chemical classification based on the carbon skeleton is the most accepted way of classification, here we will use the pharmacological one depending on the physiological response. In medicine, alkaloids mainly exhibit marked pharmacological activity in some serious disorders like cardiovascular and metabolic disorders, cancer, blood pressure, inflammation, infectious diseases, neurodegenerative diseases, and miscellaneous problems. They have been used as bronchodilator, cardiac stimulant (quinidine), muscle relaxant, pain killer, analgesic (codeine), antioxidant, anticancer (berberine), antimicrobial and amebicidal, anti-inflammatory, central nervous system stimulants or depressants, sympathomimetics, purgative, vasodilator (vincamine), etc. Various pharmacological alkaloids are used in medicine with some examples as listed: atropine is widely used as an antidote to cholinesterase inhibitors and also used in drying cough secretions; morphine and codeine are narcotic analgesics, and codeine is also an antitussive agent; colchicine is used as a gout suppressant; caffeine is a central nervous system stimulant further used as a cardiac and respiratory stimulant and as an antidote to barbiturate and morphine poisoning; emetine is used in the treatment of amebic dysentery and other protozoal infections; epinephrine or adrenaline is used as a bronchodilator and cardiac stimulant and antiallergic, anesthesia, and cardiac arrest; vincristine is used as anticancer drug; and ephedrine is used in blood pressure. Galantamine plays a vital role in treating cognitive disorders that cognitive dysfunction is a major health problem in the twenty-first century, by influencing the function of receptors for the major inhibitory neurotransmitters [22, 30, 54, 55, 59, 60].

6. Alkaloids with anesthetic effects and the related mechanisms

Local anesthetics are the most effective drugs used for the provision of anesthesia and analgesia both intra- and postoperatively in medicine. They are also used to decrease temperature, touch proprioception, and skeletal muscle tone. Alkaloids in local anesthetics have been used in a variety of clinical situations such as topical application to the skin or mucosa membranes; injectable agents for peripheral, central, or spinal nerve block; and also anorectal or ophthalmic use. Local anesthetics consist of a lipophilic (soluble in lipids) aromatic ring connected to a hydrophilic amine ring (amide group) in the molecular structure. In all clinically used local anesthetics (except cocaine), these lipophilic and hydrophilic groups bind via an amide or ester, and the nature of this bond determines many of the properties of the agent (**Figure 2**). Cocaine, procaine, tetracaine, chlorprocaine, benzocaine, and amethocaine can be given as examples to esters, whereas lidocaine (also known as lignocaine), bupivacaine, mepivacaine, prilocaine, etidocaine, dibucaine, ropivacaine, and levobupivacaine for amides. As can be noticed, the suffix “-caine” is a common ending for drugs containing alkaloids. The ester bond is less stable than amide bond so it can easily be broken in solution and cannot be stored for as long as amides. Amino esters undergo hydrolysis to derivatives of para-aminobenzoic acid (PABA) during the metabolic process in the blood which cause allergic reactions that range from urticaria to anaphylaxis. In contrast, amino amides are metabolized by enzymes in the liver, have long duration of activity, are heat stable, also rarely trigger an allergic reaction, and therefore are more commonly used than esters.

When using the local anesthetics, it should be adjusted according to the duration of the surgical procedure and the anticipated degree of pain. For example, a short-acting agent (e.g., mepivacaine) will be useful for creation of excellent intraoperative conditions with minimum postoperative pain for a short operation. On the other hand, a long-acting anesthetic (e.g., ropivacaine) selection will be appropriate for a rotator cuff repair which involves a greater degree of postoperative pain. A given local anesthetic has different block durations and onset depending on the nerve or plexus blockade.

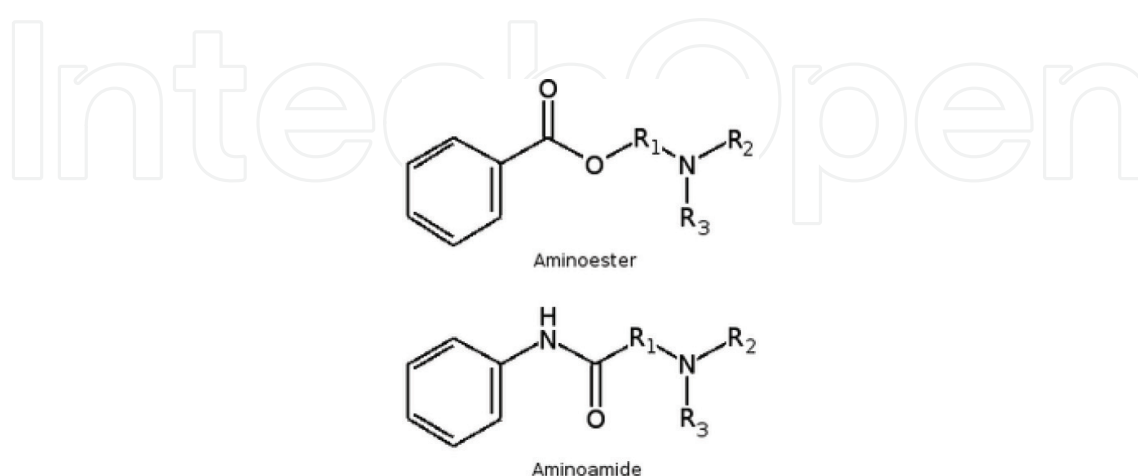


Figure 2. Para-aminobenzoic derivatives of local anesthetics (hydrolyzed by pseudocholinesterase in plasma).

All local anesthetics (except cocaine) are vasodilators where vasodilation occurs via direct relaxation of peripheral arteriolar smooth muscle fibers. The enhanced vasodilator activity of a local anesthetic agent results in shorter duration of action because of faster absorption. A vasoconstrictor counteracts this vasodilatation by providing delayed vascular adsorption of local anesthetics and increases the duration of contact with nerve tissues. Epinephrine vasoconstricts arteries, in concentrations of 5 mcg/ml (1:200,000), and is commonly used to decrease the adsorption of lidocaine when combined with local anesthetics solution. This dosage of epinephrine will significantly reduce nerve blood supply of lidocaine regardless of the site of administration. Decrease in the absorption provides increased neuronal uptake, enhanced quality of anesthesia, and prolonged duration of action [22, 23, 41, 56, 59, 61].

The first local anesthetic used in the clinical practice was cocaine, an alkaloid from the leaves of *Erythroxylum coca*. The natives of South America have chewed the leaves of *E. coca* which grows wild in the Andes Mountains in Peru for the stimulant effect, and the systemic effects of chewing these leaves had reached Europe from the time of the Spanish conquest. In 1860, Niemann isolated the pure alkaloid responsible for the properties of the coca leaves and produced pure white crystals which he named cocaine. He noted that it had a bitter taste and produced numbness of the tongue, rendering an almost devoid sensation. A Russian physician Vassily von Anrep in 1880 demonstrated that subcutaneous injection of cocaine produces sensory block where the skin is insensitive to the prick of a pin. This had attracted the attention of Sigmund Freud, and he conducted a study of the anesthetizing properties of cocaine with assistance of his friend Carl Koller. Koller introduced its topical use into ophthalmology and found that cocaine is able to block signal conduction in nerves which led to its rapid medical use as a “local anesthetic” in both dentistry (1884) and in surgery (1885) in spite of its dangers (dangerous effect on the central nervous system, drug of addiction, mydriasis in eye surgery) [62–64].

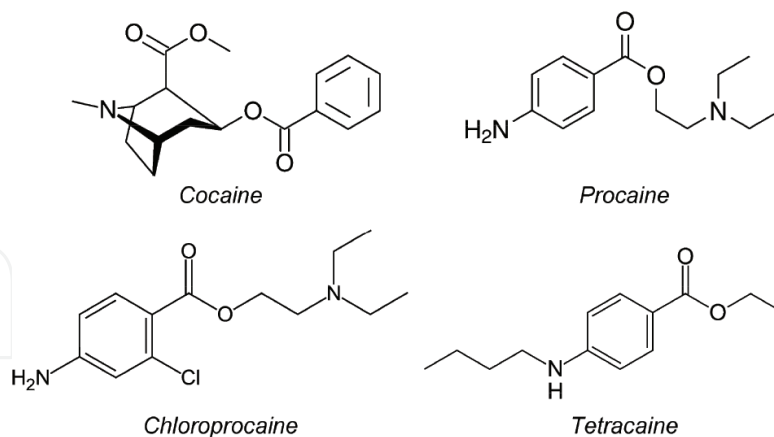
In 1885, Leonard Corning produced spinal anesthesia both in a dog and a patient and produced block of the lower half of the body. Even though he suggested its feasibility, it could be performed in surgery several years after that. Quincke showed that lumbar puncture was a practical procedure in 1891 and the first spinal blocks for surgery was performed by August Bier in 1898.

The early use of cocaine was largely limited to topical application because of the toxicity of cocaine, difficulties in sterilization, drug addiction, and short duration of action. Later on, others have been discovered with less abuse potential, low toxicity, and safer drugs like procaine and procainamide. The latest is lidocaine (synthetic local anesthetic considered prototype) where all new local anesthetics like amino amides have been introduced into clinical practice (Figure 3) [46, 47, 65].

6.1. Mechanism of action

Local anesthetics block the generation and the conduction in peripheral nerves by disruption of ion channel function within the neuron cell membrane preventing the transmission of the neuronal action. This is achieved by specific binding of alkaloids in anesthetics reversibly to sodium (Na^+) channels, preventing the passage of Na^+ through Na^+ channels, and interaction

Esters



Amides

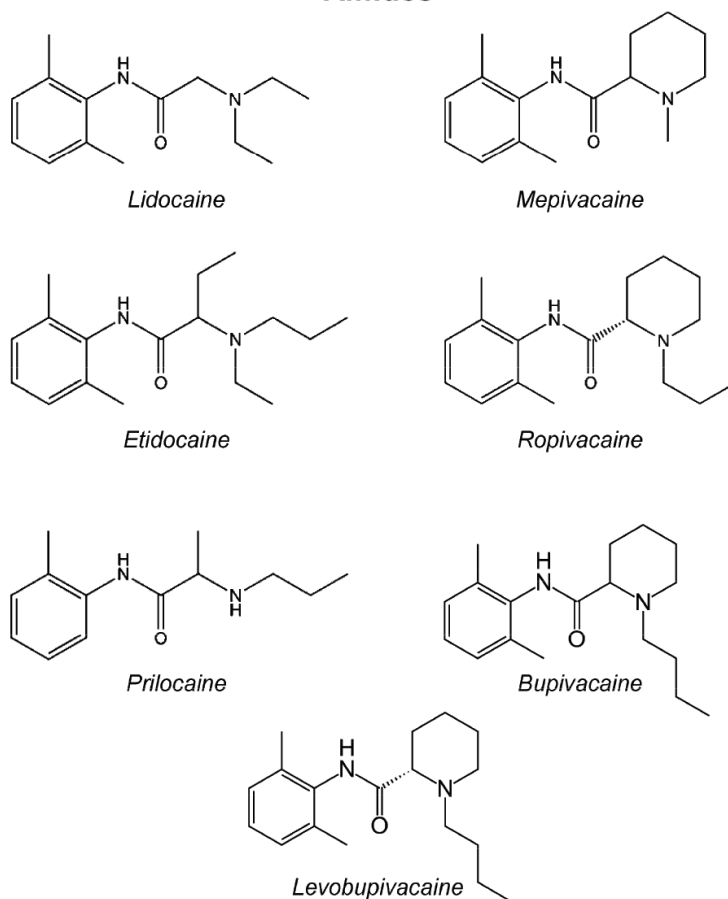


Figure 3. Chemical structures of ester and amide local anesthetics.

with receptors, holding them in an inactive state so that no further depolarization can occur. Local anesthetics primarily have the ability to bind to sodium channel pore when it is in activated state, although may bind during the resting inactivated state to make it impermeable to Na⁺ [62, 66–68].

Sodium influx through these channels is necessary to function within the neuron cell membrane for the transmission of the neuronal action potential and subsequent propagation of an impulse along the course of the nerve. Thus, the loss of sensation in the area supplied by the nerve provides loss of pain, temperature, touch, proprioception, and then skeletal muscle tone, respectively. When local anesthesia is used, people may still feel touch but not pain.

Physiologic activity of alkaloidal local anesthetics depends on lipid solubility, affinity for protein binding, percent ionization at physiologic pH, and vasodilating properties. Lipid solubility is directly in correlation with the potency of the local anesthetic where the nerve cell membrane is composed of lipid and a depot of drug forms in the perineural lipid-rich tissues.

Through the lipid solubility, lidocaine penetrates in nerve membranes and binds to acute-phase protein of α 1-acid glycoprotein (AAG) which is responsible for binding lidocaine and other basic drugs. Although lidocaine can bind to albumin (low affinity, high capacity), AAG (low capacity, high affinity) is the major drug-binding macromolecule even with lower plasma concentration. Albumin is considered as the principal binding protein for acidic compounds, and AAG is the principal binding protein for basic drugs [69–72].

Alkaloids are weak bases and exist in ionized and nonionized forms which are defined by the dissociation constant (pK_a) of a weak base and the pH of the tissues (usually at range 7.6–8.9). Alkaloids are able to self-regulate by changing their structural chemical configurations and biological activity in different cell conditions according to pH changes. The neutral base form of the local anesthetic is more lipophilic that makes pK_a greater than 7.4 for most local anesthetics. A decrease in pH increases the proportions of ionized form and results the delayed onset of action. In the presence of inflammation, local anesthetics are less effective, and onset of action is slow. On the contrary, an increase in pH results increased nonionic form, and nonionized drug form is more ready to pass through the lipid cell membrane. Therefore, more nonionized drug at physiological pH will reach its target site more quickly and will have a faster onset of action. This explains why lignocaine has an enhanced onset of action than bupivacaine [69–72].

Local anesthetic is exposed to the more acidic axoplasmic side of the nerve when passed in the cell membrane. This leads to ionized form of the molecule which binds the sodium channel for blockade. Local anesthetics bind to serum α 1-acid glycoproteins and other proteins. The duration of action for local anesthetics is based on high affinity against protein. As long as local anesthetic remains bound to nerve membranes, it provides an increased duration of action. Thus, the availability of free drug in the blood decreases which reduce the potential for toxicity.

Clinically, sodium bicarbonate is used to increase the pH of local anesthetic solutions. Nevertheless, it should be avoided from precipitation of anesthetic molecules over with alkalization. Protein binding is also correlated to enhance continued blockade that alkaloid more firmly binds to the protein of the sodium channel. All local anesthetics are vasodilators (except cocaine) where the vasodilator activity leads to faster absorption and thus shorter duration of action. Addition of different alkaloids in local anesthetic solutions, i.e., mostly preferred epinephrine or norepinephrine and phenylephrine, produces vasoconstriction and provides less absorption through vascular beds. Thus, more local anesthetic will be available for neural blockade.

Local anesthetic sensitivity of nerve fibers differs to block generation and the conduction of nerve impulses. Small nerve fibers tend to be blocked more easily than larger fibers, and myelinated fibers are blocked sooner than non-myelinated fibers of the same diameter [22, 24, 40, 56, 57, 59, 73, 74].

6.2. Cocaine

Cocaine is a natural alkaloid produced from leaves of the coca that blocks nerve impulses and local vasoconstriction secondary to inhibition of local norepinephrine reuptake. However, it has a limited clinical use because of its toxicity and the potential for abuse. In modern medicine, cocaine is used primarily in topical anesthesia of the upper respiratory tract, where it's combined with vasoconstrictor and local anesthetic properties [56, 59, 75].

6.3. Lidocaine

Lidocaine was developed by Lofgren after procaine, the most widely used cocaine derivative with a low pKa (7.7). Lidocaine is a local anesthetic of the amide type as well as cardiac depressant (antiarrhythmic) which has an ingredient of lidocaine hydrochloride alkaloid ($C_{14}H_{22}N_2O \cdot HCl$). Lidocaine hydrochloride is a white powder freely soluble in water where injection of sterile, nonpyrogenic solution of it is indicated for production of local or regional anesthesia by infiltration techniques (percutaneous injection) and intravenous regional anesthesia by peripheral nerve block techniques (brachial plexus and intercostal) and by central neural techniques (lumbar and caudal epidural blocks). Further, it has been administered by continuous intra-articular infusion (to control postoperative pain). Lidocaine binds to neuronal membrane to stabilize and inhibit voltage-gated sodium channels for the initiation and conduction of impulses. Lidocaine has a very rapid onset of action that typically begins working within 4 min and an anesthetic half-life of about 1.6 h (30 min to 3 h). Therefore, lidocaine is suitable for infiltration, block, and surface anesthesia where its actions are more intense and its effects are more prolonged (when compared to procaine). Subdural and epidural anesthetics bupivacaine or prilocaine are preferred as longer-acting substances [37, 57, 58, 76].

The rapid metabolism by the liver enzymes leads to biotransformation of lidocaine in some pathways including oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. The pharmacologically active metabolites monoethylglycinexylidide and inactive glycinexylidide are produced as a result of N-dealkylation biotransformation that is a primary metabolism. Monoethylglycinexylidide has a longer half-life but also less potent than lidocaine. The rate of biotransformation of an amide local anesthetic significantly influences the anesthetic blood levels where increased blood levels can potentially increase toxicity. Approximately 90% of the dose of injected lidocaine undergoes biotransformation and is excreted in the form of various metabolites in the kidney, whereas less than 10% is excreted and unchanged.

The concentration of AAG and the concentration of free lidocaine affect the predictability of lidocaine toxicity where higher doses of lidocaine can be tolerated before encountering toxicity based on surgery type and certain disease states. For example, surgery, trauma, postoperative

inflammation, cancer, and myocardial infarctions cause an increase in α 1-acid glycoprotein and lidocaine binding, thus reducing the free lidocaine plasma concentration [77].

Through the lipid solubility, lidocaine penetrates in nerve membranes and binds to acute-phase protein of α 1-acid glycoprotein (AAG) which is responsible for binding lidocaine and other basic drugs. Although lidocaine can bind to albumin (low affinity, high capacity), AAG (low capacity, high affinity) is the major drug-binding macromolecule even with lower plasma concentration. Albumin is considered as the principal binding protein for acidic compounds, and AAG is the principal binding protein for basic drugs [37, 57, 58, 76, 78, 79].

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6.4. Procaine

Procaine, the first synthetic derivative of cocaine, was created in 1904 with the trade name of Novocaine, from the Latin nov- (new) and -caine, a common ending for alkaloids used as anesthetics. Procaine, an amino ester, is a short-acting local anesthetic that is used as an injection for local infiltration and peripheral nerve block during surgery and other medical and dental procedures. Low potency, slow onset, and short duration of action are the characteristics of procaine. Although its clinical use is largely confined to infiltration anesthesia and peripheral nerve block as sterile solutions in concentrations of 1 and 2% for injection, this drug is no longer available in the United States.

Procaine has a pKa of 8.9 where commercially prepared solutions have a pH of 5.5 to 6.0. Due to rapid hydrolysis by plasma cholinesterase, it has very short plasma half-life that is thought to be approximately 20 seconds. It has a very short duration of action based upon extremely poor protein binding. While toxicity associated with the use of procaine is quite a little, the use of procaine produces metabolite para-aminobenzoic acid which is associated with an increased rate of allergy [57, 80].

6.5. Benzocaine

Benzocaine is an amino ester that is a derivative of procaine with a pKa of 8.5 and pH in preparation between 4.5 and 6.0. Benzocaine binds to sodium channels and reversibly depolarizes the neuronal membrane, consequently blocking the initiation and conduction of nerve impulses. It has a slow onset, short duration, and moderate toxicity. Benzocaine is considered an oral anesthetic because it numbs the mouth by dulling the nerve endings in painful areas [81].

6.6. Chlorprocaine

Chlorprocaine is a short-acting amino ester which is a chlorinated derivative of procaine. Because it is the most rapidly metabolized local anesthetic (by cholinesterase), it has an extremely short plasma half-life. Chlorprocaine has a pKa of 8.9, whereas prepared solutions have a pH of 2.5 to 4.0. Although it has a high pKa value, characterized by rapid onset of action, it also has the least toxicity in the central nerve system and/or cardiovascular system among current agents in use.

Chlorprocaine has clinical usage mostly in epidural anesthesia and also in peripheral blocks with short duration, whereas combined usage with other long-acting, slow-onset local anesthetics such as bupivacaine and tetracaine to achieve rapid onset with prolonged duration is common.

Owing to the short duration of spinal chlorprocaine, it is a strong alternative to lidocaine for surgical blocks and short or ultrashort surgical procedures for outpatient anesthesia. Its use in a dose ranging between 30 and 60 mg for procedures lasting >60 min has been suggested in the literature [82].

6.7. Tetracaine

Tetracaine is a long-acting amino ester with a pKa of 8.6, and commercially prepared solutions have a pH between 4.5 and 6.5. It has been used in spinal anesthesia if long duration of action is needed and also in various topical anesthetic preparations. When compared to the other commonly used ester local anesthetics, tetracaine is more slowly metabolized and considerably more toxic. It is significantly more potent and has a longer duration of action than procaine or chlorprocaine. Tetracaine is not recommended for peripheral nerve blocks owing to its slow onset and potential for systemic toxicity (may be greater if used with epinephrine). It has clinical use in spinal anesthesia with and without the use of epinephrine leading in a considerably reliable and long-onset spinal anesthetic [80].

6.8. Mepivacaine

Mepivacaine is an intermediate-duration amino amide local anesthetic with a pKa of 7.6. In terms of pharmacologic properties, mepivacaine is often compared to lidocaine where mepivacaine has similar onset of action with a slightly longer duration for infiltration anesthesia. When an intermediate-duration blockade is desired for peripheral nerve block techniques, 1.5% mepivacaine is an attractive local anesthetic, particularly in high-risk cardiac patients. Low toxicity, rapid onset, dense motor block, and excellent diffusion properties through tissue can be listed as characteristic of mepivacaine. Mepivacaine is clinically used as a local anesthetic for an epidural or spinal block and also used as an anesthetic for dental procedures. Some addictive people try to obtain this drug and inject it themselves because large doses of mepivacaine cause sedation, immobility, confusion, dissociation, and amnesia [83].

6.9. Bupivacaine

Bupivacaine is introduced in 1963 since then it has been one of the most commonly used long-acting local anesthetics in regional and infiltration anesthesia. The structural difference of bupivacaine from lidocaine is the amine-containing group that is a butylpiperidine. Bupivacaine is capable of producing prolonged anesthesia and analgesia, thus reducing the need for repeated administration and rarely required the addition of epinephrine. Epinephrine can be prolonged even further duration of blockade. Bupivacaine produces more sensory than motor block where anesthesia duration is from 4 to 16 h depending upon the site of injection and the concentration used. Bupivacaine stabilizes the neuronal membrane and is widely used both in neuraxial and peripheral nerve blockade. Bupivacaine hydrochloride has higher lipid solubility ($\log D_{pH\ 7.4} = 2.54$) and a much decreased rate of hepatic degradation when compared to lidocaine. This characteristic makes bupivacaine more cardiotoxic than lidocaine. Because of its greater tendency to produce cardiotoxicity, large doses of bupivacaine should be avoided and is not recommended for intravenous regional analgesia. 0.5% bupivacaine is as effective as 2% lignocaine. Bupivacaine is widely used both in neuraxial and peripheral nerve blockade, infiltration anesthesia, spinal anesthesia, and epidural and caudal anesthesia. It is not recommended for intravenous regional analgesia because of cardiotoxicity which is much more than other local anesthetics. When bupivacaine is used, the smallest effective dose is aimed to administer [84–86].

6.10. Ropivacaine

The studies on reducing the cardiotoxicity of bupivacaine resulted to development of ropivacaine with similar physicochemical properties of onset, potency, and duration to those of bupivacaine. Ropivacaine is used in concentrations of 0.5% or higher and produces dense blockade with a slightly shorter duration than bupivacaine. The onset of blockade is almost as fast as 1.5% mepivacaine or 3% 2-chloroprocaine in concentrations of 0.75%. Having less cardiotoxicity and central nerve system toxicity, reduced motor block, and an absolute difference in potency are mentioned in the literature as the advantages of ropivacaine over bupivacaine. However, it can be suggested that there may be no more than slight differences in onset, but no difference between ropivacaine and bupivacaine in duration of block. For these reasons, both drugs have been used as an effective long-acting local anesthetic in peripheral nerve blockade [84, 87, 88].

6.11. Levobupivacaine

Despite the effectiveness of bupivacaine as anesthetic, there are safety concerns related to cardiovascular and/or central nerve system toxicity. As a result levobupivacaine is being associated with a lower risk of toxicity alternative to bupivacaine. Levobupivacaine contains a single enantiomer of bupivacaine hydrochloride (the S-(-)-enantiomer of (±)-bupivacaine) where dexbupivacaine (R-(+)-enantiomers) is the other enantiomer of bupivacaine. The route of administration and concentration effects the onset and duration of sensory and motor block where levobupivacaine, dexbupivacaine, or bupivacaine has similar potency as an anesthetic.

However, levobupivacaine is consistently less toxic than bupivacaine. The clinical use of levobupivacaine includes surgical anesthesia or pain management during labor, postoperative analgesia, lumbar epidural or intrathecal anesthesia, thoracic epidural anesthesia, peripheral nerve block, and infiltration anesthesia that have mostly investigated and compared with bupivacaine [84, 88].

6.12. Opiates

Opiate describes any of the narcotic opioid alkaloids found in opium plant (*Papaver somniferum*) that are morphine, codeine, thebaine, and papaverine or synthetic opioids that are derived from morphine and thebaine (oxycodone and hydrocodone). Opiates and its synthesized derivatives are prescribed in medications used for pain relief with even stronger analgesic properties than their predecessors do. Opium itself contains over 25 different alkaloids, whereas only morphine and codeine are used as opiate analgesics from the point of view of clinical significance. The majority of drugs appearing on a synthetic opioid list are derivatives of these medications. The list of opiate drugs includes natural opiate drugs from natural opium alkaloids and synthetic (synthetic and semisynthetic) opiate drugs, also called as opioids, made by chemical synthesis in the laboratory according to the chemical structures found in natural alkaloids.

Natural opiate drugs can be listed as morphine, codeine, thebaine, and oripavine. Synthesized versions of natural opiate drugs are Demerol, Fentanyl, Dilaudid, Norco, Lortab, Atarax, Methadone, and Buprenorphine. Semisynthetic medications are derived from the naturally occurring alkaloids where small concentrations of natural opium alkaloids go into the making of semisynthetic opiates, thus, a part of synthetic opiates. Semisynthetic opiate drugs include:

- Oxymorphone—contains the natural alkaloid, thebaine.
- Hydrocodone—contains the natural alkaloid, codeine.
- Oxycodone—contains the natural alkaloid, thebaine.
- Hydromorphone—contains the natural alkaloid, morphine.

The studies in the laboratory were focused on eliminating the risk for addiction of natural opioid alkaloids and make even more effective than opium itself for relatively safe alternatives for treatment. However, opiates in any form always carry a risk for addiction. Fully synthetic alkaloids are synthesized from other chemicals and molecules that do not come from alkaloids found in plants [61, 89].

Both of these natural and synthetic types of drugs bound to the active site on the receptors (called opioid receptors) from certain nerve cells in the brain, spinal cord, and gastrointestinal tract. Once the opioids injected into the epidural or subarachnoid space to manage acute or chronic pain, bound to the specific nerve cells in the brain, block a specific receptor site and sent inaccurate measures of the severity of the pain so that the person who has taken the drug will experiences less pain. Thus, opiate is used in combinations with a local anesthetic to both enhance the blockade and prolong analgesia in neuraxial blockade. Nevertheless, opioid

receptors do not exist in peripheral nerve so opiates do not have an effective clinical role in peripheral nerve blockade. Taking drugs in these classes also affect how the brain feels pleasure, in other words addictive [21, 90–94].

Completely synthetic alkaloid molecules called opioids are originally synthesized by pharmaceutical companies because of their potency as an analgesic for the treatment of severe pain. As opposed to an opiate (natural opium alkaloid), they are very similar in structure to morphine, whereas the exact geometry of the molecule largely effects on determining the painkilling activity. For example, the drugs Levorphan and Dextrorphan are both mirror images of one another with quite similar structure to morphine. Levorphan, the left-handed molecule like naturally left-handed morphine, is several times more potent than morphine and is strongly addictive, while Dextrorphan, the right-handed molecule, has no analgesic ability and is also nonaddictive [21, 90–94].

6.12.1. Morphine

The main alkaloid morphine in opium poppy is a naturally occurring analgesic opioid and one of the most potent pain relievers. One of the most important uses of morphine in today's clinical practice is relief of pain caused by heart attack or myocardial infarction. Morphine helps to ease the pain particularly before, during, and after major surgeries and acts as an anesthetic without decreasing consciousness. Morphine is a weak base with the pKa of about 8.0 and has relatively low lipid solubility at physiological pH (**Figure 4**). Morphine exists mostly in ionized form that does not favor passage through the lipid membrane; thus, onset of action is relatively slow (15–30 min). The basic mechanism depends on the shape of the morphine molecule and its binding to the active site on the receptor protein. The ability of morphine to fit into the active site and block a specific receptor site on a nerve cell gives its analgesic properties. In this way the action of the pain receptor rules out and intercepts the pain signals reaching the brain. The specific opiate receptors are classified mainly as mu (μ), kappa (κ), and sigma (σ). In terms of analgesia effects, the mu (μ) is the most important receptor type including at least two subtypes, μ_1 and μ_2 , in which μ_1 probably mediates analgesia. Morphine produces relaxation and sedation by depressing the nervous system [91, 93, 95].

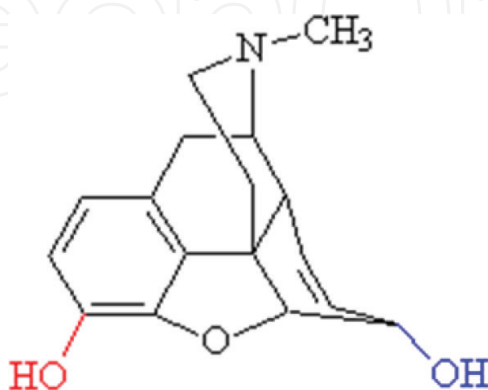


Figure 4. Morphine structure, replacing the —OH group shown in red with —OCH_3 , produces codeine where heroin derives from replacing both the red and blue —OH groups with OCOCH_3 .

Hydromorphone is synthesized from morphine that is much stronger than morphine but has less side effects and a lower dependency rate. It is prescribed to treat severe pain or dry coughing (Dilaudid and Palladone).

Completely synthetic alkaloid molecules called opioids are originally synthesized by pharmaceutical companies because of their potency as an analgesic for the treatment of severe pain. As opposed to an opiate (natural opium alkaloid), they are very similar in structure to morphine, whereas the exact geometry of the molecule largely effects on determining the painkilling activity. For example, the drugs Levorphan and Dextrorphan are both mirror images of one another with quite similar structure to morphine. Levorphan, the left-handed molecule like naturally left-handed morphine, is several times more potent than morphine and is strongly addictive, while Dextrorphan, the right-handed molecule, has no analgesic ability and is also nonaddictive.

6.12.2. Codeine

Codeine is another powerful analgesic derived from morphine (although it is less potent than morphine) by replacing one of the —OH groups with a methoxy group (—OCH_3) and was first used as a therapeutic antitussive (see structure below in **Figure 5**). When codeine is metabolized, the —OCH_3 group converted back to —OH and regenerates morphine. Although morphine, heroine, and codeine are all derived from opium, codeine has a slight difference in chemical structure from morphine and heroine. It is often sold as a salt in the form of either codeine sulfate or codeine phosphate, while codeine hydrochloride is more common worldwide. In therapeutic doses, codeine is much less effective as an analgesic than morphine therefore often combined with other medications including Empirin with codeine, Fiorinal with codeine, and Tylenol with codeine. The prescription medications of codeine is available in pill form but also can be injected into the muscle. It is not given through IV as it can cause convulsions. Codeine is used for its analgesic, antitussive, antidiarrheal, antihypertensive, anxiolytic, antidepressant, sedative, and hypnotic properties [21, 96].

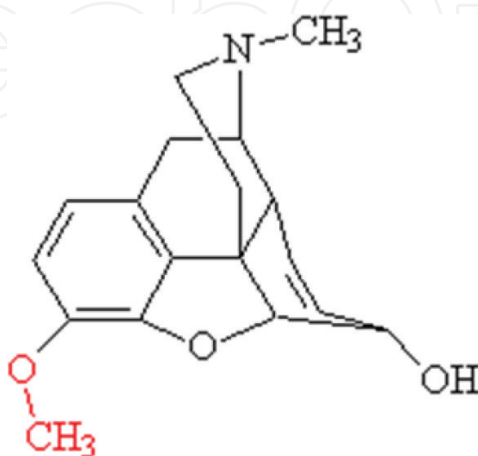


Figure 5. Replacing the —OH group of morphine shown in red with —OCH_3 produces codeine.

6.12.3. Heroin

Heroin was synthesized from morphine to be used as a nonaddictive cure; however, it was turned out that heroin is highly addictive and more potent than morphine. Heroin exhibits euphoric, anxiolytic, and analgesic central nervous system properties so classified as a Schedule I drug that possession or trading of it is illegal. Heroin (diacetylmorphine or diamorphine) is derived from the morphine alkaloid by acetylation of the two hydrogen-bonding hydroxyl groups ($-\text{OH}$) with acetyl chloride ($-\text{OCOCH}_3$) (**Figure 6**). Acetylation makes heroin more soluble in nonpolar solvents (i.e., oils and fats) and provides rapid pass through the blood-brain barrier which makes heroin much more potent than morphine because heroin is converted back to morphine in the brain. Patients with heroin addiction should seek advice from healthcare providers [91, 93, 95].

6.12.4. Thebaine

Thebaine is a natural alkaloid that is extracted from the opium poppy plant, due to its origin classified as opiates. Though thebaine is toxic and unsuitable for use as drug, pharmaceutical companies use thebaine alkaloids to create semisynthetic therapeutic drugs including Naloxone, Naltrexone, and Buprenorphine by breaking down it into smaller metabolites and also alter the chemical structure such as oxycodone. In spite thebaine binds to opioid receptors in the central nervous system, it stimulates the nervous system, while morphine and codeine produce relaxation and sedation by depressing the nervous system.

Thebaine is used to create semisynthetic pain relievers, such as oxymorphone and oxycodone. Oxycodone is synthesized from thebaine and used to treat moderate to severe pain for patients after surgery. Oxycodone is usually prescribed in tablet forms (Percocet, Percodan, or OxyContin) and widely combined with other drugs such as aspirin. Hydrocodone is synthesized from either codeine or thebaine and prescribed to treat moderate to severe pain and heavy coughs (Vicodin, Lorcet, Dolorex, Forten, and Anexsia).

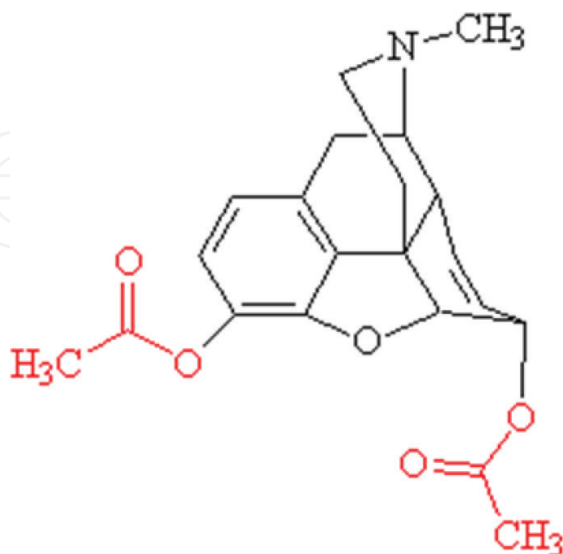


Figure 6. Chemical structure of heroin derived from morphine.

6.12.5. Oripavine

Oripavine is not produced by traditionally cultivated varieties of opium poppy where a chain of chemical processes are used to extract oripavine from the opium poppy plant. First of all opium is broken to major alkaloid metabolites, codeine, morphine, and thebaine. Oripavine is the major metabolite of thebaine that is produced by altering the chemical structure of thebaine for more effective or safer medications. Despite its development based on high therapeutic value and low-abuse potential compounds, it has severe toxicity and low therapeutic index. Even though oripavine is a strong pain reliever with comparable analgesic potency to morphine, it does not have clinical use. It is used as convenient source for the production of several synthetic opioid pharmaceuticals [97].

6.12.6. Fentanyl

Fentanyl is one of the most lipophilic opioids with rapid onset of action (10–15 min) and short duration (2–5 h) that found a wide usage epidural and intradural for postoperative pain. The clinical studies also focused on the beneficial effect of the combination of intrathecal fentanyl as lipophilic opioids with intrathecal local anesthetic in ambulatory surgery. Intrathecal bupivacaine is commonly preferred for local anesthesia in ambulatory surgery due to neurological toxicity of lidocaine. The fact remains that a high level of the sympathetic block can take place in high doses of intrathecal bupivacaine. The combination of intrathecal opioids added to low-dose local anesthetics provides a faster onset of blockade and better intraoperative and immediate postoperative analgesia that prevents increasing the degree of motor blockade or delaying discharge [98–100].

6.13. Other anesthetic alkaloids

Tropane alkaloids are synthesized from the amino acids ornithine, putrescine (decarboxylated ornithine), and proline or obtained by extraction from plants. The important drugs and alkaloids in this group are atropine, hyoscyamine, and scopolamine. These alkaloids have effects on the central nervous system, including nerve cells of the brain and spinal cord that may also affect the autonomic nervous system. The chemical structure of these includes a methylated nitrogen atom $N-CH_3$ at one end of the molecule which is also found in the neurotransmitter acetylcholine. Hence, they are capable of blocking or inhibiting nerve impulses between nerves in the brain and neuromuscular junctions. Atropine is an alkaloid which stimulates the central nervous system. Its sulfate salt is injected intramuscularly prior to induction of anesthesia. Reduction in pulse range and cessation of cardiac action are attributable to increased vigil activity administered intravenously during surgery. Scopolamine or hyoscyne is an alkaloid that has a depressant activity on the central nervous system. Thus, scopolamine hydrobromide is used for preanesthetic sedation in conjunction with analgesics. Diterpenoid alkaloids (DAs) isolated from *Delphinium* and *Aconitum* plant species possess local anesthetic activity by suppressing sodium currents of excited membranes [22, 59, 101, 102].

6.14. Alkaloids for pain and pleasure

Despite alkaloids and other psychoactive chemicals came from nature act as defensive molecules for the organisms that made them, these types of molecules can be quite addictive drugs to humans. Many alkaloid substances like cocaine, caffeine, nicotine, opium (morphine, heroine), etc. act on the peripheral nervous system with the psychological side effects that produce a state of relaxed, mental excitement, and euphoria which are referred to addiction.

Medically useful alkaloids morphine and codeine are the pain relievers but also addictive drugs. Morphine is stronger than codeine, while codeine is often prescribed for moderate pain and also an effective cough suppressant. Heroin is another abused alkaloid drug derived from morphine by a simple chemical modification. However, heroin is metabolized to morphine once it enters the body; thus, these two alkaloids drugs are considered completely equivalent.

Cocaine is produced from the coca plant and classified as narcotic. The effects of cocaine can be sorted, excited, and elated, an impression of enhanced physical strength and mental ability feelings. There after elevated heart rate and blood pressure are accompanied to these feelings. However, cocaine produces a state of euphoric hyperarousal for a short duration; hence, the addicted person needs high dose of the drug that may lead to fibrillation and death. Cocaine usage over time can result in paranoid schizophrenia.

Nicotine is another alkaloid that is pleasurable and addictive mainly known for tobacco plants, whereas potatoes, eggplant, cauliflower, and tomato can be listed as nicotine sources. Nicotine alkaloids have primarily stimulation properties and produce either relaxation or arousal.

There are other alkaloids which are not addictive, but stimulants such as caffeine and the analog compounds theophylline and theobromine are. Caffeine occurs naturally in coffee, tea, cocoa and chocolate, cola drinks, and a variety of other plants. Tea contains small amounts of theophylline apart from caffeine, while theobromine is the major stimulant in cocoa. Cocoa and chocolate contain neuroactive alkaloids known as tetrahydro-beta-carbolines that possibly have influences on mood and behavior [23, 24, 103–108].

Author details

Havva Sayhan^{1*}, Serbülent Gökhan Beyaz² and Ahmet Çeliktas³

*Address all correspondence to: hsayhan@gmail.com

1 Sakarya University Training and Research Hospital, Sakarya, Turkey

2 Sakarya University Training and Research Hospital, Korucuk Campus, Department of Anesthesiology and Pain Medicine, Sakarya, TURKEY

3 Tubitak Bilgem Yital, Kocaeli, TURKEY

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