General and local anesthetics

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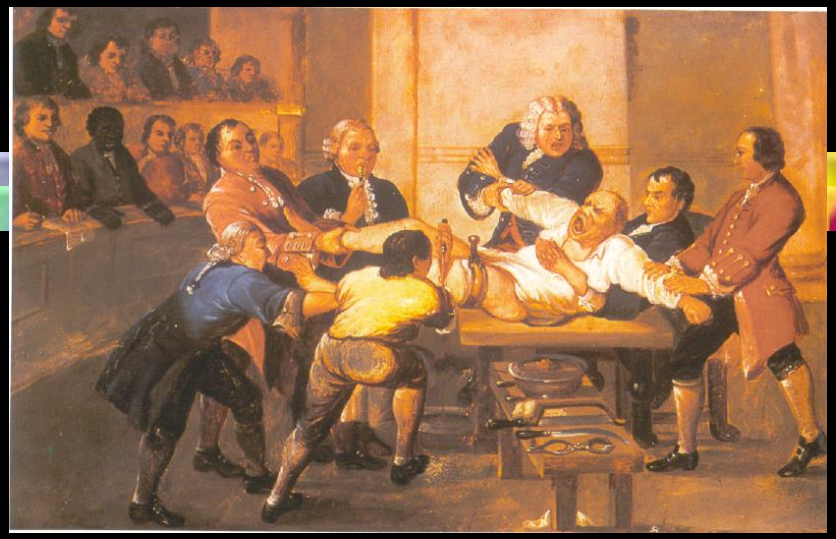


General anesthetics

Introduction

- general anesthetics produce a state of unconsciousness with the absence of pain sensation

- they are given systemically, and exert their effects on the CNS ⇨ contrast to LA (local block of sensory nerves impulses from periphery to the central nervous system)

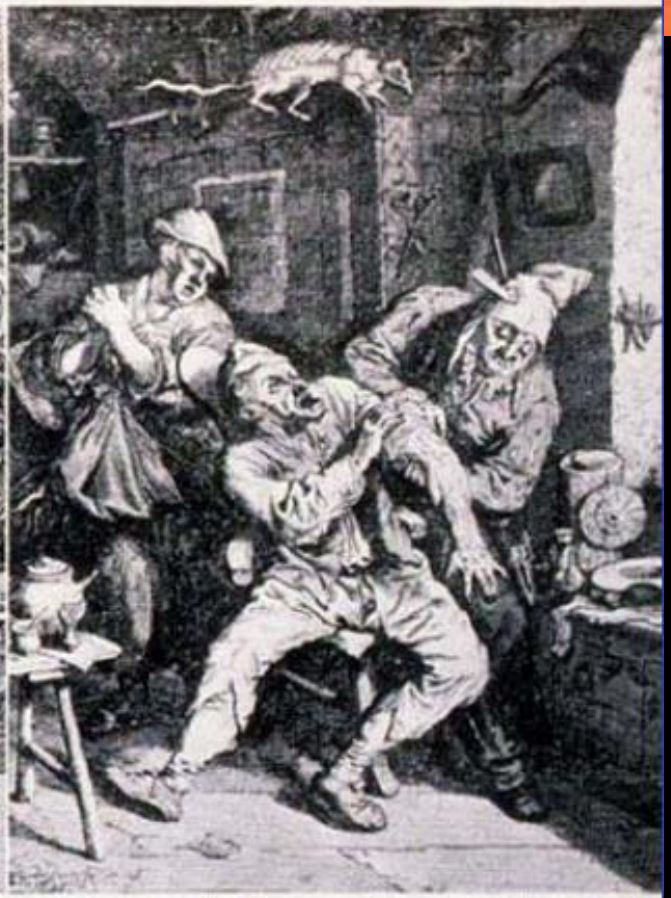
Surgery Before Anesthesia

Mural of Dr. Villander, Hôtel de Dieu, Paris.

A

From *Behind the Doctor*, by Logan Clendenning, published by Alfred A. Knopf.

B



From *Devils, Drugs and Doctors*, by Howard W. Haggard, M.D., published by Harper and Brothers.

C

PICTORIAL RECORDS OF THE AGONY ENDURED IN OPERATIONS BEFORE THE ADVENT OF ANESTHESIA

A. A surgeon cutting with his big saw.
B. A very painful operation of the seventeenth century.
C. A surgeon torturing his patient.

History of Anesthesia

Joseph Priestly – discovers **N_2O** in 1773

Sir Humphrey Davy – experimented with N_2O, reported loss of pain, euphoria

Horace Wells 1844. Demonstrated N_2O for tooth extraction

William Morton, dentist – first demonstration of successful surgical anesthesia with **ether** 1846

Crawford W. Long – 1842. Country Dr. in Georgia first used ether for neck surgery. Did not publicize; tried to claim credit after Morton's demonstration but…

Important lesson learned – if you don't publish it, it didn't happen.

John C. Warren, surgeon at MGH says "Gentlemen, this is no humbug!" – birth of modern anesthesia

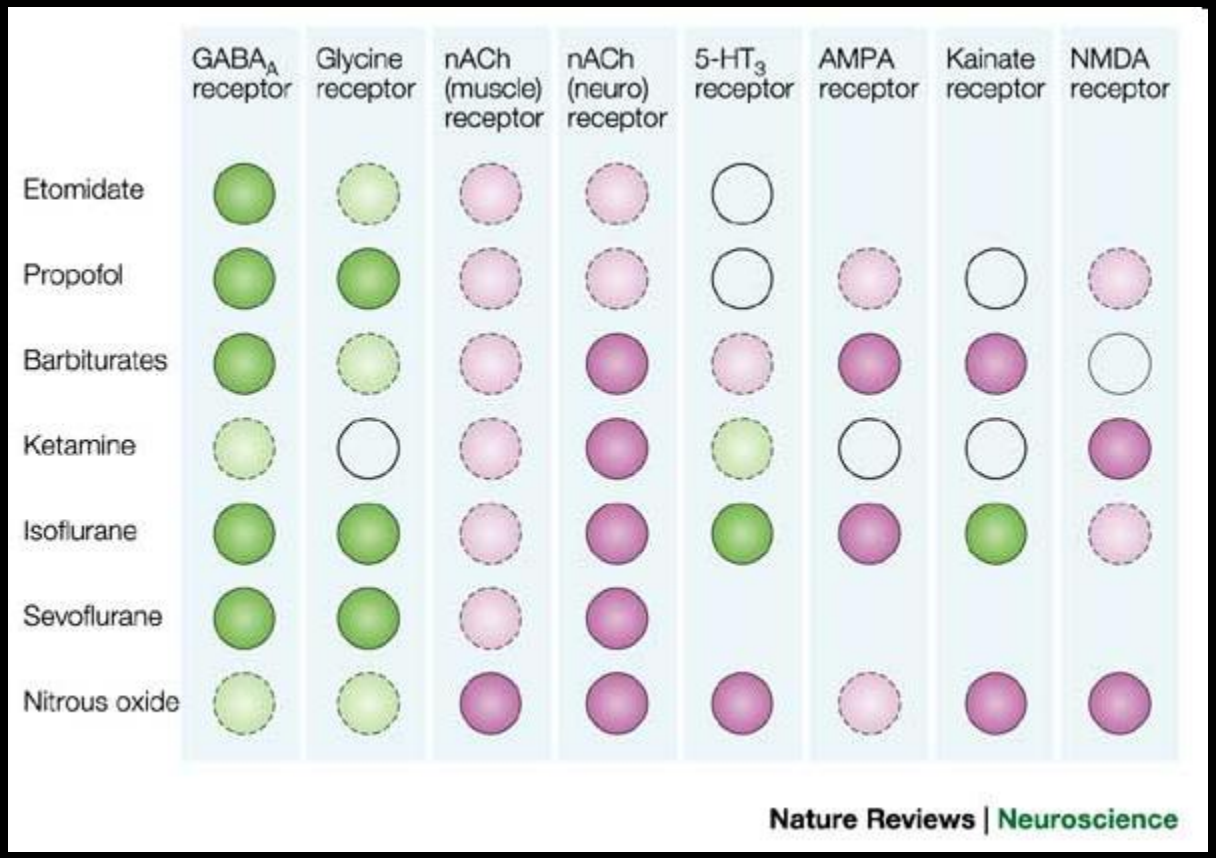
Dr. John Snow administers chloroform to Queen Victoria (1853)– popularizes anesthesia for childbirth in UK
He becomes the first anesthesia specialist.

MOLECULAR MECHANISM OF ANESTHESIA

Inhalational anesthetics

- **is poorly understood**
- **activation of GABA and glycine receptors**
- **Inhibition of glutamate**

Effect of CA on ligand controled ion channels



Dark green = potentiation; dark pink = inhibition; light green= weak potentiation; light pink= weak inhibition; empty = no effect

Intravenous anesthetics

- most of them have well-documented effect at membrane receptor
- thiopental (barbiturate) - GABA-receptor
- BDZ - GABA-receptor
- ketamine binds to the phencyclidine receptor - block the action of glutamic acid (principal excitatory neuromediator)

Stages of anesthesia

Stage I: analgesia

- loss of pain sensation - interference with sensory transmission in the spinothalamic tract
- patient is conscious and conversational

Stage II: excitement

- patient losses consciousness
- no respond to non-painful stimuli
- respond to the pain stimuli (reflex)
- other reflexes (cought) are present and are often exaggerated
- patient may move, talk incoherently, vomit
- dangerous state - modern anesthetics procedures are designed to eliminate it

Stage III: Surgical anesthesia

- regular respiration and relaxation of the skeletal muscle
- eye reflexes decrease progresivelly, until the eye movment stop
- surgery may proceed during this stage

Stage IV: medullary paralysis

- severe depression of the respiratory and vasomotor center
- death occurs within a few minutes

Stage III:

Plane 1: “light” anesthesia

Plane 2: Loss of corneal reflex, regular respiration . Surgical procedures can be performed at this stage.

Plane 3: Deep anesthesia. Shallow breathing, assisted ventilation needed. Level of anesthesia for painful surgeries

Plane 4: Diaphragmatic respiration only, assisted ventilation is required. Cardiovascular impairment.

Anesthetic Techniques

- **Inhalational anesthesia**

  Anesthetics in gaseous state are taken up by inhalation

- **Total intravenous anesthesia**

- **Inhalational plus intravenous (“Balanced Anesthesia”)**

  Most common

Inhalational anesthetics

October 17, 1846: First public demonstration of the use of ether in anesthesia at Massachusetts Gen Hosp.

Painting by Robert C. Hinckley, Francis A. Countway Library of Medicine, Boston

Inhaled Anesthetic Agents

Generic name	*Year of introduction*	*Currently in use?*
Diethyl ether	1842	No
Nitrous oxide	1844	Yes
Chloroform	1847	No
Cyclopropane	1933	No
Trichloroethylene	1934	No
Fluroxene	1954	No
Halothane	1956	Rare
Methoxyflurane	1960	No
Enflurane	1974	Rare
Isoflurane	1980	Rare
Desflurane	1992	Yes
Sevoflurane	1995	Yes

General Actions of Inhaled Anesthetics

- **Respiration**

  Depressed respiration and response to CO_2

- **Kidney**

  Depression of renal blood flow and urine output

- **Muscle**

  High enough concentrations will relax skeletal muscle

Cont’

- **Cardiovascular System**

  Generalized reduction in arterial pressure and peripheral vascular resistance. Isoflurane maintains coronary function better than other agents

- **Central Nervous System**

  Increased cerebral blood flow and decreased cerebral metabolism

Inhaled Anesthetics - Historical

- Ether – Slow onset, recovery, explosive
- Chloroform – Slow onset, very toxic
- Halothane (Fluothane) – first halogenated ether (non-flammable)
    - 50% metabolism by P450, induction of hepatic microsomal enzymes; chloride, bromide released
    - Myocardial depressant (SA node), sensitization of myocardium to catecholamines
    - Hepatotoxic
    - + suxamethonium - malignant hypertemia
- Methoxyflurane (Penthrane) - 50 to 70% metabolized
    - Releases fluoride, oxalic acid
    - Nephrotoxic

Inhaled Anesthetics – currently

Desflurane

- analogue of isoflurane
- least blood soluble of all the anesthetics - most rapid induction
- very pungent - severe laryngospasm, secretion, apnea
- rapid recovery (5 minutes) - CAUTION - ensure adequate analgesia is in place
- no metabolism - no liver toxicity, but respiratory depres.
- contraindicated as sole anesthetic agent in cases of coronary artery disease
- malignant hyperthermia still a risk

Sevoflurane

- nonpungent, no respiratory tract irritation
- poor solubility - rapid induction
- excellent induction agent
- 5% metabolism
- no tachycardia
- malignant hyperthermia still a risk

Nitrous oxide

- strong analgesic, but weak anesthetic properties
- it does not produce surgical anesthesia ⇨ it cannot be used on its own for anesthesia
- it is used in conjuction with other more potent anesthetics (halothane, enflurane, isoflurane)
- nitrous oxide/oxygen mixture (50/50) ⇨ rapid analgesia in subanesthetic doses ⇨ obsteric analgesia
- it is generalle non-toxic

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Inhaled Anesthetics – rare

Isoflurane

- less CV or respiratory depression than enflurane but more than halothane
- little risk of dysrhythmia through sensitization to catecholamines.
- minimal liver toxicity since little (metab. <0.5%)
- potentiation of non-depolarizing myorelaxants
- risk of malignant hyperthermia
- no convulsant EEG pattern
- mildly pungent; bronchial irritation and secretion

Xenon

- It interacts with many different receptors and ion channels
- Anesthetic property of xenon is mainly conferred by the inhibition of NMDA receptors in the CNS
- Short induction times foranaesthesia
- Xenon is not associated with malignant hyperthermia
- No hepatic or renal toxicity, less cardiovascular depression, neuroprotection, profound analgesia.

- Too expensive

Metabolism of inhaled anesthetics

Agent	*% metabolized*
Halothane	20
Sevoflurane	2-5
Enflurane	2.4
Isoflurane	0.2
Desflurane	0.02
Nitrous Oxide	0.004

Malignant Hyperthermia

- **Malignant hyperthermia (MH) is a pharmacogenetic hypermetabolic state of skeletal muscle induced *in susceptible individuals* by inhalational anesthetics and/or succinylcholine**

- Genetic susceptibility- RYR1 (ryanodine receptor)

- Excess calcium ion leads to excessive ATP breakdown/depletion

- **Signs: tachycardia, tachypnea, metabolic acidosis, hyperthermia, muscle rigidity, sweating, arrhythmia**
- **May be fatal**
- **Treated with dantrolene**

Intravenous anesthetics

- are often used for rapid induction of anesthesia ⇨ then combination with some inhalation agent

- ADVANTAGES - Rapid onset, controlled dosage, ease of administration.
- DISADVANTAGES - Overdose not readily corrected, prolonged after effects

Thiopental

- most widely used intravenou agent
- ultra-short-acting barbiturate, high lipid solubility
- quickly enter the CNS and depress function (less than 1 min)
- diffusion out of the brain is also rapid - redistribution of thiopental - brain - skeletal muscle - adipose tissue
- it has no analgesic properties - supplementation of analgesic drugs

Thiopental – *cont.*

- it depresses the arterial BP ⇨ decrease of cardiac output caused by cardiac depression
- there is no changes in peripheral resistance
- thiopental depresses respiratory center (dose-dependent manner) and decrease its sensitivity to carbon dioxide
- decrease cerebral blood flow and oxygen consumption by brain
- induction often accompanied by coughing, sneezing or laryngospasm: prevent with atropine or scopolamine
- barbiturate solutions VERY ALKALINE → avoid extravasation
- thrombophlebitis a risk with i.v. injection

Ketamine

- short acting non-barbiturate anesthetic
- strong analgesic effect
- blocks both nicotinic ACh and NMDA (glutamic acid) receptors
- it increases sympathetic nervous system activity
- dissociative anesthesia - catatonia, amnesia, analgesia

Ketamine

- recovery from anesthesia may be complicated by: hallucinations, disorientation, amnesia
- it may be used in risk surgical patients (poor myocardial function), in patients with burns, in short diagnostic or surgical preceduress
- it may be used also in pediatrics patients

Etomidate

- potentiates GABA inhibitory effect
- during induction may cause involuntary movements and can cause post-operative nausea and vomiting
- low cardiovascular risk, weaker effect on BP
- prolonged use - etomidate suppress the adrenal cortex - increase mortality in severely ill patients - therefore it is used only as an induction agent

Propofol

- introduced in 1983, similar to thiopental
- it lacks the tendency to cause involuntary movement and to suppress adrenal cortex
- recovery is rapid and there is less nausea and vomiting in comparison with thiopental
- significant but transient fall in BP and a rise in heart rate

Benzodiazepines

- common drugs are diazepam or lorazepam
- midazolam - water soluble but slower in onset than barbiturates
- prolonged recovery with amnesia
- MAINLY USED PREOPERATIVELY
- flumanezil - receptor antagonist; used to speed recovery, or act as antidote in overdose

Preanesthetic medication

- some drugs are administered prior to anesthesia to allay anxiety, reduce pain, decrease excess salivation and to combat nausea

A) Anxiolytic drugs

- benzodiazepines are used to to provide preoperative sedation (diazepam)
- barbiturates may be also used

B) Opioid analgesic

- morphine or fentanyl are often combined with general anesthetics
- neuroleptic drugs (promethazine) and antihistamine (hydroxyzine) are often administered concominantly with opioids to increase the analgesic action of opioids

C) Anticholinergic drugs

- atropine and scopolamine are used routinely for reduction of bronchial and salivary secretion and to supress the parasympathetic overactivity

D) Neuroleptics

- promethazine, chlorpromazine - these agents sedate and have useful antiemetic properties

E) Muscle relaxant

- they are used for tracheal intubation, to facilitate assisted ventilation
- to prevent laryngeal spasm during operation
- to produce sufficient muscle paralysis during surgery

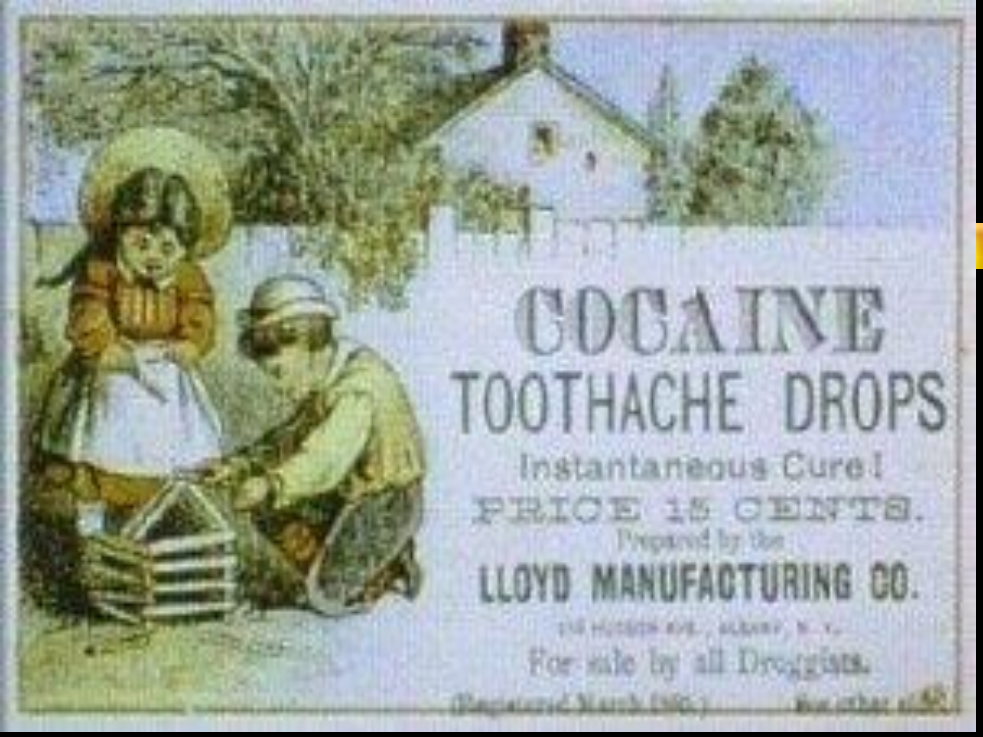
F) H_2-blockers

- to prevent stress gastric ulcer

Local anesthetics

History of Local Anesthetics

- Incas used cocaine as a topical anesthetic, dating back to 3000 B.C.
- Cocaine isolated 1856
- 1884 cocaine used in occular surgery
- 1880's Regional anesthesia plexus
- 1898 cocaine used in spinal anesthesia
- 1905 1st synthetic LA (procaine) introduced
- 1943 lidocaine synthesized
- Mepivacaine (1957), Bupiv ('63), Ropiv ('96)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A local anesthetic is an agent that interrupts pain impulses in a specific region of the body without a loss of patient consciousness. Normally, the process is completely reversible - the agent does not produce any residual effect on the nerve fiber.

Mechanism action

- these drugs bind selectively to the intracellular surface of **sodium channels** and block entry of sodium into the cell ⇨ eliminate the depolarisation necessary for action potential propagation
- LA have high potency to block sodium channels in open state
- great practical importance ⇨ LA will preferentially block nerves in which sodium channels are open ⇨ mainly sensory neurons

Nerve Sensitivity

1. Autonomic
2. Pain
3. Temperature
4. Touch
5. Skeletal muscle tone

pH and local anaesthetic activity

- LA are weak bases pK_a ⇨ 8-9
- at normal body pH most of the drugs will be in ionisated form ⇨ only 1-10% of the drugs will be nonionisated
- this minor nonprotonated fraction cross the cell membrane and accumulates in the cytoplasm
- once across the membrane, equilibrium is reestablished, and most of the drug will again be ionisated
- this fraction of drug (cytoplasmatic, ionisated) is able to block voltage-dependent sodium channel

Effect of pH, and pKa

- The pKa of amides ranges from 7.6 to 8.1. At physiologic pH (7.4), most of the local anaesthetic is in the ionized state (a charged base).

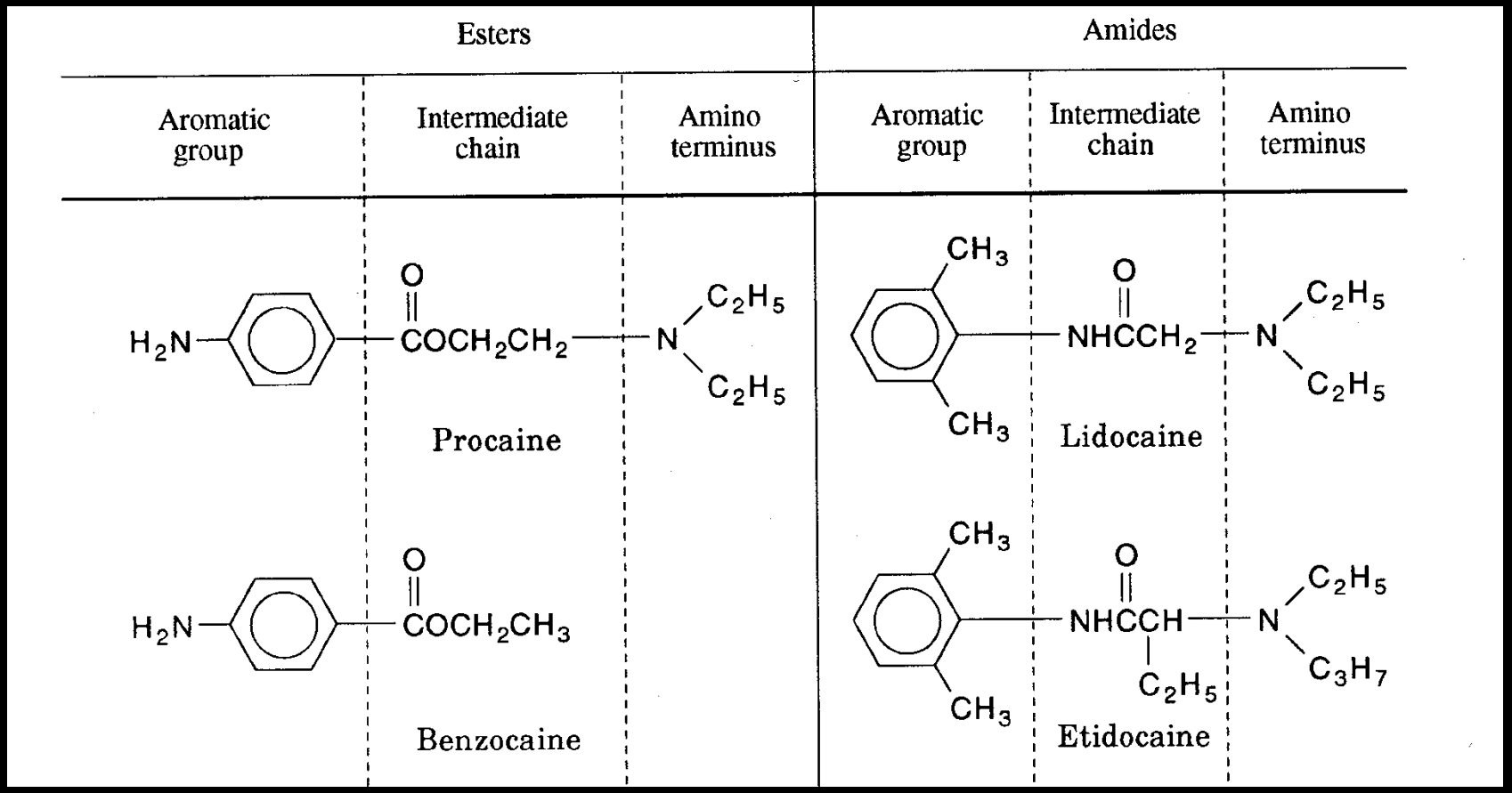
- For example, lidocaine has a pKa of 7.9. The above formulat determines that at physiologic pH, lidocaine exists in a ratio of 3:1 ionized to non-ionized.

Low pH

- The pH of the tissue becomes relevant in conditions of infection or inflammation, in which the natural pH may be more acidic.
- This acidity results in a greater proportion of the ionized (charged) form of the anaesthetic, thereby delaying or preventing the onset of action.
- For example, if lidocaine (pKa 7.9) is administered into an area of infection (pH 4.9) emanating from a dental abscess, then the resulting ratio of 1,000:1 ionized to non-ionized indicates a poorer penetration into the nerve tissue and therefore a less effective nerve block

Chemical structure

- all LA consists of a hydrophilic amino group linked through a connecting intermediate chain to a lipophylic aromatic residue
- aromatic group allows the drug to enter the cell (penetrate the membrane) and reach its actual site of action
- amino group allows the drug to diffuse to the nerve
- esters (PABA derivatives)
- amides (aniline derivatives)


Esters
Amides
Aromatic group
Intermediate chain
Amino terminus
Aromatic group
Intermediate chain
Amino terminus
Procaine
Lidocaine
Benzocaine
Etidocaine

Esters

- these include cocaine, procaine, tetracaine, and chloroprocaine.
- they are hydrolyzed in plasma by pseudo-cholinesterase.
- One of the by-products of metabolism is paraaminobenzoic acid, the common cause of allergic reactions seen with these agents

ESTERS

- **Chloroprocaine and Procaine-** have low potency and lipid solubility and also low duration and protein binding.
- **Cocaine-** has intermediate potency and solubility and intermediate duration and protein binding
- **Tetracaine-** has high potency and lipid solubility along with a long duration of action and high protein binding

Amides

- these include lidocaine, mepivicaine, prilocaine, bupivacaine, and etidocaine
- they are metabolized in the liver to inactive agent
- true allergic reactions are rare (especially with lidocaine)

AMIDES

- **Bupivacaine, Etidocaine and Ropivacaine- very high potency and lipid solubility, very long duration and protein binding also.**
- **Lidocaine, Prilocaine and Mepivacaine- have intermediate potency and lipid solubility and intermediate duration of action and protein binding.**

Metabolism of LA

- **esters** are primarily inactivated in plasma by hydrolysis (pseudocholinesterase)
- they generally have a relatively short half-life in the body
- in spinal fluid (absence of esterase activity) duration of anaesthesia is extended
- metabolites are excreted by urine
- liver disease ⇨ cumulation of drugs ⇨ higher risk of toxicity

Metabolism of LA - cont.

- **amides are metabolized by liver microsomes**

⇨**initial N-dealkylation is followed by hydrolysis**

- **some metabolites possess local anaesthetic activity**

Properties of Local Anesthetic Agents

PROPERTIES	AMINOESTERS	AMINOAMIDES
Metabolism	rapid by plasma cholinesterase	slow, hepatic
Systemic toxicity	less likely	more likely
Allergic reaction	possible - PABA derivatives form	very rare
Stability in solution	breaks down in ampules (heat,sun)	very stable chemically
Onset of action	slow as a general rule	moderate to fast
pKa's	higher than PH = 7.4 (8.5-8.9)	close to PH = 7.4 (7.6-8.1)

Types of local anesthesia

Surface anesthesia

- this type of anesthesia is accomplished by the application of a local anesthetic to skin or mucous membranes
- surface anesthesia is used to relieve itching, burning, and surface pain (for example, as seen in minor sunburns)
- relatively high doses are often used ⇨ tetracaine (2%), lidocaine (2-10%), cocaine (1-4%)
- cocaine is restricted to ophtalmological procedures and for nasal surgery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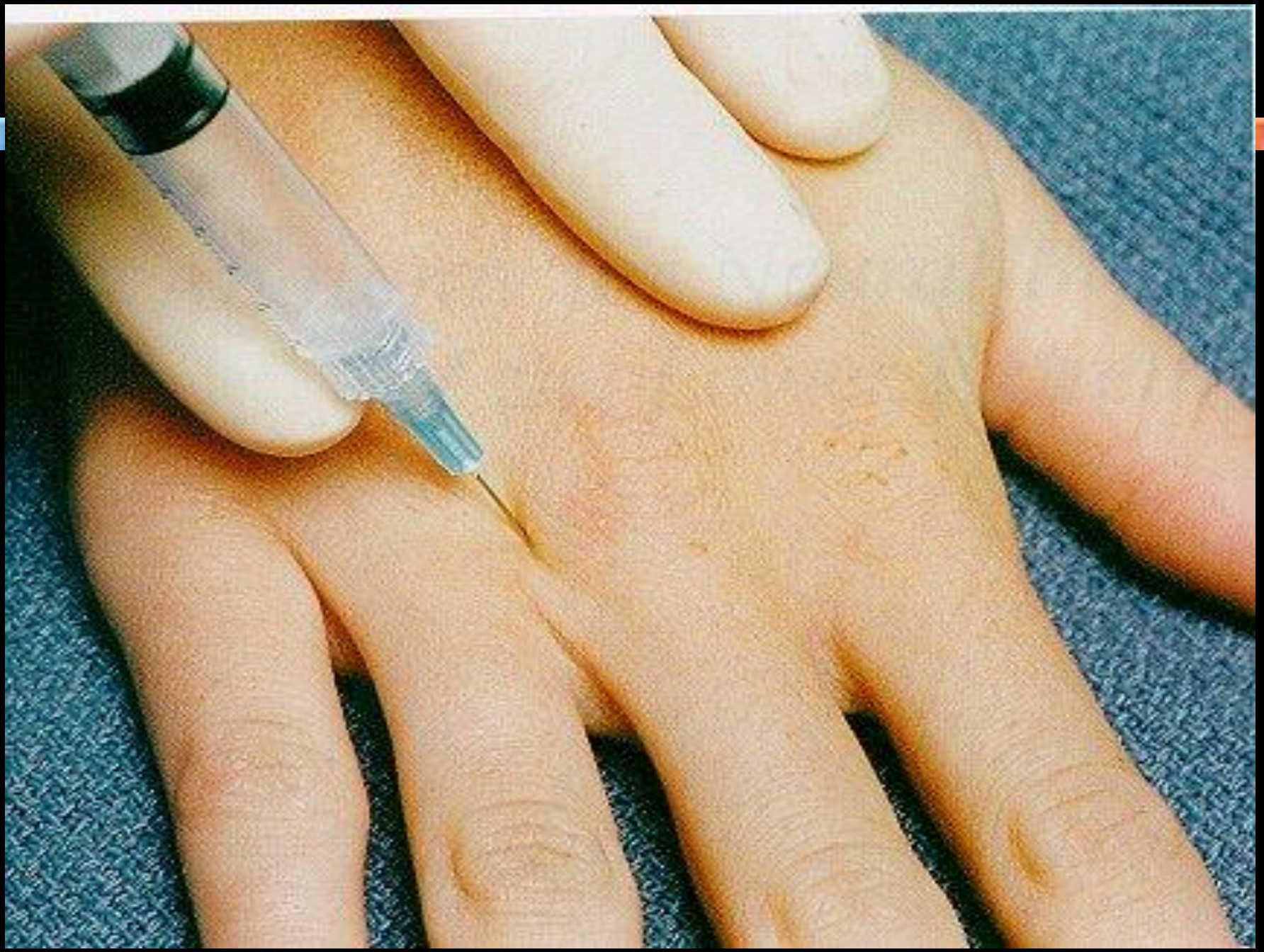
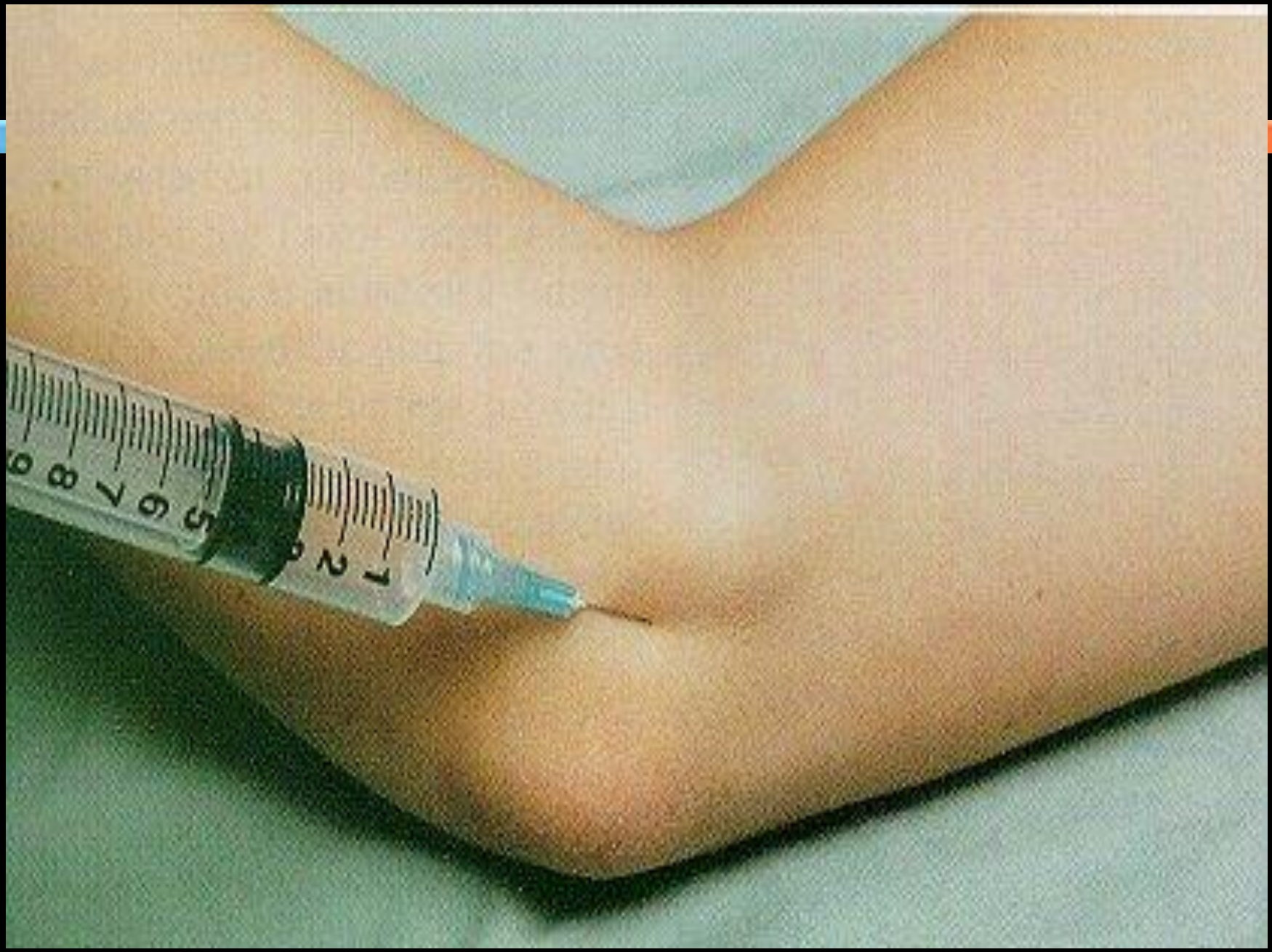
Local infiltration

- local infiltration occurs when the nerve endings in the skin and subcutaneous tissues are blocked by direct contact with a LA, which is injected into the tissue
- local infiltration is used primarily for surgical procedures involving a small area of tissue (for example, suturing a cut)
- most frequently used LA ⇨ lidocaine (0.5-1%), procaine (0.5-1%), bupivacaine (0.125-0.25%)

Nerve block

- in this type of anesthesia, a LA is injected around a nerve that leads to the operative site
- usually more concentrated forms of LA solutions are used for this type of anesthesia
- it is a widely used methods ⇨ much less anesthetics are needed than for infiltration anesthesia
- procaine (0.5-1%), lidocaine (1-2%), mepivacaine (1-3%), bupivacaine (0.25-0.75%)





Intrathecal anesthesia

Epidural anesthesia

- his type of anesthesia is accomplished by injecting a local anesthetic into the epidural space
- the peridural space is one of the coverings of the spinal cord

Spinal anesthesia

- in spinal anesthesia, the local anesthetic is injected into the subarachnoid space of the spinal cord

- in both cases the anaesthetic works mainly on the spinal roots
- advantage ⇨ relatively small doses of LA are needed ⇨ reduced risk of toxicity
- main unwanted effects in spinal anaesthesia are:
  - ⊙ vasodilatation
  - ⊙ bradykardia
  - ⊙ marked fall in arterial pressure
- hypotension is usually less severe in epidural anaesthesia
- used for surgery to the abdomen, pelvis, and lower limbs in patients unsuitable for general anaesthesia
- epidural anaesthesia is also frequent use for painless childbirth

IV Block - “Bier” block

- **Injection of local anesthetic intravenously for anesthesia of an extremity**
- **Uses**
  - any surgical procedure on an extremity
- **Advantages:**
  - technically simple, minimal equipment, rapid onset
- **Disadvantages:**
  - duration limited by tolerance of tourniquet pain, toxicity

IV Block

August Bier (1908)

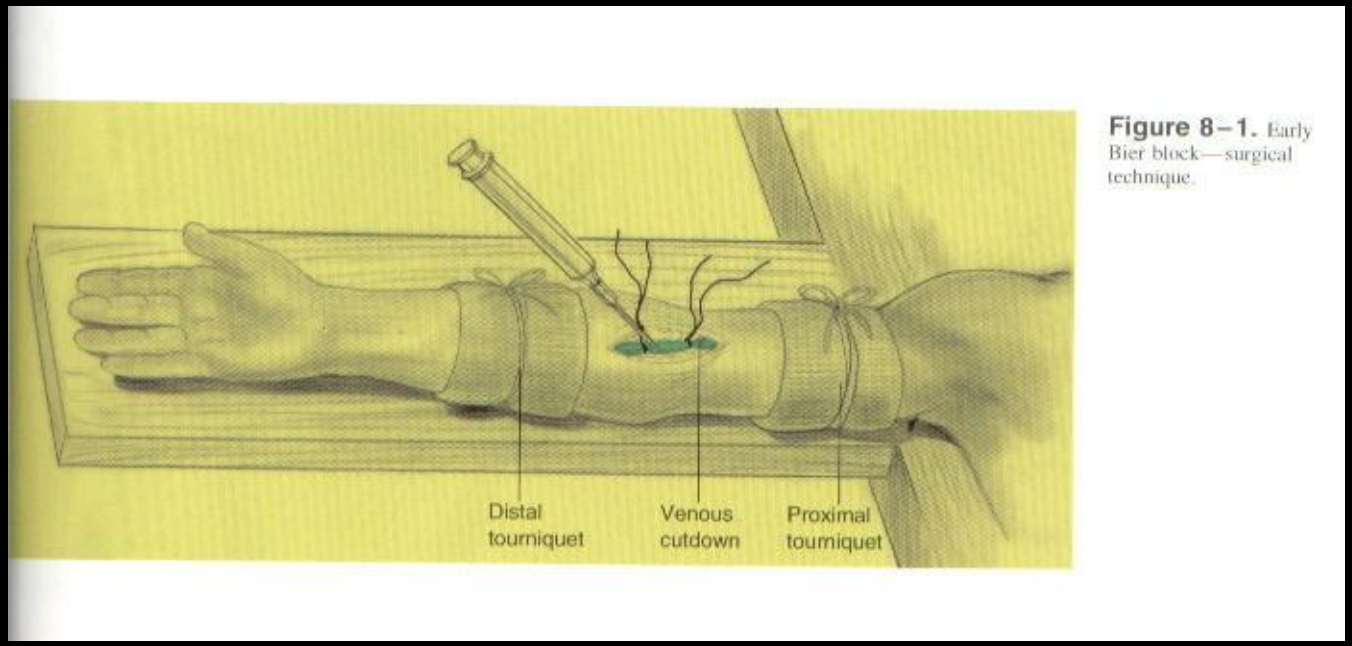


Figure 8–1. Early Bier block—surgical technique.

Toxicity of local anesthetics

- all systemic toxic reactions associated with local anesthetics are the result of over-dosage leading to high blood levels of the agent given

- to avoid a systemic toxic reaction to a local anesthetic, the smallest amount of the most dilute solution that effectively blocks pain should be administered

CNS toxicity

- LA, if absorbed systematically in excessive amounts, can cause central nervous system (CNS) excitement
- if absorbed in even higher amounts, can cause CNS depression
- Excitement - tremors, shivering, and convulsions
- Depression - respiratory depression and, if enough drug is absorbed, respiratory arrest

CVS toxicity

- LA if absorbed systematically in excessive amounts can cause depression of the CVS
- peripheral vascular action arteriolar dilation (except cocaine which is vasoconstrictive)
- hypotension and a certain type of abnormal heartbeat (atrioventricular block) characterize such depression
- these may ultimately result in both cardiac and respiratory arrest

- signs of toxicity occur on a continuum
- from early to late stages of toxicity, these signs are:
- circum-oral and tongue numbness, tinnitus, visual disturbances, muscular twitching, convulsions, unconsciousness, coma, respiratory arrest, then cardiovascular collapse.

Treatment of overdose

- **Airway:**
  - 100% oxygen
  - Intubate if necessary to ventilate
- **CNS:**
  - Break seizure with propofol, thiopental, or midazolam
- **Cardiovascular**
  - Amiodarone has demonstrated efficacy.
  - Resuscitation difficult with bupivacaine, more frequently successful in animal studies following ropivacaine and levobupivacaine overdose.

Hypersensitivity

- some patients are hypersensitive (allergic) to some local anesthetics
- although such allergies are very rare, a careful patient history should be taken in an attempt to identify the presence of an allergy
- there are two basic types of local anesthetics (the amide type and the ester type). a patient who is allergic to one type may or may not be allergic to the other type.

Vasoconstrictors

- vasoconstrictors decrease the rate of vascular absorption which allows more anesthetic to reach the nerve membrane and improves the depth of anesthesia.
- there is variable response between LA and the location of injection as to whether vasoconstrictors increase duration of action. 1:200,000 epinephrine appears to be the best vasoconstrictor.