Physiology and Pharmacology of Local Anesthetic Agents†

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Local anesthetic drugs may be defined as pharmacological agents which are capable of producing a loss of sensation in a circumscribed area of the body. This localized form of anesthesia is due to an inhibition of excitation at nerve endings or to a blockade of the conduction process in peripheral nervous tissue. Regional anesthesia originated in 1884 when Koller described the topical anesthetic properties of cocaine, an alkaloid that had been isolated from the leaves of the Erythroxylin coca bush. Procaine, which was synthesized by Einhorn in 1905, was the first injectable agent of clinical value for the production of local anesthesia. Following the introduction of procaine, numerous compounds of similar chemical structure were developed. Tetracaine and chloroprocaine are the procaine-like agents which have persisted to this day as clinically useful local anesthetic drugs.

In 1943, Lofgren synthesized lidocaine, which represented a new chemical class of local anesthetic compounds. Whereas the procaine-like drugs are ester derivatives of para-aminobenzoic acid, lidocaine, is an amide derivative of diethylamino acetic acid. Since the advent of lidocaine, many other amide substances, such as mepivacaine, prilocaine, bupivacaine, and etidocaine, have been introduced into clinical practice as local anesthetic agents each with its own pharmacological profile.

Mechanism of Local Anesthesia

Local anesthetic agents exert their primary pharmacological action by interfering with the excitation-conduction process of peripheral nerve fibers and nerve endings. The electrophysiological properties of the nerve membrane are dependent on: (a) the concentration of electrolytes in nerve cytoplasm and extracellular fluid; and (b) the permeability of the cell membrane to various ions — particularly, sodium and potassium. The ionic composition of the cytoplasm and extracellular fluid differ markedly. The intracellular concentration of potassium is approximately 110 to 170 meq/liter. In extracellular fluid the situation is reversed. The concentration of sodium is approximately 140 meq/liter, chloride is 110 meq/liter, and potassium is 5 meq/liter. This ionic asymmetry on either side of the cell membrane is due in part to the selectively permeable characteristics of the membrane. The resting membrane is fully permeable to potassium ions but only slightly permeable to sodium ions, which accounts for the low intracellular concentration of sodium. The high intracellular concentration of potassium is maintained by the attractive forces of the negative charges, mainly on proteins, within the cell, which counterbalances the tendency of potassium ions to diffuse out of the cell by passive movement along a concentration gradient and across a freely permeable membrane.

During the period of nerve inactivity, a negative electrical potential (resting potential) of approximately −90 mv exists across the cell membrane. Thus, at rest, the nerve cell behaves as a potassium electrode which would react to intra or extracellular changes in potassium but not sodium concentrations. Excitation of a nerve results in an increase in the permeability of the cell membrane to sodium ions. The initial flux of sodium ions from the extracellular space to the interior of the nerve cell results in a depolorization of the cell membrane from the resting potential level to the threshold or firing level of approximately −50 to −60 mv. At this point, a maximum increase in the permeability of the cell membrane to sodium ions occurs and an explosively rapid influx of sodium ions into the axoplasm follows. At the end of depolarization or at the peak of the action potential, the nerve membrane is essentially transformed from a potassium electrode to a sodium electrode with a positive membrane potential of +40 mv.

At the conclusion of the depolarization phase, the permeability of the cell membrane to sodium ions again decreases and high potassium permeability is restored. Potassium moves out of the cell, resulting in repolarization of the membrane until such time as the original electrochemical equilibrium and resting potential is re-achieved. The flux of sodium ions into the cell during depolarization and potassium ions out of the cell during repolarization is a passive phenomenon, since each ion is moving down its concentration gradient. Under normal conditions this entire process of depolarization and repolarization occurs within 1 msec. The depolarization phase occupies approximately 30 percent of the entire action potential, whereas repolarization accounts for the remaining 70 percent.

Following return of the membrane to the resting potential level, a very slight excess of sodium ions is present within the cell and a very slight excess of potassium ions exists outside of the nerve cell. Restoration of the normal ionic gradient across the nerve membrane requires the expenditure of energy for the active transport of sodium ions from the

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inside to the outside of the nerve cell against a concentration gradient. This active transport of sodium ions is made possible by the function of the so-called "sodium pump." The energy required to drive the sodium pump is derived from the oxidative metabolism of adenosine triphosphate. This metabolic pump, which actively extrudes intracellular sodium ions, also is believed responsible, in part, for the transport of potassium ions from the extracellular space to the interior of the nerve cell, since potassium ions also must move against a concentration gradient in order to restore the normal K_i/K_o ratio across the cell membrane. Potassium will return to the interior of the cell until the electrostatic attraction of the intracellular negative charges balances the chemical concentration gradient.

Electrophysiological studies have failed to show any alteration in the membrane resting potential of isolated nerves following exposure to varying concentrations of different local anesthetic agents such as procaine or lidocaine.[1] In addition, little or no change in the threshold potential occurs following application of local anesthetic agents to an isolated nerve. The predominant change occurs during the depolarization phase of the action potential. A decrease in the maximum rate of rise of the action potential of the isolated lumbar spinal ganglion of the frog from a control value of 190 v/sec to 120 v/sec has been observed after 15 minutes exposure to a solution of 0.005 percent (0.2 mmolar) lidocaine.[1] This decrease in the rate of depolarization is not accompanied by any significant change in the rate of repolarization. When depolarization is not sufficient to reduce the membrane potential of an individual fiber to the threshold potential level, a propagated action potential fails to develop.

Since the depolarization phase is related to an influx of sodium ions across the cell membrane, the action of local anesthetic agents on sodium permeability has been investigated. Direct measurements of sodium and potassium conductance by voltage clamp techniques have shown that local anesthetic agents block neural sodium currents.[2] Lidocaine causes a complete inhibition of sodium conductance, but only a 5 percent decrease in potassium conductance. In addition, tetrodotoxin, the puffer fish poison which possesses potent local anesthetic activity, completely inhibits sodium conductance and conduction in nerves at a concentration of 30 nM with no discernible effect on potassium conductance.

Local anesthetic agents are believed to act at the sodium channel of the nerve membrane. However, the specific receptor location varies according to the type of local anesthetic agent. The conventional agents, such as lidocaine and procaine, are believed to bind at receptor sites located on the inner surface of the nerve membrane. Biotoxins, such as tetrodotoxin and saxitoxin, act at receptor sites located on the external surface of the membrane. Finally, agents such as benzocaine and benzyl alcohol act by penetrating the nerve membrane, causing membrane expansion and a resultant decrease in the diameter of the sodium channel.[3]

In summary, the mechanism of action of local anesthetic agents is related to the following sequence of events: (a) binding of local anesthetic molecules to receptor sites in the nerve membrane; (b) reduction in sodium permeability; (c) decrease in the rate of depolarization; (d) failure to achieve threshold potential level; (e) lack of development of a propagated action potential; and (f) conduction blockade.

Active Form of Local Anesthetic Agents

Most of the clinically useful local anesthetic preparations are available in the form of solutions of a salt, e.g., lidocaine is usually prepared as an 0.5 – 2.0 percent solution of lidocaine hydrochloride. In solution, the salts of these local anesthetic compounds exist as uncharged molecules (B) and as positively charged cations (BH^+). The relative proportion between the uncharged base (B) and charged cation (BH^+) depends on the pK_a of the specific chemical compound and the pH of the solution, i.e., $pH = pK_a - \log (BH^+/B)$. Since pK_a is constant for any specific compound, the relative proportion of free base and charged cation will be dependent essentially on the pH of the local anesthetic solution ($BH^+ \; B + H^+$). As the pH of the solution is decreased and the H^+ concentration increased, the equilibrium will shift towards the charged cationic form and relatively more cation will be present than free base. Conversely, as the pH is increased and the H^+ concentration decreased, the equilibrium will shift towards the free base form and relatively more of the local anesthetic agent will exist in the free base form. Both the uncharged base form (B) and the charged cationic form (BH^+) of local anesthetic agents are involved in the process of conduction block.[4,5] The base diffuses more easily through the nerve sheath and so is required for optimal penetration which is reflected clinically in onset of anesthesia. Following diffusion through the epineurium, equilibrium reoccurs between B and BH^+ and the charged cation actually binds to the receptor site in the nerve membrane. Therefore, the cationic form is ultimately responsible for the suppression of electrophysiological events in peripheral nerve which is reflected clinically in the profoundness of anesthesia.

Pharmacological Basis of Local Anesthesia

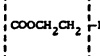
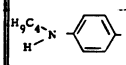
Chemical compounds that demonstrate local anesthetic activity usually possess the following chemical arrangement:

Aromatic portion — Intermediate chain — Amine portion

The agents of clinical importance can be categorized into two distinct chemical groups. Local anesthetics with an ester link between the aromatic portion and the intermediate chain are referred to as amino-esters and include procaine, chloroprocaine, and tetracaine (Table 1). Local anesthetics with an

TABLE 1

Chemical Structure and Primary Anesthetic Use of Ester and Amide-type of Local Anesthetics

AGENT	CHEMICAL CONFIGURATION			PRIMARY ANESTHETIC USE
	Aromatic Lipophilic	Intermediate Chain	Amine Hydrophilic	
A. Esters				
PROCAINE				Infiltration
CHLOROPROCAINE				Obstetrical Epidural
TETRACAINE				Spinal
B. Amides				
MEPIVACAINE		NHCO		Infiltration Peripheral nerve block Surgical epidural
BUPIVACAINE		NHCO		Peripheral nerve blocks Surgical and Obstetrical epidural
LIDOCAINE		$NHCOCH_2$		Infiltration Peripheral nerve blocks Surgical epidural Obstetrical spinal
PRILOCAINE				Infiltration Peripheral nerve blocks Surgical epidural
ETIDOCAINE				Peripheral nerve blocks Surgical epidural

amide link between the aromatic end and intermediate chain are referred to as amino-amides and include lidocaine, mepivacaine, prilocaine, bupivacaine and etidocaine (Table 1). The basic difference between the ester and amide compounds resides in (a) the manner in which they are metabolized and (b) their allergic potential. The ester agents are hydrolyzed in plasma by pseudocholinesterase, whereas the amide compounds undergo enzymatic degradation in the liver. Para-aminobenzoic acid is one of the metabolites formed from the hydrolysis of ester-type compounds. This substance is capable of inducing allergic-type reactions in a small percentage of the general population. The amide, lidocaine-like, drugs are not metabolized to para-aminobenzoic acid and reports of allergic phenomena with these agents are extremely rare.

The anesthetic profile of a chemical compound is dependent on its (a) lipid solubility, (b) protein-binding, (c) pK_a, (d) non-nervous tissue diffusibility, and (e) intrinsic vasodilator activity. Lipid solubility appears to be a primary determinant of intrinsic anesthetic potency (Table 2). The lipid solubility of procaine, as determined by partition coefficient measurements, is less than one and this drug is least potent in suppressing conduction in an isolated

TABLE 2

Relationship of Physical Chemical Properties to Local Anesthetic Activity

Agent	Relative In Vivo Potency	Approximate Lipid Solubility	Duration (Min)	Approximate Protein Binding
LOW POTENCY — SHORT DURATION				
Procaine	1	< 1	60-90	5
INTERMEDIATE POTENCY/DURATION				
Mepivacaine	2	1	120-240	75
Prilocaine	2	1.5	100-240	55
Lidocaine	2	4	90-200	65
HIGH POTENCY — LONG DURATION				
Bupivacaine	8	30	180-600	95
Tetracaine	8	80	180-600	85
Etidocaine	6	140	180-600	94

nerve. On the other hand, the partition coefficient of bupivacaine, tetracaine and etidocaine vary from approximately 30 to 140, indicating an extremely high degree of lipid solubility for these agents. These drugs produce conduction blockade in an isolated nerve at very low concentrations such that their intrinsic anesthetic potency is approximately 20 times greater than that of procaine.[6] The relationship of lipid solubility to intrinsic anesthetic potency is consistent with the biochemical composition of the nerve membrane. Chemical analysis of the axolemma of the first stellar nerve of the giant squid has revealed that approximately 90 percent of the axolemma consisted of lipids.[7] Therefore, local anesthetic agents which are highly lipid soluble penetrate the nerve membrane more easily, which is reflected biologically in increased potency.

The protein-binding characteristics of local anesthetic agents primarily influence the duration of action (Table 2). Agents such as procaine are poorly bound to proteins and basically possess a relatively short duration of action. Conversely, tetracaine, bupivacaine and etidocaine are highly bound to proteins and display the longest duration of anesthesia.[6] The relationship between protein-binding of local anesthetic agents and their duration of action is again consistent with the basic structure of the nerve membrane.[7] Proteins account for approximately 10 percent of the nerve membrane. Therefore, agents which penetrate the axolemma and attach more firmly to the membrane proteins will tend to possess a prolonged duration of anesthetic activity.

The pK_a of a chemical compound may be defined as the pH at which its ionized (BH^+) and nonionized (B) forms are in complete equilibrium. As previously indicated, the uncharged base form (B) of a local anesthetic agent is primarily responsible for diffusion

across the nerve sheath. The onset of anesthesia is directly related to the rate of epineural diffusion which, in turn, is correlated with the amount of drug in the base form. The percentage of a specific local anesthetic drug which is present in the base form when injected into tissue whose pH is 7.4 is inversely proportional to the pK_a of that agent. For example, lidocaine, which has a pK_a of 7.74, is 65 percent ionized and 35 percent nonionized at a tissue pH of 7.4. On the other hand, tetracaine, with a pK_a of 8.6, is 95 percent ionized and only 5 percent nonionized at a tissue pH of 7.4. Both in vitro and in vivo studies have confirmed that local anesthetic drugs such as lidocaine, whose pK_a is closer to tissue pH, have a more rapid onset time than agents with a high pK_a, such as tetracaine (Table 3).[8]

TABLE 3

Relationship of pK_a to Percent Base Form and Time for 50 Percent Conduction Block in Isolated Nerve

Agent	Chemical Class	pK_a	Δ Base at pH 7.4	Onset (Min)
Prilocaine	Amino-amide	7.7	35	2-4
Lidocaine	Amino-amide	7.7	35	2-4
Etidocaine	Amino-amide	7.7	35	2-4
Bupivacaine	Amino-amide	8.1	20	5-8
Tetracaine	Amino-ester	8.6	5	10-15
Procaine	Amino-ester	8.9	2	14-18

In an isolated nerve, onset time is a function of the rate of diffusion of a compound through the epineurium which, in turn, is related to percentage of drug in the base form. However, in vivo, a local anesthetic must diffuse initially through non-nerve connective tissue barriers. Differences do exist between the rate of non-nervous tissue diffusion for various agents. For example, procaine and chloroprocaine have similar pK_a's of 9.1 and similar onset times for conduction blockade in an isolated nerve. However, in vivo, the onset of anesthesia for chloroprocaine is significantly shorter than that of procaine, which is indicative of a more rapid rate of non-nervous tissue diffusibility. Similarly, in the amide series, lidocaine and prilocaine possess the same pK_a and onset of action in isolated nerves, whereas lidocaine has a slightly faster onset of anesthesia in vivo. The factors that determine diffusibility through non-nervous tissue are unclear.

Finally, intrinsic vasodilator activity of different local anesthetic agents will influence their apparent potency and duration of action in vivo. The degree and duration of nerve block is related to the amount of local anesthetic drug which diffuses to the receptor site at the nerve membrane. Following injection of a local anesthetic agent, some of the drug will be taken up by the nerve and some will be absorbed by the vascular system. The degree of vascular absorption is related to the blood flow through the area in which the drug is deposited. All local anesthetic drugs, except cocaine, are vasodilator in nature. However, the degree of vasodilation produced by the various agents does differ. In vitro studies have shown that the intrinsic anesthetic potency of lidocaine is significantly greater than that of mepivacaine, while their durations of action are similar. However, in vivo, mepivacaine is similar in potency and produces a longer duration of anesthesia than lidocaine. These differences between in vitro and in vivo results are attributable to the greater vasodilator activity of lidocaine which results in greater vascular absorption such that less lidocaine is available for nerve blockade.

In summary, chemical alterations within an homologous group produce quantitative changes in physico-chemical properties, such as lipid solubility and protein-binding, which can alter the anesthetic properties of the compounds. Within the ester series, the addition of a butyl group to the aromatic end of the procaine molecule increases lipid solubility and protein-binding and results in a compound, tetracaine, which has a greater intrinsic anesthetic potency and longer duration of anesthetic activity. In the amide series, the addition of a butyl group to the amine end of mepivacaine transforms this agent into a compound, bupivacaine, which is more lipid soluble, more highly protein-bound, and, biologically, possesses a greater intrinsic potency and longer duration of action. In the case of lidocaine, substitution of a propyl for an ethyl group at the amine end, and the addition of an ethyl group to the alpha carbon in the intermediate chain yields etidocaine, which is more lipid soluble, more highly protein-bound, and, biologically, a local anesthetic agent of greater potency and longer duration.

On the basis of differences in anesthetic potency and duration of action, it is possible to classify the clinically useful injectable local anesthetic compounds into three categories:

Group I — Agents of low anesthetic potency and short duration of action: e.g., procaine and chloroprocaine.

Group II — Agents of intermediate anesthetic potency and duration of action: e.g., lidocaine, mepivacaine, and prilocaine.

Group III — Agents of high anesthetic potency and long duration of action: e.g., tetracaine, bupivacaine, and etidocaine.

Physiological Disposition of Local Anesthetic Agents

The vascular absorption, tissue distribution, metabolism and excretion of local anesthetic agents are of particular importance in terms of their potential toxicity. Absorption varies as a function of site of injection, dosage, addition of a vasoconstrictor agent, and the specific agent employed.[9] In general, the greater the vascular supply of the tissue (e.g., muscle mucous membranes), the greater the absorp-

tion without a vasoconstrictor. For intra-oral injections, the infiltration of two cartridges (1.8 ml) of lidocaine 20 mg/ml or 76 mg will produce a peak blood level of 0.5-2 μg/ml within 20-30 minutes. An equal dose applied topically in the uncharged base form can reach higher levels within 5 minutes approaching intravenous administration. An inferior alveolar block, with reduced vascularity at the site of injection, will have the lowest blood level and be least influenced by a vasoconstrictor. The blood level of local anesthetic agents is related to the total dose of drug administered rather than the specific volume or concentration of solution employed.[9] A linear relationship tends to exist between the injected amount of drug and the peak anesthetic blood level.

Addition of a vasoconstrictor agent to local anesthetic solutions decreases the rate of absorption of certain agents. 5 μg/ml of epinephrine (1:200,000) reduces the peak blood levels of lidocaine and mepivacaine by approximately 30 percent, irrespective of the site of administration.[6] Epinephrine will decrease the peak blood levels of prilocaine, bupivacaine, and etidocaine achieved after peripheral nerve blocks, but has little influence on the absorption of these drugs following lumbar epidural administration.[9,10] Phenylephrine, and norepinephrine can also reduce local anesthetic absorption, but not as effectively as epinephrine.[11]

The rate and degree of vascular absorption varies between various agents. Lidocaine is absorbed more rapidly than prilocaine, while bupivacaine is absorbed more rapidly than etidocaine.[12] The lower blood levels of prilocaine probably reflects its tendency to produce less vasodilation than lidocaine or mepivacaine. The lower peak blood levels of etidocaine compared to bupivacaine may be related to the greater lipid solubility and uptake by peripheral fat of etiodcaine.

Following absorption from the injection site, local anesthetic agents distribute throughout total body water. An initial rapid disappearance from blood (alpha phase) occurs which is related to uptake by rapidly equilibrating tissues, i.e., tissues with a high vascular perfusion. A secondary, slower disappearance rate (beta phase) reflects distribution to slowly perfused tissues and metabolism and excretion of the compound. The disappearance rate of prilocaine is significantly more rapid than that of lidocaine or mepivacaine.[13] The rate of tissue redistribution for these latter two agents is similar. Similarly, the alpha and beta half-lives of etidocaine are significantly shorter than those of bupivacaine, which indicates a more rapid rate of tissue redistribution for etidocaine.[14] Although all tissues will take up local anesthetics, the highest concentrations are found in the more highly perfused organs, such as lung and kidney.[15] The greatest percentage of an injected dose of a local anesthetic agent distributes to skeletal muscle due to the large mass of this tissue in the body.

The metabolism of local anesthetic agents varies according to their chemical classification. The ester or procaine-like agents undergo hydrolysis in plasma by plasma cholinesterases. Chloroprocaine shows the most rapid rate of hydrolysis (4.7 μmole/ml/hr) compared to procaine (1.1 μmole/ml/hr) and tetracaine (0.3μmole/ml/hr).[16] Less than 2 percent of unchanged procaine is excreted, while approximately 90 percent of para-aminobenzoic acid, which is the primary metabolite of procaine, appears in urine. On the other hand, only 33 percent of diethylaminoethanol, the other major metabolite of procaine, is excreted unchanged.

The amide, or lidocaine-like, agents undergo enzymatic degradation primarily in the liver. Prilocaine undergoes the most rapid rate of hepatic metabolism. Lidocaine, mepivacaine, and etidocaine are intermediate in terms or rate of degradation, while bupivacaine is metabolized most slowly. Some degradation of the amide-type compounds may occur in non-hepatic tissue as indicated by the formation of certain metabolites following the incubation of prilocaine with kidney slices. The metabolism of the amide-type agents is more complex than that of the ester drugs. The complete metabolism for all the amide compounds has not been elucidated. Lidocaine, which has been studied most extensively, undergoes primarily oxidative deethylation to monoethylglycinexylidide, followed by a subsequent hydrolysis to hydroxyxylidine.[17] Less than 5 percent of unchanged amide-type drugs is excreted into the urine. The major portion of an injected dose appears in the form of various metabolites. For example, 73 percent of lidocaine can be accounted for in human urine by hydroxyxylidine. The renal clearance of the amide agents is inversely related to their protein-binding capacity. Prilocaine, which has a lower protein-binding capacity than lidocaine, has a substantially higher clearance value than lidocaine. Renal clearance also is inversely proportional to the pH of urine, suggesting urinary excretion by nonionic diffusion.[18]

Systemic Toxicity of Local Anesthetic Agents

The toxicity of local anesthetic agents mainly involves the central nervous system and cardiovascular system.

a) *CNS effects:* Local anesthetic agents readily cross the blood-brain barrier and toxic levels can produce signs of CNS excitation and depression. The initial symptoms of local anesthetic toxicity in man consist of a generalized feeling of lightheadedness and dizziness, followed by auditory and visual disturbances, such as difficulty in focusing and tinnitus. Drowsiness, disorientation, and a temporary lack of consciousness may also occur. Slurred speech, shivering, muscle twitching, and tremors of the face and extremities appear to be the immediate precursors of a generalized convulsive state. A further increase in the dose of local anesthetic agents during the excitation period, results in cessation of convulsive

activity, respiratory arrest, and a flattening of the brain wave pattern consistent with generalized central nervous system depression.

The signs and symptoms of CNS excitation followed by depression are related to an inhibition of cerebral cortical neurons. An initial selective blockade of inhibitory cortical neurons or synapses allows facilitory fibers to function unopposed leading to excitation and convulsions. Further increases in dosage depress both inhibitory and facilitory pathways causing a generalized state of central nervous system depression.[19]

Local anesthetic toxicity is due usually to an inadvertent rapid intravenous injection or extravascular administration of an excessive dose. CNS toxicity following rapid intravenous administration is related to the intrinsic anesthetic potency of the agent.[20] Procaine is least potent anesthetically and least toxic following a rapid intravenous injection. Bupivacaine, tetracaine, and etidocaine are the most potent compounds in terms of intrinsic anesthetic and CNS convulsive activity. Lidocaine, mepivacaine, and prilocaine are intermediate in anesthetic potency and convulsive activity. For example, blood levels in excess of 20 μg/ml of procaine are associated with CNS symptoms in man. Lidocaine, mepivacaine, and prilocaine demonstrate CNS effects at levels of 5-10 μg/ml, while bupivacaine, and etidocaine show CNS effects at venous blood levels of 1.5 to 4 μg/ml.

The potential toxicity of local anesthetic agents administered extravascularly will be influenced by factors such as rate of absorption, tissue redistribution, and metabolism. Prilocaine and lidocaine are similar in terms of intrinsic anesthetic potency and rapid intravenous toxicity, whereas prilocaine is approximately 60 percent less toxic than lidocaine following subcutaneous administration due to its slower absorption and more rapid clearance. Similarly, etidocaine and bupivacaine are equitoxic following rapid intravenous injection, but etidocaine is only half as toxic as bupivacaine after subcutaneous injection. Intravenous chloroprocaine is intrinsically more toxic than procaine, but is four times less toxic than procaine following subcutaneous adminsitration due to its rapid hydrolysis in plasma.

Other factors, such as acid-base status of the patient, will influence local anesthetic toxicity. An inverse relationship exists between pCO_2 level and convulsive threshold of local anesthetic agents. The convulsive threshold of procaine in cats decreases from approximately 35 mg/kg to 15 mg/kg when the pCO_2 is elevated from 25-40 torr to 65-81 torr.[20]

b) *Cardiovascular effects:* Local anesthetic agents can produce profound cardiovascular changes by a direct cardiac and peripheral vascular action and, indirectly, by conduction blockade of autonomic nerve fibers. Lidocaine concentrations of 5-10μg/ml may cause a prolongation of conduction through various portions of the heart (increased P-R interval and QRS duration), an increase in diastolic threshold and decreased automaticity, as reflected by sinus bradycardia. Lethal concentrations of lidocaine produce asystole. Hemodynamically, lidocaine doses and blood levels considered non-toxic (2-5 μg/ml) cause no alterations in myocardial contractility, diastolic volume, intraventricular pressure, and cardiac output.[21] Blood levels of 5-10 μg/ml result in decreased myocardial contractility, increased diastolic volume, decreased intraventricular pressure, and decreased cardiac output.[21] At these blood levels, lidocaine also produces a decrease in peripheral vascular resistance, due to a direct relaxant effect on the smooth muscle of peripheral arterioles. This negative inotropic and peripheral vasodilator action can cause profound hypotension and circulatory collapse. All local anesthetic agents show a similar pattern of cardiovascular toxicity. The doses of local anesthetic agents employed for most regional anesthetic procedures result in peak blood levels which, generally, are not associated with a cardiodepressant effect. However, inadvertent, rapid, intravenous injection, or administration of an excessive dose may cause significant cardiovascular alterations.

c) *Allergy:* True allergic reactions to local anesthetic agents are rare. Ester derivatives of paraaminobenzoic acid, such as aprocaine and tetracaine, are responsible for most of the suspected allergic phenomena associated with the use of local anesthetic agents. Reports of allergic reactions to amide-type compounds (i.e., lidocaine and mepivacaine) have been extremely rare. Multiple dose vials of some amide agents contain a preservative, methylparaben, which may cause cutaneous signs of allergic-type reactions.[22]

Summary

Local anesthesia provides a safe and efficacious method of preventing or relieving pain in circumscribed areas of the body and so is particularly useful in dentistry. These agents inhibit excitation in nerve endings and fibers by a decrease in sodium permeability which, in turn, depresses the rate and degree of membrane depolarization. The clinically useful local anesthetic agents can be divided chemically into the amino-esters, e.g., procaine, chloroprocaine and tetracaine, and amino-amides, e.g., lidocaine, mepivacaine, prilocaine, bupivacaine and etidocaine. Pharmacologically, these agents can be categoried as agents of low potency and short duration of action, e.g., procaine and chloroprocaine; agents of intermediate potency and duration of action, e.g., lidocaine, mepivacaine and prilocaine; and agents of high potency and long duration, e.g., tetracaine, bupivacaine and etidocaine.

Local anesthetic agents can produce toxic reactions which usually involve the central nervous system of cardiovascular system. Toxic blood levels, which are due most often to an inadvertent rapid intravenous injection or the extravascular adminis-

tration of an excessive dose, may result in overt convulsions followed by CNS depression and cardiovascular collapse due to a direct negative inotropic action on the heart and peripheral vasodilator effect. Intravenous toxicity of local anesthetic agents is directly related to their anesthetic potency, whereas toxicity subsequent to extravascular overdose is related to the disposition characteristics of the various drugs. The judicious use of local anesthesia requires knowledge of the pharmacological properties of the various agents, technical skill in the performance of regional anesthetic procedures, and an evaluation of the patient's clinical status.

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