Inhaled and intravenous general anesthesia

Prof. Tassonyi Edömér
Content of the lecture

- Short history
- Concept and clinical importance of GA
- Pharmacodynamics and mechanism of action of anesthetics
- Pharmacokinetics of anesthetics
- Clinical application, advantages, disadvantages
- Side effects, metabolism and toxicity
- Conclusions
The first public demonstration of ether anesthesia at MGH on October 16, 1846
Ether anesthesiasia in Hungary

- In February 1847, Balassa first used ether in volunteers
- Surgical anesthesia was carried out soon after
- The first Hungarian monograph of anesthesia was written by Joseph Rosenfeld in 1847
A
KÉNÉGÉNYGŐZ
HATÁSA,
KÜLÖNÖSEN SEBORVOSI TEKINTETBŐL;
TAPA SZTALATI ADATOKRA ÉPÍTVE
S TUDOMÁNYOSAN FELVILÁGSÍTVA.

İRTA
ROSENFLD JÓZSEF, [Zövsoy]

ORVOSTUDOK, SZÜLÉSZ-MESTER, A' KIR. MAGYAR EGYETEMI ORVOSKIR,
A BUDAPESTI KIR. ORVOSEGYESÜLET, S A KIR. MAGYAR TERMÉSZETTUDOMAMNYI TÁRSULATI RENDES TAGA; A HÖN İZRAELİTAK KÖZÖTT MAGYAR
NYELVET TERJEDÉSÚ FEJLESZTŐ PESTI EGYSZÉTÉN K I. MASOD-ELSŐJE, GYAKORLÓ
ORVOS PESTEN.

EGY KÖRE METSZETT TÁBLÁVAL.

PEST.
HECKENAST GUSZTÁV TULAJDONA.

1847.
Inhaled anesthetics no more in clinical use

- Chloroform
- Cyclopropan
- Methoxyflurane
- Trichlorethylene
- Fluroxene
- Diethyl ether
- Divinil ether
Modern inhaled anesthetics

- **Halogenated**
  - Halothane
  - Enflurane
  - Isoflurane
  - Sevoflurane
  - Desflurane
- **Nonhalogenated**
  - Xenon
  - $\text{N}_2\text{O}$
Early development of intravenous anesthesia

- PC. Ore was the first to give an intravenous anesthesia to human with chloralhydrate, in 1827

- The morphine-scopolamine combination became popular during the First World War

- Fischer synthetised the first sedative barbiturate in 1930-ban
Further progress of intravenous anesthesia

- Bensodiazepines appeared during the ’60s and ’70’s: diazepam, midazolam
- NLA was developed and popular during the ’60s and ’70s (fentanyl-droperidol)
- Ketamine has been in clinical use since 1966
- Etomidate was introduced in 1973
- Propofol was first used in 1977
- TIVA and TCI were developed during the ’80s and ’90s
Phenylpiperidin opioids have key role in general anesthesia
Muscle relaxants

- **1942** *d-Tubocurarine*, Griffith & Jonson
- **Succinylcholine**, 1951 Bovet, Nobel price
- **Non-depolarising NMBAs:**
  - D-Tc
  - Metocurine
  - Pancuronium
  - Pipecuronium
  - Vecuronium
  - Atracurium
  - Cis-atracurium
  - Rocuronium
Main components of GA

- Hypnosis, Amnesia
- Analgesia
- Muscle relaxation
- Immobility
Main conditions of GA

- Pharmacological conditions
- Technical conditions
- Logistics
- Human factors
Importance and epidemiology of GA

- Anesthesia makes surgery possible
- Ensures the quality and security of intraoperative patient care. Low mortality (1:10 000-1:100 000)
- Protects patients against operative stress
- Ensures patients comfort
- About 10% of the population receive GA/year
Pharmacodynamics and mechanisms of action of anesthetics

- Relative potencies:
  - $\text{ED}_{50}$
  - Minimal alveolar concentration (MAC)
- The Meyer-Overton rule
- The membran lipoid theory
- Receptor proteins
The MAC is the alveolar anesthetic concentration in human that produces immobility in 50% of subjects exposed to a noxious stimulus (skin incision).
Meyer-Overton rule

The MAC is in close correlation with the oil/gas partition coefficient (O/G) of anesthetics; *more an anesthetic is lipid soluble more potent it is.* The possible target site for inhaled anesthetics would be the membran lipid bilyer

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<thead>
<tr>
<th></th>
<th>MAC</th>
<th>O/G</th>
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<tr>
<td>Halothane</td>
<td>0.8</td>
<td>224</td>
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<tr>
<td>Isoflurane</td>
<td>1.15</td>
<td>90</td>
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<tr>
<td>Sevoflorane</td>
<td>1.7</td>
<td>53</td>
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<tr>
<td>Desflurane</td>
<td>6.0</td>
<td>18</td>
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<tr>
<td>N₂O</td>
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<td>1.4</td>
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Possible target sites for inhaled anesthetics

Receptors involved in the action of anesthetics

**Inhibition**
GABA<sub>A</sub>

**Excitation**
NMDA

**Agonistes**: Inhaled agents, benzodiazepines, propofol, etomidate, barbiturates

**Antagonistes**: ketamine, xenon, N<sub>2</sub>O

Ca<sup>2+</sup>K<sup>+</sup>Na<sup>+</sup>
Anesthetics enhance inhibitory synaptic transmission
Mechanisms of loss of consciousnes

1. inhibition of glutamaterg transmission
2. facilitation of GABAerg transmission
Effect of propofol and sevoflurane on the cortical GABA receptors (C-flumazenil-PET)

Propofol 9.0±3.0 µg/ml  
BIS 28±8

Sevoflurane 2%  
BIS 35±6

Salmi L A&A 2004
Propofol and isoflurane reduce the metabolic and electric activities of the brain

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<th>PET</th>
<th>% BMR</th>
<th>BIS</th>
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_Alkire MT Anesthesiology 1998_
Pharmacokinetics of inhaled anesthetics

**Inspiratory concentration** \((F_i)\)
- Depends on:
  1. \((F_i)\)
  2. Alveolar ventilation
  3. Blood uptake \(= [(\lambda) \times (Q) \times (P_A - P_V)]\)

**Alveolar = arterial concentration** \((F_A = \text{End-tidal})\)
- Direct equilibration with CNS in a short time independently of uptake and distribution to other tissues

**CNS concentration**
- Blood supply
- Redistribution

**Tissue uptake** \((P_A - P_V)\)
- Metabolism
- Excretion
The rise in alveolar concentration toward inspired concentration is most rapid with the least soluble anesthetics.
Simulated time course of plasma levels of propofol after an induction dose of 2 mg/kg
Tissue distribution of thiopental after an iv. bolus dose
Context-sensitive-half times of iv anesthetics
Context sensitive half times of opiates

Clinical application

- Anesthesia with inhaled agents
- Anesthesia with ketamine
- Balanced anesthesia
- Total intravenous anesthesia (TIVA)
- Target controlled infusion (TCI)
Advantages and drawbacks of inhaled anesthetics

- « Easy » to administer (except Xe)
- Induction without venous line possible
- Direct measurement of CNS concentration
- Relative analgesia
- Environmental pollution (except Xe)
- Instability with open airways
- PONV with N₂O
- Toxicity of metabolites (except Xe and N₂O)
- Malignant hyperthermia (except Xe and N₂O)
Advantages and drawbacks of intravenous anesthetics

- Rapid induction
- Friendly to environment
- Antiemetic, amnesic, anxyolitic, anticonvulsiv
- Stable in open airway cases
- Can be antagonised
- Can be used outside hospital
- ANALGESIA WITH OPIATES
- Difficulties to ensure a venous line
- Technical difficulties in delivery
- Allergy may happen
- Inaccurate dosage, frequently overdosed
Pulmonary effects of anesthetics

- **Inhaled anesthetics:**
  - potent bronchodilators
  - depress mucociliary function
  - reduce tidal volume and minute ventilation: enflurane > desflurane > isoflurane > sevoflurane > halothane
  - affect inspiratory and expiratory muscles to various degrees
  - depress the ventilatory responses to hypercarbia and hypoxia

- **Intravenous anesthetics and opioids:**
  - central respiratory depressing effect
  - apnoea may occur after an induction dose of propofol or thiopental
Cardiovascular effects of anesthetics

- **Inhaled anesthetics:**
  - dose-related depression of myocardial contractility
  - complex effects on the arterial and venous vasculature
  - sensitize the myocardium to the arrhythmogenic effect of epinephrine
  - important cardioprotective effects against myocardial ischemia
  - N₂0 causes negative inotropic and slight hypertensive effects

- **Intravenous anesthetics and opioids:**
  - arterial blood pressure reduction after propofol and barbiturates due to central and peripheral effects
  - increase in HR and SBP after ketamine
  - benzodiazepines and etomidate have minimal CV effects
  - slight decrease in HR after opioids
Side effects of N₂O

- Increases in CBF, CMR, ICP
- Sympathomimetic effect
- Negative inotropic effect
- Volume changes of closed gaz spaces
- Can oxidize vitamine B₁₂ and inhibit its coenzyme function
- Can induce hepatic enzyme after prolonged use
The effects of drug metabolism on excretion

Weinhilsboum R: Inheritance and drug response NEJM 2003
The liver is the major site of metabolism

Pharmacogenomics affect drug metabolism

Trifluoroacylated metabolites of halothane (20%), enflurane (2.5%), isoflurane (0.2%), desflurane (0.02%) may be hepatotoxic

Sevoflurane’s major base-catalysed breakdown product (compound A) is a nephrotoxic vinil ether

Xenon and N₂O are not metabolised

Intravenous anesthetics and opioids are metabolised in the liver
Conclusions

- GA is a crucial issue in modern medicine
- About 10% of the population receive GA/year
- GA is relatively safe, mortality is low
- Anesthetics are high quality drugs with low toxicity
- Pharmacogenetics are major determinant of individual drug actions
- Appropriate equipment and logistics are determinant for patient safety and quality
- Human factor remains the main issue in the practice of anesthesia