Anesthetics

HISTORY:

Ether (1846)

Chloroform (1847)

Nitrous oxide (1868)

Cyclopropane (1929)

Thiopental (1935)

Halothane (1956)

A GRAND EXHIBITION

OF THE EFFECTS PRODUCED BY INHALING

NITROUS OXIDE, EXHILERATING, OR

LAUGHING GAS!

WILL BE GIVEN AT The Masonic Hall

Saturday EVENING, 15th

10 GALLONS OF GAS

will be

prepared and administered

to all in the audience

who desire to inhale it.

MEN will be invited from the audience, to protect those under the influence of the Gas from injuring themselves or others. This course is adopted that no apprehension of danger may be entertained. Probably no one will attempt to fight.

THE EFFECT OF THE GAS is to make those who inhale it, either

LAUGH, SING, DANCE, SPEAK OR FIGHT, &c. &c.

according to the leading trait of their character. They seem to retain consciousness enough not to say or do that which they would have occasion to regret.

N. B. The Gas will be administered only to gentlemen of the first respectability. The object is to make the entertainment in every respect, a genteel affair.

Those who inhale the Gas once, are always anxious to inhale it the second time. There is not an exception to this rule.

No language can describe the delightful sensation produced. Robert Southey, (poet) once said that "the atmosphere of the highest of all possible heavens must be composed of this Gas."

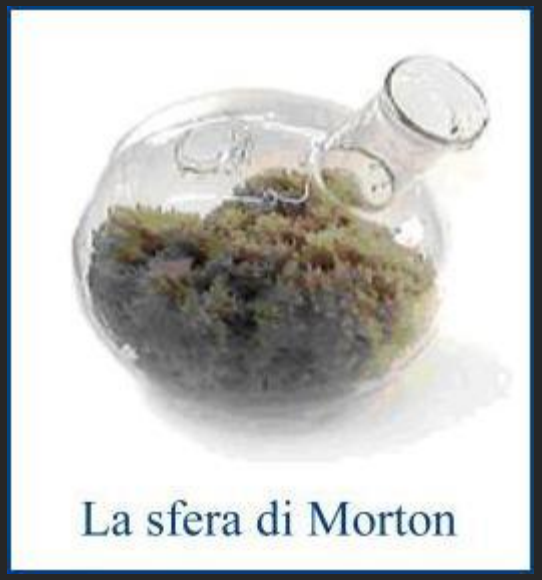
For a full account of the effect produced upon some of the most distinguished men of Europe, see Hooper's Medical Dictionary, under the head of Nitrogen.

Date: 1845

1796

Opium 1700

(Horace Wells, 1815-1848)



La sfera di Morton

1846

(William Thomas Green Morton, 1819-1868)

Ether monument, Boston

Anesthesia phases: induction, modulation, recovery

Amnesia
Loss of consciousness
Analgesia
Muscle relaxation
Reflex suppression

Medications:
1) Pre-anesthetic medication
2) General anesthetic
3) Relaxing skeletal muscles

MEDICAZIONE PREANESTETICA

- Anticolinergici
- Antiemetici
- Antiistaminici
- Barbiturici
- Benzodiazepine
- Miorilassanti
- Oppiacei

ANESTETICI GENERALI

INALATORI

- *Alotano*
- *Desflurano*
- *Enflurano*
- *Isoflurano*
- *Protossido d'azoto*
- *Sevoflurano*

ENDOVENOSI

- Barbiturici
- Benzodiazepine
- *Etomidato*
- *Ketamina*
- Oppiacei
- *Propofol* *

ANESTETICI LOCALI

- *Bupivacaina*
- *Lidocaina*
- *Procaina*
- *Tetracaina*

Drugs used as an adjunctive medication

-**Benzodiazepines**, diazepam (anxiety), midazolam effect (amnesia) barbiturates (sedation)

-**Neuromuscular blockers** (vecuronium, atracurium) and BZ Muscle relaxation

-**Antihistamines** (allergic reactions);

-**Anti H2**, ranitidine (gastric acidity, reflux)

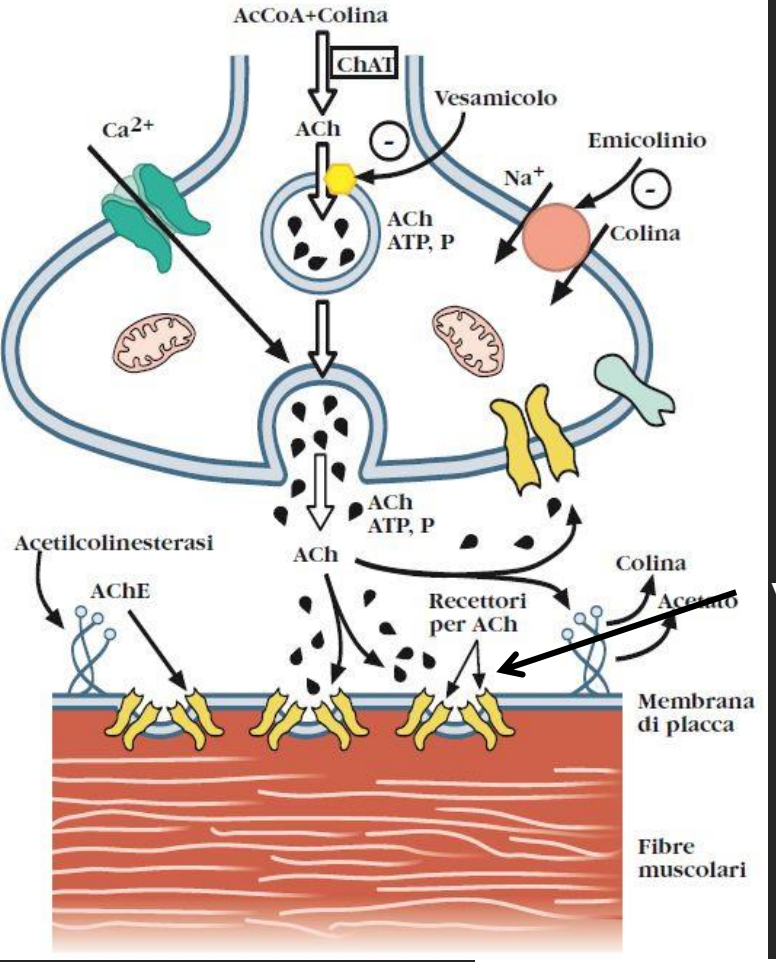
-**Alpha 2 agonists** (sedation, hypotension) (clonidine or dexmedetomidine)

-**Antiemetics**, ondansetron (prevent aspiration of stomach contents)

-**Opiates**, fentanyl (analgesia)

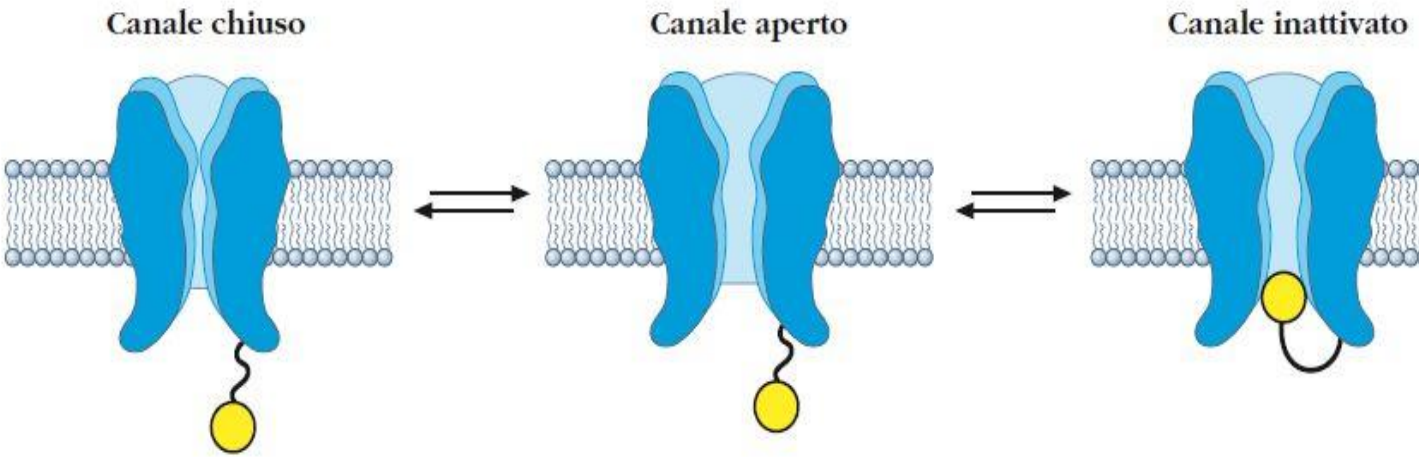
-**Anticholinergics**, scopolamine (preventing secretion respiratory tract)

Muscle relaxation

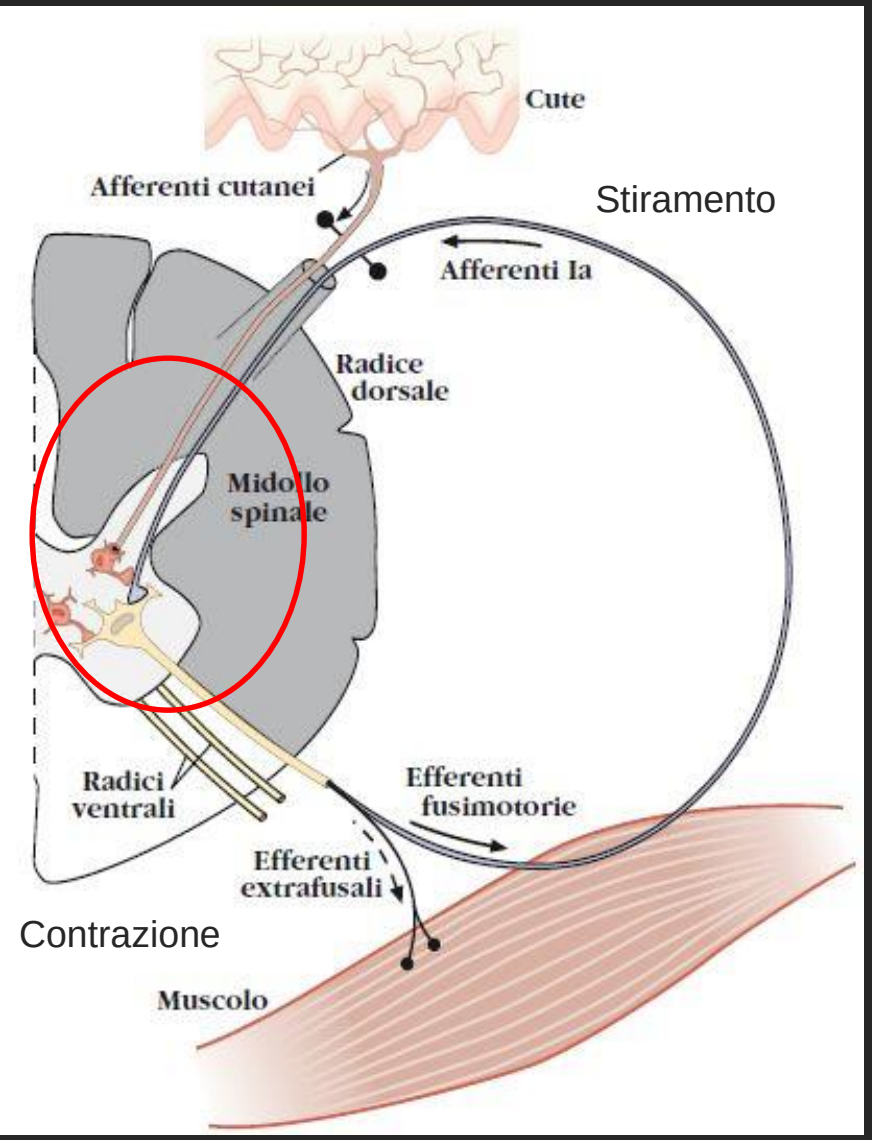


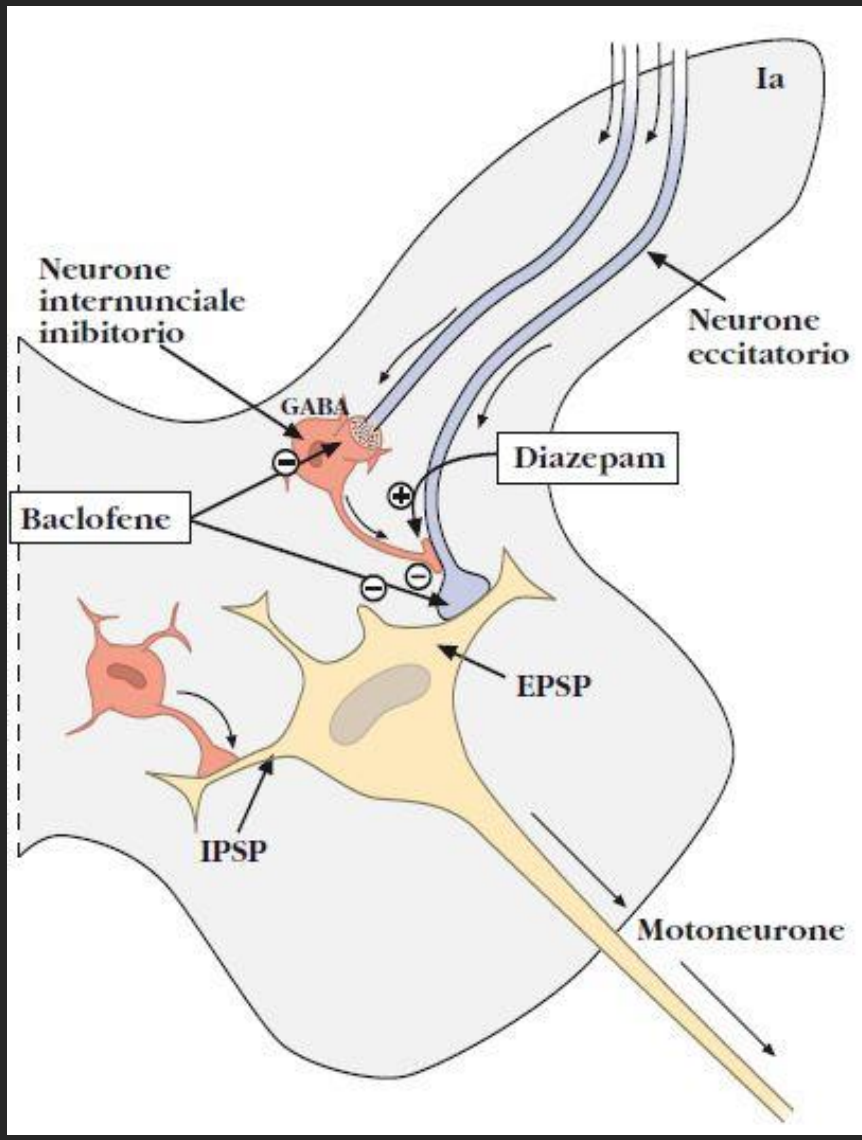
Vecuronium, atracurium

Succinylcholine



Myorelaxant effects of BZ and GABA agonists





Anesthesia effects

Hemodynamic pressure decrease, vasodilation, myocardial depression, sympathetic tone reduction, baroreceptor tone attenuation (nitrous oxide)

Hypothermia environmental temperature, exposure cavities, cold fluids, thermoregulation, metabolism, vasodilation / vasoconstriction

Respiratory reduction respirators: ventilation, esophageal sphincter (etc. nitrous oxide and ketamine)

Nausea-Vomiting CTZ (front 5-HT3, front D2)

General Anesthetics

Inhalation anesthetics

Individual inhalation anaesthetics

- The main agents in current use in developed countries are halothane, nitrous oxide, isoflurane, enflurane, desflurane and sevoflurane. Ether is largely obsolete.
- **Halothane**:
  - —widely used agent
  - —potent, non-explosive and non-irritant, hypotensive; may cause dysrhythmias; about 30% metabolised
  - —hangover likely, because of high lipid solubility
  - —risk of liver damage if used repeatedly.
- **Nitrous oxide**:
  - —low potency, therefore must be combined with other agents
  - —rapid induction and recovery
  - —good analgesic properties
  - —risk of bone marrow depression with prolonged administration.
- **Enflurane**:
  - —halogenated anaesthetic similar to halothane
  - —less metabolism than halothane; therefore, there is less risk of toxicity
  - —faster induction and recovery than halothane (less accumulation in fat)
  - —some risk of epilepsy-like seizures.
- **Isoflurane**:
  - —similar to enflurane but lacks epileptogenic property
  - —may precipitate myocardial ischaemia in patients with coronary disease.
  - —Irritant to respiratory tract
- **Desflurane** and **sevoflurane** are similar to isoflurane but have faster onset and recovery and lack of respiratory irritation.
- **Ether**:
  - —obsolete except where modern facilities are not available
  - —easy to administer and control
  - —slow onset and recovery, with postoperative nausea and vomiting
  - —analgesic and muscle relaxant properties
  - —highly explosive
  - —irritant to respiratory tract.

Principal inhalation anesthetics

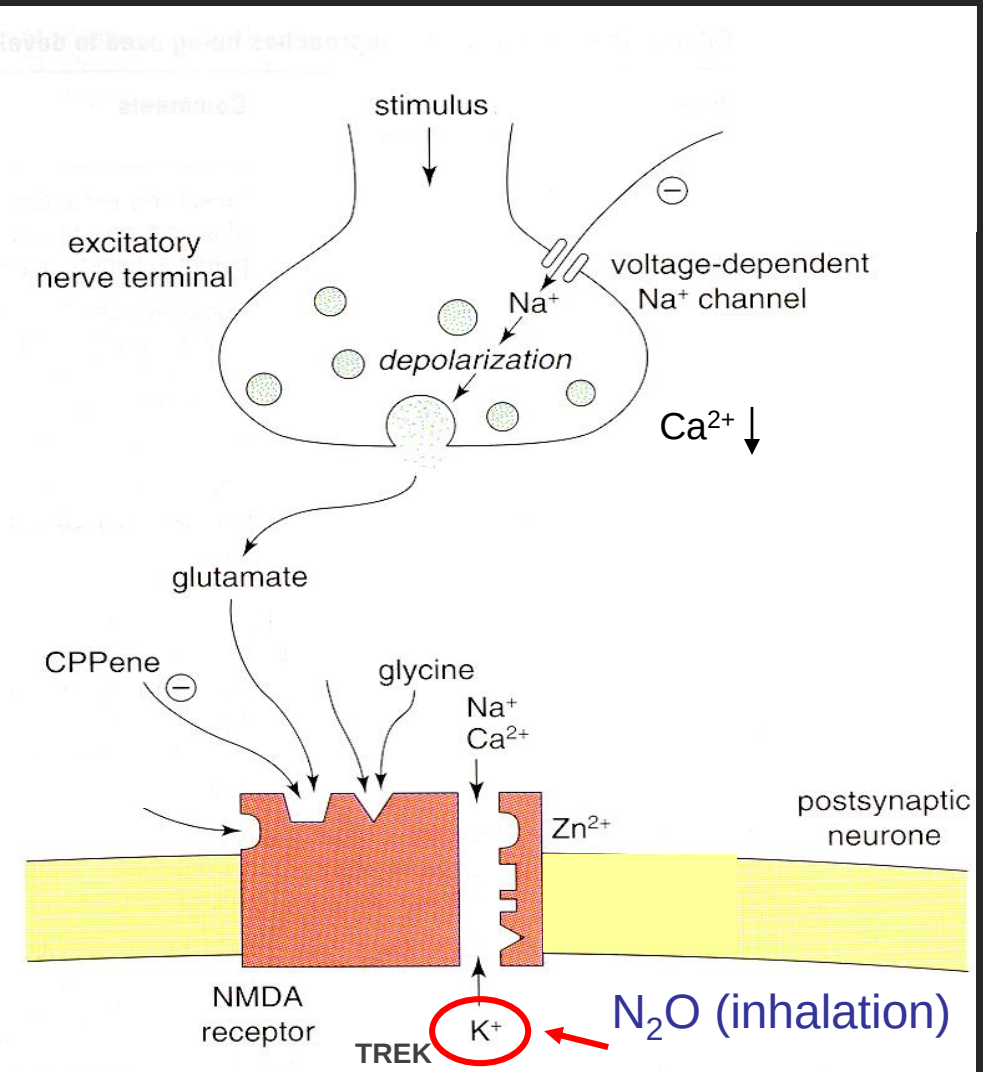


Fig. 3. Possible sites of interaction of antiepileptic drugs on glutamate-mediated transmission. The NMDA receptor is associated with an ion channel permeable to Na^+ and Ca^{2+}, and is associated with a number of modulatory sites, including a strychnine-insensitive glycine-binding site. Glycine is an absolute requirement for the receptor–channel complex to enter the open state. CPPene, 3-(2-carboxypiperazin-4-yl)-1-propenyl-phosphonic acid.

Release of the neurotransmitter and channel ligand / regulated membrane modulated by anesthetics

Side Effects

Kidney and Liver (fluoride, bromide metabolic products)

Respiratory system (asthma, depression newborn breathing)

Pregnancy (no diazepam)

Cardiovascular system (hypotension, reduced perfusion pressure and ischemic damage)

Nervous system (epilepsy, malignant hyperthermia)

Factors that determine the anesthetic drug's properties (potency)

- minimum alveolar concentration
- blood / gas distribution coefficient
- oil / gas distribution coefficient
- soft tissue / fat distribution

Minimum alveolar concentration (MAC)

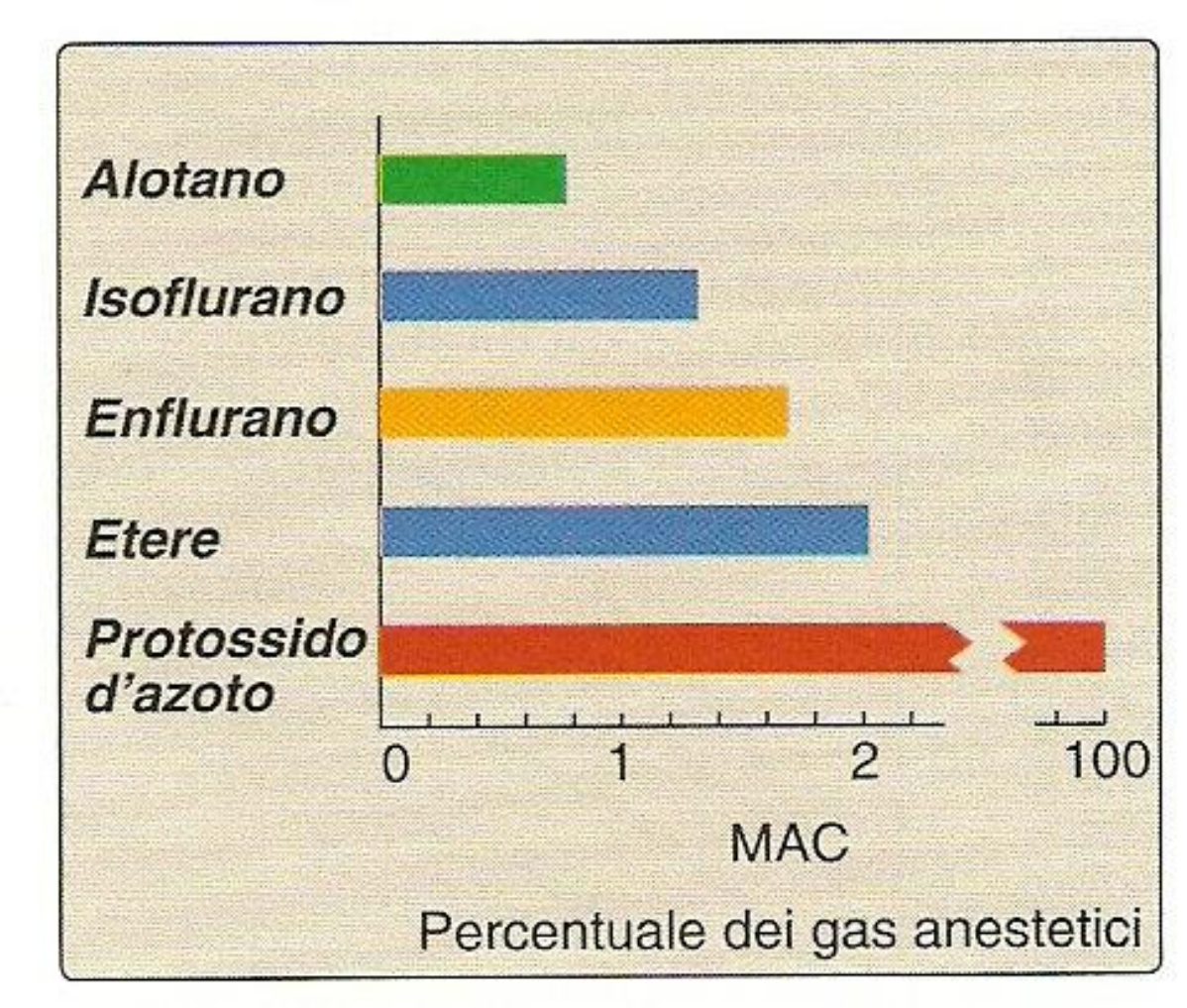
ANESTHETIC POTENCY = MAC

↓ potent anesthetic: halothane

↑ less potent anesthetic: nitrous oxide (protossido di azoto)

Equilibrium = partial gas pressure is equal between blood and gas

Minimum alveolar concentrations (MAC) of inhalation anesthetics



MAC of some inhalation general anesthetics

	MAC	MAC risveglio
Isoflurano	1,2	0,4
Enflurano	1,6	0,4
Alotano	0,7	0,4
Sevoflurano	2,0	0,6
Desflurano	6,0	2,4
Protossido d'azoto	105,0	60,0

Blood / gas partition coefficient

Oil / gas distribution coefficient

Pharmacokinetic properties

Low blood-gas partition coefficient =
Rapid induction and recovery

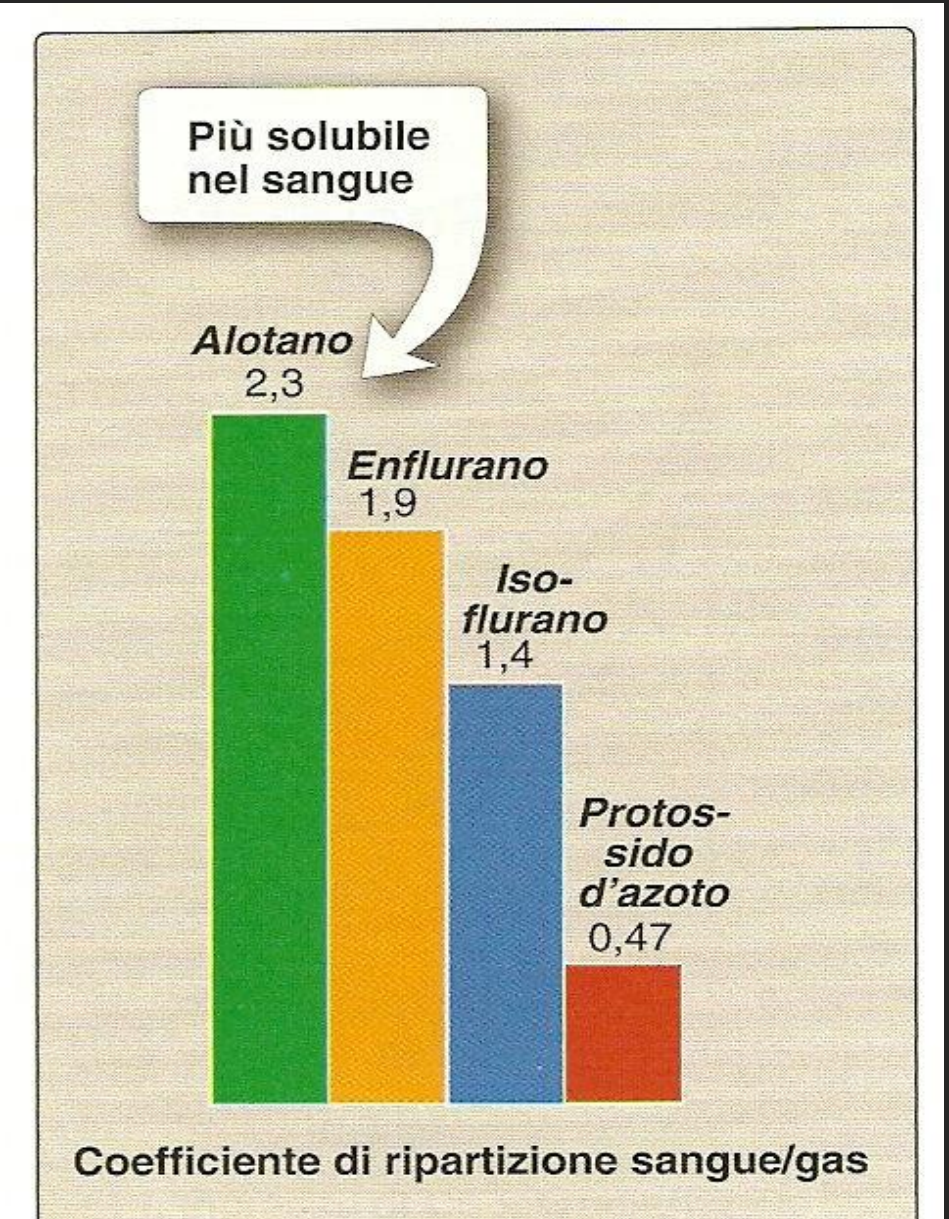
Not very soluble in the
Blood + fast balance
blood 50 / gas 100

High blood-gas partition coefficient =
Slow induction and recovery

Very soluble in blood
- fast balance
blood 200 / gas 100

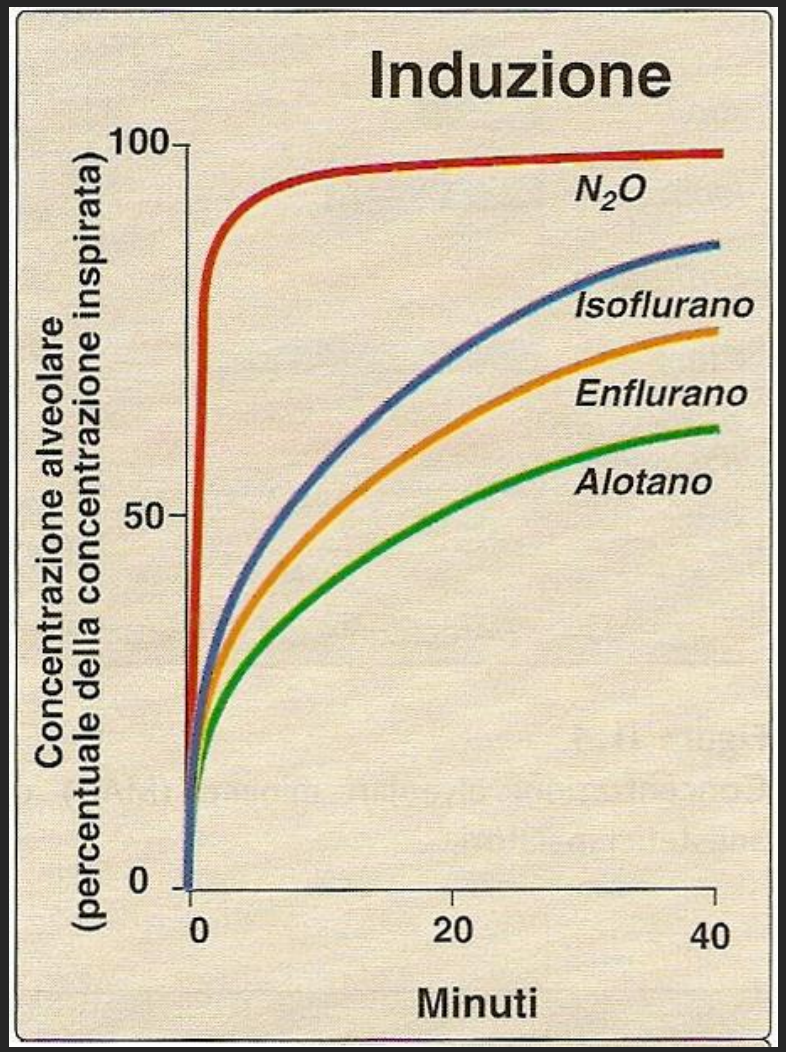
Blood / gas partition coefficients of some inhalation anesthetics (induction and recovery)

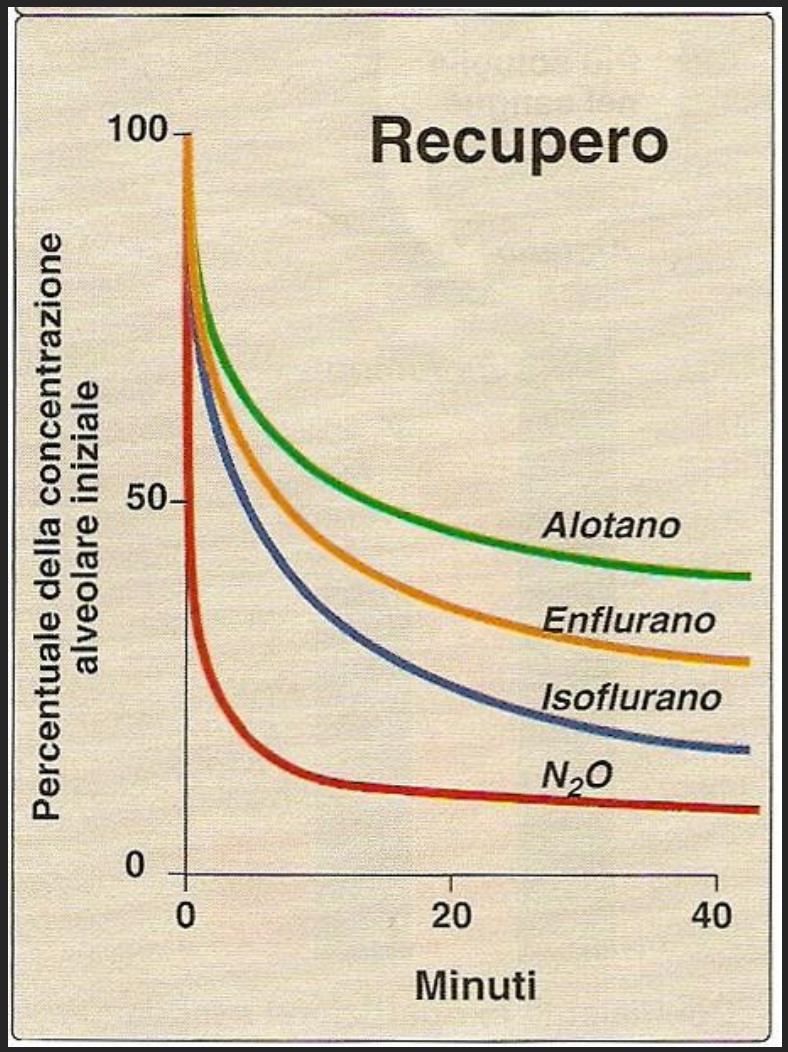
blood 23 / gas 10



blood 47 / gas 100

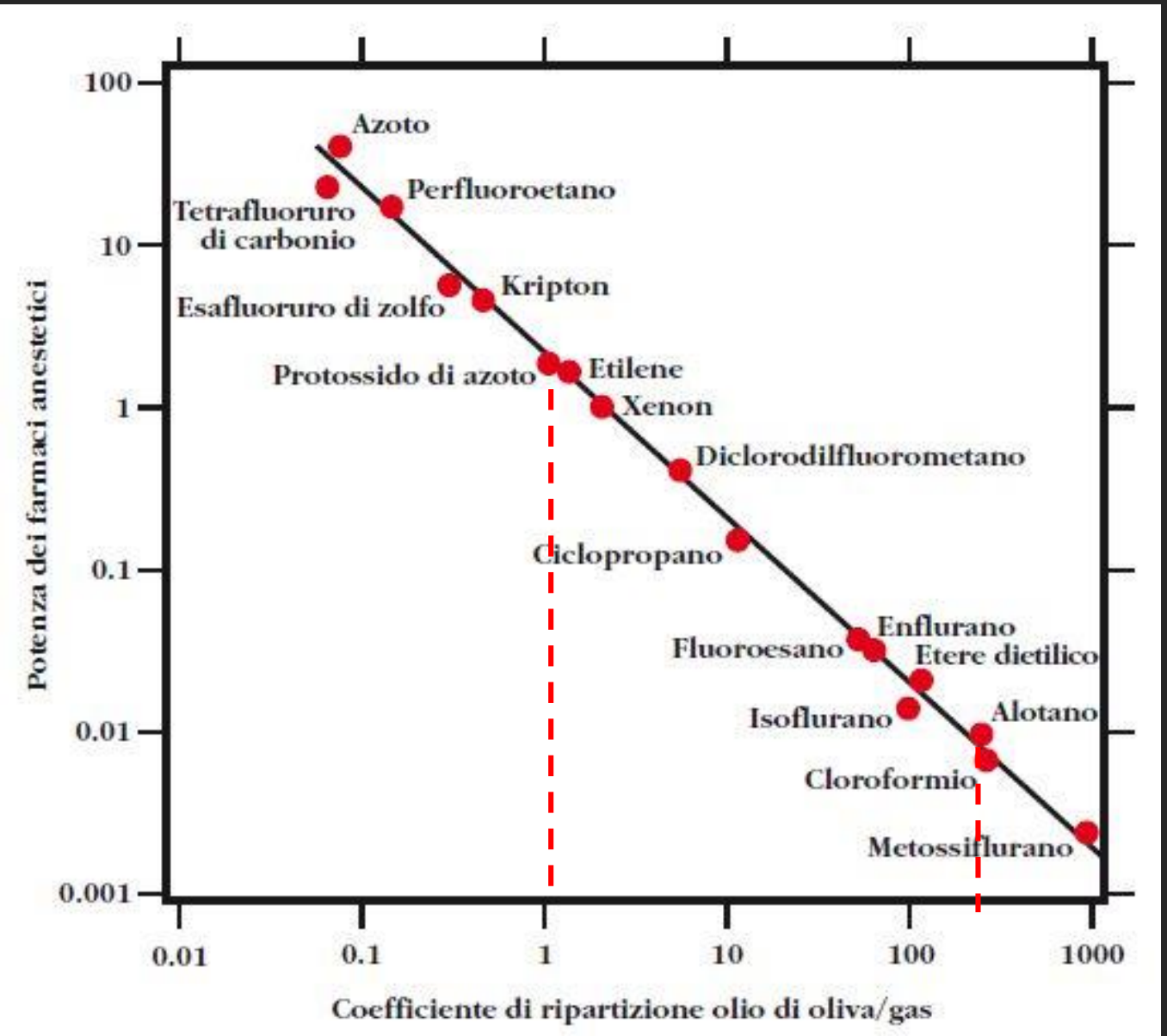
Temporal modifications of alveolar concentration of some inhalation anesthetics





If slightly soluble, a certain partial pressure is reached with a lower absorption of the drug

Correlation between the anesthetic potential (MAC) and the oil / gas partition coefficient



oil 300 / gas 1 (high)
oil 2 / gas 1 (low)

MAC inversely proportional to the potency

Distribution of anesthetics in body areas

- **Brain, heart, liver, kidney, endocrine glands:**

rapid stationary state

- **Skeletal muscles:**

slow steady state

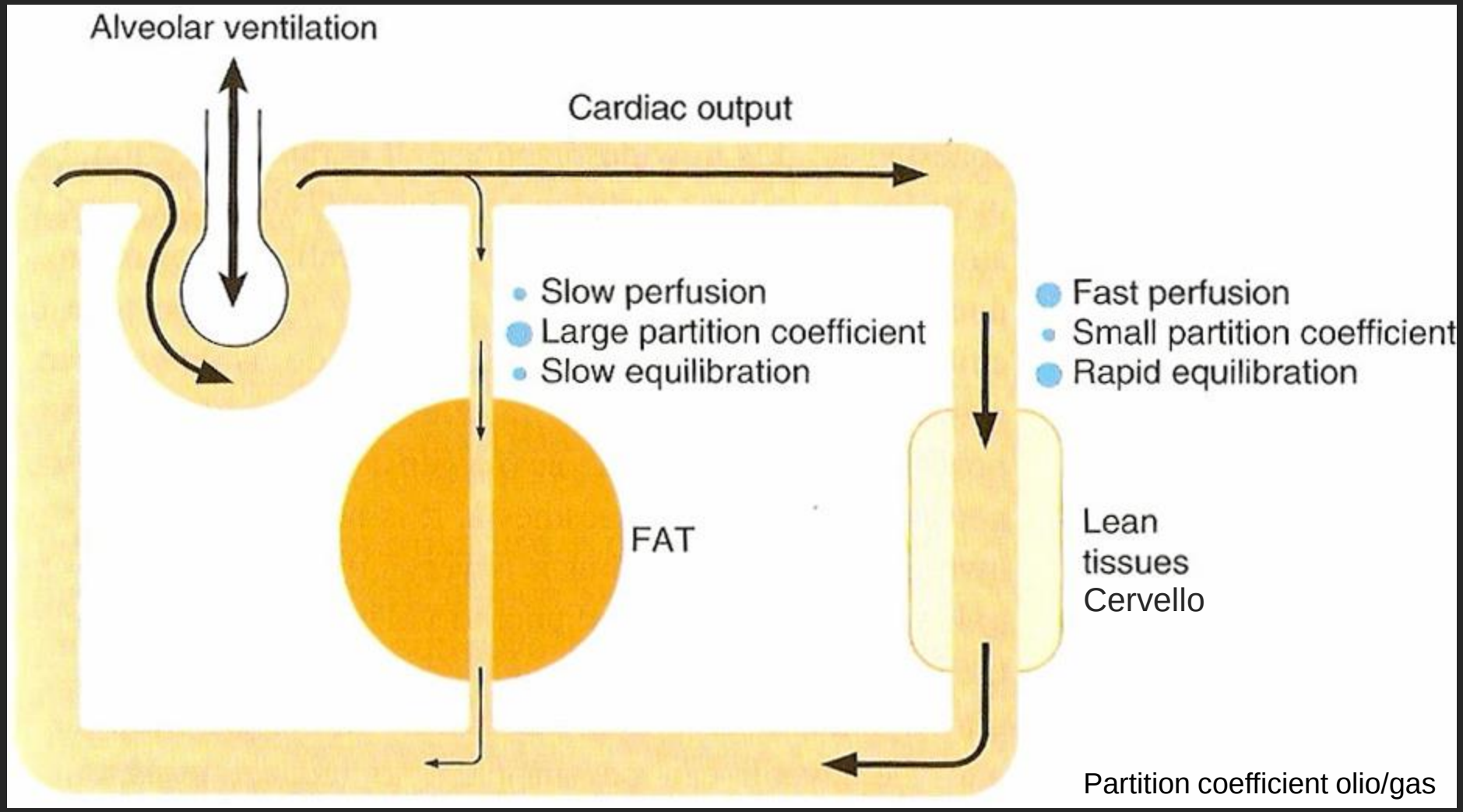
- **Adipose tissue:**

large storage capacity

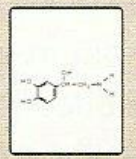
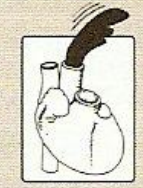
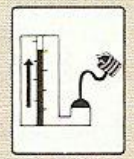
- **Bones, ligaments, cartilage:**

low storage capacity

Factors that influence the speed of equilibrium in the body



Risks and side effects

	Alotano	Enflurano	Isoflurano
 Aritmie	↑ Aumento	—	—
 Sensibilità alle catecolamine	↑ Aumento	↑ Lieve aumento	—
 Gittata cardiaca	↓ Diminuzione	Diminuzione… … poi recupera	↓ Diminuzione
 Pressione sanguigna	↓ Diminuzione	Diminuzione… … poi recupera	↓ Diminuzione
 Riflessi respiratori	↓ Inibiti	↓ Inibiti	↑ Iniziale stimolazione
 Tossicità epatica	↑ Rischio elevato	↑ Rischio moderato	↑ Rischio moderato

Drug	Partition coefficients		MAC (% v/v)	Induction/ recovery	Main adverse effects	Notes
	Blood:gas	Oil:gas				
Etere	12.0	65	1.9	Slow	Respiratory irritation Nausea and vomiting Explosion risk	Now obsolete, except where facilities are minimal
Alotano	2.4	220	0.8	Medium	Hypotension Cardiac arrhythmias Hepatotoxicity (with repeated use) Malignant hyperthermia (rare)	In common use, but declining in favor of newer agents Significant metabolism to trifluoracetate
Protossido azoto	0.5	1.4	100[a]	Fast	Few adverse effects Risk of anemia (with prolonged or repeated use)	Good analgesic effect Low potency precludes use as sole anaesthetic agent—normally combined with other inhalation agents
Enfluorano	1.9	98	0.7	Medium	Risk of convulsions (slight) Malignant hyperthermia (rare)	Widely used Similar characteristics to halothane, with less risk of hepatic toxicity
Isofluorano	1.4	91	1.2	Medium	Few adverse effects Possible risk of coronary ischemia in susceptible patients	Widely used as alternative to halothane
Desfluorano	0.4	23	6.1	Fast	Respiratory tract irritation, cough, bronchospasm	Used for day-case surgery, because of fast onset and recovery (comparable to nitrous oxide)
Sevofluorano	0.6	53	2.1	Fast	Few reported Theoretical risk of renal toxicity owing to fluoride	Recently introduced Similar to desflurane

Portion of general inhalation anesthetics that are biotransformed in the liver

Isoflurano	0,2%
Enflurano	2,4%
Alotano	17-20%
Sevoflurano	3%
Desflurano	0,02%
Protossido d'azoto	0,004%

Intravenous anesthetics

- Most commonly used for induction of anaesthesia, followed by inhalation agent.
- Thiopental, etomidate and propofol are most commonly used; all act within 20–30 seconds if given intravenously.

- **Thiopental:**
  - —barbiturate with very high lipid solubility
  - —rapid action because of rapid transfer across blood–brain barrier; short duration (about 5 minutes) becaue of redistribution, mainly to muscle
  - —slowly metabolised and liable to accumulate in body fat; therefore, may cause prolonged effect if given repeatedly
  - —no analgesic effect
  - —narrow margin between anaesthetic dose and dose causing cardiovascular depression
  - —risk of severe vasospasm if accidentally injected into artery.
- **Etomidate:**
  - —similar to thiopental but more quickly metabolised
  - —less risk of cardiovascular depression
  - —may cause involuntary movements during induction
  - —possible risk of adrenocortical suppression.
- **Propofol:**
  - —rapidly metabolised
  - —very rapid recovery; no cumulative effect
  - —useful for day-case surgery
- **Ketamine:**
  - —analogue of phencyclidine, with similar properties
  - —action differs from other agents; probably related to effect on NMDA-type glutamate receptors
  - —onset of effect is relatively slow (2–5 minutes)
  - —produces 'dissociative' anaesthesia, in which patient may remain conscious, though amnesic and insensitive to pain
  - —high incidence of dysphoria, hallucinations, etc. during recovery; used mainly for minor procedures in children.

Principal Intravenous anesthetics

↓ **Cerebral metabolism (O_2)**
(cerebral ischemia)
Respiratory System

↓ **Cerebral metabolism**
(cerebral ischemia)

↑ **Cerebral blood flow**
Blood pressure
Frequency and cardiac output

Release of the neurotransmitter and channel ligand / regulated membrane modulated by anesthetics

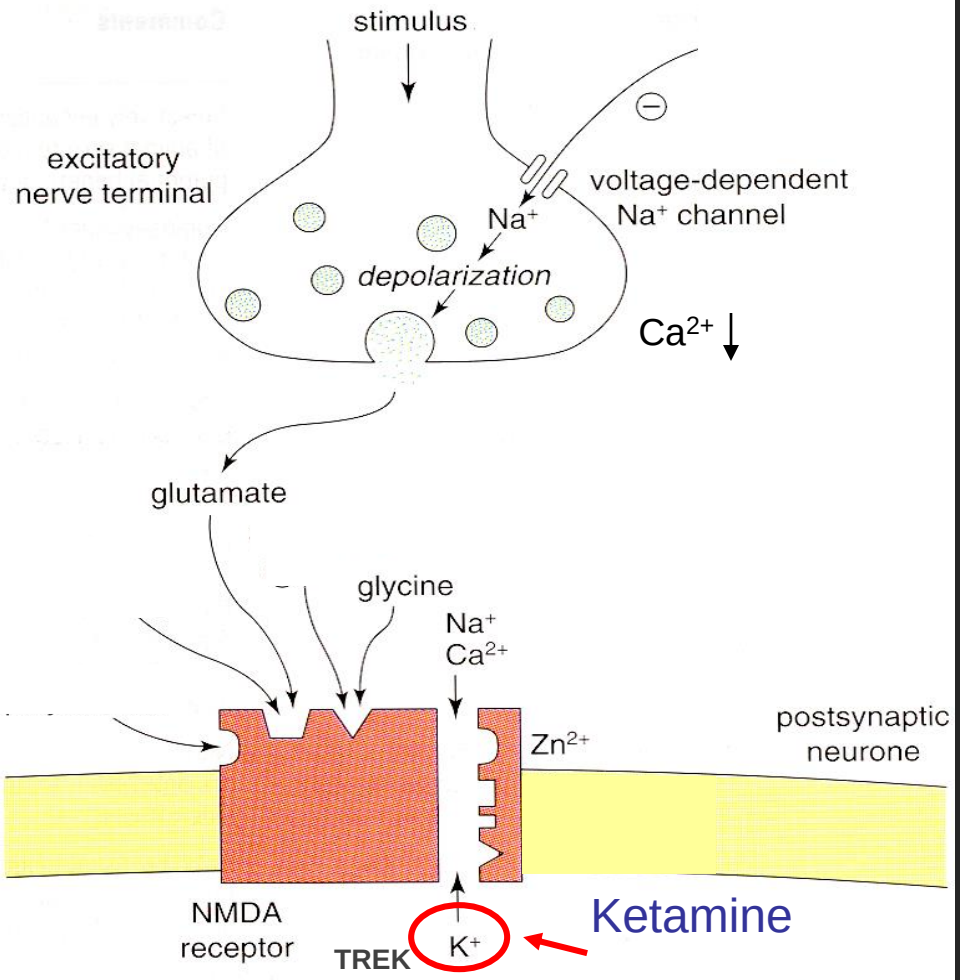
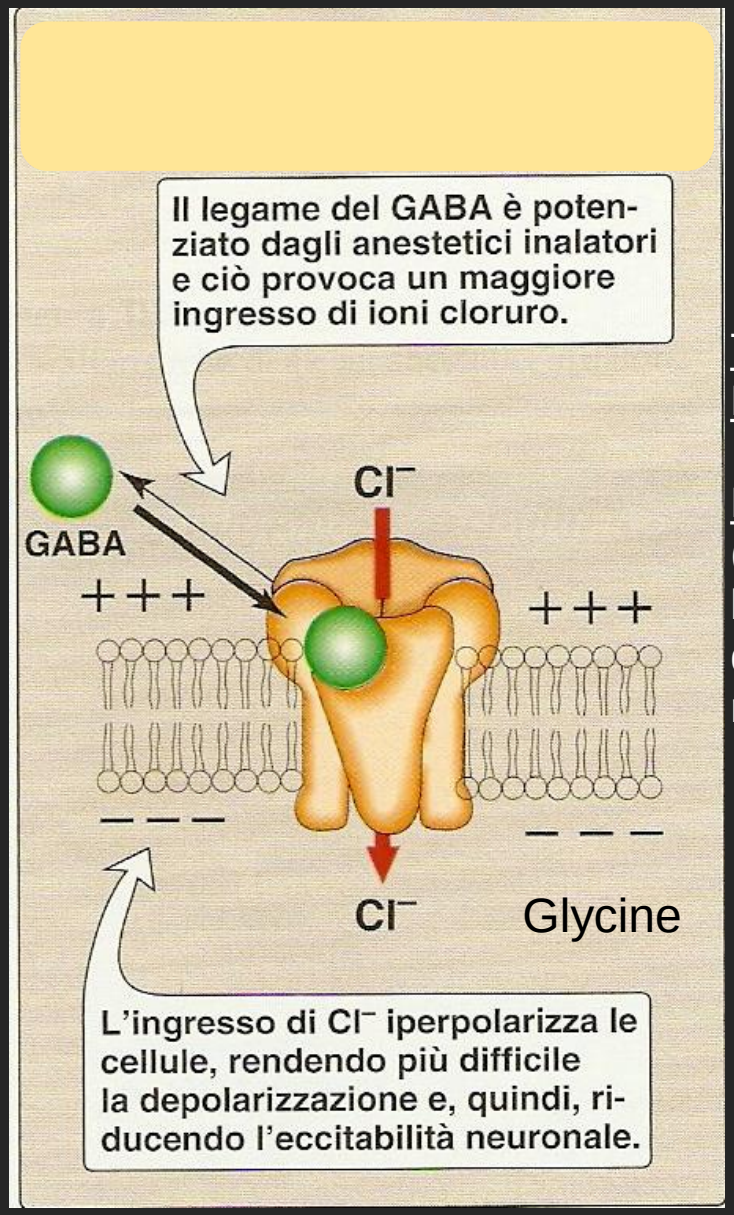


Fig. 3. Possible sites of interaction of antiepileptic drugs on glutamate-mediated transmission. The NMDA receptor is associated with an ion channel permeable to Na^+ and Ca^{2+}, and is associated with a number of modulatory sites, including a strychnine-insensitive glycine-binding site. Glycine is an absolute requirement for the receptor–channel complex to enter the open state. CPPene, 3-(2-carboxypiperazin-4-yl)-1-propenyl-phosphonic acid.

Ligand / regulated membrane channel modulated by anesthetics

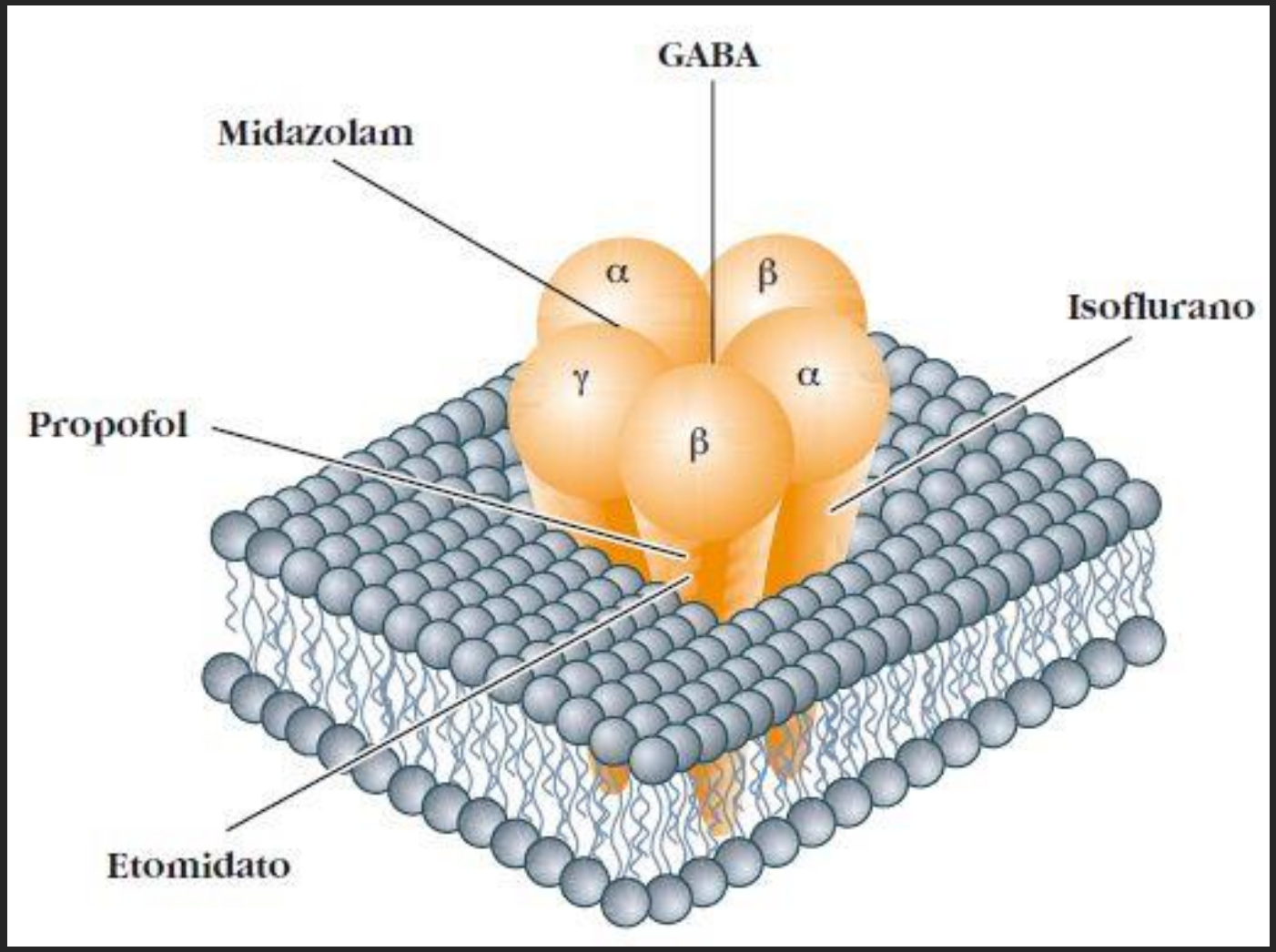


Thiopental
Propofol

Etomidate
(quick and short action, little respiratory depression,
no histamine release)

Propofol
GABA and glycine receptor
Reduces O2 consumption
Used in ischemia

Site of action of general anesthetics on the GABA-A receptor



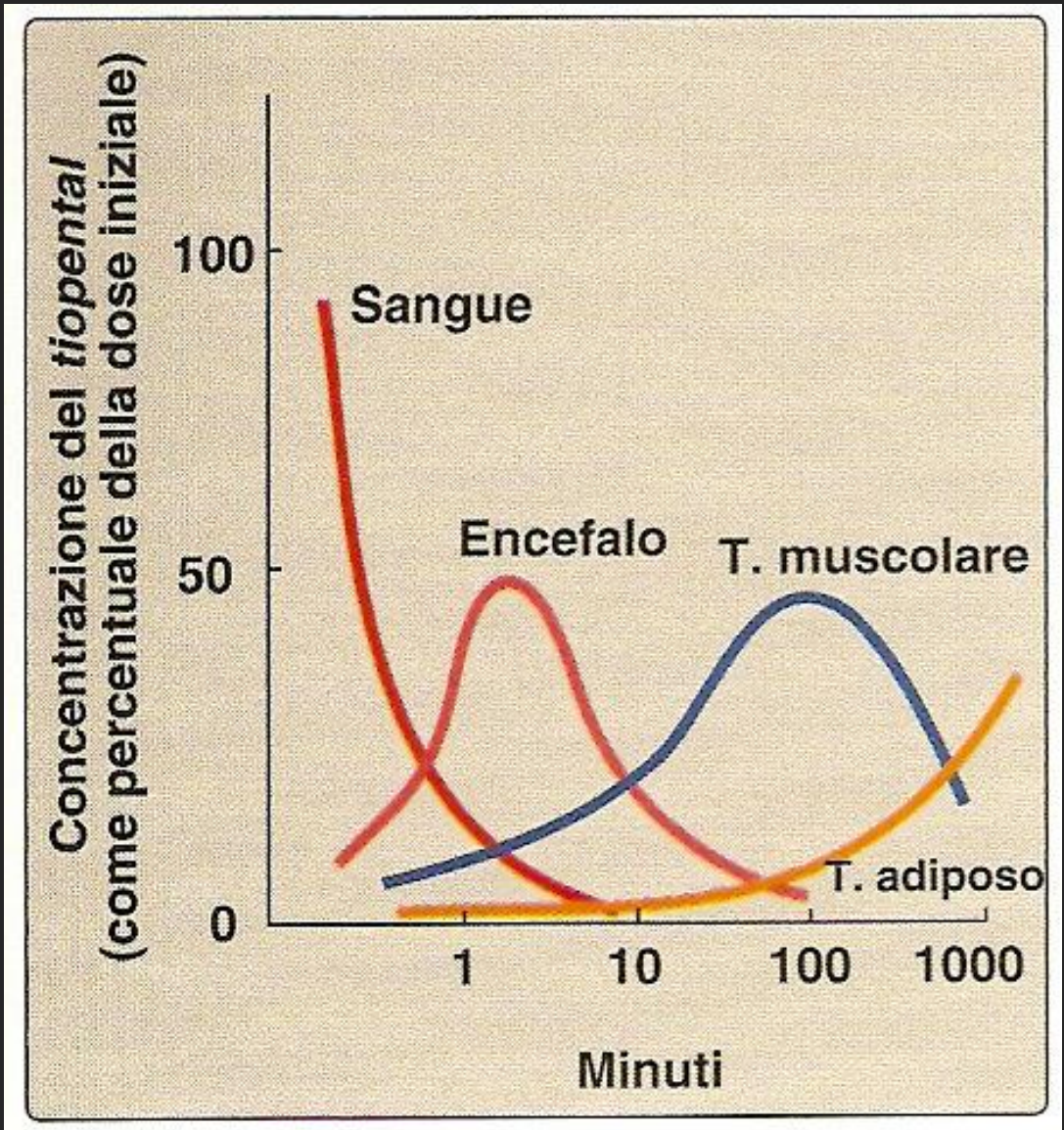
Characteristics of parenteral anesthetics

Tabella 13-2

Caratteristiche farmacologiche degli anestetici per via parenterale

FARMACO	FORMULAZIONE	DOSE mg	LIVELLO MINIMO µg/ml	DURATA min	T1/2 ore	CLEARANCE ml/min	PROTEINE %
Tiopentale	25 mg/ml in soluzione acquosa + 1.5 mg/ml Na_2CO_3; pH = 10-11	3-5	15.6	5-8	12.1	3.4	85
Metoesitale	10 mg/ml in soluzione acquosa + 1.5 mg/ml Na_2CO_3; pH = 10-11	1-2	10	4-7	3.9	10.9	85
Propofol	10 mg/ml in olio di semi di soia 10%, glicerolo 2.25%, fosfolipidi di uovo 1.2%. EDTA 0.005% o metabisolfito di Na 0.025%; pH = 4.5-7	1.5-2.5	1.1	4-8	1.8	30	98
Etomidato	2 mg/ml in propilenglicole 35%; pH = 6.9	0.2-0.4	0.3	4-8	2.9	17.9	76
Ketamina	10, 50 o 100 mg/ml in soluzione acquosa; pH = 3.5-5.5	0.5-1.5	1	10-15	3	19.1	27

Redistribution of thiopental from the encephalon to muscle and fat tissue



Other uses of general anesthetic Drugs intravenously (Cerebral ischemia)

Thiopental (+ on respiration inhibition)

Propofol (++ on respiration inhibition)

Etomidate (+ on respiration inhibition)

reduce **oxygen consumption**, blood flow, cerebral intracranial pressure

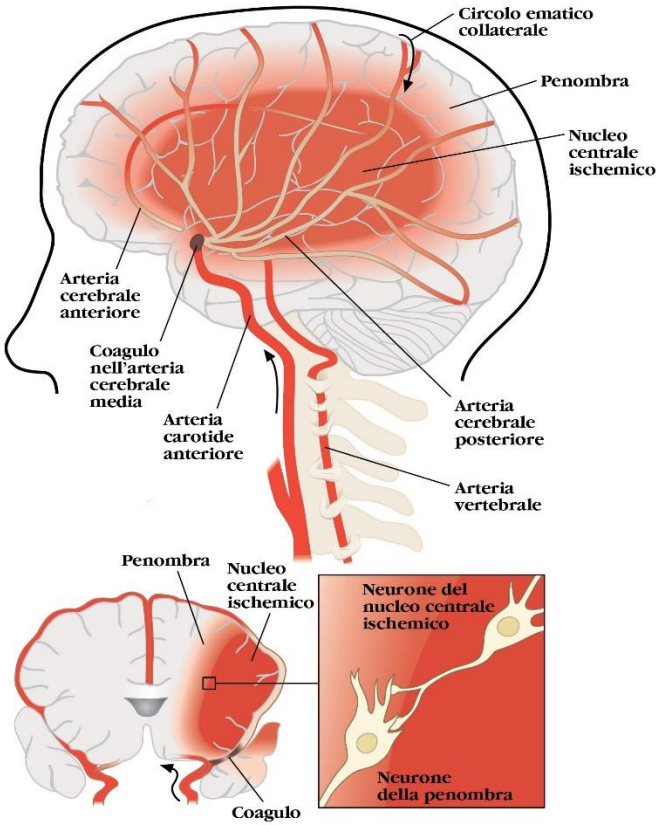
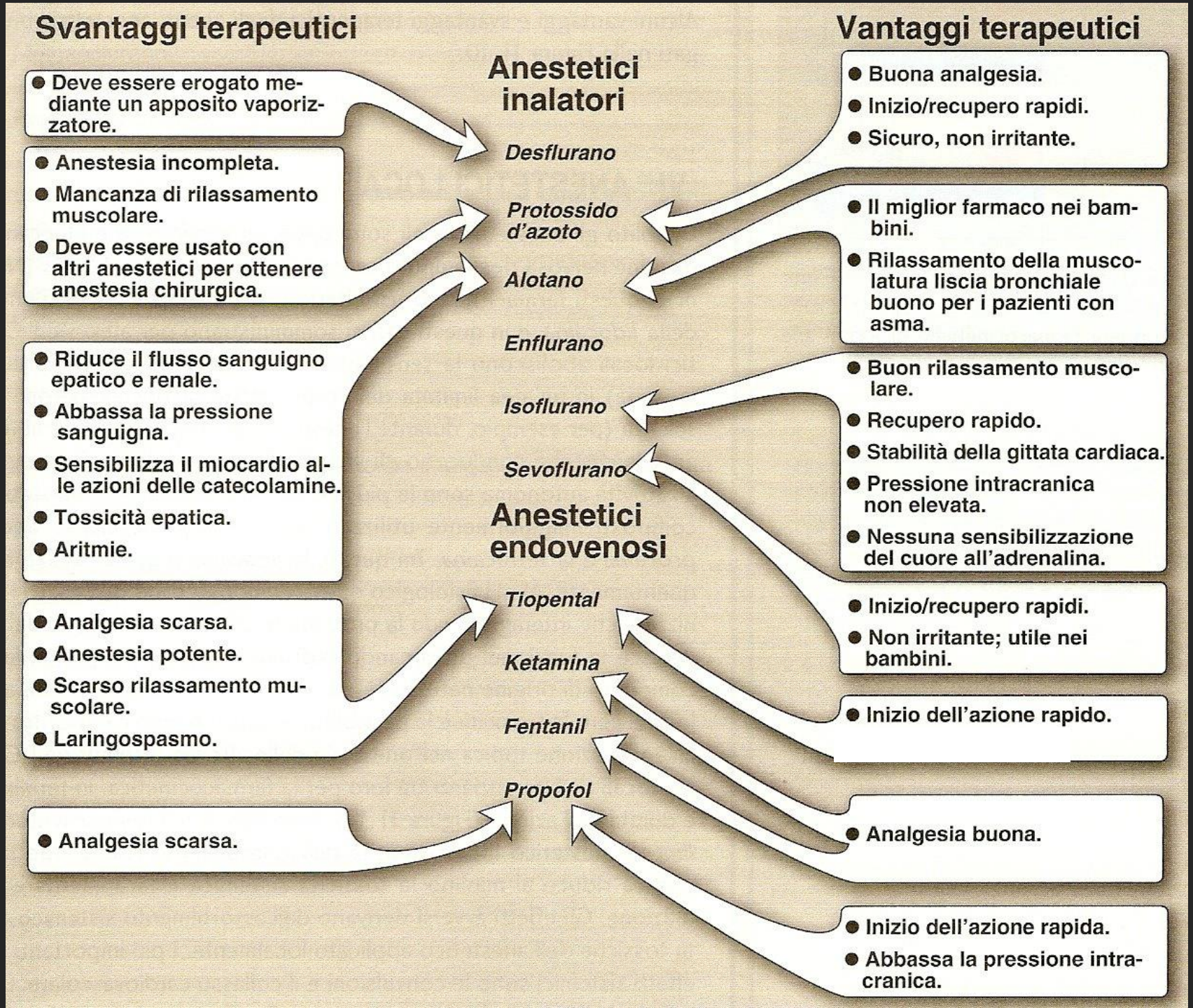
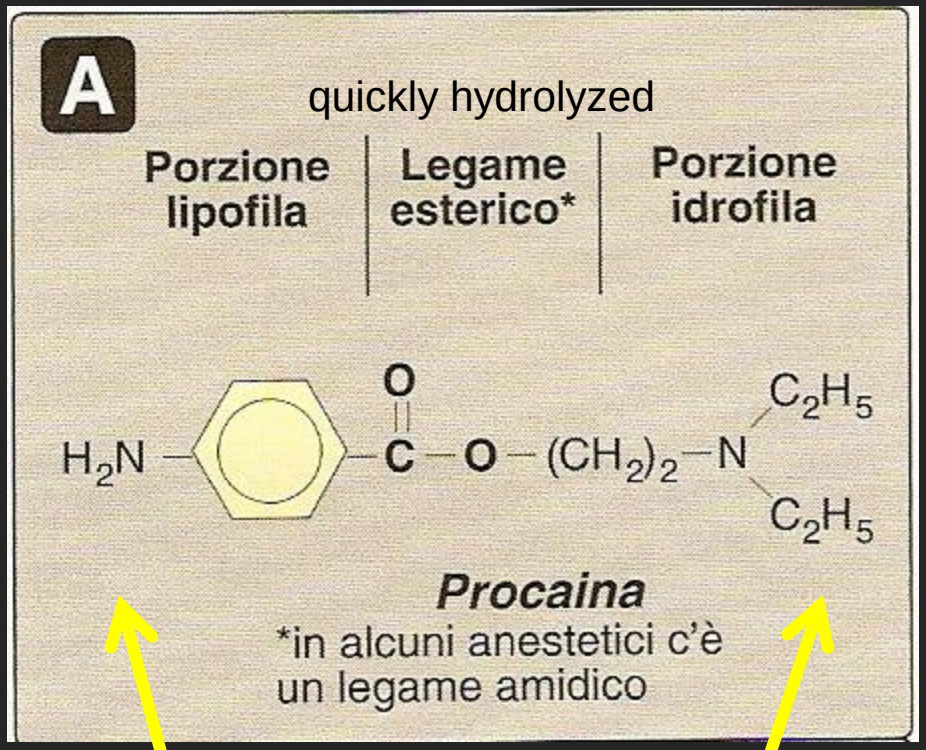


Figura 29.1. Un comune esempio di ictus ischemico. Nella sezione sagittale è presente un coagulo che occl l'arteria cerebrale media e causa una zona di necrosi (core ischemico) ed una zona di sofferenza (area pen bra). Sia la "penombra" che il "core" sono visibili anche nella sezione coronale.

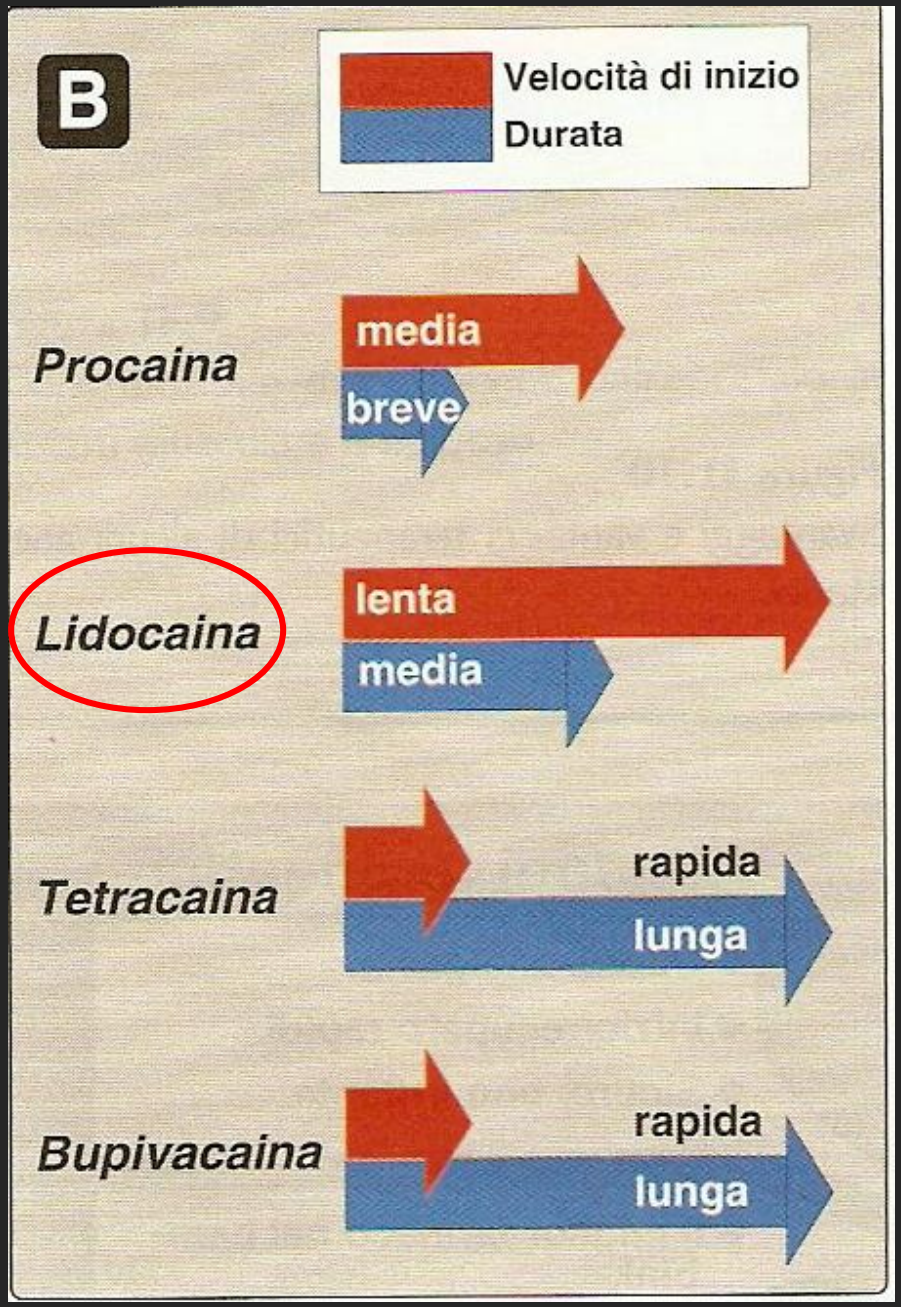

Svantaggi terapeutici
Vantaggi terapeutici
Anestetici inalatori
Deve essere erogato mediante un apposito vaporizzatore.
Anestesia incompleta.
Mancanza di rilassamento muscolare.
Deve essere usato con altri anestetici per ottenere anestesia chirurgica.
Riduce il flusso sanguigno epatico e renale.
Abbassa la pressione sanguigna.
Sensibilizza il miocardio alle azioni delle catecolamine.
Tossicità epatica.
Aritmie.
Desflurano
Protossido d'azoto
Alotano
Enflurano
Isoflurano
Sevoflurano
Buona analgesia.
Inizio/recupero rapidi.
Sicuro, non irritante.
Il miglior farmaco nei bambini.
Rilassamento della muscolatura liscia bronchiale buono per i pazienti con asma.
Buon rilassamento muscolare.
Recupero rapido.
Stabilità della gittata cardiaca.
Pressione intracranica non elevata.
Nessuna sensibilizzazione del cuore all'adrenalina.
Anestetici endovenosi
Analgesia scarsa.
Anestesia potente.
Scarso rilassamento muscolare.
Laringospasmo.
Analgesia scarsa.
Tiopental
Ketamina
Fentanil
Propofol
Inizio/recupero rapidi.
Non irritante; utile nei bambini.
Inizio dell'azione rapido.
Analgesia buona.
Inizio dell'azione rapida.
Abbassa la pressione intracranica.

Local Anesthetics



aromatic

amino-basic



Unwanted effects and pharmacokinetics of local anaesthetics (LAs)

- LAs are either esters or amides. Esters are rapidly hydrolysed by plasma cholinesterase, and amides are metabolised in the liver. Plasma half-lives are generally short, about 1–2 hours.
- Unwanted effects result mainly from escape of LAs into systemic circulation.
- Main unwanted effects are:
  - —CNS effects, agitation, confusion, tremors progressing to convulsions and respiratory depression
  - —cardiovascular effects, namely myocardial depression and vasodilatation, leading to fall in blood pressure
  - —occasional hypersensitivity reactions.
- LAs vary in the rapidity with which they penetrate tissues, and in their duration of action. Lidocaine penetrates tissues readily and is suitable for surface application; bupivacaine has a particularly long duration of action.

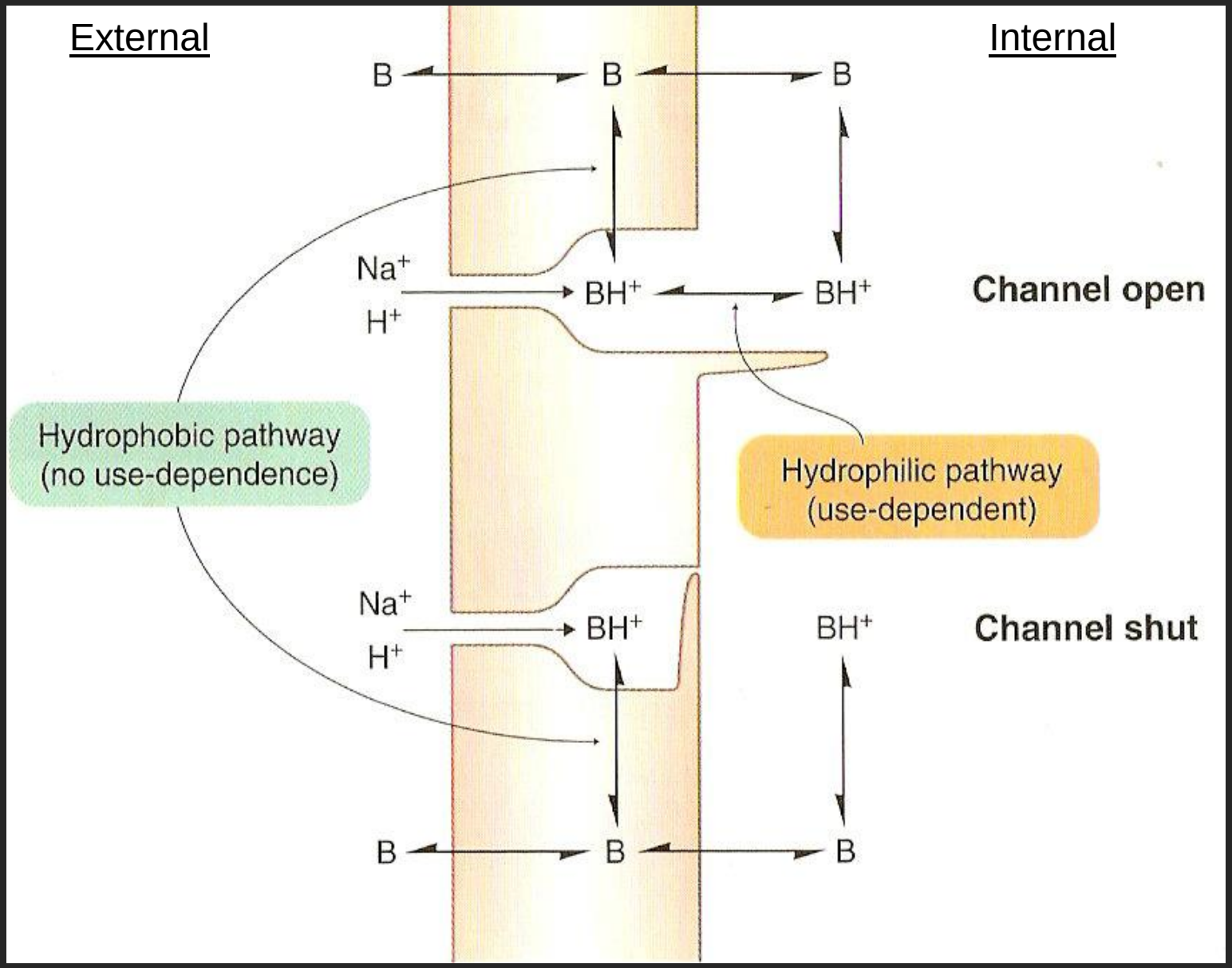
Adrenaline (vasoconstrictor)

Procaine

Bupivacaine (cardiotoxic)

Procaine

Interaction of local anesthetics with sodium channels



Method	Uses	Drugs	Notes and adverse effects
Surface anaesthesia	Nose, mouth, bronchial tree (usually in spray form), cornea, urinary tract Not effective for skin[a]	Lidocaine, tetracaine, (amethocaine) dibucaine, benzocaine	Risk of systemic toxicity when high concentrations and large areas are involved
Infiltration anaesthesia	Direct injection into tissues to reach nerve branches and terminals Used in minor surgery	Most	**Epinephrine (adrenaline)** or **felypressin** often added as vasoconstrictors (not with fingers or toes, for fear of causing ischaemic tissue damage) Only suitable for small areas; otherwise, serious risk of systemic toxicity
Intravenous regional anaesthesia	LA injected intravenously distal to a pressure cuff to arrest blood flow; remains effective until the circulation is restored Used for limb surgery	Mainly lidocaine, prilocaine	Risk of systemic toxicity when cuff is released prematurely; risk is small if cuff remains inflated for at least 20 minutes
Nerve-block anaesthesia	LA is injected close to nerve trunks (e.g. brachial plexus, intercostal or dental nerves) to produce a loss of sensation peripherally Used for surgery, dentistry, analgesia	Most	Less LA needed than for infiltration anaesthesia Accurate placement of the needle is important Onset of anaesthesia may be slow Duration of anaesthesia may be increased by addition of vasoconstrictor
Spinal anaesthesia	LA injected into the subarachnoid space (containing CSF) to act on spinal roots and spinal cord Glucose sometimes added so that spread of LA can be limited by tilting patient Used for surgery to abdomen, pelvis or leg, mainly when general anesthesia cannot be used	Mainly lidocaine	Main risks are bradycardia and hypotension (owing to sympathetic block), respiratory depression (owing to effects on phrenic nerve or respiratory center); avoided by minimising cranial spread Postoperative urinary retention (block of pelvic autonomic outflow) is common
Epidural anaesthesia[b]	LA injected into epidural space, blocking spinal roots Uses as for spinal anesthesia; also for painless childbirth	Mainly lidocaine, bupivacaine	Unwanted effects similar to those of spinal anaesthesia but less probable, because longitudinal spread of LA is reduced Postoperative urinary retention common

Infusion sites of anesthetics