

General anesthetic (GA) agents

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- Different drugs in anesthetic room used regularly
- Knowledge of individual agents, their pharmacology & reasons for administration essential to understanding art of anesthesia

Classes of drugs

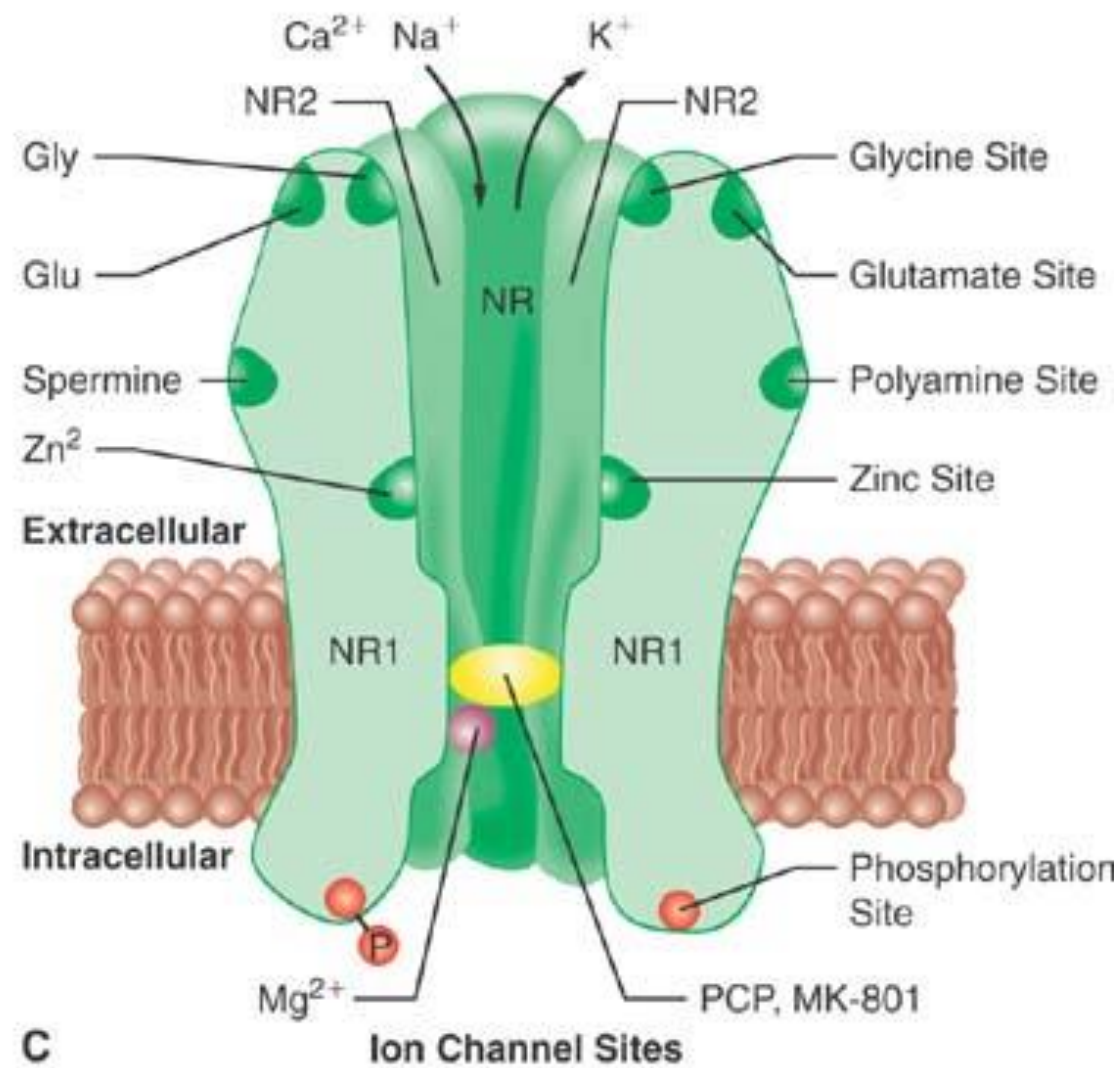
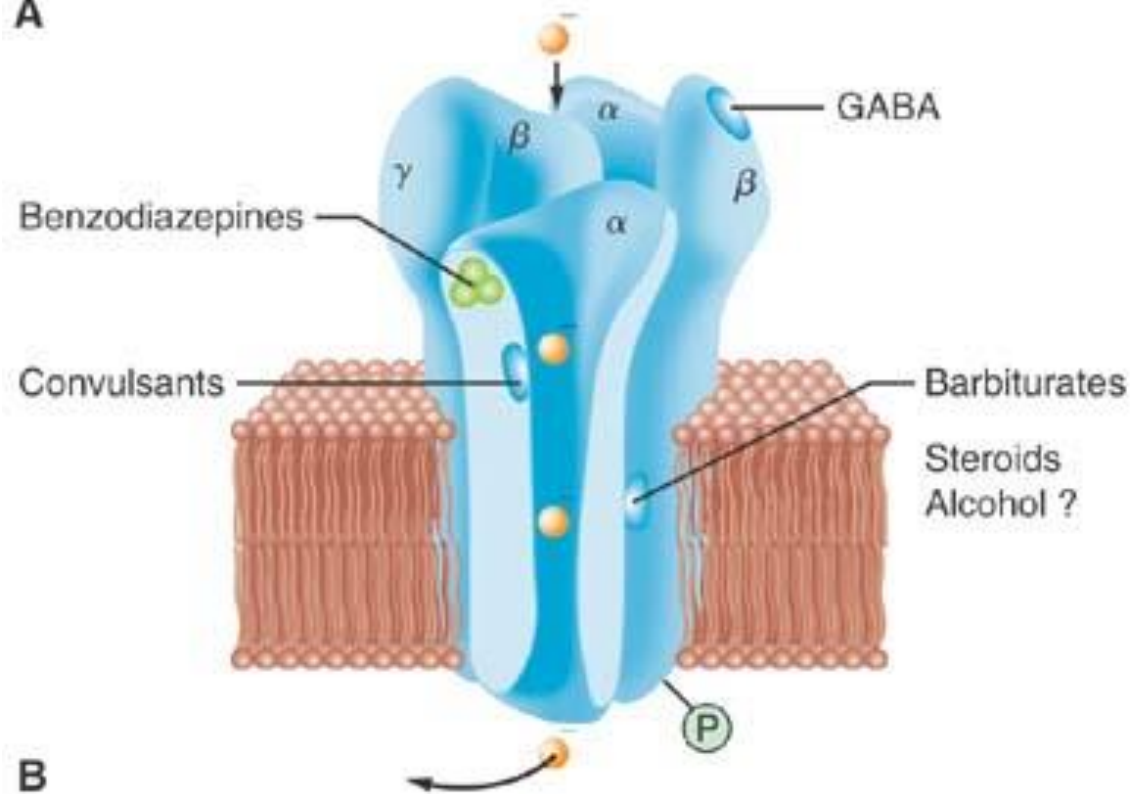
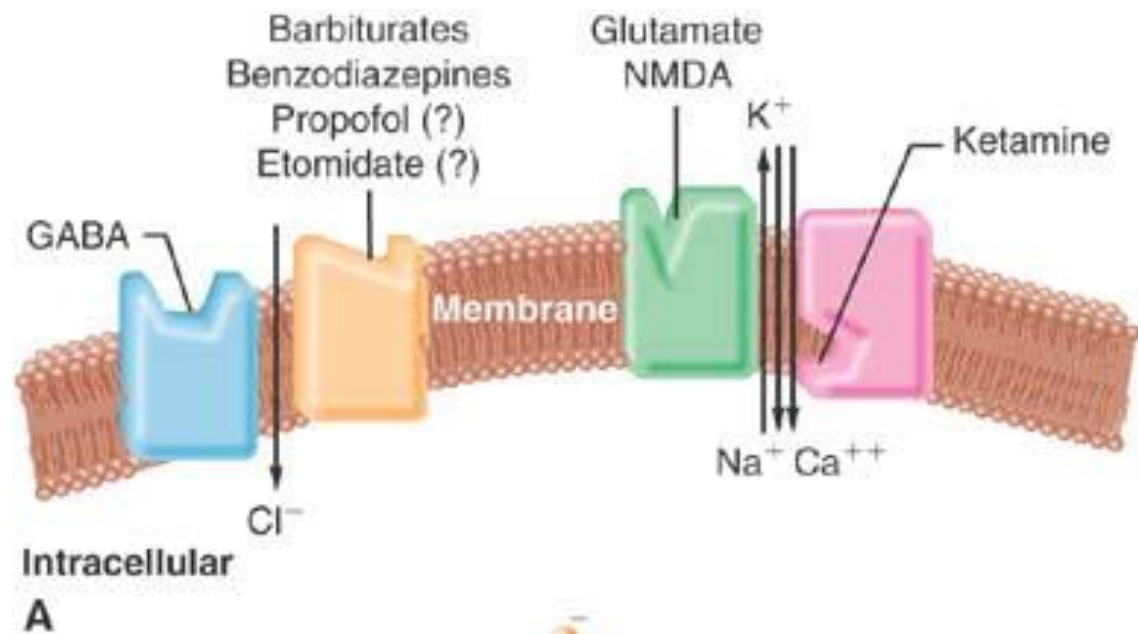
- General anesthetics
- Muscle relaxants: neuromuscular blockers
- Anti-cholinesterases
- Local anesthetics

General anesthetics

- Anesthetic drugs used for induction of anesthesia, maintenance or sedatives depending on dose
- Given intravenously as liquid or inhaled as gas
- Most cases **intravenous (IV)** agents used for **induction** & **inhaled** agents used for **maintenance**

Mechanisms of action

- γ -Aminobutyric acid (GABA) $\rightarrow$ main inhibitory neurotransmitter within CNS
- Acts via two different receptors: GABA_A and GABA_B
- Benzodiazepines (BDZs) acts via GABA_A receptors $\rightarrow$ anxiolytic, sedative & anticonvulsant



GA effects at central receptors

	Inhibitory neurotransmitters		Excitatory neurotransmitters	
	GABA _A	Glycine	NMDA	Neuronal nACh
Propofol	+++++	++	0	—
Thiopental	+++++	++	0	—
R-etomidate	+++++	0	0	0
S-etomidate	0	0	0	0
Ketamine	0	0	—	0
Isoflurane	+++++	+++	0	—
Nitrous oxide	0	0	—	0
Xenon	0	0	—	0

+: enhances effect of neurotransmitter; -: reduces effect of neurotransmitter; 0: no effect on neurotransmitter. nACh: central nicotinic acetylcholine receptor.

Intravenous anesthetic agents

Definition

- Agents induce loss of consciousness in one arm–brain
circulation time

Barbiturates (**Thiopental**)

- Derived from barbituric acid
- Pale yellow powder
- Strongly alkaline solution (pH 10.5)
- 2.5% solution stable for many days & **bacteriostatic** due to its alkaline pH

Thiopental



Uses

- Induction of anesthesia (3–7 mg/kg IV)
- Status epilepticus
- Continuous IV infusion → isoelectric EEG → ↓cerebral oxygen requirements

- Speed of induction:
 - 30 - 45 seconds (one arm to brain circulation time)
- Advantages:
 - Rapid, smooth induction to anesthesia
 - ↓ Cerebral metabolic rate of oxygen consumption (propofol is similar)

- Side-effects:
 - Hypotension
 - Respiratory depression
 - Coughing, laryngospasm & bronchoconstriction due to poor suppression of laryngeal reflexes
 - Pain on injection and tissue damage
- Elimination: Liver

Intra-arterial injection

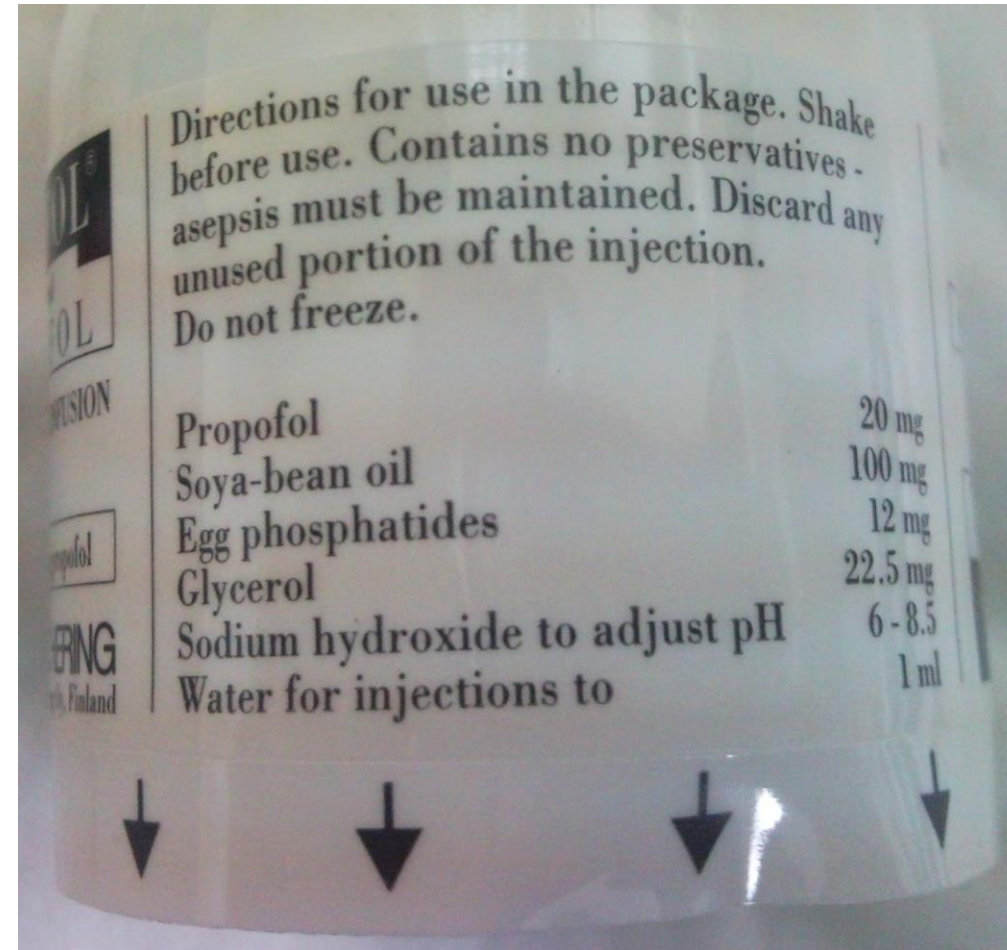
- Injection into artery → ischemia & pain
- **Treatment:** begin immediately
 - Intraarterial injection of papaverine or procaine
 - Analgesia
 - Sympathetic block of the limb
 - Anticoagulation
- Peri-vascular injection painful & tissue necrosis if large doses extravasate

Propofol

Presentation

- Phenolic derivative
- Highly lipid-soluble
- Presented as 1% or 2% lipid–water emulsion (soya bean oil & purified egg phosphatide)

Propofol



Uses

- Induction & maintenance of GA
- Sedation of ventilated patients in ICU
- Induction dose is 1–2 mg/kg

- Speed of induction:
 - 30 - 45 seconds (one arm to brain circulation time)
- Duration of action:
 - 4 - 7 minutes
- Advantages:
 - Depresses upper airway reflexes, anti-emetic, anti-pruritic

- **Side-effects:**

- Hypotension
- Apnea of up to 60 seconds
- Respiratory depression
- Pain on injection
- Involuntary movements
- Hiccoughs
- propofol infusion syndrome

Ketamine

- Phencyclidine derivative

Presentation & uses

- Available as 10, 50 & 100 mg/ml
- IV 1–2 mg/kg or IM 5–10 mg/kg for **induction of anesthesia**
- IV 0.2–0.5 mg/kg for **analgesia**
- Oral, rectal route for **sedation**
- Intrathecal & epidural routes for analgesia

- Mode of action:
 - Acts on N-methyl-d-aspartate & opioid receptors → anesthetic & analgesic effect
- Speed of induction:
 - 50 - 70 seconds.
- Advantages:
 - Analgesia; does not cause respiratory depression

- **Side-effects:**

- Hallucinations with vivid dreams & psychosis
- Diplopia
- Temporary blindness
- Hypertension
- Tachycardia

Ketamine



Etomidate

- Imidazole derivative & *an ester*
- Used infrequently in UK
- Withdrawn in North America & Australia



Presentation

- Prepared as 0.2% solution
- Lipid formulation also available
- Used for induction of GA at dose of 0.3 mg/kg

- **Advantages:**
 - **Produces least cardiovascular disturbance**
- **Side effects**
 - Even with single dose → Suppresses adrenocortical function → inhibition of cortisol & aldosterone synthesis
 - Pain on injection
 - Excitatory movements
 - **Nausea & vomiting more than others**
 - Porphyric crisis

Pharmacological properties of some intravenous anaesthetics.

	Thiopental	Propofol	Ketamine	Etomidate
BP	↓	↓↓	↑	→
CO	↓	↓↓	↑	→
HR	↑	↓→	↑	→
SVR	↑↓	↓↓	→	→
RR	↓	↓	↑	↓
ICP	↓	↓	↑	→
IOP	↓	↓	↑	→
Pain on injection	No	yes	no	yes
Nausea and vomiting	no	? reduced	yes	yes

Benzodiazepines

- **Uses:**

- Premedication
- Sedate patients during minor procedures
- Anxiolytics
- Hypnotics
- Anticonvulsants

Midazolam (Dormicum)

- Uses:
- I.V.
 - Sedate patients for minor procedures
 - Sedate ventilated patients in intensive care
 - Amnesic
- P.O, intranasally or I.M as premedication

- Short duration of action
- Metabolized by hydroxylation in liver
- Renal excretion
- Elimination half-life of 1–4 hours

Inhaled anesthetic agents

Inhaled anesthetic agents

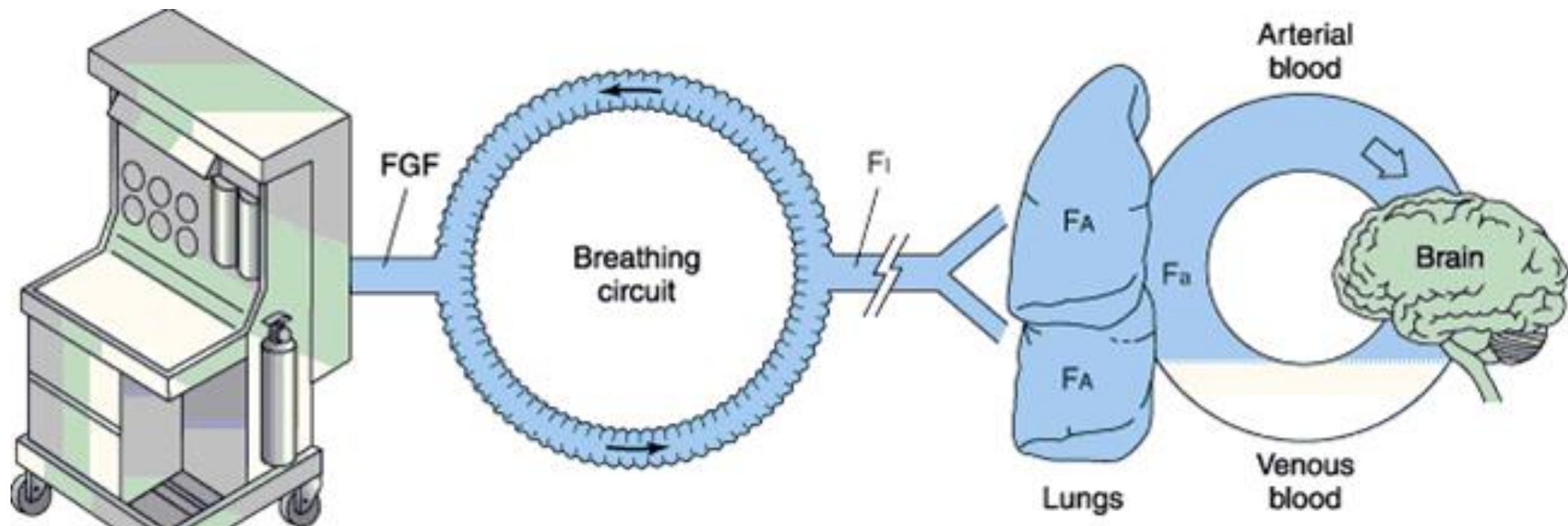
- Volatile liquids (**Halogenated** compounds)
 - Halothane
 - Isoflurane
 - Sevoflurane
 - Desflurane
- Nitrous oxide (N_2O)

Minimum alveolar concentration (MAC)

- A measure of potency
- Defined as: *the minimum alveolar concentration that prevents reaction to a standard surgical stimulus (skin incision) in 50% of subjects*

Minimum alveolar concentration (MAC)

Agent	MAC %
Halothane	0.75
Isoflurane	1.2
Sevoflurane	2
Desflurane	6
Nitrous oxide	104



Anesthesia machine

FGF (fresh gas flow)

F_i (inspired gas concentration)

F_A (alveolar gas concentration)

F_a (arterial gas concentration)

Nitrous oxide (N₂O)

- Used alongside volatile agents
- In combination with oxygen (O₂) as **entonox**
- High MAC

Effects

Respiratory

- ↓TV & ↑RR

Cardiovascular

- Mild direct myocardial depressant effects
- ↑Sympathetic activity

CNS

- ↑CBF (avoided in ↑ICP)
- Analgesia & sedation

Contraindications

- N_2O cause rapid expansion of any air-filled space
(pneumothorax, vascular air embolus & intestinal lumen)
- Prolonged use interferes with vitamin B12, protein & DNA synthesis

Halothane

- Clear, colorless liquid
- Contains thymol → prevents degradation by light
- Characteristic sweet smell
- MAC 0.75
- 20-50% metabolized in liver

Pharmacodynamic properties

CVS

- Dose dependent ↓ Cardiac contractility, ↓ HR & ↓ SVR
- Sensitizes myocardium to circulating catecholamines & cause arrhythmias

RS

- Dose dependent ↓ TV & ↑ RR
- Bronchodilatation
- Non-irritant

Pharmacodynamic properties

CNS

- Cerebral vasodilatation, ↑ CBF & ↑ ICP

Other

- Autoimmune hepatitis

Isoflurane

- Clear, colorless liquid
- Not degraded by light
- Doesn't contain preservatives
- Pungent smell
- MAC 1.2
- 0.2 % metabolized in liver

Pharmacodynamic properties

CVS

- Mild ↓ Cardiac contractility
- Dose dependent ↓ SVR & ↓ MAP
- Reflex tachycardia
- Coronary vasodilatation

Pharmacodynamic properties

RS

- Dose dependent ↓TV & ↑RR
- Bronchodilatation
- Respiratory irritant

CNS

- Low concentrations (< 1 MAC) do not increase CBF & ICP

Other

- Reduces muscle tone in pregnant uterus

Sevoflurane

- Clear, colorless liquid
- Not degraded by light
- Doesn't contain preservative
- Reacts with soda lime to form compound A
- MAC 2
- 3-5% metabolized in liver

Pharmacodynamic properties

CVS

- Dose dependent ↓CO, ↓SVR & ↓MAP
- Does not reduce HR

RS

- Less respiratory depression than other drugs
- Bronchodilatation & non-irritant

CNS

- Has similar actions as isoflurane

Other

- ↓Muscle tone in pregnant uterus

Desflurane

- Clear, colorless liquid
- Can be degraded by light
- Doesn't contain preservatives
- MAC 6
- 0.02% metabolised in liver
- Rapid onset & offset

Pharmacodynamic properties

CVS

- Dose dependent ↓ myocardial contractility, SVR & MAP
- ↑ HR

RS

- Dose dependent ↓ TV & ↑ RR
- It is potent irritant

CNS

- < 0.8 MAC → does not cause increase intracranial pressure

Other

- ↓ Renal blood flow

Analgesics

Pain

- Defined as “An unpleasant sensory & emotional experience associated with, or resembling that associated with, actual or potential tissue damage,”
- Nociceptive pain is the result of stimulation of nociceptors by noxious stimuli

Commonly used agents

- Opioids & related drugs
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Other analgesics

Classification of opioid receptors

Receptor	Effects
MOP, μ , mu	analgesia, meiosis, euphoria, respiratory depression, bradycardia, inhibition of gut motility
KOP, κ , kappa	analgesia, sedation, meiosis
DOP, δ , delta	analgesia, respiratory depression

Opioids

```
graph TD; A[Opioids] --- B[Agonist]; A --- C[Agonist-Antagonist]; A --- D[Antagonist];
```

The diagram is a simple tree structure. At the top is a blue rounded rectangle containing the word 'Opioids' in red. A vertical line descends from the bottom center of this box. Three horizontal lines branch off to the right from this vertical line, each connecting to a second blue rounded rectangle. The first rectangle contains the word 'Agonist', the second contains 'Agonist-Antagonist', and the third contains 'Antagonist'. All text is in red.

Agonist

Agonist-Antagonist

Antagonist

- Agonist–antagonist
 - Causes **agonism** at **certain receptors** & **antagonism** at **others**
- Pentazocine
 - Agonist at kappa (κ) & weak antagonist at mu receptor (μ)
- Butorphanol
 - Partial agonist at μ - & agonist at κ - & antagonist at delta receptor (δ)
- Nalbuphine κ -agonist/ μ -antagonist analgesic
- Agonist–antagonist opioids have a **lower addiction potential** but lower analgesic efficacy & more likely produce psychotomimetic effects
- Agonist–antagonist opioids that block delta while activating mu opioid receptors produce analgesia without the development of tolerance

Classification of opioid

Strong Agonists

- Morphine
- Methadone
- Meperidine / Pethidine
- Oxycodone
- Hydromorphone
- Fentanyl
- Sufentanil
- Alfentanil
- Remifentanyl

Moderate Agonists

- Codeine
- Hydrocodone
- Propoxyphene

Classification of opioid

Antagonists

- Naloxone
- Naltrexone

Indications

- Pre-, intra-, postoperative analgesia
- Induction & maintenance of anesthesia
- ↓MAC of volatile anesthetics
- Post operative analgesia by subarachnoid or epidural routes

Morphine

- Naturally occurring
- Reference opioid with which all others are compared

Presentation & uses

- Tablets, suspensions, suppositories & slow-release capsules & granules
- Oral dose 5–20 mg 4-hourly
- Parenteral preparation contains 10–30 mg/ml
- IM dose 0.1–0.2 mg/kg 4-hourly
- IV dose titrated to effect, but total dose is similar

Presentation & uses

- Relatively low lipid solubility
 - SC route avoided due to slow absorption
 - *Delayed respiratory depression* following intrathecal or epidural administration may occur

Effects

- Analgesia
 - Visceral pain > sharp or superficial pain
- Respiratory depression
 - ↓ RR > TV
 - Antitussive
- Nausea & vomiting
- CNS
 - Sedation, euphoria & dysphoria

Effects

- CVS
 - Mild bradycardia
- Gut
 - Constricts sphincters of gut & spastic immobility of bowel → constipation
 - Sphincter of oddi is contracted

Effects

- Histamine release
 - Hypotension, bronchospasm, rash & pruritus
- Pruritus
 - Following intrathecal or epidural
- Chest wall muscle rigidity
- Meiosis
- Urinary
 - ↑ Tone of bladder & sphincter → urinary retention

Fentanyl

- Synthetic with rapid onset of action
- *Less likely to precipitate histamine release*

Presentation

- Colorless solution for injection 50 µg/ml
- Transdermal patches release 25 to 100 µg per hour for 72 hours

Uses

- Minor surgery 1–2 $\mu\text{g}/\text{kg}$ IV & has duration of 30 minutes
- High doses (50–100 $\mu\text{g}/\text{kg}$) used for opioid-based anesthetic & duration of action extended to 6 hours
- Infusion for sedation but duration of action significantly prolonged
- Augment effects of local anesthetics in spinal 10–25 μg & epidural 25–100 μg

Alfentanil

- Synthetic

Presentation & uses

- Colorless solution 500 µg or 5 mg/ml
- Short term analgesia 5–25 µg/kg
- Infusion for sedation but duration of action is significantly prolonged

Remifentanyl

- Pure μ -receptor agonist
- Synthetic

Presentation

- Crystalline white powder in glass vials containing 1, 2 or 5 mg
- Not licensed for spinal or epidural administration

Uses

- IVI
- Diluted before use
- Stable for 24 hours
- Given as initial bolus of 1 $\mu\text{g}/\text{kg}$ over not less than 30 seconds, followed by infusion
- Usual dose 0.05–2.00 $\mu\text{g}/\text{kg}/\text{min}$

Effects

- Ultra-short duration of action → nausea & vomiting less common
- Characteristically ↓ HR & ↓ BP

Kinetics

- Rapidly broken down by non-specific plasma esterase →
elimination $t_{1/2}$ 3–10 minutes
- Inactive metabolite excreted in urine
- Impaired hepatic & renal function do not prolong its effects

Pethidine / Meperidine

- Synthetic

Presentation

- Solution for injection containing 10–50 mg/ml
- IV & IM dose 0.5–1.0 mg/kg, repeated 2–3 hourly

Uses

- Often used during labor !!!
- High lipid solubility → significant amounts cross placenta & reach fetus → metabolism → less lipid-soluble norpethidine → accumulates in fetus → levels peak 4 hours after initial maternal IM dose
- ↓ Fetal clearance → ↑ $t_{1/2}$ of both pethidine & norpethidine by factor of three

Effects

- Anticholinergic effects
 - Dry mouth & tachycardia
- If administered with monoamine oxidase inhibitors (MAOI) → coma, labile circulation, convulsions & hyperpyrexia

Tramadol

Presentation

- Tablets, capsules or sachets (50–400 mg)
- Solution for IV or IM containing 100 mg in 2 ml
- Analgesic potency one-fifth to one-tenth that of morphine

Effects

- Less respiratory depression & constipation
- Interact with tricyclic antidepressants → seizures
- Should not be used in epilepsy

Opioids Used in Anesthesia

Agent	Potency	Duration
Morphine	1	4 Hours
Pethidine	1/6 to 1/10	3 Hours
Fentanyl	100	1 Hour
Sufentanil	1000	1 Hour
Alfentanil	10-20	30 Minutes
Remifentanyl	400	Ultra-short

Opioid Antagonists

- **Naloxone & Naltrexone**
 - Competitively inhibit opioid receptors, *predominantly mu receptors*
- **Naloxone**
 - **Short acting** ($T_{1/2} = 1$ hour); effects of narcotic may return when naloxone wears off
- **Naltrexone**
 - ($T_{1/2} = 10$ hours); less likely to see return of narcotic effects unless narcotic levels very high

Side effects

- Agitation
- Sweating
- Tachycardia
- Hypertension
- Re-emergence of pain
- Pulmonary edema
- Seizures

Neuromuscular blocking agents

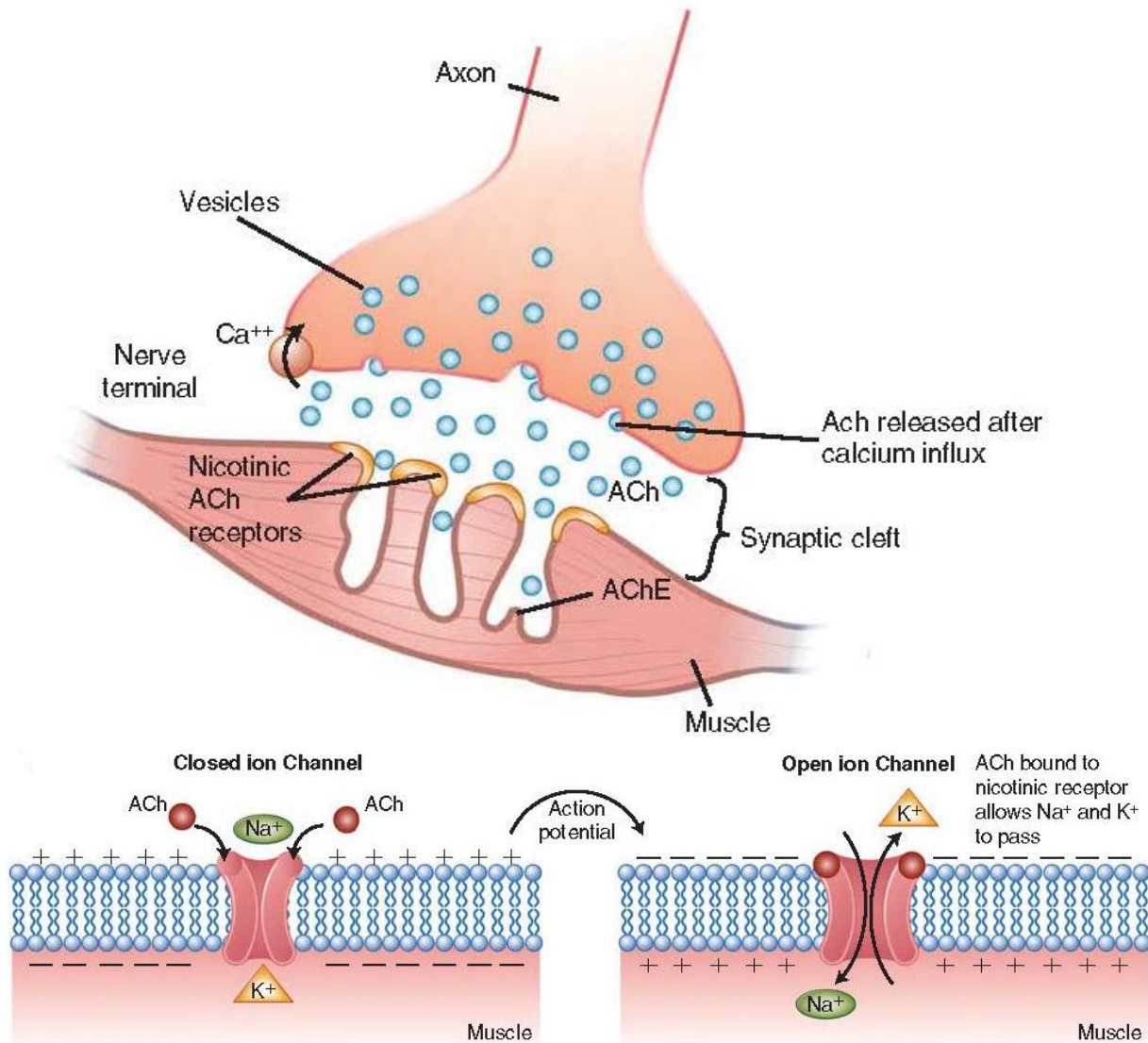
Introduction

- One of the primary anesthetic goals is akinesia → enhance surgical exposure & ↓ total anesthetic dose
- Muscle relaxants = neuromuscular relaxants = neuromuscular blockers (NMB)

Introduction

- Induce state of pharmacologic paralysis by interfering with normal processes of neurotransmitter– receptor interaction at neuromuscular junction (NMJ)

Neuromuscular junction



Classification of muscle relaxants

- Two main types:
 - Depolarizing
 - Nondepolarizing

Depolarizing / Succinylcholine

- Physically resemble Ach
 - Two Ach molecules joined

Mechanism of action

- Depolarization of skeletal muscle membrane & muscle contraction (fasciculations) followed by flaccid paralysis
- Higher affinity for Ach receptor as compared with Ach
- Remains bound & blocks subsequent stimulation

Metabolism

- Rapidly cleared by nonspecific plasma esterases
- Only small fraction of administered dose reaches NMJ
- Hypothermia & medications affect plasma cholinesterase activity prolong duration
- Deficiency of pseudocholinesterase prolonged paralysis (Heterozygous or homozygous)
- Treated with mechanical ventilation & ? FFP

Dosage & uses

- Adult 0.5–1.5 mg/kg
- Pediatric 2.0 mg/kg
- Muscle paresis occurs within 45 seconds
- Ideal drug for rapid sequence induction (RSI)
- Duration of action 5–10 min
 - Short case
 - Difficult airways
 - Patients prone to hypoxia
 - Electroconvulsive therapy
 - Emergent intramuscular administration
 - Laryngospasm rescue

Side effects

- ↑ Potassium (0.5 to 1 mEq/L)
- Myalgias
- Transient ↑ IGP, ↑ ICP & ↑ IOP
 - ↓ by pretreatment with “defasciculating dose = 1/10 intubating dose” of nondepolarizing agent & intravenous lidocaine
- Masseter muscle spasms
- Malignant hyperthermia
- Anaphylaxis
- Bradycardia (pediatric)

Contraindications

- Severe burns
- Myopathy
- Extensive degenerative neuropathy
- Hyperkalemia
- Prolonged paralysis with previous use
- Family history of malignant hyperthermia

Nondepolarizing

- Competitive antagonists of Ach at postsynaptic membrane
- Several nondepolarizing muscle relaxants
- Subclassified by:
 - Chemical structure
 - Duration of action
 - Potency

Chemical structure

- **Aminosteroid**

- Vagolytic → ↑HR, ↑MAP & ↑CO

- **Benzylisoquinolines**

- Stimulate release of histamine → hypotension, tachycardia, bronchospasm & facial flushing

Chemical structure

Aminosteroid	Benzy Isoquinolines
Rocuronium	Atracurium
Vecuronium	Cisatracurium
Pancuronium	Mivacurium

Duration of action

Ultra-Short	Short	Intermediate	Long
Succinylcholine	Mivacurium	Vecuronium Atracurium Cis-atracurium Rocuronium	Pancuronium

Rocuronium

- Intubating dose 0.6–1 mg/kg
- RSI 0.6–1.2 mg/kg
- Rapid onset of 0.9–1.7 min
- Alternative to succinylcholine in RSI
- Duration of action is 36–73 min
- Minimal cardiovascular effects
- Hypersensitivity reactions & anaphylaxis
- Excreted through biliary system & in urine minimally
- Duration prolonged in hepatic impairment

Vecuronium

- Intubating dose 0.08–0.1 mg/kg
- Onset 2–3 min
- Duration of action is 40–45 min
- Hypersensitivity
- Minimal cardiovascular effects
- ICU patients paralyzed → higher incidence of prolonged blockade & critical illness polyneuropathy
- Metabolized in liver & excreted through biliary system
- Hepatic disease & severe renal impairment prolong duration of action

Pancuronium

- Intubating dose 0.06–0.1 mg/kg
- Onset 3–4 min
- Duration of action is 85–100 min
- Vagolytic effects
- hypersensitivity reactions
- Metabolized in liver
- Avoided in renal impairment

Atracurium

- Intubation Dose 0.2–0.3 mg/kg
- Onset 3 mins
- Duration of action 45 mins
- Metabolized by Hoffman elimination & plasma esterases
 - Hoffman elimination is enzyme-independent hydrolysis relies on physiologic pH & temperature
- Laudanosine is byproduct → cross BBB → convulsion
- Histamine release

Cisatracurium

- Intubating dose 0.15–0.2 mg/kg
- Onset of 2–8 mins
- Duration of action of 45–90 min
- Hoffman elimination
- Amount of laudanosine produced from cisatracurium < atracurium
- Does not release histamine

Mivacurium

- Metabolized by plasma pseudocholinesterase
- Duration of action prolonged in renal & liver failure
- Histamine release
- No longer available in the United States

Local anesthetic (LA)

Definition

- Drug reversibly prevents transmission of nerve impulse
without affecting consciousness

Structural classification

- Amides
- Esters

Amides

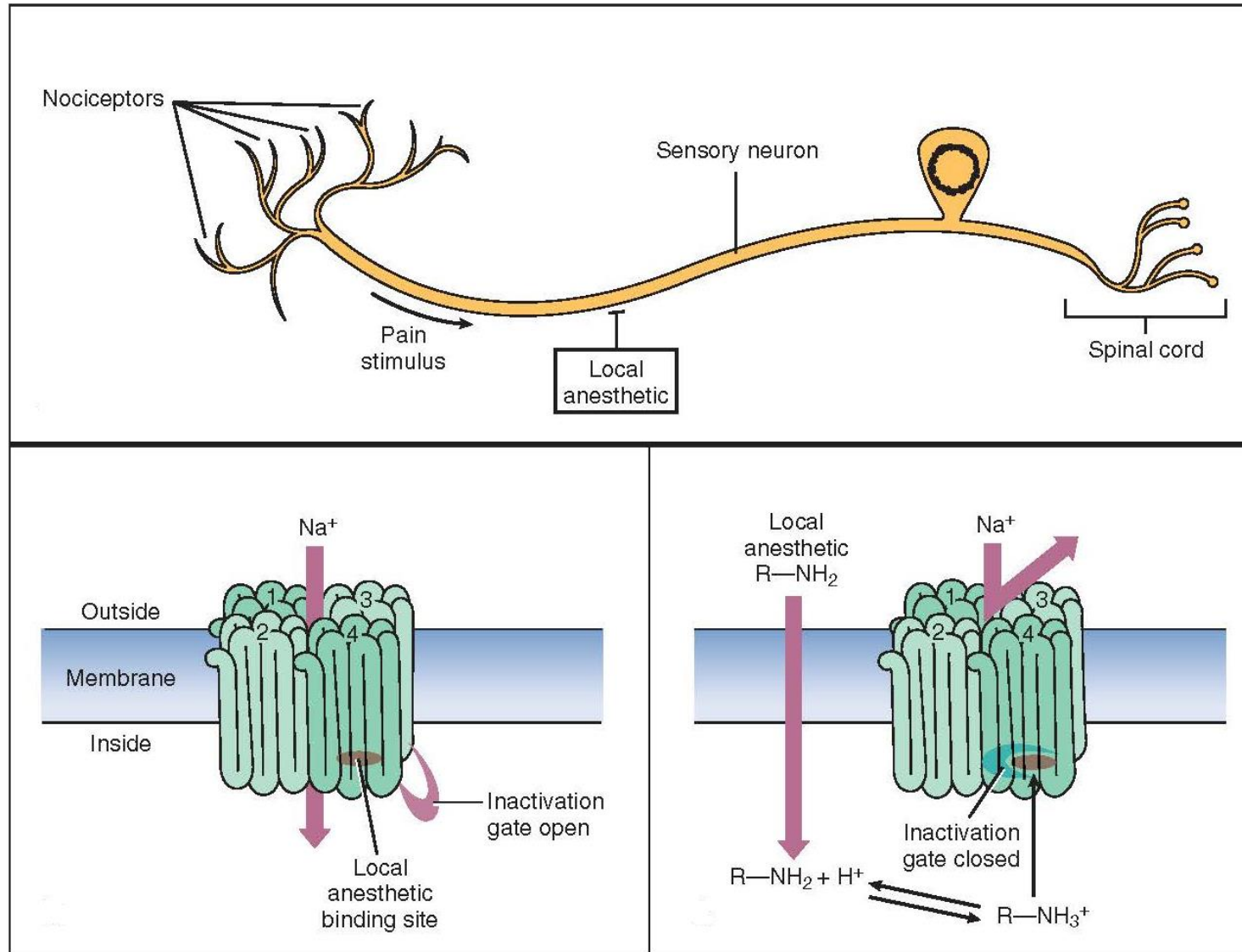
- Bupivacaine
- Prilocaine
- Lidocaine
- Ropivacaine
- Etidocaine
- Mepivacaine

Esters

- Cocaine
- Amethocaine
- Chloroprocaine
- Procaine
- Tetracaine

- Metabolism of esters results in production of para-aminobenzoate (PABA) which is associated with allergic reaction
- Amides very rarely cause allergic phenomena
- Amides more commonly used than esters

Mechanism of action



Mechanism of action

- Block voltage-gated sodium channels from inside the cell → interfering with sodium influx associated with membrane depolarization → impulse conduction slows until action potential no longer generated & impulse propagation abolished

- Loss of nerve function proceeds as pain, temperature, touch, proprioception then skeletal muscle
- This is why people may still feel touch but not pain when using

LA

Comparative Pharmacology of Local Anesthetics

Classification	Potency	Onset	Duration after Infiltration (min)	Maximum Single Dose for Infiltration (mg)	Toxic Plasma Concentration ($\mu\text{g/mL}$)	pK	Protein Binding (%)
Esters							
Procaine	1	Slow	45–60	500		8.9	6
Chloroprocaine	4	Rapid	30–45	600		8.7	
Tetracaine	16	Slow	60–180	100 (topical)		8.5	76
Amides							
Lidocaine	1	Rapid	60–120	300	>5	7.9	70
Prilocaine	1	Slow	60–120	400	>5	7.9	55
Mepivacaine	1	Slow	90–180	300	>5	7.6	77
Bupivacaine	4	Slow	240–480	175	>3	8.1	95
Levobupivacaine	4	Slow	240–480	175		8.1	>97
Ropivacaine	4	Slow	240–480	200	>4	8.1	94

Onset of action

- Onset of action depends on relative concentration of non-ionized lipid-soluble form & ionized water-soluble form, expressed by pKa
- LA with pKa closest to physiological pH will have higher concentration of non-ionized that can pass through nerve cell membrane & more rapid onset

Potency

- Potency correlates with lipid solubility
- The higher the lipid solubility, the higher the potency

Duration

- The greater the protein binding, the longer the duration

Absorption

- Rate of systemic absorption is proportionate to the vascularity of the site of injection:
- **IV** > tracheal > intercostal > caudal > paracervical > epidural > brachial plexus > sciatic > subcutaneous

LA + vasoconstrictors

- Epinephrine is added LA in dilute concentrations
- This causes local tissue vasoconstriction → limiting up taking of LA into the vasculature → prolonging its effect & reducing its toxic potential

Contraindication of additives vasoconstrictors

- Unstable angina pectoris
- Cardiac dysrhythmias
- Peripheral nerve blocks to fingers, toes, penis
- Uncontrolled hypertension
- Intravenous regional anesthesia

Metabolism

- Ester LA metabolized by non-specific plasma esterase
- Amide LA metabolized by P-450 enzymes in liver

Toxicity

- CNS is the site of premonitory signs of overdose in awake patients
- Symptoms
 - Circumoral numbness & tongue paresthesia
 - Dizziness
 - Tinnitus
 - Blurred vision
 - Restlessness
 - Agitation
 - Nervousness
 - Tonic–clonic seizures

- Unintentional IV injection of bupivacaine during regional anesthesia produces severe cardiotoxic reactions
 - Hypotension
 - Atrioventricular heart block
 - cardiac arrest Ventricular tachycardia & fibrillation

Management of LA toxicity

- Oxygenation
- Fluids
- Hypotension → ephedrine 10-30mg bolus
- Seizures → diazepam 5-10mg, midazolam (0.05–0.10 mg/kg)
- Intravenous infusion of 20% lipid emulsion (Intralipid 20%)

Thanks