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Chemical Aspects of Local Anesthetic Agents

HISTORICAL NOTES

Local anesthesia may be defined as a loss of sensation in a circumscribed area of the body due to a depression of excitation in nerve endings or an inhibition of the conduction process in peripheral nervous tissue. This localized state of anesthesia may be produced by such different means as mechanical trauma, low temperature, anoxia, and a variety of chemical irritants. In general, only substances that produce a transient and completely reversible state of insensibility are employed in clinical practice. Neurolytic agents such as alcohol or phenol may be useful to induce a relatively permanent state of anesthesia in patients with intractable pain.

The use of chemical substances to prevent or treat local pain had its origin in South America during the nineteenth century. It was known that central nervous system stimulation occurred among the natives of Peru who chewed the leaves of an indigenous plant (*Erythroxylon coca*). Circumoral numbness was believed to have occurred as a by-product of this custom. Attempts to isolate the active principle from leaves of the *Erythroxylon coca* bush resulted in the extraction of the alkaloid, erythroxylon, by Gaedcke in 1855 and finally in the isolation of the alkaloid, cocaine, by Niemann in 1860.[1] The potential use of cocaine as a local anesthetic agent was initially described by a Peruvian army surgeon, Moréno y Maïz, in an obscure monograph.[2] However, the clinical usefulness of cocaine was not appreciated until 1884, when Koller reported that instillation of cocaine into the conjunctival sac resulted in topical anesthesia of the eye.[3] These observa-

tions led to the widespread use of cocaine as a topical anesthetic agent in ophthalmology. Within a year after Koller's discovery of the topical anesthetic properties of cocaine, Halstead administered this substance by injection for the production of peripheral nerve blockade. By 1898, spinal anesthesia with cocaine had been performed by Bier. These early experiments represented a major advance in surgery. However, a number of adverse effects, both acute and chronic, were observed with the clinical use of cocaine. The acute effects were due to systemic toxicity and the chronic effects were due to cocaine's addicting properties. The severity of these adverse reactions resulted in an intense effort to develop chemical substances possessing the beneficial local anesthetic properties of cocaine, but without such serious side effects. One of the major programs in the present field of local anesthesia is to develop local anesthetic drugs with a more favorable therapeutic ratio.

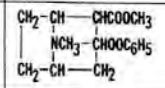
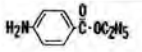
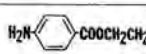
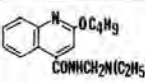
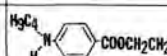
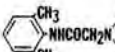
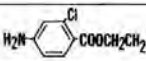
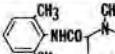
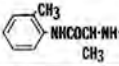
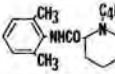
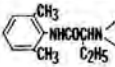
The chemical identification of cocaine as a benzoic acid ester led to the synthesis of numerous compounds which were basically benzoic acid ester derivatives. Benzocaine, a poorly water-soluble local anesthetic agent, was identified by Ritsert in 1890.[4] Because its low water solubility limited its usefulness as an injectable agent, this compound was neglected for many years. Ultimately, benzocaine was recognized as an effective topical anesthetic agent and persists today as a valuable drug for the production of surface anesthesia of mucous membranes. In 1905, Einhorn and Braun reported the synthesis of procaine, an ester of para-aminobenzoic acid.[5, 6] Procaine was water soluble, fairly stable in solution, and possessed an acceptable margin of local and systemic safety for clinical use as an injectable agent in regional anesthesia.

Following the introduction of procaine, numerous similar compounds were synthesized. Tetracaine, the most potent ester of the benzoic acid series appeared in 1930[7] and chloroprocaine, the least toxic of this chemical group, was initially described in 1952.[8] These two para-aminobenzoic acid derivatives are still widely used clinically as local anesthetic agents.

Until the mid-twentieth century, most compounds synthesized as local anesthetic agents were, like tetracaine and chloroprocaine, benzoic acid derivatives. Unfortunately, the major drawback to this chemical class of substances has been their propensity for producing allergic or sensitizing-type reactions. A major breakthrough in the chemistry of local anesthetic agents occurred in 1943 when Löfgren synthesized lidocaine.[9] Lidocaine represented a major chemical de-

Table 1

REPRESENTATIVE LOCAL ANESTHETIC AGENTS IN COMMON CLINICAL USE

Generic* and Common Proprietary Name	Chemical Structure	Approx. year of Initial Clinical Use	Main Anesthetic Utility	Representative Commercial Preparation
Cocaine		1884	Topical	bulk powder
Benzocaine Americaine*		1900	Topical	20% ointment 20% aerosol
Procaine Novocain*		1905	Infiltration Spinal	10 and 20 mg/ml solutions 100 mg/ml solution
Dibucaine Nupercaine*		1929	Spinal	0.667, 2.5 and 5 mg/ml solutions
Tetracaine Pontocaine*		1930	Spinal	Niphanoid crystals - 20 mg/ml 10 mg/ml solutions
Lidocaine Xylocaine*		1944	Infiltration Peripheral Nerve Blockade Epidural Spinal Topical "	5 and 10 mg/ml solutions 10, 15 and 20 mg/ml sol'ns 10, 15 and 20 mg/ml sol'ns 50 mg/ml solution 2.0% jelly, viscous 2.5%, 5.0% ointment
Chloroprocaine Nesacaine*		1955	Infiltration Peripheral Nerve Blockade Epidural	10 mg/ml solution 10 and 20 mg/ml solutions 20 and 30 mg/ml solutions
Mepivacaine Carbocaine*		1957	Infiltration Peripheral Nerve Blockade Epidural	10 mg/ml solution 10 and 20 mg/ml solutions 10, 15 and 20 mg/ml solutions
Prilocaine Citanest*		1960	Infiltration Peripheral Nerve Blockade Epidural	10 and 20 mg/ml solutions 10, 20 and 30 mg/ml solutions 10, 20 and 30 mg/ml solutions
Bupivacaine Marcaine*		1963	Infiltration Peripheral Nerve Blockade Epidural	2.5 mg/ml solutions 2.5 and 5 mg/ml solutions 2.5, 5 and 7.5 mg/ml solutions
Etidocaine Duranest*		1972	Infiltration Peripheral Nerve Blockade Epidural	2.5 and 5 mg/ml solutions 5 and 10 mg/ml solutions 5 and 10 mg/ml solutions

* USP nomenclature

parture from the previous local anesthetic drugs, since it was not an ester but an amide derivative of diethylamino acetic acid. Not only did this new class of amide-type local anesthetic agent offer certain advantages in terms of anesthetic activity, but more importantly, perhaps, such compounds appeared to be relatively free of the sensitizing reactions characteristic of the ester-type derivatives of para-

aminobenzoic acid. Since the advent of lidocaine, all newer local anesthetic agents introduced into clinical practice have been essentially amide-type structures. Thus, mepivacaine, prilocaine, bupivacaine, and etidocaine, which represent the most recent additions to the local anesthetic armamentarium, are amide-type chemical compounds similar to lidocaine, that differ somewhat in their pharmacological profile from lidocaine and from each other.

Representative local anesthetic agents presently in common clinical use are listed in Table 1. The generic name, trade name, and chemical structure of each of these compounds are presented, in addition to their main anesthetic utility and the various types of available commercial preparations.

CHEMICAL CLASSIFICATION OF LOCAL ANESTHETIC AGENTS

Blockade of nerve conduction can be produced by a great variety of chemical structures. Substances that can be classified in broad terms as amino-esters, amino-carbamates, amino-ketones, amidines, alcohols, thioesters, thioethers, thioamides, ureas, phosphoric esters, polyethers, and simple amines are capable of impeding the conduction process in isolated or intact nerves.[10] In general, those local anesthetic agents of proven clinical utility have been the amino-esters and amino-amides.

Amino-Esters

As mentioned previously, most of the agents in this category are ester derivatives of para-aminobenzoic acid. Benzocaine (ethyl 4-aminobenzoate), the oldest of the currently available ester-type agents, is still used widely as a topical anesthetic agent, particularly in nonprescription preparations recommended for dermal pain from minor abrasions or sunburn. Procaine (2-diethylaminoethyl 4-aminobenzoate) was for many years the standard injectable local anesthetic agent for use in infiltration, peripheral nerve blockade, and central neural blockade. Procaine possesses poor topical anesthetic properties and its current clinical role is limited essentially to infiltration procedures. Other similar compounds that still enjoy wide clinical utility are tetracaine and chloroprocaine. Tetracaine (2-dimethylaminoethyl 4-butylaminobenzoate), most potent of the amino-ester agents in clinical use, is employed as both an injectable

and a topical analgesic compound. Tetracaine still remains the most commonly used drug for spinal anesthesia. Chloroprocaine (2-diethylaminoethyl 4-amino-2-chlorobenzoate), the least toxic agent in this class, is particularly suitable for short surgical procedures in poor-risk patients. The structures of benzocaine, procaine, tetracaine, and chloroprocaine are presented in Table 1.

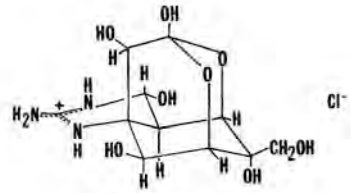
Amino-Amides

Lidocaine (2-diethylaminoacet-2, 6-xylidide), which was the first compound in this series of chemical structures to demonstrate clinical utility as a local anesthetic agent, represented such a significant pharmacological advance over procaine that it soon replaced procaine as the standard local anesthetic drug. Chemically related amide compounds have been introduced into clinical practice during recent years. Prilocaine (2-propylamino-2'-propionotoluidide) differs chemically from lidocaine in that it is a toluidine derivative and secondary amine, whereas lidocaine is a xylidine derivative and tertiary amine.[11] The main clinical advantage of this agent is its relatively low systemic toxicity. Etidocaine (2-N-ethylpropylamino-2',6'-butyroxylidide), the most recent local anesthetic agent introduced into clinical practice, also is structurally similar to lidocaine, but possesses a greater anesthetic potency and a longer duration of action.[12]

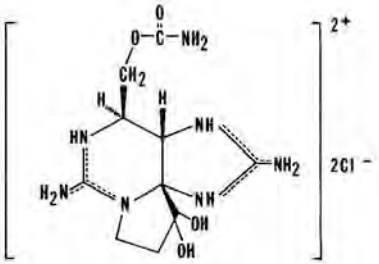
Ekenstam, Egner, and Pettersson described a series of amino-amides in which the chain amino group was made part of a ring system by joining one of the aminoalkyl groups with the intermediate acyl chain.[13] Mepivacaine (1-methyl-2',6'-hexahydropicolinylxylidide) was the initial compound in this series to be introduced into clinical practice.[14] This agent has properties similar to those of lidocaine but lacks topical anesthetic qualities. Bupivacaine (1-butyl-2',6'-hexahydropicolinylxylidide), a homologue of mepivacaine, possesses a greater anesthetic potency and prolonged duration of action compared to mepivacaine.[15]

Guanidine-Type Structures

A third category of substances possessing potent local anesthetic activity includes the guanidine-type molecules. Tetrodotoxin and saxitoxin, representatives of this group, appear in Figure 1-1.[16, 17] Tetrodotoxin is derived from the ovaries and other organs of the puffer fish found most commonly along the coast of Japan.[18] Saxitoxin is produced by certain marine dinoflagellates which can contami-



TETRODOTOXIN



SAXITOXIN

Fig. 1-1. Chemical structures of tetrodotoxin as described by Goto *et al.*[16] and saxitoxin as suggested by Schantz *et al.*[17]

nate shellfish and cause paralytic shellfish poisoning in man.[19] Both of these biotoxins are quite different chemically from other types of local anesthetic agents, since they contain guanidine moieties, resulting in compounds that are stronger bases than either the amino-esters or amino-amides. These substances are the most potent inhibitors of nerve conduction studied to date. Although not presently available for clinical use, such compounds as tetrodotoxin and saxitoxin may be of importance in the future. A classification of these chemical substances according to their biological site of action will be presented in a later chapter.

STRUCTURE-ACTIVITY RELATIONSHIPS

As indicated above, a great variety of chemical structures may produce conduction blockade in nerves. Therefore, it is difficult to define precisely the relationship between the chemical structure and biological activity of local anesthetic agents. However, compounds that demonstrate clinical utility as local anesthetic agents, in general, possess the following chemical arrangement:

Aromatic Portion—Intermediate Chain—Amine Portion

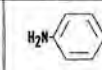
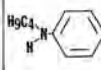
The aromatic portion of the molecule is believed responsible for the lipophilic properties, whereas the amine end is associated with hydrophilicity. Alterations in the aromatic portion, amine portion, or intermediate chain of a specific chemical compound will modify its anesthetic activity. For example, an increase in molecular weight within an homologous series of compounds, achieved by lengthening the intermediate chain or by the addition of carbon atoms to either the aromatic or amine portion of the molecule, will tend to increase intrinsic anesthetic potency up to a maximum, beyond which a further increase in molecular weight results in a decrease in anesthetic activity.[10] Changes in the aromatic or amine portion of a local anesthetic substance will alter its lipid/water distribution coefficient and its protein-binding characteristics which, in turn, will markedly alter the anesthetic profile within a series of homologous compounds. The relationship between chemical structure, partition coefficient, protein-binding, and anesthetic activity of various homologous anesthetic agents is presented in Table 2. A comparison between procaine and tetracaine, which are both ester derivatives of para-aminobenzoic acid, reveals that the addition of a butyl group to the aromatic end of the procaine molecule produces a greater than 100-fold increase in lipid solubility and a ten-fold increase in protein-binding.[20] Such changes in physicochemical properties are reflected in marked alterations in biological activity. For example, the intrinsic anesthetic potency of tetracaine as determined on an isolated nerve is approximately 16 times greater than that of procaine, whereas the duration of its anesthetic activity as determined in vivo in the rat sciatic nerve preparation is approximately four times longer than that of procaine.

Similar relationships exist in the amide series of compounds. The addition of a butyl group to the amine end of mepivacaine, forming bupivacaine, results in a 35-fold increase in partition coefficient[21] and a significantly greater degree of protein-binding as compared to mepivacaine. The chemical alterations of mepivacaine to bupivacaine and the subsequent modification of physicochemical properties result in a four-fold increase in intrinsic anesthetic activity and a significant prolongation of anesthetic duration.

Another example of the relationship between modification of chemical structure and biological activity is found in the comparison of lidocaine and etidocaine. Substitution in the lidocaine molecule of a propyl for an ethyl group at the amine end and the addition of an ethyl

Table 2

STRUCTURE - ACTIVITY RELATIONSHIP OF LOCAL ANESTHETIC AGENTS

AGENT	CHEMICAL CONFIGURATION			PHYSICO-CHEMICAL PROPERTIES		BIOLOGICAL PROPERTIES		
	Aromatic Lipophilic	Intermediate Chain	Amine Hydrophilic	Partition Coefficient	% Protein Binding	Equi-Effective* Anesthetic Conc.	Approx. Anesthetic* Duration (min)	Site of Metabolism
A. Esters								
PROCAINE				0.6[1]	5.8[3]	2	50	Plasma
TETRACAINE				80[1]	75.6[3]	0.25	175	Plasma
B. Amides								
MEPIVACAINE				0.8[2]	77.5[4]	1	100	Liver
BUPIVACAINE				27.5[2]	95.6[4]	0.25	175	Liver
LIDOCAINE				2.9[2]	64.3[4]	1	100	Liver
ETIDOCAINE				141[2]	94[4]	0.25	200	Liver

[1] oleylalcohol / pH 7.2 buffer
[2] n-heptane / pH 7.4 buffer
[3] nerve homogenate binding
[4] plasma protein binding - 2μg/ml
* data derived from rat sciatic nerve blocking procedure

group at the alpha carbon in the intermediate chain yields etidocaine. These chemical changes in structure produce an increase in partition coefficient of approximately 50-fold and a significant increase in protein-binding.[22] As in the previous examples, these alterations in chemical structure and physicochemical properties are reflected in significant changes in biological activity, such that etidocaine possesses an intrinsic anesthetic potency four times greater than that of lidocaine and a duration of anesthetic action approximately twice that of lidocaine.

The rate of degradation and subsequently intrinsic toxicity also will be affected by alterations in the chemical structure of homologous compounds. A comparison of the three ester local anesthetic agents—i.e., tetracaine, procaine, and chloroprocaine—reveals a considerable difference in the rate of enzymatic hydrolysis and intrinsic toxicity of these three agents (Table 3). Tetracaine, which is hydrolyzed quite slowly, shows an LD_{50} value of 48 mg/kg following

Table 3

RELATIONSHIP BETWEEN THE RATE OF HYDROLYSIS AND SUBCUTANEOUS TOXICITY OF SEVERAL ESTER-TYPE LOCAL ANESTHETIC AGENTS

Agent	Rate of Hydrolysis (μ moles/ml/hr)	Subcutaneous Toxicity in mice (LD_{50} values)	Main Products of Metabolism
CHLOROPROCAINE	4.7	1,396	2 chloro,4-aminobenzoic acid, diethylaminoethanol
PROCAINE	1.1	615	4-aminobenzoic acid, diethylaminoethanol
TETRACAINE	0.3	48	4-butylaminobenzoic acid, diethylaminoethanol

subcutaneous administration in mice,[23] whereas chloroprocaine, which undergoes rapid hydrolysis, has an LD_{50} value of 1396 mg/kg in mice. Procaine is intermediate between chloroprocaine and tetracaine, both in terms of rate of hydrolysis and intrinsic toxicity (LD_{50} value of 615 mg/kg). A similar relationship exists within the amide series between lidocaine and prilocaine. Prilocaine is metabolized at a significantly more rapid rate by liver enzymes than is lidocaine and possesses an intrinsic toxicity significantly less than that of lidocaine.[24] A further comparison of prilocaine and lidocaine reveals an interesting aspect of structure-activity relations. The presence of methyl groups in the 2,6-position of the benzene ring of lidocaine results in the formation of 2,6-xylidine as one of the metabolites of lidocaine. On the other hand, prilocaine, lacking the methyl group in the 6-position of the benzene ring has as one of its primary metabolites, o-toluidine. The formation of o-toluidine can induce the production of methemoglobin and is responsible for the methemoglobinemia observed clinically in patients receiving high doses of prilocaine.[25] Lidocaine administration does not result in the formation of methemoglobin.

Alterations in chemical structure within an homologous series of local anesthetic agents are reflected in changes in intrinsic anesthetic potency, duration of action, rate of degradation, and intrinsic toxicity. The basic differences between heterologous local anesthetic agents, i.e., the ester and amide compounds, are: (a) the manner in which they are metabolized and (b) their allergic potential. The ester derivatives of benzoic acid are hydrolyzed primarily in plasma by the enzyme pseudocholinesterase.[26] Members of the amide series of local anesthetic compounds undergo enzymatic degradation primarily in the liver.[27, 28] The difference in site of metabolism between these two main classes of local anesthetic agents is of clinical relevance. Patients possessing a genetic deficiency in the enzyme, pseudocholines-

terase, are unable to hydrolyze these drugs at a normal rate and show reduced tolerance to ester-type local anesthetic agents. Moreover, pseudocholinesterase is responsible for the degradation of neuromuscular blocking agents of the depolarizing types such as succinylcholine. The concomitant use of neuromuscular blocking agents such as succinylcholine and ester-type local anesthetic agents may result in a prolonged duration of neuromuscular blockade and increased toxicity of the local anesthetic agent.[29] Use of a local anesthetic agent of the amide-type in such clinical situations is preferable, since these agents do not depend on the enzyme, pseudocholinesterase, for their metabolism. On the other hand, patients with liver disease may show reduced tolerance to the amide-type local anesthetic drugs, since they are metabolized mainly by hepatic microsomal enzymes. In such patients, the normal dose of an amide agent should be reduced or a compound of the ester-type substituted.

Since the ester agents are derivatives of para-aminobenzoic acid, this substance occurs as a metabolite following hydrolysis of the parent compound. This metabolite is responsible for the allergic-type reactions observed in a small percentage of the general population exposed to such agents. The amide lidocaine-like drugs are not metabolized to para-aminobenzoic acid and reports of allergic phenomena with this group of agents are extremely rare. No evidence of cross sensitivity between the amino-esters and amino-amides has been reported.

SUMMARY

1. Isolation of cocaine from the *Erythroxylon coca* bush marked the start of the local anesthetic era in clinical medicine.
2. The clinically useful drugs presently available essentially fall into two chemical categories: (a) agents with an ester link between the aromatic end of the molecule and the intermediate chain (procaine-like); (b) agents with an amide link between the aromatic portion and the intermediate group (lidocaine-like).
3. Chemical alterations within an homologous group produce quantitative changes in: (a) physicochemical properties, i.e., lipid solubility and protein-binding, which, in turn, alter the anesthetic profile of the compounds; (b) rate of metabolism and type of metabolites formed, which affect systemic toxicity in a quantitative and qualitative fashion.
4. The chemical difference between heterologous groups is reflected

biologically in (a) site of metabolism, i.e., ester compounds are hydrolyzed in plasma whereas amide compounds undergo enzymatic degradation in the liver, and (b) allergic potential, i.e., a greater frequency of sensitizing reactions is observed with the ester derivatives of para-aminobenzoic acid.