Lec 4 General and Local Anesthetics

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4th stage/ 1st course

• General anesthetic drugs:

- are drugs which produce reversible loss of Sensation and consciousness.
- General anesthetic agents can be administered by different routes: mostly Intravenous injection and inhalation
- The drugs which are given as anesthetics by I.V administration are used for specific purpose as quickly acting general anesthetics for few minutes or as a supplement with another general anesthetic agents as:
- Thiopental (I.V anesthetic agent), Nitrous oxide, ether and halothane (Inhalation agents).
- As a supplement in order to produce the induction of anesthesia in a short period, because the inhalational anesthetic agents need a time about 15-20 minutes for production of induction.
- During this 15-20 minutes, the patients will start into what we called stages of general anesthesia.

Guedel (1920) described four stages with Ether anesthetic agent.

Stage I (Analgesia):

- **The subject is conscious but drowsy.**
- **Responses to painful stimuli are reduced.**
- **The degree of analgesia actually varies greatly with different agents.**
- **It is pronounced with Ether and Nitrous oxide but not with Halothane.**
- **During this stage all reflexes are present.**
- **The respiration remains normal.**
- **Small and pain sensation are lost toward the end of this stage.**

Stage II Excitement:

✓**The patient experiences delirium and possibly violent, combative behavior.**

✓ **Rise and irregularity in blood pressure.**

✓**Respiratory rate may increase.**

To avoid this stage of anesthesia, a short-acting barbiturate, such as *thiopental*, is given intravenously before inhalation anesthesia is administered

Stage III Surgical anesthesia:

✓Regular respiration and relaxation of the skeletal muscles occur in this stage.

✓Eye reflexes decrease progressively, until the eye movements cease and the pupil is fixed.

Surgery may proceed during this stage.

Stage IV Medullary paralysis:

✓Severe depression of the respiratory and vasomotor centers occur during this stage.

✓ **Death** can rapidly ensue unless measures are taken to maintain circulation and respiration.

- **General anesthesia is essential to surgical practice, because it renders patients analgesic, amnesic, and unconscious, and provides muscle relaxation and suppression of undesirable reflexes.**
- **No single drug is capable of achieving these effects both rapidly and safely.**
- **Several different categories of drugs are utilized to produce optimal anesthesia.**

Patient Factors in Selection of Anesthesia

1. **Liver and kidney:** release of fluoride, bromide, and other metabolic products of the halogenated hydrocarbons can affect these organs,
2. **Respiratory system:**

Respiratory system must be considered if inhalation anesthetics are indicated.

- asthma and ventilation or perfusion abnormalities complicate control of an inhalation anesthetic.
- All inhaled anesthetics depress the respiratory system.
- Additionally, they also are bronchodilators.

3-Cardiovascular system:

The hypotensive effect of most anesthetics is sometimes desirable, but ischemic injury of tissues could follow reduced perfusion pressure.

4-Nervous system:

(for example, epilepsy or myasthenia gravis)

- ➢ influences the selection of an anesthetic.
- ➢ halogenated hydrocarbone induced malignant hyperthermia.

5-Pregnancy

- ✓ *nitrous oxide* can cause aplastic anemia in the unborn child.
- ✓ Oral clefts have occurred in the fetuses of women who have received benzodiazepines.
- ✓ *Diazepam* should not be used routinely during labor, because it results in temporary hypotonia and altered thermoregulation in the newborn.

Induction, Maintenance, and Recovery from Anesthesia

A. Induction

- The period of time from the onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient.
- Essential to avoid the dangerous excitatory phase (Stage II delirium) during induction.
- General anesthesia is normally induced with an intravenous anesthetic like *thiopental*, which produces unconsciousness within 25 seconds after injection.
- At that time, additional inhalation or intravenous anesthetic combination may be given to produce the desired depth of surgical (Stage III) anesthesia.

[Note: This often includes coadministration of an intravenous skeletal muscle relaxant to facilitate intubation and relaxation].

B. Maintenance of anesthesia

- The period during which the patient is surgically anesthetized.
- Anesthesia usually maintained by the administration of volatile anesthetics, because these agents offer good minute-to-minute control over the depth of anesthesia.
- Opioids, such as *fentanyl*, are often used for pain along with inhalation agents, because the latter are not good analgesics.

C. Recovery

- The return of the patient to consciousness.
- The reverse of induction; that is, redistribution from the site of action

  (rather than metabolism of the anesthetic).

General aspects of anesthesia:

- The practice of anesthetist has three main parts:

❖ **Before surgery (pre-medication):**

- The principle is to provide:

A. Sedation and amnesia (to reduce anxiety and stress).

- -The patient who is going to do operation is normally afraid, so this patient needs some explanation about his operation that it is simple, it needs not long time to do the operation and so on.
- -Sedation and amnesia may produce by a drug like diazepam.

B. Analgesia.

- This is very important when there is an existing pain, or to produce analgesia as a supplement to a weak anesthetic agent.
- Analgesia is not required if there is no existing pain.
- However if post operation is expected an analgesic drug may be given at the end of the operation without waiting for the patient to complain of pain.

- e.g. of drug produces analgesia pethedine or morphine.

C. Inhibition of para-sympathetic autonomic system (Antimuscarinic agent).

1. To reduce bronchial secretion. Mostly happen with the use of an irritating drug such as ether. Bronchial secretion may cause bronchospasm.

2. To reduce secretion of salivary glands, because the saliva may enter the larynx causes laryngospasm.

3. To reduce reflex bradycardia and hypotention.

- e.g. of drug produces inhibition of para-sympathetic. Atropine or Hyoscine.
- So Typical combination drugs used in premedication include:

Morphine or Pethedine + Hyoscine or Atropine } These combination are usually given 1h before operation

-During surgery:

- **The most important is to produce sleep, analgesia and muscle relaxation by using a single drug or more than one drug.**

-After surgery:

- **The anesthetist ensures that the effects of hypnotic, analgesic and muscle relaxant are adequate.**
- **The patient must never be left alone until he is conscious that may be he needs:**

Antibiotic, analgesic, sedative, tranqulizer, purgative, enemas, hypotensive or hypertensive agent, anticoagulant, steroid, diuretic, bronchodilaters ……..etc.

Types of general anesthetic agents

Inhalation agents

Volatile (liquid at room temp.)

- Ether (diethyl ether)
- Halothane
- Methoxyflurane
- Enflurane
- Isoflurane

Gas (with a boiling point below room temp.)

- Nitrous oxide
- Cyclopropane
- Ethylene

I.V

- Thiopental
- Ketamine
- Propofol

Inhalation Anesthetics

- The mainstay of anesthesia
- Used primarily for the maintenance of anesthesia after administration of an intravenous agent.
- Depth of anesthesia can be rapidly altered by changing the concentration of the drug (not available with IV anesthetics).
- Inhalation anesthetics are also reversible, because most are rapidly eliminated from the body by exhalation.

Common features

- Nonflammable, nonexplosive agent.
- Decrease cerebrovascular resistance, resulting in increased perfusion of the brain.
- Bronchodilation and decrease both minute ventilation hypoxic pulmonary vasoconstriction
- Movement of these agents from the lungs to the different body compartments depends upon their **solubility** in blood and tissues as well as **on blood flow**

Uptake and distribution of inhalation anesthetics

- The deriving force of inhaled anesthetic is partial pressure.
- moves the anesthetic into the alveolar space and, then, into the blood, which delivers the drug to the brain and various other body compartments.
- **a steady state** is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture.

Mechanism of action

- **increase the sensitivity of ($GABA_A$)** receptors to the neurotransmitter, GABA, at clinically effective concentrations of the drug…. causes a prolongation of the inhibitory chloride ion current after a pulse of GABA release. Postsynaptic neuronal excitability is thus diminished .
- **Increase activity of the inhibitory glycine** receptors in the spinal motor neurons.
- **block the excitatory postsynaptic current of the nicotinic receptors**.

Halothane

- ✓ potent anesthetic, relatively weak analgesic.
- ✓ usually co-administered with *nitrous oxide*, opioids, or local anesthetics.
- ✓ relaxes both skeletal and uterine muscle, and it can be used in obstetrics when uterine relaxation is indicated.
- ✓ not hepatotoxic in pediatric patients (unlike its potential effect on adults), and combined with its pleasant odor, this makes it suitable in children for inhalation induction.

Pharmacokinetics:

- metabolized in the body to tissue-toxic hydrocarbons (for example, tri fluoro ethanol) and bromide ion.
- This reaction begins as a fever, followed by anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis.
- To avoid this condition, *halothane* anesthesia is not repeated at intervals of less than 2 to 3 weeks.

Adverse effects:

- **Cardiac effects:**

✓ *halothane* is vagomimetic and causes *atropine*-sensitive bradycardia.

✓ cardiac arrhythmias.

✓ concentration-dependent hypotension.

✓ Malignant hyperthermia

Enflurane

- less potent than *halothane*, but it produces rapid induction and recovery.
- **Contraindicated** in patients with kidney failure (metabolized to fluoride ion, which is excreted by the kidney).
- fewer arrhythmias, less sensitization of the heart to catecholamines.
- greater potentiation of **muscle relaxants** due to a more potent c*urare*-like effect.
- A disadvantage of *enflurane* is that it causes **CNS excitation** (not used in patients with seizure disorders.)

Isoflurane

- **very stable** (little metabolism; little fluoride produced), not tissue toxic.
- not induce cardiac arrhythmias and not sensitize heart to action of catecholamines.
- beneficial in patients with **ischemic heart disease**:

✓ ***produce concentration-dependent hypotension due to peripheral vasodilation.***

✓ ***dilates coronary vasculature, increasing coronary blood flow and oxygen consumption by the myocardium.***

Desflurane

- a popular anesthetic for outpatient surgery (due to rapidity of action).
- **not used** to induce extended anesthesia (irritating to the airway and can cause laryngospasm, coughing, and excessive secretions).

Sevoflurane

- suitable for **induction in children**(rapid uptake without irritating the airway during induction)….replace halothane
- low solubility in blood and is rapidly taken up and excreted.
- Recovery is faster than with other anesthetics.
- It is metabolized by the liver, releasing fluoride ions; thus, like *enflurane*, it may prove to be nephrotoxic.

Nitrous oxide

- **potent analgesic but a weak general anesthetic**.
- *nitrous oxide* at 80 percent (without adjunct agents) cannot produce surgical anesthesia.
- frequently combined with other, more potent agents to attain pain-free anesthesia.
- the least hepatotoxic of the inhalation anesthetics (**safest one**).

Intravenous Anesthetics

- For **rapid induction of anesthesia**,
- Must be injected **slowly** (due to rapidity of induction)
- **Recovery** from intravenous anesthetics is due to redistribution from sites in the CNS.

A. Barbiturates ..thiopental, methohexital

- Potent anesthetic but a weak analgesic.
- ultra short-acting barbiturate and has a **high lipid solubility.**
- quickly enter the CNS and depress function, (less than 1 minute).
- diffusion out of the brain occur very rapidly (because of redistribution of the drug to other body tissues).

- **The short duration of anesthetic action** is due to the decrease of its concentration in the brain to a level below that necessary to produce anesthesia.
- may contribute to severe hypotension in patients with hypovolemia or shock.
- All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm.

- contraindicated in patients with acute porphyria.

B- Benzodiazepines

- used in conjunction with anesthetics to sedate the patient.

Midazolam…most commonly used

Lorazepam
diazepam
} alternatives

- All three facilitate amnesia while causing sedation.
- facilitate GABA-mediated inhibition at $GABA_A$ receptors

C- Opioids

- facilitate GABA-mediated inhibition at $GABA_A$ receptors
- Interact with μ ,κ , and δ receptors for endogenous opioid peptides .
- frequently used together with anesthetics (**Because of analgesic property)**

example, the combination of **morphine & NO**.. provides good anesthesia for cardiac surgery.

- ***fentanyl , sufentanil* or *remifentanil***, commonly used because they induce analgesia more rapidly than *morphine* does.
- not good amnesic, all cause hypotension, respiratory depression, and muscle rigidity as well as post anesthetic nausea and vomiting.
- Opioid effects can be antagonized by ***naloxone***

D- Etomidate

- facilitate GABA-mediated inhibition at $GABA_A$ receptors.
- used to **induce anesthesia**.
- a **hypnotic agent** but **lacks analgesic activity**.
- rapid Induction , short-acting.
- only used for patients with **coronary artery disease or cardiovascular dysfunction**, such as shock (no effect on the heart and circulation).

E- Ketamine

- Blocks excitation by glutamate at N-methyl-D-aspartate (NMDA) receptors
- a short-acting, non-barbiturate anesthetic
- induces a **dissociated state** in which the patient is unconscious but appears to be awake and does not feel pain.
- stimulates the central sympathetic outflow, which, in turn, causes stimulation of the heart and increased blood pressure(beneficial in patients with hypovolemic or cardiogenic shock or patients with asthma).

F- Propofol

- an **intravenous sedative/hypnotic** used in the induction or maintenance of anesthesia.
- facilitate GABA-mediated inhibition at $GABA_A$ receptors
- Onset is smooth and occurs within about 40 seconds of administration.
- Supplementation with **narcotics** for analgesia is required.
- accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, or hiccups.

- **decreases blood pressure** without depressing the myocardium.
- **reduces intracranial pressure**.
- widely used and has replaced ***thiopental*** as the first choice for anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause post anesthetic nausea and vomiting.
- very useful for resection of spinal tumors (has much less of a depressant effect than the volatile anesthetics on CNS-evoked potentials,

• *Local anesthetic drugs*

- **Are drugs employed to produce reversible loss of sensation in certain area of the body by interfering with nerve conduction.**
- **They must be:**
  - **Water soluble, not irritant, not cause any permanent damage to nerve structure, have rapid onset of action, the duration of action must be suitable to the operation performed and must be nontoxic locally when absorbed or when reach the circulation.**

• Mechanism of action:

- **Local anesthetics act on all nervous tissue to prevent the nerve impulse from arising that means by block the nerve conduction.**
- **This effect is by altering the permeability of ions particularly the sodium influx through the cell membrane which is necessary for generation the action potential.**
- **So first to be blocked is sympathetic sensory fibers for pain, cold warmth and touch and then the motor nerve which affected or inhibited induces skeletal muscle relaxation.**
- **The tissue pH under normal condition is slightly alkaline this alkaline medium causes with the local anesthetic agent free base.**

- **Procaine H Cl + Na OH ⟶ NaCl + Procain base**

Can penetrate lipid membrane produces local anesthetic effect

- **If pH of tissue is acidic as in inflammation the base will not form, so there is no anesthetic effect as in pre-apical abscess in tooth.**
- **Some points about local anesthetic agents:**

❖ **- Action of local anesthetic depends on fiber dimeter, mylenation physiological firing rate.**

❖ **- sodium bicarbonate enhances the activity of weakly basic anesthetic.**

❖ **-repeated epidural injection in anesthetic may cause tachyphylaxis.**

❖ -oral and parenteral forms of local anesthetic are used adjunctive in neuropathic pain states.

❖ -all local anesthetic may produce toxic effects due to CNS include light-headedness or sedation, restlessness, nystagmus and tonic – clonic convulsion. Sever convulsion then coma and cardiovascular depression.

❖ -all L.A vasodilator effects. May develop heart block

❖ -bupivicaine may produce sever cardiovascular toxicity.

❖ -procain is some what more allergic

- **Systemic action:**
- **On C.V.S:**
- **Local anesthetics exert their effect on the cardiovascular system if absorbed in great amount from site of injection.**
- **In toxic doses of L.A agent. It decreases the maximal depolarization of purkinjes fibers, reduces conduction velocity and it may have direct inotropic effects. It has quindine like action on the heart (enhanced contractility of myocardium).**

- **On C.N.S**
- **The usual doses of L.A produce no effects, with the increasing doses may cause excitatory effect resulting anxiety restlessness, tremors, euphoria, agitation and even convulsion.**
- **Other effects of LA may depress ganglionic transmission and neuromuscular transmission.**

- **Vasoconstrictors and local anesthetics**
- **-Vasoconstrictors particularly epinephrine or nor-epinephrine is commonly added to LA solution to delay the absorption and to prolong its action locally and reduce systemic reaction.**
- **Concentration used for this purpose in L.A is 1:200.000 or 1:400.000 and in dentist 1: 80.000.**

- -Vasoconstrictors should not be used for nerve block of extremity (e.g. finger, nose, penis and toe) because they may cause cut of blood supply (gangrene), so that the organ may be damaged or even lost.
- -Enough adrenaline or nor-adrenaline can be absorbed to affect the heart and circulation and reduce the plasma potassium.
- This can be dangerous in cardiovascular disease. An alternative vasoconstrictor is Felypressin (synthetic vasopressin). This agent does not affect in-patients with cardiovascular disease as with Ad or nor-Ad.
- -Local anesthetics are usually effective within 5min of application and have a useful duration effect 1-2 hrs that may be doubled by adding a vasoconstrictor agents.

- **Local anesthetics are classified according to their chemistry:**
  - **They are either esters or amides**
  - **1.Ester compounds: as (cocaine, procaine, tetracaine, benzocaine) are hydrolyzed by liver and plasma esterase (their effect may be prolonged when there is genetic enzyme deficiency). The hydrolysis of all ester-linked local anesthetics leads to the formation of para amino benzoic acid (PABA), which is known to be allergenic. Therefore, some people have allergic reactions to the ester class of local anesthetics.**
- **2.Amide compounds: as (lidocaine, prilocaine, mepivacaine and bupivacaine) are dealkylated in the liver.**

- **Classification of L.A according to clinical usage.**
- **1.Surface anesthesia: the agent is used direct on the skin or to the eye, nose, ear, mouth, throat, trachea, bronchi, rectum …etc. that means external application. The preparation of surface anesthetic agents are either a solution, ointment, jells, cream or lozenges NFE3W. e.g benzocain, lidocaine and prilocaine.**

- **2.Infiltration anesthesia: to paralyze the sensitive nerve ending and small cutaneous nerve. The agent is used for minor operation as incision, excision, extraction of teeth….etc. e.g. lidocaine, bupivacaine, procaine, mepivicaine and prilocaine.**

- **3.Regional anesthesia: 4 types.**

a. **Intravenous anesthesia: mostly used for limbs, that we inject the local anesthetic in the vein. It is rarely used. e.g lidocain and prilocain**

b. **Nerve block: to anesthetize a region by inject the drug around the nerve (individual nerve is blocked) as sciatic nerve, facial nerve ….etc. e.g lidocaine and bupivacaine.**

c. **Extradural (epidural) anesthesia: the agent is injected in the spinal dural space to anesthetize the nerve roots. Widely used in obstetrics, thoracic, lumber and sacral block. e.g lidocaine and bupivacaine.**

d. **Subarachnoid (intrathecal) block or called spinal anesthesia. The problem with this type of anesthesia. It causes prolonged headache, hypotention and probably infection e.g. lidocaine, tetracaine and procaine.**

- **Adverse reaction:**
- **Excessive absorption results in paraesthesia (face and tongue), nervousness, tremor, and even convulsion which is very danger may be followed by respiratory depreesion. Diazepam or thiopentone or even suxamethonium may be necessary to control convulsion.**

- **Other adverse reactions: nausea, vomiting, abdominal pain and allergic reactions as skin rash and asthma.**

- **Individual L.A:**

- **Procaine (novocaine):** **It was standard drug to which all L.A are compared, now replaced by lidocaine. It has the disadvantage of producing poor topical anesthesia.**
- **Only effective when given by injection.**

- **Lignocaine (xylocaine, lidocaine):** **1st choice for surface as well as for injection, more potent than procaine. Structurally lignocaine differs from most other local anesthetics.**
- ✓ ***It is used as an alternative for other local anesthetic which has allergy to some patients.**
- ✓ **It can produce sedation along with time of anesthesia.**
- ✓ **Control of Cardiac Arrhythmias as lidocaine the primary drug for treating cardiac arrhythmias.**

- **Benzocaine:** poorly soluble, therefore poorly absorbed from mucous membrane, provide potent and safe local anesthetic.

- **Tetracaine:** It has longer duration of action, rapidly absorbed topically. The total dose should be carefully calculated and should not exceed 0.5mg/Kg body weight. Several fatalities have been reported from its topical misuse.

- **Prilocaine:** Is used similarly to lignocaine, but it is less toxic. It may cause methemoglobinemia. It is mixed with lignocaine to form eutectic emulsion (good soluble) that penetrate the skin easily (new preparation EMLA). It is used Bupivicaine: it has a longer duration of action. It is used in chronic pain in patient with malignancy (topical and injection).

- **Cocaine:** This drug is too toxic to be injected to the tissue. So it is used only topically. It causes vasoconstriction, addiction and abuse toxicity.