Pharmacology of Local Anesthetics

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Definition

Local anesthesia is the drug-induced, reversible loss of sensation in a part of the body without the loss of consciousness and without the impairment of central systems controlling vital functions.
History

• 1905: Procaine (Novocain)
• 1930: Tetracaine (Pontocaine)
• 1944: Lidocaine (Xylocaine)
• 1957: Mepivacaine (Carbocaine)
• 1963: Bupivacaine (Marcaine)
• 1992: Ropivacaine (Naropin)

• These are the most widely used local anesthetics in clinical practice today.

Miller’s Anesthesia, Sixth Edition, 2005, Table 14-1
Chemistry:
Structure-Activity Relationships

- A lipophilic group (an aromatic ring), an intermediate chain (an ester or amide), an ionizable group (usually a tertiary amine).
- Nature of linking group determines some of the pharmacological properties.
- Ester links are more prone to hydrolysis than amide links; thus agents with ester links have a shorter duration of action.
Chemistry of Local Anesthetics

- weak bases ($pK_a$ 8 to 9)
- marketed as salts re: solubility and stability
- exist in the body as the uncharged base or as a cation
- cationic form is the most active form at the receptor site
- uncharged form is important for rapid penetration of biological membranes
Cationic form of local anesthetics at pH 7.4 as a function of pK$_a$

- Chlorprocaine
- Tetracaine
- Bupivacaine
- Tetracaine
Pharmacokinetics: Factors Affecting Absorption

- dosage
- site of injection
- drug-tissue binding
- presence of vasoconstrictors
- physicochemical properties of the drug
Vasoconstrictors and Local Anesthetics

- Duration of local anesthetic action is proportional to the time during which the drug is in contact with the nerve.
- Vasoconstrictors decrease absorption, thus prolong action of local anesthetics.
- Vasoconstrictors also decrease toxicity.
- Local anesthetics are often formulated with vasoconstrictors, usually epinephrine.
Pharmacokinetics: Distribution

- Amide local anesthetics are widely distributed after intravenous bolus administration, and initial uptake is rapid into highly perfused organs (brain, liver, kidney, heart).
- Ester agents are rapidly degraded, which limits distribution.
Pharmacokinetics: Metabolism and Excretion

- Toxicity of local anesthetics depends largely on the balance between rates of absorption and elimination.
- Rates of degradation vary among drugs.
- Toxicity is related to the free concentration of drug, thus binding to serum proteins and tissues reduces toxicity.
Pharmacokinetics:
Metabolism and Excretion

- Local anesthetics are converted in liver or plasma to water soluble metabolites and excreted in the urine.
- Ester type local anesthetics are hydrolyzed rapidly in blood by butyrylcholinesterase (pseudocholinesterase) (half life < 1 min).
- Cerebrospinal fluid contains little or no esterase.
Pharmacokinetics:
Metabolism and Excretion

- The amide linkage is hydrolyzed by liver microsomal cytochrome P450.
- Thus, local anesthetic toxicity is more likely to occur in patients with liver disease.
- Many other anesthesia-related drugs also are metabolized by the same P450 systems (e.g., alfentanil, midazolam).
Pharmacodynamics: Mechanism of Action

- Local anesthetics prevent the generation and conduction of the action potential by blocking voltage-gated sodium channels.
- The active site within the sodium channel is accessible only from within the cell.
- Thus, local anesthetics must penetrate the axonal membrane in order to block nerve conduction.
Voltage-Gated Sodium Channels
Local Anesthetic Receptor Site

extracellular

plasma membrane

intracellular
Pharmacodynamics: Mechanism of Action

- Sodium channels exist in one of three states: resting, activated, or inactivated.
- Binding of local anesthetics stabilizes the inactivated state of sodium channels.
- This binding causes a reversible blockade of nerve conduction
Resting State of the Sodium Channel

- predominates in the fully polarized membrane
- m gate is closed, blocking Na+ current
- h gate is open, permits access to LA receptor
- low affinity for local anesthetics
Activated State of the Sodium Channel

- activating stimulus opens m gate; Na+ flows into axon
- affinity for local anesthetics increases
- local anesthetic receptor site accessible from inside the axonal membrane
Inactivated State of the Sodium Channel

- ≈ 1 msec later, h gate closes, shutting off the Na$^+$ current
- additional stimuli can not open inactivated Na$^+$ channels
- local anesthetics stabilize inactivated state
Key Points

- Membrane repolarization causes local anesthetics to dissociate from their receptors.
- Local anesthetics must be bound to block conduction.
- Local anesthetic action is voltage-dependent and frequency-dependent.
- Thus, a depolarized membrane potential and a high frequency of stimulation favor local anesthetic action.
Degree of nerve block depends on:

- membrane potential, frequency of firing, and duration of action potential
- size and myelination of the nerve
- hydrophobicity (lipid solubility) of the drug
- molecular size of the drug
- pH of surrounding solution
- metabolic fate of the drug
Preferential Block of Sensory Fibers

- Small diameter B and C fibers are blocked first, and A delta fibers are blocked next.
- Sensory (especially pain) fibers have a higher firing rate and longer action potential duration (up to 5 msec) than motor fibers.
- Thus, pain fibers are blocked first; touch, temperature, and deep pressure are blocked next; and motor function is blocked last.
Hydrophobicity of Local Anesthetics

- increases potency and duration of action
- enhances partitioning of drug to its sites of action
- decreases the rate of metabolism by plasma esterases and liver enzymes
- receptor site is hydrophobic, thus has higher affinity for more hydrophobic drugs increases toxicity
Molecular Size of Local Anesthetics

• influences association and dissociation rates of local anesthetics from the receptor
• smaller drugs have better access to and escape more rapidly from the receptor site
• important in rapidly firing neurons, because local anesthetics bind during the action potential and dissociate during membrane repolarization
pH of Local Anesthetics

- exist as uncharged base or cation unprotonated form is necessary for diffusion across the axonal membrane
- cationic form binds to the receptor site
- at pH 9.6, nerve conduction will not be blocked; changing pH to 7.2 will block conduction with same drug concentration
Toxicity of Local Anesthetics

- Local anesthetics block Na\(^+\) channels in all excitable cells, including nerve, heart, and muscle.
- Local anesthetics ultimately are absorbed from their site of administration.
- Adverse effects are proportional to the concentration of local anesthetic achieved in the circulation.
Central Nervous System Toxicity

- Low concentrations cause circumoral and tongue numbness, sleepiness, lightheadedness, visual and auditory disturbances, and restlessness.
- Higher concentrations cause nystagmus, muscular twitching, and convulsions.
- Stimulation is followed by depression, and death is caused by respiratory failure.
Central Nervous System Toxicity

- The excitatory phase results from the initial suppression of inhibitory neuron activity.
- Airway management and mechanical ventilation are essential for treatment.
- Hyperoxemia is beneficial.
- Benzodiazepines or barbiturates are used to treat seizure activity.
Cardiovascular System Toxicity

- The primary site of action is via direct effects on cardiac and smooth muscle.
- Blockade of cardiac Na\(^+\) channels depresses abnormal cardiac pacemaker activity, excitability, and conduction.
- Local anesthetics also have indirect effects by blocking autonomic nerves.
Clinical Uses:
Choice of Local Anesthetic

is determined by duration of action required
- short-acting: procaine and chloroprocaine
- intermediate duration: lidocaine, mepivacaine, prilocaine
- long-acting: tetracaine, bupivacaine, etidocaine, ropivacaine
Clinical Uses:
Routes of Administration

- topical
- infiltration
- subcutaneous (field block)
- injection around nerves (nerve block)
- intravenous
- spinal (intrathecal)
- epidural
Topical Application

- for ophthalmic use and for anesthesia of mucous membranes of the nose, mouth, throat, tracheobronchial tree, esophagus, and genitourinary tract
- tetracaine and lidocaine are used most frequently
- rapid absorption into the circulation, thus risk of systemic toxicity
Infiltration Anesthesia

- injection of local anesthetic directly into tissue without taking into consideration the course of cutaneous nerves
- lidocaine, procaine, and bupivacaine are used most frequently
- large amounts of drug used to anesthetize small areas, thus good for minor, not major, surgery
Field Blocks

- subcutaneous injection to anesthetize region distal to the injection
- can be applied to forearm, scalp, anterior abdominal wall, lower extremities
- lidocaine, procaine, and bupivacaine are used most frequently
- use less drug to anesthetize a greater area compared to infiltration anesthesia
Nerve Blocks

- injection around individual peripheral nerves or nerve plexuses
- brachial plexus, intercostal nerves, cervical plexus, sciatic and femoral nerves, nerves of wrist and ankle, sensory cranial nerves
- choice of drug is determined by the nerves and types of fibers to be blocked, duration of desired block, size, and health of patient
Nerve Blocks

Factors determining onset of block:

- proximity of injection to the nerve
- concentration and volume of drug
- degree of drug ionization
Intravenous Injection

• also called Bier’s block
• used with tourniquet to prevent drug spread away from area of interest
• used most often for surgery of forearm and hand; can be adapted for foot and distal leg
• lidocaine is drug of choice
Spinal and Epidural Administration

- Epidural block
- Spinal block
- Epidural space
- Intrathecal space
- Dura
- Base of spinal cord
- Cauda equina
- S2, S1, L5, L3, L1, T12
Spinal (Intrathecal) Injection

- injection of local anesthetic into the cerebrospinal fluid of the lumber spine
- for surgery of lower abdomen or lower extremities, post-operative pain, chronic pain, cancer pain
- lidocaine, tetracaine, and bupivacaine are used most frequently
Epidural Injection

- for analgesia during labor, post-operative pain, chronic pain, cancer pain
- catheters are placed into the epidural space to permit continuous infusion or repeated bolus administration
- bupivacaine is commonly used with fentanyl to provide analgesia for labor and delivery
Epidural Injection

- etidocaine is used for surgical anesthesia, because it also provides muscle relaxation
- lidocaine is used most frequently for intermediate duration procedures
- dose of local anesthetic used can produce high concentrations in blood following absorption from epidural space; this is in contrast to spinal administration