ANAESTHETIC AGENTS

Westmead Primary Exams

STAGES OF ANAESTHESIA

- Stage 1 - Analgesia
    - Analgesia without amnesia, later in stage one both analgesia and amnesia are produced
- Stage 2 - Excitement
    - Patient often appears delirious, there is amnesia
- Stage 3 - Surgical anaesthesia
    - This stage begins with recurrence of regular respiration and extends to complete cessation of spontaneous respiration
- Stage 4 - Medullar depression - without circulatory and respiratory support, death rapidly ensues

INHALED ANAESTHETICS

- Pharmacokinetics - the rate at which effective brain concentrations are achieved depends of multiple pharmacokinetic properties

- These factors effect dose which in turn effects recovery

ABSORPTION AND DISTRIBUTION

- The concentration of an inhaled anaesthetic in a mixture of gases is proportional to its partial pressure
- Needs to go from alveolar air —> blood —> brain
- This rate of therapeutic concentration depends on:
    - Solubility
    - Concentraiton
    - Volume of pulmonary ventilation
    - Pulmonary blood flow
    - Partial pressure gradient between arterial and mixed venous blood anaesthetic concentrations

SOLUBILITY

- One of the most important factors influencing the transfer of an anaesthetic from the lungs to the arterial blood is its solubility
    - Desflurane and N20 which are both relatively insoluble in blood have very low Blood:Gas partition coefficients
        - When an anaesthetic with low blood solubility diffuses from the lung into the arterial blood, relatively few molecules are required to raise its partial pressure —> therefore arterial tension rises rapidly —> this leads to rapid equilibration with the brain and fast onset of action and fast offset of action.
- Conversely, an anaesthetic with moderate to high solubility such as Isoflurance —> more molecules dissolve before partial pressure changes and therefore arterial tension increases less rapidly

ANAESTHETIC CONCENTRATION IN THE INSPIRED AIR

- Has direct effects on the maximum tension that can be achieved in the alveoli and the rate of increase in its tension in the arterial blood

- Higher concentration will increase the rate of diffusion into the blood (FICK's LAW)

- In addition moderately soluble anaesthetics are often administered in combination with a less soluble agent to reduce time required for LOC and anaesthesia

PULMONARY VENTILATION

- The rate of rise of anaesthetic ga tension in the arterial blood is directly dependent on both the rate and depth of ventilation i.e. MV (TV x RR)

- Therefore hyperventilation will increase the speed of induction

PULMONARY BLOOD FLOW

- Increase in blood flow (increase in CO) slows the rate of rise in arterial tension, particularly for those agents with high solubility

- In patients with circulatory shock, the combined effects of decreased CO and increased ventilation will accelerate induction of anaesthetia

AV CONCENTRATION GRADIENT

- The anaesthetic concentration gradient between arterial and mixed venous blood is dependent mainly on uptake of the anaesthetic by tissues including non neuronal tissues

- The greater this difference in gas tension the MORE time it will take to achieve equilibrium with brain tissue

    - This is because it suggests that other tissues might also be obtunding the circulating concentration i.e. adipose tissues

    - The degree to which these tissues effect the AV gradient depends on this perfusion, so despite most anaesthetic agents being soluble in fat, fat is not so highly perfused and so the delay to anaesthesia will be minimal

ELIMINATION

- Time to recovery depends on the rate of elimination from the brain
- Inhaled agents that are relatively insoluble in blood and brain are eliminated faster rates
- In the case of more soluble anaesthetics can also have a marked effect on recovery time - especially in the case of more soluble anaesthetics
    - Accumulation in various tissues increases with prolonged inhalation particularly in obese patients as a result blood tension may decline slowly during recovery as the anaesthetic is gradually eliminated from these tissues
    - Clearance via the lung is the major route of elimination from the body

PHARMACODYNAMICS

- MOA: Primary molecular target of GA is the GABA receptor - this is the major mediator of inhibitory synaptic transmission

- Ketamine does not produce its effects via facilitation of GABA a receptor function —> NMDA

- In addition to GABAa activity, many general anaesthetic agents also alter K permeability in the cell

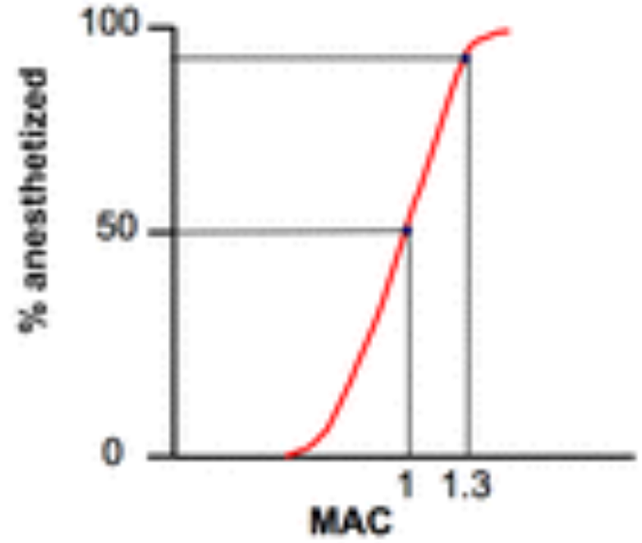
- They also decrease the duration of opening of nicotinic receptor activated cation channel

CONCEPTS OF MAC

- Dose response characteristic of gazes anaesthetics are difficult to measure and concentrations in brain tissue are impossible to measure under clinical conditions
- During GA, the partial pressure of inhaled anaesthetics in the brain = that in the lung = steady state
- MAC = median concentration that results in immobility in 50% of patients when exposed to a noxious stimulus (e.g. surgical incision)
    - It thus represents one point - ED50 on a conventional dose response curve
- The dose of an inhaled agent is therefore calculated in number of MAC
- MAC values decrease with age and body temperature
- MAC values of various GAs are additive

POTENCY OF GENERAL ANESTHETICS

- Only 50% of individuals may fail to respond to stimulation at 1.0 MAC, but 95% may fail to respond to stimulation at about 1.1 - 1.3 MAC.



17

ORGAN SYSTEM EFFECTS

- CV system - All decrease MAP in direct proportion to their MAC
    - Iso, des and sevo have minimal effect of CO
    - Des and Iso increase HR
- Resp system
    - Except NO, all inhaled anaesthetics decrease TV and increase RR
    - The increase rate cannot compensate for the decrease volume and so there is a decrease in overall minute ventilation
    - Depress mucocillary function
    - Sevoflurane and halothane cause bronchodilator effects

ORGAN SYSTEM EFFECTS

- Effects on CNS
  - Decrease metabolic rate
  - The more volatile agents increase cerebral blood flow because they decrease cerebral vascular resistance
  - Risk of increasing ICP

TOXICITY

- Hepatotoxicity - halothane can have hepatic dysfunction
- Nephrotoxicity - Sevoflurane —> formation of fluride ions which can effect long term renal function
- Malignant hyperthermia -
    - Autosomal dominant genetic disorder - effects individuals undergoing sedation with volatile agents and some muscle relaxants
- Consists of:
    - Rapid onset tachycardia and HTN
    - Severe muscle rigidity
    - Hyperthermia
    - Hyperkalemia
    - Acidosis
- Rare but important cause of anaesthetic morbidity and mortality

TOXICITY

- Malignant hyperthermia
  - biochemical abnormality is an increase in free calcium concentration
  - Treat with Dantrolene and reduce body temperature and restore electrolyte and acid base balance

IV ANAESTHETICS - BARBITURATES

- Thiopental
- Pharmacokinetics
    - A: IV
    - D: Rapidly crosses BBB - and if in sufficient dosage produces LOC in one brain arm circulation time
        - Plasma, brain equilibrium occurs rapidly < 1 min because of high lipid solubility
        - Redistributed into muscle and fat rapidly and so only causes a brief LOC
    - M:
    - E: Renal

IV ANAESTHETICS - BARBITURATES

- With large doses there is a dose dependent decrease in arterial blood pressure
- These haemodynamic effects are due primarily to a myocardial depressant effect and increased venous capacitance
- Thiopental is also a respiratory depressant
- Cerebral metabolism and oxygen utilisation are decreased after barbituate administration
- Can exacerbate acute intermittent prophyria

IV ANAESTHETICS - PROPOFOL

- Becomes the most popular IV anaesthetics - rate of action is similar to barbituate agents but the recovery is more rapid
- Also has anti emetic properties
- Pharmacokinetics:
    - A: IV Administration
    - D: half life is 2 - 8 minutes
        - Redistribution half life is 30 - 60 minutes, the drug is rapidly metabolised in the liver
        - Less than 1% of the parent drug is excreted unchanged
    - M: total body clearance is > than hepatic blood flow, suggesting extra hepatic
    - E: Renal
- Dose dependent resp depression and hypotension are main side effects
- Pain near injection site

IV ANAESTHETICS - ETOMIDATE

- Good in patents with limited cardiovascular reserve
- Causes minimal cardio-resp depressant effects
- Drug has NO analgesia effects
- Pharmacokinetics:
    - A: IV
    - D: Rapidly and widely distributed with biphasic plasma concentration showing initial and intermediate re-distribution half lives of 3 and 30 minutes
    - M: Liver
    - E: Renal
- S/E: history of PONV, pain on injection, myoclonic activity

IV ANAESTHETICS KETAMINE

- The drug produces a dissociative anaesthetic state - characterised by catatonia, amnesia, analgesia without LOC
- May involve NDMA antagonism
- Pharmacokinetics:
    - A: IV
    - D: highly lipophilic drug that is rapidly redistributed
- Only IV anaesthetics thats a direct cardiac stimulant
- Increases cerebral blood flow - therefore can have negative impact on ICP
- Emergence phenomena