General Anaesthetics

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Surgery in 18th century


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Demonstration of ether

General Anaesthetics

Definition:-

GA are the agents which are used to produce loss of all modalities of sensation specially pain, alongwith controlled reversible loss of consciousness, adequate muscular relaxation & loss of reflex activity to carry out operative procedures safely in a patient.

GENERAL ANESTHSIA

- It is a global but ***reversible state of depression of CNS function*** resulting in the loss of perception of response to all external stimuli along with amnesia

- anesthetic state a collection of "component" changes in behavior or perception

COMPONENTS OF ANESTHETIC STATE

a) Amnesia (for the procedure)
b) Immobility in response to noxious stimuli
c) Attenuation of autonomic responses to noxious stimuli(e.g heart rate ,blood pressure)
d) Analgesia
e) unconscious

Balanced Anaesthesia:

- Preanaesthetic Medication
- Use of both I/V GA (for Induction) and Inhalational GA
- Use of NM Blockers intraoperatively

PROPERTIES OF IDEAL General Anesthetic

- Rapid & smooth induction
- Rapid recovery
- Amnesia, analgesia ,
- Adequate skeletal muscle relaxation
- No postoperative complications

MECHANISM OF GA

- ANATOMIC SITES OF ANESTHETIC ACTION

a)immobilization to surgical incision-----spinal cord

b) sedation------ tuberomamillary nuleus(GABAergic anth)
lous ceruleus (alpha 2 agonist)

c) unconsciousness--------thalamus

d) amnesia--------- hippocampus

MOLECULAR ACTIONS OF GA

a)GABAergic

b) Glycine actions

c)Inhibition of nicotinic cholinergic recep

d) Inhibition of NMDA recep

e) Activation of 2 pore K+ channels

STAGES OF GA

- STAGE 1(stage of analgesia)

Loss of pain without amnesia,at the end of this stage there is amnesia

STAGE 2 (stage of excitement)

delirium, patient may be vocal but amnesia

respiration irregular in rate &volume

retching and vomiting

at the end of this stage resp becomes regular

- STAGE 111(stage of surgical anesthesia)

Starts with recurrence of regular resp & extends to apnea

Loss of purposeful motor &ANS response to noxious stimuli(trapezius muscle squeez ,eye lash reflex)

STAGE1V(stage of medullary depression)

- **resp & vasomotor center depression if not supported** ***death may ensue***

SYSTEMIC EFFECTS OF GA

- HEMODYNAMIC EFFECTS

hypotension due to

direct vasodilation

myocardial depression

blunting of barorecptor tone

generalized dec in sympth tone

hypotensive eff is enhanced if preexisting vol depletion(compensatory sympth discharge is blocked)

- **RESPIRATORY SYSTEM**

a)decrease or eliminate resp drive

b) decrease reflexes to maintain airway patency (loss of gag reflex &cough reflex is blunted)

endotracheal intubation reduces chances of aspiration

NAUSEA & VOMITING

Caused by action of GA on CTZ& vomiting centre due to stimulation of 5-HT, histamine ,Ach & dopamine

may be **prevented/treated**

i)by giving metoclopramide,ondansetron,dexamethasone

ii)using ketorolac for analgesia &propofol for induction in place of opioids

iii)Avoiding NO2

- **HYPOTHERMIA**

  temperature below 36% due to

  a) exposure of body cavities

  b)lower the core temp set point

  c) decreased body metabolism& O2 consumption so reduced body temp

  d) infusion of cool I/V fluids

  RISK

INHALED GA

A)NITROUS OXIDE

B)VOLATILE LIQUIDS(halogenated)

Halothane

Enflurane

Isoflurane

Desflurane,

sevoflurane

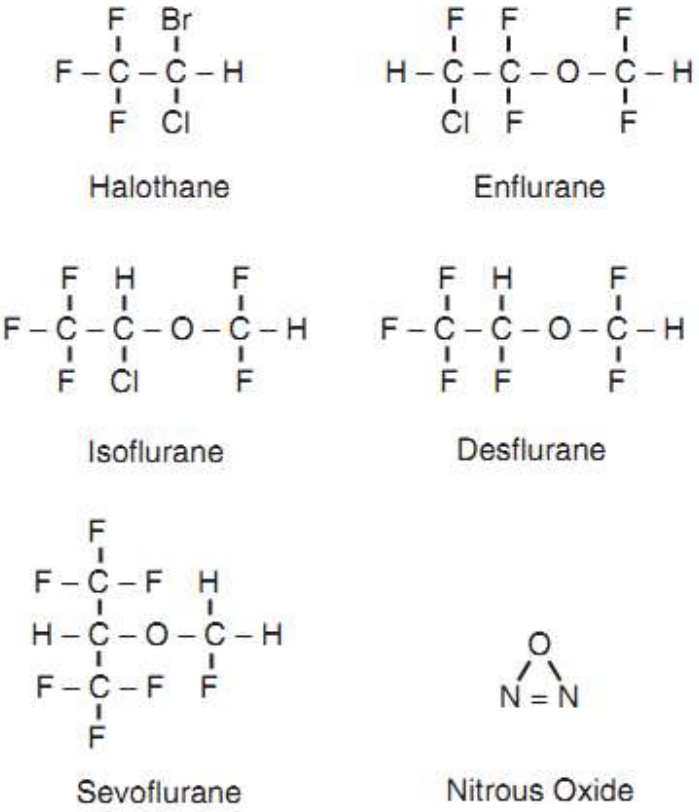


FIGURE 13–3 ***Structures of inhaled general anesthetics.*** Note that all *inhaled* general anesthetic agents except nitrous oxide and halothane are ethers and that fluorine progressively replaces other halogens in the development of the halogenated agents. All structural differences are associated with important differences in pharmacological properties.

Pharmacokinetics of inhaled GA

UPTAKE&DISTRIBUTION

:Solubility (Blood: Gas Partition coefficient)

GA Concentration in the inspired air.

Pulmonary ventilation.

Pulmonary blood flow

Arteriovenous concentration gradient

- **SOLUBILITY**

depends *on* ***blood:gas partition coefficient*** **i.e**

relative affinity of the inhaled anesthetic for the blood compared with that of air

inverse relation between blood solubility of an anesthetic& rate of rise of tension in arterial blood

- ANESTHETIC CONC IN INSPIRED AIR

Higher the conc in inspired air,-----

more will be the max tension of the drug in alveoli ,

rapid will be the rate of rise of the anestheic tension in the blood,

Rapid will be the rate of induction

- PULMONARY BLOOD FLOW

inverse relation between pulmonary blood flow &rate of induction of anesthesia (only for more soluble anesthetics)

Contd

ARTERIOVENOUS CONC GRADIENT

Anesthetic entry in the tissues depends on

a) tissue :blood partition coefficient(relative solubility in blood & tissues)

b)perfusion of the tissue(rate of blood flow)

c)anesth gas tension/conc diff between art & venous blood(greater the diff more time it will take to reach eq with brain tissue)

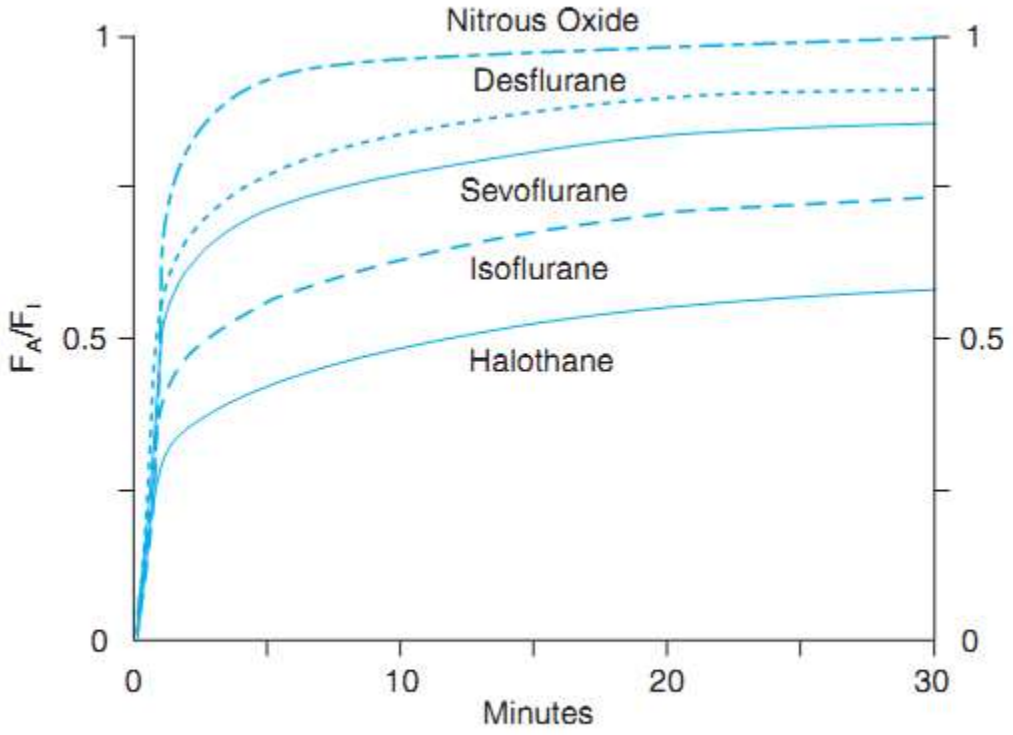


FIGURE 13–4 ***Uptake of inhalational general anesthetics.*** The rise in end-tidal alveolar (F_A) anesthetic concentration toward the inspired (F_I) concentration is most rapid with the least soluble anesthetics, nitrous oxide and desflurane, and slowest with the most soluble anesthetic, halothane.

ELIMINATION OF HALOGENATED GA

Mainly through lungs,less solublity----rap exhalation

- Some metab in liver

i)**halothane** ---- 40% oxidative metabreleasing Br& Cl ions ,& forming TFAA, in low O2 tension converted to ***chlorotrifluoroethyl*** free radical

ii) **methoxyflurane**-*---70%,renotoxic levels of*

iii) ***enflurane***---10% (also metab by betalyase in kidney)

iv) **isoflurane ,desflurane**-----least metab

v) **sevoflurane**------degraded by contact with CO2 absor in anesthesia machine ,forming "comp A" , in large amounts may be nephrotoxic

Recovery depends on

- Mirror image of induction, depends upon
- Blood: Gas partition cofficient
- Pulmonary Blood Flow
- Pulmonary Ventilation
- Tissue solubility of anesthetic

  Duration of exposure to G.A(more imp for more soluble agents).

Minimum Alveolar concentration (MAC)

The potency of an inhaled G.A is defined quantitatively as the MAC.

One MAC is the concentration which will prevent movement in response to surgical incision in 50% of patients.

MAC is expressed as percentage of Alveolar gas mixture/ partial pressure of G.A as % of 760 mm of Hg.

MAC is small for more potent G.A.

MAC is large for less potent G.A.

Ether

- The oldest G.A obsolete except where modern facilities are not available
- Highly inflammable, explosive
- Irritant to respiratory tract
- Long and hazardous stage II if used on its own.

- Easy to administer and control
- Slow onset and recovery, with postoperative nausea and vomiting
- Analgesic and muscle relaxant properties

Chloroform

Not used because of

- Hepatotoxicity
- Cardiotoxicity

Cyclopropane

- Not used because it is explosive
- Cardiotoxic

ORGAN SYSTEM EFFECTS OF HALOGENATED GA

- **CVS**

Hypotension directly proportional to alveolar conc due to

a) **myocardial depression,decreased** CO-----halothane, enflurane

b)decreased TPR, ----isoflurane,desflurane, sevoflurane

Heart rate due to direct effect on SA node or indirectly by action on ANS

bradycardia-----halothane ,due to excessive vagal stim

tachycardia-----isoflurane,esp desflurane due to direct symp stimulation

Ventricular arrythmia -----halothane, to lesser extent iso flurane senstise myocardium to circulating catecholamines, so arrythmias in cardiac disease

- **Respiratoy system**

CENTRAL EFFECTSdose dependent decrease in tidal vol

decrease minute ventilation

increased heart rate

resp depression &lack of CO_2 driven resp (counteracted by surgical stimulation)

increase resting P_{aCO_2}

prevented by----mechanical ventilation

EFFECT ON LUNGS

a)depress mucociliary function,pooling of mucus, atelectasis,post opereative resp infction

b)bronchodilation ,airway irritation esp halothane& sevoflurane

c)pungent smell ---desflurane

- **CENTRAL NERVOUS SYSTEM**

a)They decrease cerebral metbolic rate

b)Increase cerebral blood flow especially more soluble bcoz they decrease cerebral vascular resistance so increased cerebral volume, increase intracranial pressure, can be minimized by hyperventilation before giving the drug

c)depressent effect on EEG ---halothane, isoflurane, enflurane

d) at large doses stimulant eff like myoclonic activity ---- enflurane ,sevoflurane

KIDNEY

Decrease GFR & renal blood flow

Increase filtration fraction

Impair renal vascular auto regulation

- **EFFECT ON LIVER**
- 15 -45% decrease in base line hepatic blood flow

- **EFFECT ON UTERINE SMOOTH MUSCLE**

dose dependent relaxation of uterine muscles

CLINICAL USES OF HALOGENATED GA

- 1- Used as a part of balanced anesthesia combined with I/V GA
- 2-rarely used as sole anesthetic for induction & maintenance in children
- 3- ind agents in asthmatics or air way dis— halothane,sevoflurane

- 4-”short stay”basis anesthetic----- desflurane& sevoflurane

  5-intrauterine fetal manipulation& manual extraction of retained placenta

  6-status asthmaticus(as last resort)----- halothane with ventilatory support

ADVERSE EFFECTS OF HALOGENATED GA

- **HEPATOTOXICITY**

HALOTHANE HEPATITIS repeated exposure

life threatening hepatitis (1in 20to35 thousand) may be

i)immune mediated ***TFA protiens*** formed in hepatocyte during biotransformation

ii) Direct hepatocellular damage due to ***free radicals***

NEPHROTOXICITY

i) F ion released from metabolism of methoxyflurane ,enflurane,

by beta-lyase in kidneys ***decrease renal conc ability***

ii) sevoflurane to compound A, which is converted to thioacylhalide in kid may ***cause renal tubular necrosis***

- **MALIGNANT HYPERTHERMIA**

  genetically predisposed individual when volatile agents are given with succinylcholine
- More common with halothane
- **RESP SYS**
- Pooling of secretions & atelectasis if proper suction is not done

INCREASED POSTPARTUM UTERINE BLEEDING

if used for intrauterine manipulation of fetus or manual delivery of placenta

- **CHRONIC TOXICITY**
- **Mutagenicity**

- **Carcinogenicity**

- **Effect on reproductive organs**

CONTRAINDICATIONS

- Increased intracranial press
  - head injury
  - tumor of brain
- Preexisting renal dysfunction

- Patient or relatives have h/o malignant hyperthermia

- DRUG INTERACTIONS/PRECAUTIONS

  Decreased dose req/rapid onset in circulatory shock due to decreased pulmonary flow

  increased ventilation

  Additive with other GA

  Second gas effect

  Dilutional hypoxia

B) Overview of VOLATILE LIQUIDS(halogenated)

Halothane(light sensitive,potent,lipid soluble,hepatotoxic,direct depression of SA node,sensitize myocardium to adrenaline,inhibits hypoxic pulmonary vasoconst ,cerebral vasodil)

Enflurane(lipid sol,min effect on heart,seizure,M relax,F nephrotox

Isoflurane(mod lipid sol,pungent,airwairrit,,lesscerebvasod,potent coronary vasodil,dec myocardial O2 consump,tachyc,may sensitize myoc)

Desflurane(insoluble,high volatility, needs heated vap, pungent,airway irrit, cough,response to hypocapnia maintained,sympathetic sti ,tachy,)

sevoflurane(unstable,least soluble,non irrit,most effec broncchodila release F,no tachycardia,response to hypocapnia retained ,adm with fresh gas flow of 2L/min to dec accumulation of comp A)

NITROUS OXIDE(NO2)

- Gas at room temp, colorless,odorless,stored in steel cylinders
- **PHARMACOKINETICS**

Least solubility

Lowest blood :gas partition coefficient o.47

&brain:blood partition coefficient 1.1

Most rapid induction

Most rapid rate of recovery

least potent,highest MAC value---- 105%

Not metabolized, totally eliminated by lungs,0.1% is degraded by interaction with vit B12 in intestinal bacteria.This may result in inactivation of methionine synthesis

- SECOND GAS EFFECTOM ALVEOLAR GAS
- Rapid uptake ofN2O from alveolar gas concentrates coadministered halogenated anesthetics so it is also absorbed rapidly
- Rapid rate of abs of halogenated anesthetic along with N2O is called second gas effect
- DFFUSIONAL HYPOXIA

  when N2O administration is discontinued it rapidly diffuses back from blood to alveoli diluting O2 in lungs. This phenomenon is called diffusional hypoxia.

  This can be prevented by giving pureO2 instead of air after discontinuation of N2O

- CLINICAL USES
- Analgesia at 20 ---50% conc
- Sedation at 30---80% conc
- As GA very low potency ,cannot be used above 80% conc ,so mainly used as an adjunct to other GA

- **ADVERSE EFFECTS**
- hepatotoxicty ,no nephrotoxicity ,muscles not relaxed no malignant hypertherthermia
- **CVS**

Increases venous tone,should be avoided in pulmonary hypertension

Effects on heart rate &BP depends on coadministered GA

RESP SYS

- Depresses ventilatory response to hypoxia so arterial O2 saturation should be measured directly
- **CNS** increases cerebral blood flow(less as compared to other

- v**EXPANSION OF AIR CONTAINING BODY CAVITIES**
- Exchanges with N2 inbody cavities ,& bcoz of differential blood:gas partition coefficient enters the cavities faster than N2 escapes ,increasing the vol/press.e.g obs middle ear ,pneumothorax,intracranial air

INTRAVENOUS GA

PHARMACOKINETIC PRINCIPLE

a)small **hydrophobic** compounds

b) preferentially partition into CNS in **single circulation time**

c) rapid redistribution out of CNS **terminating anesthesia**

d) diffuses into less perfused tissues (muscles and visceras)

e) at still slower rate to adipose tissue

- ***f)terminal/beta t1/2***

(depends upon metabolic rate & lipophilicity of drug stored in peripheral compartments

g)Less dose req –

dec cardiac output ,

septic shock

cardiomyopathy in elderly

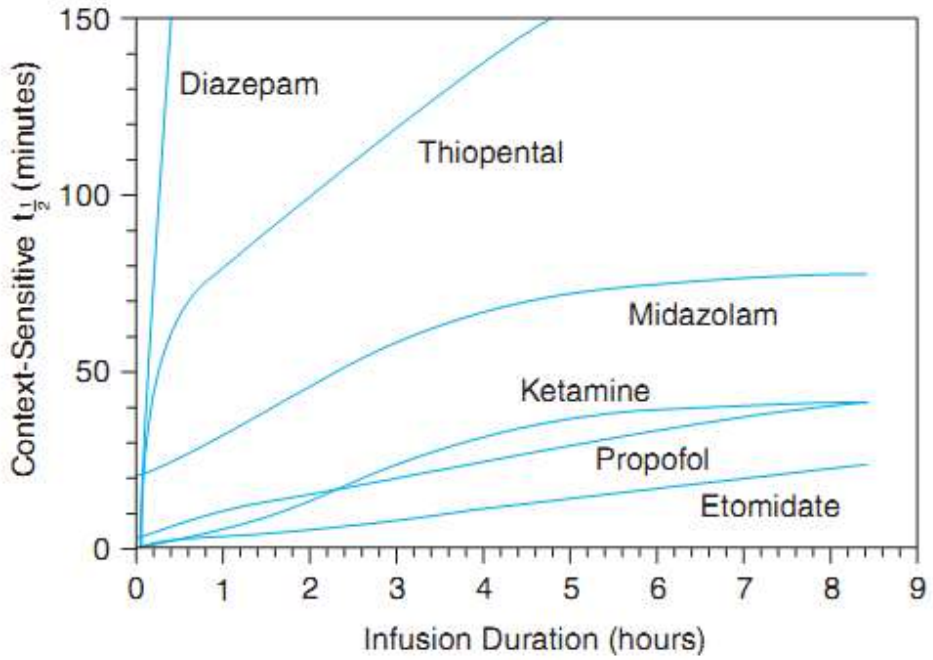


FIGURE 13–2 ***Context-sensitive half-time of general anesthetics.*** The duration of action of single intravenous doses of anesthetic/hypnotic drugs is similarly short for all and is determined by redistribution of the drugs away from their active sites. However, after prolonged infusions, drug half-lives and durations of action are dependent on a complex interaction between the rate of redistribution of the drug, the amount of drug accumulated in fat, and the drug's metabolic rate. This phenomenon has been termed the *context-sensitive half-time*; that is, the half-time of a drug can be estimated only if one knows the context—the total dose and over what time period it has been given. Note that the half-times of some drugs such as etomidate, propofol, and ketamine increase only modestly with prolonged infusions; others (*e.g.*, diazepam and thiopental) increase dramatically.

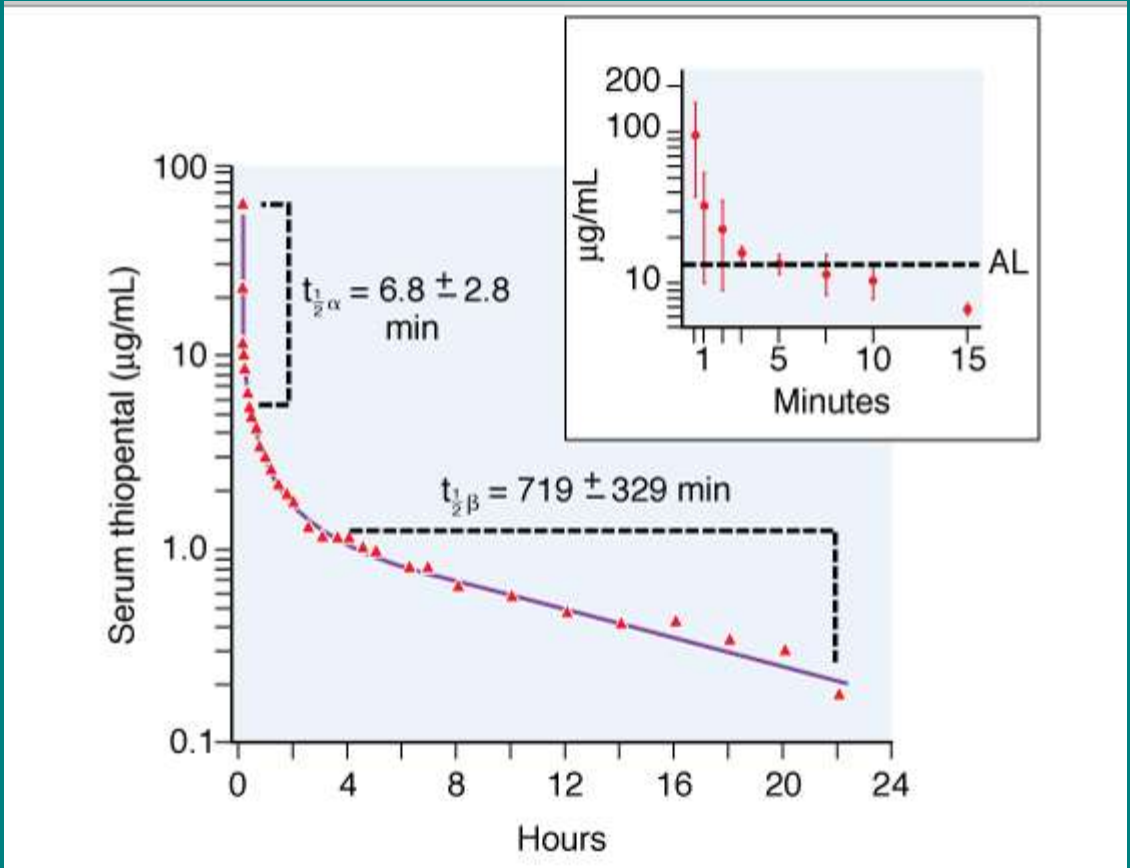
THIOBARBITURATES

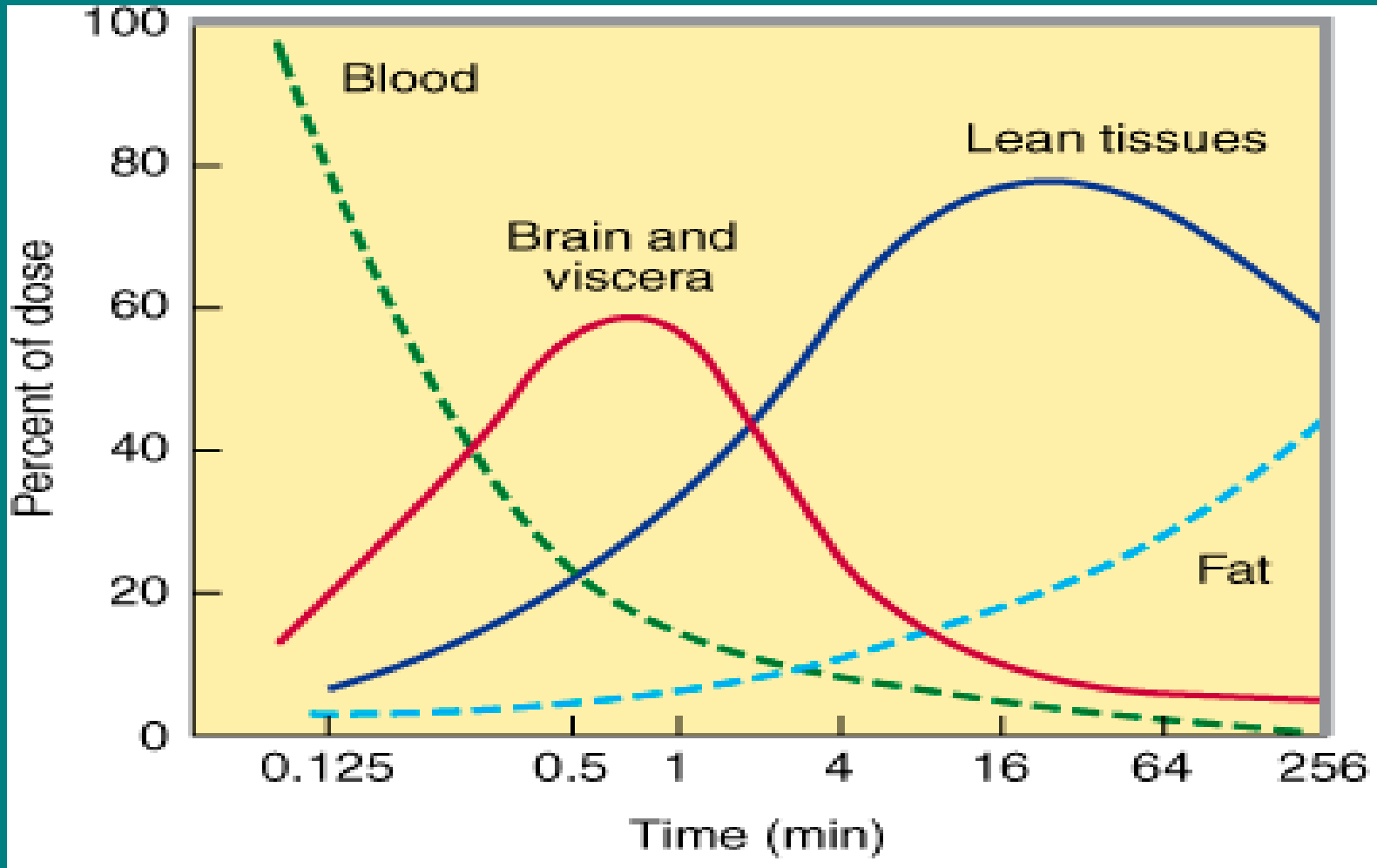
- Ultra short acting bariturates are used as I/V GA
- Thiopental sodium
- Methohexital.
- Thiamylal

THIOPENTAL SODIUM

- Stable racemic mix ,in alkaline solu
- pptates if mixed with acidic drugs
-

- **PHARMACOKINETICS**
- Induction dose-----3to5mg/kg,I/V
- Children ---higher dose ,can be given P/R(10 times the I/Vdose)
- Elderly& expectant mothers--- smaller dose
- Onset of action(unconsciousness)10----30sec
- DOA------5 to 8min
- Terminal t1/2---12 hrs(context dependent)
- High PPB
- Metab & inactivated in liver, small amount desulfurated to active pentobarbitone


100
10
1.0
0.1
Serum thiopental (µg/mL)
$t_{\frac{1}{2}\alpha}$ = 6.8 ± 2.8 min
$t_{\frac{1}{2}\beta}$ = 719 ± 329 min
0
4
8
12
16
20
24
Hours
200
100
10
µg/mL
AL
1
5
10
15
Minutes



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

PHARMACOLOGICAL ACTIONS

- **CNS**---dec $CMRO_2$,cerebral blood flow,&intracranial press
- **RESP SYS-**----potent resp depressent,dec min ventilation ,resp rate ,reflex responses to hypoxia &hypercarbia
- **CVS**----hypotension due to venodilation,
- myocardial depression,
- reflex tachycardia

CLINICAL USES

- **1-Inducing agent**,
- safe if intracranial pressure or intraocular pressure
- **2-status epilepticus**
- **3-ameliorates ischemic damage in perioperative setting**

- **ADVERSE EFFECTS**
- I)**Intraarterial** inj inflammatory & potentially necrotic reaction
- **CNS** Excitement,muscle tremor,hypertonus ,hiccups
- **CVS-**----severe hypotension in patients with hypovolemia ,valvular or coronary heart dis,or beta adrenergic blockade
- Rarely direct ***histamine release*** **allergic/anaphylactic reaction**
- porphyria in susceptable ind

METHOHEXITAL

- Rapid clearance,beta t1/2 5-8 hrs
- Short t1/2 ----may be used for short procedure
- may cause central excitatory activity

(myoclonus), used for ablation of seizure foci

Drug of choice for ECT

MILD PAIN &venoirritation at site of inj

BENZODIAZEPINES

Diazepam, midazolam, lorazepam

- Not complete GA,

-produces amnesia , muscle relaxation

no analgesia **,**

Used for:

1.Premedication– To relieve anxiety & prevent sympathetic activity.

2. Conscious sedation along with Opioids for short surgical & diagnostic procedures e.g

. Bronchoscopy . Angiography

. Gastroscopy . Cardiac catheterisation

. Cystoscopy

3. Intra operative sedation
4. Sedation of patients in ICU specially those on assisted ventilation

Disadvantages:

1- used as sole agent, Slow the recovery

- Greater incidence of anterograde amnesia

2-Diazepam , lorazepam ----- water insoluble , non – aqueos vehicles (lipid soluble at phys pH),

- pain during I/V inj ,
- Rapid inj may cause sudden resp arrest

Recovery can be accelerated by FLUMAZENIL– BDZ Antagonist

Opioid analgesics & Neurolept Analgesia

- **Morphine, Fentanyl ,Sufentanil,**

Alfentanil, Remifentanil

Uses:

- **For pre anaesthetic medication**
- **For induction of anaesthesia**
- **For Neurolept analgesia & Neurolept anaesthesia**
- **As GA in high doses--- In cardiac surgery & Low circulatory reserve**
- **For conscious sedation with BDZ**

Neurolept Analgesia/ Neurolept Anaesthesia

Neurolept Analgesia:

Definition:

Fentanyl----0.5-1 mg & Droperidol 2.5----5mg/ml

Droperidol:(Neuroleptic)

It has following properties

- Antiematic
- DISADVANTAGES OF NEUROLEPT ANALGESIA

1- Alpha adrenergic blocking activity, severe hypotension

2- Extrapyramidal symptoms

- 3-resp depression
- 4-Torsade's depontis

Fentanyl:

_IV ,supplement dose every 30 min

- **Narcotic analgesic**
- **100 times more potent than Morphine**
- **Shorter DOA**
- **Parasympathomimetic effects**

Advantages:

1. Patient is drowsy but conscious & able to co- operate during the operative procedure.

2. Much less danger of hypotension and other circulatory disturbances

3. Suppression of vomiting and coughing.

4. Continued analgesia in postoperative period.

5. Smooth onset and rapid post-operative recovery

Uses:

- Procedures on Eye
- Oral and orthopaedic surgery
- Angiocardiography
- Myelography
- Bronchoscopy
- Reduction of fractures
- As an adjunct to spinal and nerve block anesthesia
- Transdermal patches & patient controlled analgesia

- **DISADVANTAGES**

  Markes but predictable resp dep

  chest muscle tone inc if rapid I/V inj

  nausea vomiting itching

Propofol

Chemistry: 2,6 Diisopropylphenol.

insoluble in water,

I/V as 1% emulsion in

10% soyabeanoil+2.25%glycerol +1.2%purified egg phosphatide,

(disodiumEDETA/sodium metabisulphite as preservative)

KINETICS

Initial t1/2 2-8 min,Terminal T1/2 30-60 min

OOA----1min

Hepatic & extrahepatic metaolism

FOSPROPOFOL---water soluble

PRECAUTION

immediately given after removal from sterile packing

PHARMACOLOGICAL ACTION

CNS---same as barbiturates,but no anticonvulsant or cerebral protectant action

CVS---- hypotension more severe than thiopental

RESP SYSTEM-----depression of resp

GIT-----significant antiemetic activity

Advantages

1-Rapid Induction,very ***rapid recovery*** ,no hangover , no cumulative effect

2-Sig **antiemetic**

3-No bronchoconstriction

4-Safe in preg ,crosses placcental barrier,but transient depression of activity in new born infant

5-No sig.effect on renal hepatic or endocrine function

Disadvantages/adverse effects

1-Very expensive

2-Apnoea can occur

3-CVS depression, hypotension

4-Pain at site of injection

5-Clinical infections

6-muscle movements ,hypotonus,rarely tremors

Cumulative toxicity

acidosis

resp infection,neurological effects

Uses:most commonly used GA for out patient surgery

- For rapid induction
- For maintenance of G.A in day surgery
- For short operations
- For prolonged sedation in ICU

KETAMINE

- A congener of phencyclidine
- Given i/v no pain at inj site,may be given I/M,P/R& even orally

Onset of action

DOA----10 to 15 min(longest)

Hepatically metabolized to nor ketamine having reduced CNS activity

Rapid clearance,infusion doesn't lengthen DOA

Minimal PPB

MOA – blockade of NMDA receptor

Pharmacological effects

- **CNS**

Dissociative anesthesia(*seems to be awake but completely dissociated from the enviornment)*

- Amnesia ,
- profound analgesia
- unresponsive to painful stimuli
- With or without loss of consciousness

cataleptic state,increased muscle tone ,eyes open ,spontaneous movements of limbs ,

- nystagmus with pupillary dilation ,
- salivation , lacrimation,
- Inc cerebral blood flow&ICP,
- min change in CMRo2,increased intracranial press

- Emergence phenomenn

  Postoperative disorientation, sensory and perceptual illusion
- vivid dreams
- RESPIRATORY SYS

  dec resp rate

  upper airway muscle tone maintained

  reflexes intact

CNS

Inc cerebral metabolic rate ,& intracranial pressure , emergence delirium,

ANS

Dose related central stimulation of symp,

Reduce uptake of NE

- **CVS**
- ,inc heart rate rate,
- Inc CO,
- inc BP

MERITS

1-Only i/v agent having analgesic&anesthetic action

2-safe in asthmatics,dilates bronchi

no risk of RESP depression

no hypotension, d/t sympathetic stimulation

adverse effects

1- incCMRo2

2-emergence delirium

3- not given to pts of angina

uses

- 1-asthmatics
- 2-hypotensive
- 3-short procedures in children
- 4-part of monitered anesthesia
- 5-topically for arthritis

Etomidate

- Chemistry: Carboxyimidazole.
- Pharmacokinetics:

Advantages

- Minimum CVS Depression
- Minimum Respiratory Depression
- Very rapid induction within seconds
- Rapid recovery within 3-5 minutes

Disadvantages

- No analgesic effect
- Nausea & vomiting post operatively
- Pain during injection
- Myoclonus
- Adrenocortical Suppression