CENTRAL NERVOUS SYSTEM

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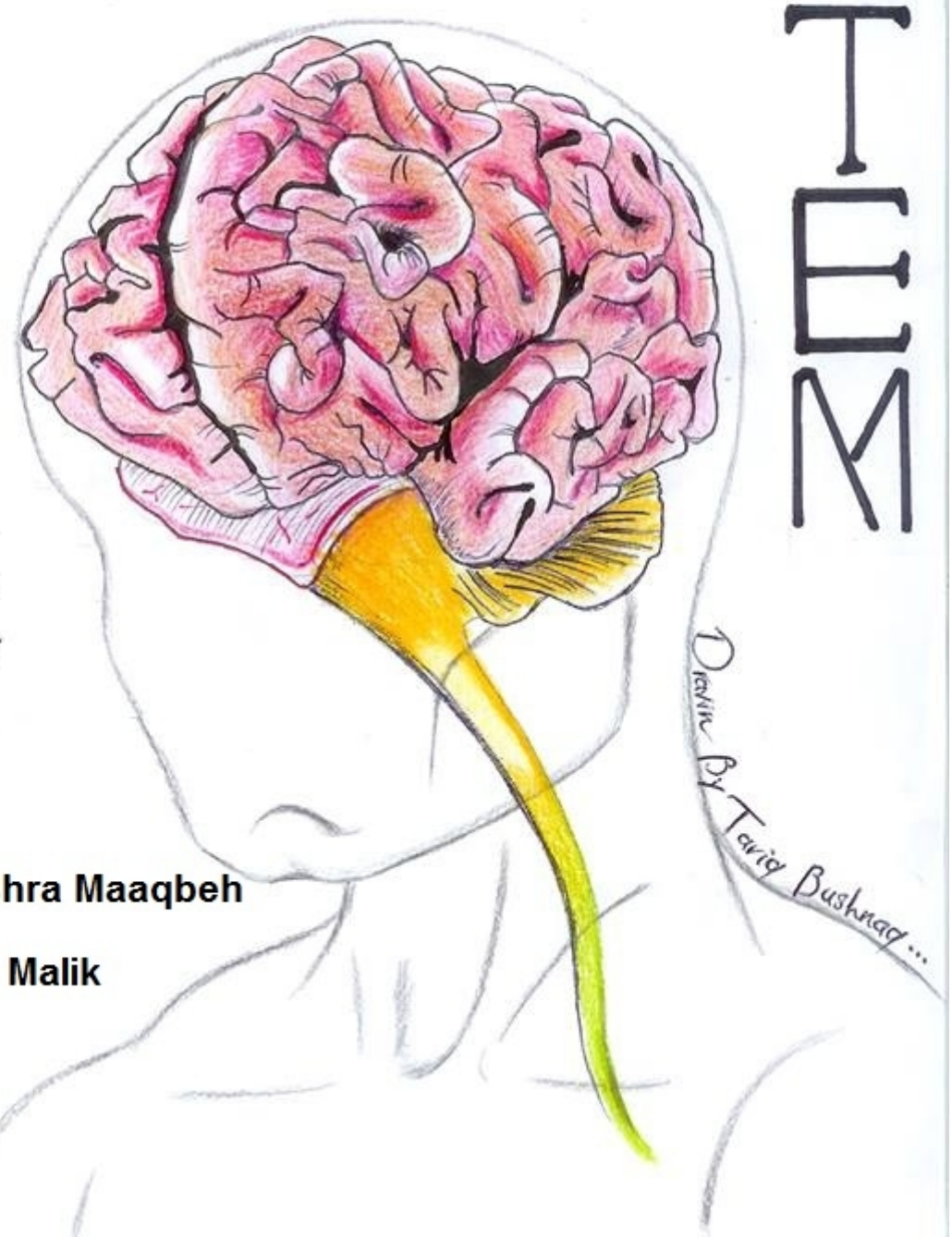

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Lec #: **5**

General Anesthesia

-We talked about opioids, anxiolytics and hypnotics (Z-drugs, Benzodiazepines, Barbiturates and Melatonin- Receptor agonists).

-Anesthesia is needed in medical procedures when we want to perform **surgeries**. Anesthesia is on different levels; we may not need general anesthesia in a minor surgery, instead we use local anesthesia. Total anesthetic effect can be induced or half anesthetic effect.

-We will talk about general anesthesia in which we completely anesthetize the patient. This includes **prevention of pain** (analgesia), **unconsciousness**, **no autonomic reflexes** and **motor reflexes should be zero** i.e. no movement at all.

-The whole idea about anesthesia is to produce something beforecoma; we can call this Artificial Coma.

-The patient is supplied with oxygen for ventilation. We keep the muscles of the chest working somehow, but they are not really performing very well → many issues are linked toward anesthesia that may, let's say, suppress the centrally oxygen/respiratory centre.

History of anesthesia

-They started with using *ether* for anesthesia in 1800s, it is very bad because it produces respiratory depression a lot so we are not using ether anymore, however, we still use it with animals. Secondly, they used *chloroform* which is very toxic to the liver and kidney.

-So we moved to the new ages of anesthesia, we will mostly talk about halogenated hydrocarbon compounds, like**Enflurane**, **Halothane** and **Isoflurane**. Those are the main three gases we use in anesthesia. Nothing has changed since 1990, those drugs are generally safe, however there is a mortality rate of 1 death per 800,000 when I use *balanced anesthesia.*

-You have to differentiate between Mono-anesthesia& Balanced anesthesia:

- ✓ **Mono-anesthesia** is when you give one anesthetic agent to induce unconsciousness, muscle relaxation and analgesia. This needs high concentrations of the drug and is linked with a mortality rate of 5 deaths in every 100,000.This is an oldapproach.
- ✓ **Balanced anesthesia**in which we try to reduce the amount of anesthetic agent we give, and reducing the mortality rate to 1 death in 800,000. This approach is the one we use in reality now.

From slides (underlined sentences are copied from the slides):

• General anesthesia is essential to surgical practice, because it renders patients analgesic, amnesia, and unconscious reflexes, while causing muscle relaxation and suppression of undesirable reflexes.

The patient should be completely relaxed and not feeling pain, because pain will induce sympathetic activation which is a problem in medical procedures since it interferes with the haemodynamics of the patient, like problems in blood flow, increases in the release of adrenaline which causes vasoconstriction in many places affecting the kidney for example.

• No single drug capable of achieving these effects both safely and effectively.

We can induce them with a single anesthetic agent but it is NOT safe with a high risk of death. It is safer when we use multiple agents.

• Potent general anesthesia are delivered via inhalation and intravenously.

• Anesthesia can be divided into three stages: induction, maintenance, and recovery.

We induce anesthesia by giving drugs like barbiturates, we use **Thiopental** to **induce** anesthesia (the first stage). This drug is given IV, it works fast (within 30 seconds or so) and finishes fast. They tell the patient who is going through a surgery to count to ten but he can maximally count to four or five.

-At high doses, barbiturates act as agonists on GABA receptors and produce hyperpolarization → CNS depression → producing unconsciousness. The first stage/ induction will not last long because those drugs work fast and finish fast.

-Then we use gases of anesthesia, they are safe and we can moment-to-moment control them. Infusion of the drug that we use in induction of anesthesia carries a lot of risk on the respiratory centre (depression), so we use volatile gases which offer good minute-to-minute control and are easily monitored. They infuse within time and make the patient under *sustained* surgical anesthetic state during the whole procedure (2, 3, 4 hours…). Those **inhaled gases** are used for **maintenance of anesthesia** after administration of an intravenous agent (the second stage).

-The third stage is the termination of anesthesia or the **recovery** stage.

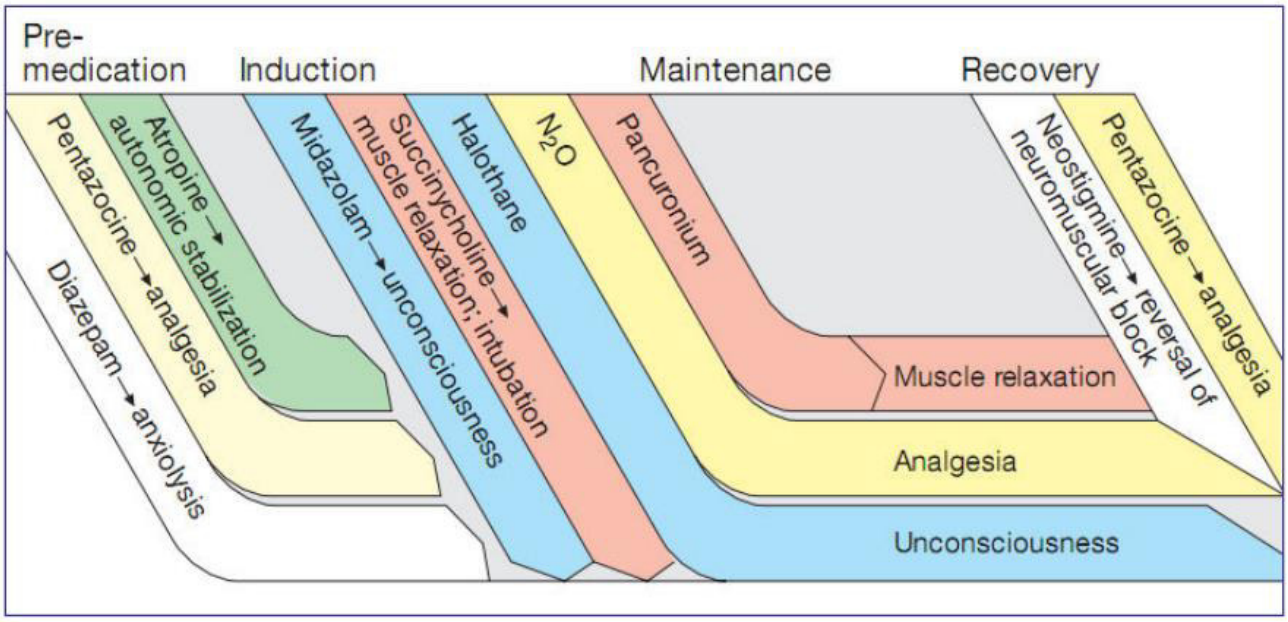
So stage ONE, the induction, starts from the patient being conscious and responding to your reflexes and talk, until you reach a state where he does not respond to your talk. As long as the patient has lost his consciousness, we go through stage TWO. On this time, the patient has activation of inhibitory activity (because we give a CNS depressant in stage one), in stage two there is a sudden increase in autonomic reflexes (patient may experience vomiting, increase in heart rate, etc), so we have to go through this rapidly by quickly putting the patient under anesthetic gases, and thus the maintenance stage. Now the patient has lost consciousness, autonomic reflexes and his muscles are relaxed and this is the ideal situation to perform any surgery, we want to be and reach this stage, stage THREE. If you overdose the patient with anesthesia, you go to stage FOUR which we really do not want to go through because there is cardiac & respiratory depression resulting in death.

-Again,in normal conditions, a pain stimulus will produce pain, autonomic reflexes and motor reflexes, we have to suppress all that in anesthesia. We can do this using a HIGH concentration of a SINGLE agent which increases the risk of respiratory depression and getting to stage four. We avoid this and decrease the risk by using BALANCED ANESTHESIA.

-In balanced anesthesia, we use drugs like halothane to produce unconsciousness, then we give agents for muscle relaxation to reduce motor reflexes like pancuronium and atracurium, also we use atropine for autonomic stabilizationand blocking the parasympathetic activation (ex. salivation), we add also agents for analgesia like fentanyl and morphine. We use balanced anesthesia in our practice, we do not want to use a lot of anesthetic agent in order not to get into stage four, So we supply the anesthesia with helpers (analgesics, agents for autonomic reflexes, muscle relaxants).

From sides:

Inhalation anesthetics are not particularly effective analgesics and vary in their ability to produce muscle relaxation; hence if they are used alone to produce general anesthesia, high concentrations are necessary. If inhalation anesthetics are used in combination with specific analgesic or muscle-relaxant drugs the inspired concentration of inhalation agent can be reduced, with an associated decrease in adverse effects. The use of such drug combinations has been termed balanced anesthesia.



-During surgery we have 3 types of drugs; pre-operation drugs, anesthetic drugs (balanced anesthesia) and recovery drugs.

1- Pre-operation drugs: include **anxiolytic** drugs like *benzodiazepines* (ex. diazepam, triazolam according to the duration of the operation). They reduce the stress and anxiety before the surgery, and diazepam gives a sort of muscle relaxation as well. We may use *opioids*instead of benzodiazepines which are anxiolytic and induce pleasure so the patient enters the theatre in a relaxed situation (*tranquilization*). We also need to **reduce the secretions** from the GI tract because those secretions may interfere with the **intubation** that you will do (intubation for ventilation needs low secretion/salivary level) →*Atropine* is good for producing this and reducing all the parasympathetic reflexes (it is an anti-muscarinic drug).

2- Balanced anesthesia: as you can notice in the figure in the previous page, we use 5 drugs here, some will be continually administrated through the operation and some will be used awhile and then stopped. We use a transient [1]**intravenous anesthetic agent** (for a short time- 5 minutes) to *induce* anesthesia (*unconsciousness*). Then we add[2]**succinylcholine**, a *muscle relaxant*, this is important for doing the *intubation* since it reduces the reflexes, it works and finishes fast. After that we give an[3]**anesthetic agent**(a volatile gas) which maintains the unconsciousness. We also give [4]**analgesic agent** that works through the whole operation. We give [5]**muscle relaxant** as well. So those three agents (anesthetics, muscle relaxants and analgesics) along with atropine are the components of balanced anesthesia. You have to be a very good anesthetist in order not to kill the patient because those drugs are CNS depressants and many things may pop up like respiratory depression or malignant hyperthermia or many other problems, so general practitioner is not allowed to anesthetize thepatient.

3- Recovery: after finishing the procedure, many of the patients experience delayed recovery not from the anesthetic agent itself, because normally once you take off the mask they (gases) are going to be expelled from the body within 15 minutes. Some of the patient will stay asleep for a long time, 1-2 hours, and you cannot wake them up. If the patient does not recover, you have to regain body activity and to *relief from muscle relaxation and improve muscle tone*, we do that by giving **Neostigmine** to stimulate the nicotinic receptors on the muscles (from the internet: neostigmine blocks the active site ofacetylcholinesterase).

-We have two types of anesthesia; intravenous anesthesia which we use in induction and inhaled anesthesia (volatile agents).

A. Inhalant anesthetics:

• Inhaled gases are the core of anesthesia, and are used primarily for the maintenance of anesthesia after administration of an intravenous agent.

• No one anesthetic is superior to another under all circumstances.

Sometimes you are going to use halothane, other times isoflurane or else. This is according to the patient condition.

• The potency of inhaled anesthesia is defined quantitatively as **median alveolar concentration (MAC)**.

Those anesthetic agents are not given Effective Dose 50 (ED50) or Inhibitory Concentration 50 (IC50), we measure their effectivity via MAC because they are gases and are inhaled so they are related to the lungs and alveoli.

• MAC is the minimum alveolar concentration of anesthetic that produces immobility in 50% of patients exposed to a standard noxious stimulus.

• MAC is usually expressed as a **percentage of gas mixture** required to achieve the effect, and is **small for potent anesthetics**.

We express MAC as a percentage not as a dose because inhaled anesthesia is not given alone, it is mixed with **oxygen** (for ventilation) and **nitrous oxide.** So the anesthetic machine has three openings one for each component of the gas mixture, the total is 100% and every drug has its own MAC.

• No specific receptors have been identified as the target of general anesthesia action.

• The fact that **chemically unrelated compounds** produce the anesthesia state argues against the existence of such receptors.

Anesthesia can be induced by ether, chloroform, halothane, isoflurane or even by nitrous oxide. Those have totally different structures so we can't link anesthesia to specific receptors. Many theories are suggested:

• For example, the general anesthesia **increase** the sensitivity of **GABA receptors**to neurotransmitters, GABA, which causes a prolongation of inhibitory chloride ion current after a pulse of GABA release. Postsynaptic neuronal excitability is thus diminished.

So they potentiate the activity of GABA like benzodiazepines and barbiturates.

• Other receptors are also affected for example, the activity of the **inhibitory glycine receptors** in the spinal motor neurons are **increased**.

Some say that the activity of **excitatory NMDA** receptors (glutamate receptors) is **decreased.**

• In addition, inhalation anesthesia **blocks excitatory** postsynaptic current of the nicotinic receptors.

At **high doses** they block acetylcholine receptors (nicotinic receptors in muscles), so **muscle relaxation** is produced **at high doses**.

-So the exact mechanism of action of general anesthetics is not known but we are sure that they induce inhibition/depression of the CNS.

Examples on inhalant anesthetics:

1- **Halothane:** the oldest, it produces toxicity in elderly but not in children (although we learned that toxicity is more common in children because they have less metabolism and so on). It is metabolized to toxic materials in the liver, so it is hepatotoxic and not usedin adults. Halothane is still used in children because the level of hepatotoxicity is low.

   • Is the prototype to which the newer inhalation anesthetics have been compared.

• It has the ability to induce anesthetic state rapidly and to allow quick recovery.

• However, with the recognition of serious side effect and the availability of other anesthetics that have less complication, halothane is largely being replaced. Especially in adults.

• Halothane is potent anesthetic, nonetheless it is relatively weak analgesic. Thus, it is co-administrated with Nitrous oxide, Opioids.

• Halothane produces bronchial smooth muscle relaxation, which make it beneficial for patients with asthma.

• Is not hepatotoxic in pediatric patients, and it has a pleasant odor, which make it suitable in children for **inhalation induction**.Some countries still use halothane for induction of anesthesia in children although not most of the countries.

• Halothane is metabolized in the body to tissue toxic materials, which may be responsible for the toxic reaction

-When halothane is used try to avoid succinylcholine because both of them induce malignant hyperthermia in which there is a drastic increase in intracellular Ca^{++} levels (it is released from its stores), excess Ca++ consumes large amounts of ATP and this generates excessive heat, the temperature of the patient increases and may reach 41.5 °C. Halothane may produce malignant hyperthermia in children that's why we have to monitor the patient and to avoid succinylcholine generally speaking.

-Halothane produces a rapid hypotension and will sensitize the heart to catecholamines (adrenaline & noradrenaline) resulting in cardia arrhythmias.

• Adverse effect: halothane causes bradycardia. It has undesirable property of causing cardiac arrhythmias.

• Halothane produces concentration dependent hypotension. It is recommended that a direct vasoconstrictor such as phenylephrine, be given.

2- **Enflurane:** it is not used anymore, not important.

3- **Isoflurane:** it is the main drug we use in maintenance of anesthesia, it is widely used in developing and developed countries. It does not produce the quick hypotensive activity like halothane, it does produce dilation but it is not too strong. You have to know this drug. Has two advantages: [1]**does not affect cardiac activity** and [2]**issafe on the liver**.

- Is widely used, and little metabolized to fluorine, thus it is not tissue toxic.
- It dilates the coronary artery and so may be beneficial for patient with ischemic heart disease.
- Does not induce cardiac arrhythmias and does not sensitized the heart to catecholamines.
- It does produce concentration dependent hypotension due to vasodilatation.
- Has been reported to cause hepatitis, but with a much lower percentage than halothane.

Drugs from 1-3 are volatile halogenated carbon anesthetic drugs.

4- **Nitrous oxide (N_2O):** commonly known as laughing gas, it is used in minor surgeries (ex. dental surgeries) to induce a little anesthesia. It is not a real anesthetic agent; it does not get the patient toward the unconsciousness but may induce sleeping and hypnotic effect. However, it is a great **analgesic** drug. The patient will sleep but won't go through the anesthetic situation. It is very common in the dental office.

• Is frequently employed at concentration of **30%** in combination with oxygen for analgesia, particularly in dental surgery.

So in many cases you do not need to use fentanyl. Nitrous oxide is added to the balanced anesthesia to produce analgesia. If the patient still needs analgesia, you should give IV fentanyl.

-30% nitrous oxide, 66-69% oxygen and the MAC of the anesthetic drug (for example it is 1.15% for isoflurane-from the internet) → this is applied in all anesthetic situations we do. By this we produce anesthesia and analgesia and we keep the oxygen supply to the patient.

The doctor will finish this topic in lecture 6.

THE END