بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

General Anesthesia

FINAL | Lecture 5

﴿ إِنِّي تَوَكَّلْتُ عَلَى ٱللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَآبَّةٍ إِلَّا هُوَ ءَاخِذٌۢ بِنَاصِيَتِهَآ ۚ إِنَّ رَبِّي عَلَىٰ صِرَٰطٍ مُّسْتَقِيمٍ ﴾

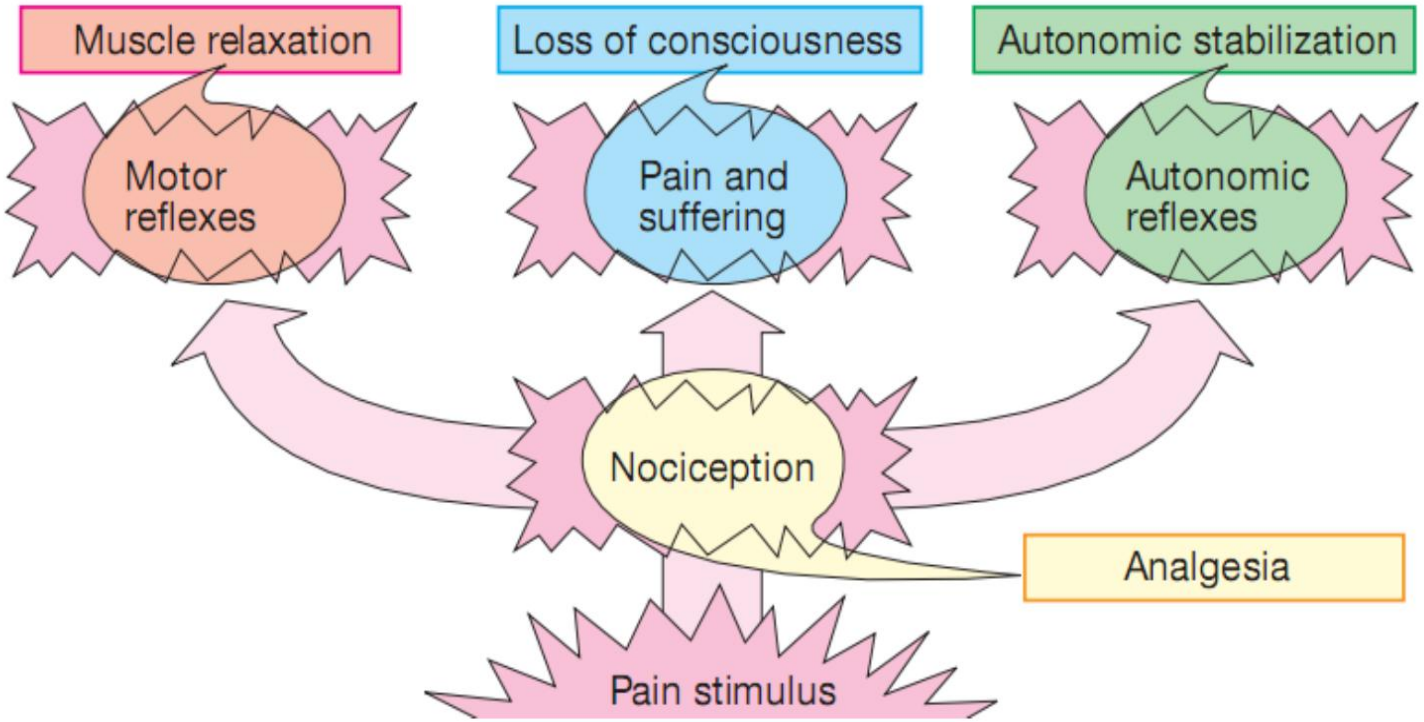
Written by: Awab Al-Hamdan
Qusai Sharkas

Reviewed by: Almothana Khalil

PHARMACOLOGY

General anesthesia

- 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.
- No single drug capable of achieving these effects both safely and effectively.
- Potent general anesthesia are delivered via inhalation and intravenously.
- Anesthesia can be divided into three stages: induction, maintenance, and recovery.



Goals of surgical anesthesia

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Usage of Anesthesia

- In surgery, there are three types of receptor responses we aim to reduce;
  - We aim to reduce the pain
  - We aim to stop the auto-motor reflexes
  - We aim to relax the muscle

The goal in surgery is to achieve these three effects for a “while”, which is entire idea behind anesthesia: to perform surgery without pain or undesired effects.

A “while” could range anywhere from 5 minutes, to multiple days, and this range that we need is one of the factors that distinguishes the different drugs, and we need to know how to use them all.

General anesthesia

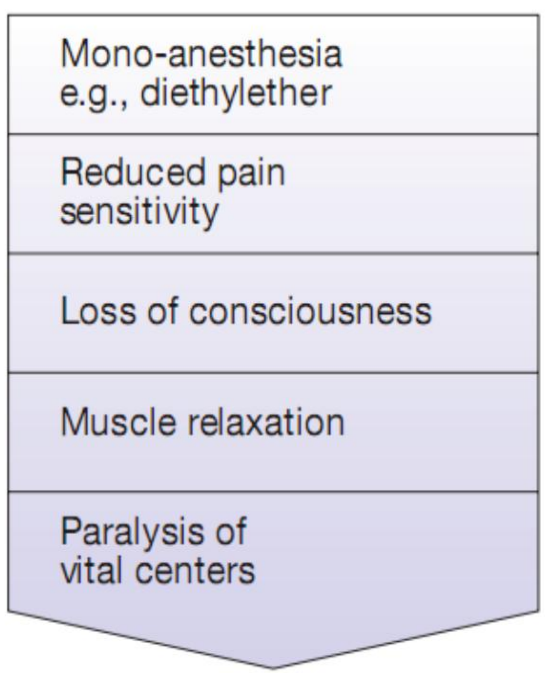
- Induction is the period time from onset of administration of the anesthetic to development of effective surgical anesthesia.
- General anesthesia is normally induced with an intravenous anesthesia that produce unconsciousness within 1 minute or so.
- After that, additional inhalation or intravenous drugs comprising anesthesia. The selected anesthesia combination is given to produce the desired depth of surgical anesthesia
- For children, without intravenous access, moderate agent, such as halothane are used to induce general anesthesia.

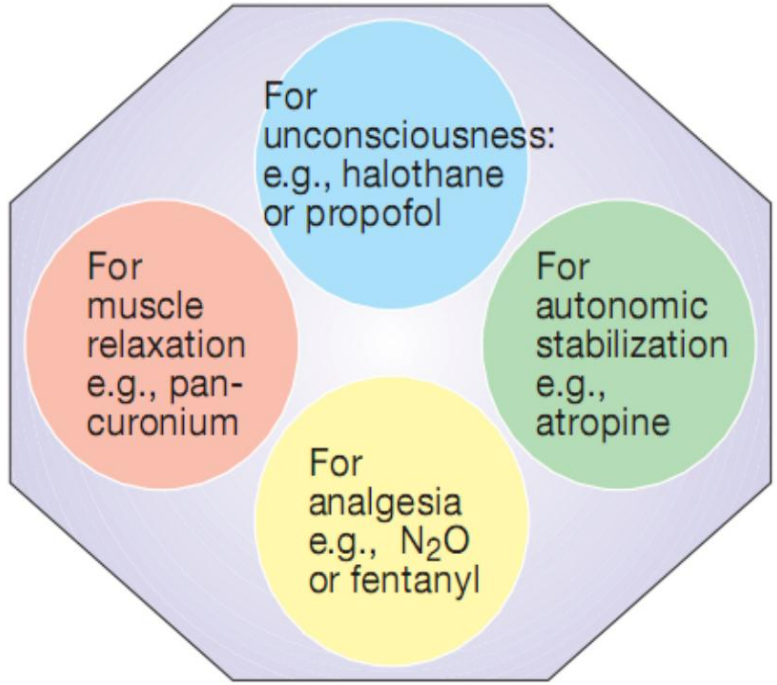
General anesthesia

- Maintenance provides a sustained surgical anesthesia.

  Usually done by administration of volatile anesthesia, because these agents offer good minute-to-minute control over the depth of anesthesia.

- Recovery is the time from discontinuation of the administration of the anesthesia until consciousness and protective physiological reflexes are regained. Recovery is reverse of induction,





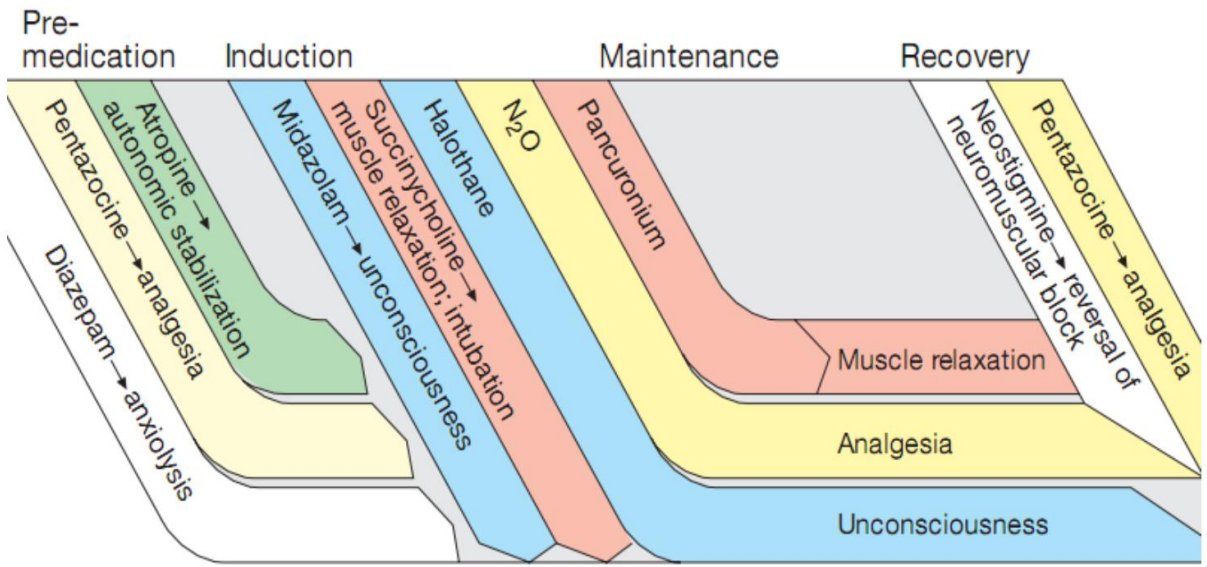
Traditional monoanesthesia vs. modern balanced anesthesia

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Evolution into Modern Anesthesia

In old medicine, we would use ether, which can achieve our three desired analgesic effects. However, it would put the patient in a state very similar to a coma, and could eventually lead to respiratory failure, so ether had a lot of death cases.

Naturally, with modern medicine, came balanced anesthesia, which utilizes multiple drugs to achieve our desired effects, which ties into the beauty of Anesthesia, in that it utilizes nearly all concepts of Pharmacology, so it's a very important science and aspect of Medicine AND Pharmacology!



Regimen for balanced anesthesia

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Phases of Anesthesia

As mentioned before, there are multiple drugs given in modern day anesthesia, split into 4 phases:

Phase 1: Pre-medication:

- Anxiolytics: Your patient would naturally be anxious, so we would want to give him an anxiolytic, such as **Diazepam**
- Analgesics: After that we would want to reduce the patient's pain, so we would use the appropriate opioid depending on the length of the surgery (for example, we would use **Fentanyl** for short-term analgesia)
- Autonomic Stabilizers: Some anesthetic drugs are inhaled, so the patient needs to be intubated so we can insert a laryngeal scope, among other things. To follow this process thoroughly, we need the patient's mouth to be dry, so we need to inhibit saliva production, so we use an anti-muscarinic drug, such as **Atropine**.

Phase 2: Induction:

- We induce unconsciousness in the patient with a drug called **Midazolam** (Induction phase is partly dependent on Benzodiazepines), however these days we use a drug called **Propofol**.
- After the patient becomes unconscious, we work on inducing muscle relaxation, using a drug called **Tubocurarine** (nicotinic antagonist) or **succinylcholine**, both of which inhibit contractibility.

Phase 3: Maintenance:

- To maintain the patient's unconsciousness, we use something called anesthetic halogenated molecules, such as **Halothane**, however Halothane has many characteristics (which will be discussed later), so we couple it with **Nitrous oxide**. These products cause a strong CNS depression, which maintains unconsciousness and all three of our desired effects (elimination of pain, muscle relaxation, and autonomic stability).

Phase 4: Recovery:

- This is the final phase of anesthesia, in which we end the maintenance phase and remove any anesthetics from the patient. When the patient wakes up, they still cannot move due to muscle relaxation, so we give him **Neostigmine** (*recall Acetylcholine Esterase inhibitors from 0503201*) to inhibit AChE, which retroactively increases Acetylcholine, restoring contractibility.
- The patient can also experience emesis, nausea, etc. After waking up from the procedure, so we give him a drug called **Ondansetron**, which blocks serotonin activity in the vagus afferents and centrally.

This is the entire process of Anesthesia.

Possible complications

- If the patient's heart rate increases during the procedure, we give him **Sotalol**.
- If the patient suffers from Hypotension post-anesthesia, we give him **Vasopressors**, such as Ephedrine, Phenylephrine, Epinephrine, etc.
- If the patient felt pain during the procedure, we give him **Fentanyl**.
- Anesthesia is so complicated and intricate, justifying it having its own specialty (anesthesiology).

Intravenous anesthesia

- Are often used for rapid induction of anesthesia, which is then maintained with appropriate inhalation agent.

- They are rapid induced anesthesia and so must injected slowly.

Intravenous Anesthetics

Anesthesia is split into two different types:

- Inhaled Anesthesia (used for maintenance)
- Intravenous Anesthesia (used for induction)

- Long ago, Barbiturates such as Thiopental above the hypnogenic dose were used to induce anesthesia. The main issue with this was that it would cause strong nausea post-surgery, which is why it was replaced by Propofol, which is commonly referred to as “milk” among medical staff because of its white color. It is also the drug of choice and the most used drug for inducing anesthesia.
- We know very little of the MOA of Propofol; all we know is that it works similar to Barbiturates in that it increases the duration of opening of the GABA-gated chloride channel.
- Propofol is also hypnotic, like Barbiturates.
- It induces unconsciousness in the patient within 10 seconds, since it is used intravenously.

Propofol

- Propofol Is an intravenous sedative/hypnotic used in the induction and maintenance of anesthesia, supplementary analgesics is required.

- Propofol is widely used and has replaced thiopental as the first choice for anesthesia induction and sedation, because it produces euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting.

  - Mechanism of action not known but may be through GABA
  - Hypotension caused mainly by vasodilatation rather than cardiac depression
  - Non-analgesic
  - Antiemetic
  - Reduces cerebral blood flow
  - Promotes bacterial growth (hence short shelf life of open solution)

Propofol appears white because it is formulated as a lipid emulsion, which allows this highly lipophilic drug to be soluble. A key component of this emulsion is egg lecithin (the phospholipid from eggs). Because it is a lipid-rich emulsion, propofol provides an ideal environment for bacterial growth. Therefore, once a bottle is opened, it should be used promptly—ideally on the same day—to minimize the risk of contamination and potential infection when administered intravenously.

Why is Propofol so good?

- As mentioned before, anesthesia is very complicated, so there are many factors we must consider when using a drug, with the most important being intracranial pressure. Most other medications cause an increase in intracranial pressure; because they are vasodilators. Propofol, however, does not, making it not just the drug of choice for induction, but also the only used drug (being antiemetic also plays into this).

Ketamine

- A short acting, induced anesthetic. It actually induce a dissociated state in which the patient is unconscious but appears to be awake and does not feel pain.
- Provides sedation, amnesia, and immobility.
- It stimulate the central sympathetic outflow, which causes stimulation of the heart and increased blood pressure, and cardiac output.
- This property is specially beneficial in patients with either hypovolemic or cardiogenic shock, as well as in patient with asthma.

Ketamine: a useful alternative

- Ketamine is another IV anesthesia inducer, but it is quite different from Propofol; it works on NMDA receptors instead. Its MOA is though to be blocking the action of glutamate on NMDA receptors, which decreases calcium entry, leading to hyperpolarized state. Naturally, this effect is dose-dependent.
- Eventually, this leads to a dissociative state, where you can see the patient looking at you, but they are not aware and are unconscious. Ketamine thus has euphoretic effects.
- Ketamine is considered a useful alternative for propofol because it does not cause hypotension, nor bradycardia. It has a short duration of action (10-15 minutes), making it useful for children, by putting them in a dissociative state while performing quick interventions without causing hypotension or interfering with their circulation.
- It can be used with adults if needed (such as in hypotensive, bradycardic, or heart failure patients).

Ketamine: a useful alternative

- Ketamine has been approved as an IV antidepressant since 2021.

- Due to its action on NMDA receptors, it causes rapid changes in the brain, leading to a quick onset of action opposite to typical antidepressants that need weeks for therapeutic effects.

- We can also use Ketamine in pain management. NMDA receptor blockers (including Ketamine, and Methadone *from the MID material*) can be used to treat resistant pain that does not respond to Morphine or other typical opioids.

All-in-all, we see Ketamine has 3 uses/applications:

1. Used as an induced anesthetic in hypotensive/bradycardic patients.
2. Used as an anti-depressant
3. Used in resistant-type pain.

Halothane, Isoflurane, Sevoflurane, Desflurane ⇔ For maintenance of anesthesia

Inhalation anesthesia

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

In other drugs, IC50 and EC50 are used.

The anesthesia device projects 3 tubes, for:

a. Oxygen
b. Nitrous Oxide (غاز الضحك)
c. Inhaled Anesthetic

Inhaled anesthetics as are liquid in the container and are vaporized for inhalation via the alveoli.

They are extremely lipophilic, so:

- They are absorbed easily to the bloodstream
- They cross the Blood-Brain Barrier.

Inhalation anesthesia

- No specific receptors has been identified as the target of general anesthesia action.
- The fact that chemically unrelated compounds produce the anesthesia state argue against the existence of such receptors.
- The focus is now on interaction of inhaled anesthetics with proteins comprising ion channels.
- For example, the general anesthesia increase the sensitivity of the gama-aminobutyric acid (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.

2 Theories emerged to explain their anesthetic effect:

1. 1951: they lodge into cell membranes of neurons, thereby disrupting neuronal conduction. *[old theory]*
2. They hyperpolarize neurons by acting on GABA (barbiturate-like effect) and NMDA (Ketamine-like effect) receptors, and potassium channels.
   [newer, more acceptable theory]

Inhalation anesthesia

- MAC is 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.

Recall the anesthesia machine with 3 tubes, it administers a mixture of Oxygen, N_2O, and an anesthetic.
Say N_2O% of the mixture is 73%, O_2% is 26%, percentage of anesthetic X is then 1%.

MAC is defined as that percentage of anesthetic in that mixture that produces immobility in 50% of patients. Therefore:

- If anesthetic X achieves this effect at **1%**, its MAC = 1%.
- If another anesthetic (Y) has a MAC of **1.5%**, it requires a higher concentration to achieve the same effect.

Ergo, Anesthetic X is more potent than Y.

Inhalation anesthesia

- Other receptors are also effected for example, the activity of the inhibitory glycine receptors in the spinal motor neurons are increased.

- In addition, inhalation anesthesia block excitatory postsynaptic current of the nicotinic receptors.

Why is halothane nice? It does not produce toxicity in children.

Halothane

- 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 series side effect and the availability of other anesthetics that have less complication, halothane is largely being replaced.
- Halothane is potent anesthetic, nonetheless it is relatively weak analgesic. Thus, it is co-administrated with Nitrous oxide, Opioids.

Halothane

- Halothane produce 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.
- Halothane is metabolized in the body to tissue toxic materials, which may be responsible for the toxic reaction that some patients (specially females) developed after anesthetic.
- The reaction begin as a fever followed by anorexia, vomiting, and patient may exhibits sighs of hepatitis.

This point was emphasized, Dr. Malik said nausea and vomiting are particularly bad with halothane, however children are spared.

Two very important points about halothane:

1. It produces bronchodilation. It is unique among inhalational anesthetics which normally produce slight bronchoconstriction; thus, Halothane is useful for asthma/COPD patients.
2. 20% of Halothane is metabolized in the liver in adults. Normally inhalational anesthetics enter and leave through the lungs without being metabolized, Halothane is an exception and only in adults, as children have not yet acquired the ability to metabolize it into its harmful metabolite that is associated with hepatotoxicity.

Halothane

- 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.
- In a very small percentage of patients halothane has the potential to induce malignant hyperthermia.

All inhalational anesthetics produce hypotension

As hypotension ensues, the heart compensates by becoming more sensitive to catecholamines, which is the principal reason that heart arrythmias happen with Halothane and other anesthetics.
Sevoflurane is best in this regard, as it causes the least sensitization and least hypotension, and of course, that reflects in its price, being most expensive.

Halothane causes the worst, most pronounced hypotension and bradycardia.

Vasoconstrictors, such as Alpha-1 agonists, are used in combination with inhalation anesthetics to compensate.

Not required for the exam

Enflurane

- Is less potent than halothane, but produce rapid induction and recovery.
- About 2 % is metabolized to fluoride ion, which is excreted by the kidney, therefore Enflurane is contraindicated in kidney failure patient.
- Enflurane exhibit the following differences from halothane:

  (1) Fewer arrhythmia, (2) less sensitizing the heart to catecholamines, and (3) greater potentiation of muscle relaxants due to more “curare-like” effect.
- Disadvantage of Enflurane is that it does cause central nervous system excitation, and so is contraindicated in patients with seizure disorder.

Isoflurane

Inhaled... Exhaled.
"Zero" Metabolism, "Zero" Hepatotoxicity.

- 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.

➔ Inaccurate, it does produce sensitization but not severe.

Even though Sevoflurane produces less adverse effects, isoflurane is most widely used because of its good cost-to-adverse reaction ratio.

Isoflurane and desflurane
cause hypotension, but not bradycardia.

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

Widely used in dental procedures

Nitrous oxide

The 3rd pipe. It is potent and is used because it accelerates the effect of inhaled anesthesia.

Click Here for a Story from Dr. Malek

- Is a potent analgesic, but a weak general anesthetic (at 80% cannot produce surgical anesthesia).
- Therefore, it combined with other potent anesthetic agent to obtained a surgical anesthesia
- Is frequently employed at concentration of 30% in combination with oxygen for analgesia, particularly in dental surgery.
- Because of its fast uptake from the alveolar gas, Nitrous oxide produce what is called “second gas effect”, which result from the ability of Nitrous oxide to concentrate the halogenated anesthetics (Halothane, Enflurane, Isoflurane) in the alveoli when they are coadministrated,

It is called "غاز الضحك" because it produces euphoria.

Important point, Which anesthetic has a second gas effect? Its Nitrous Oxide.
The diffusion capacity for N_2O is much higher than that for oxygen *(Recall RS)* when the patient takes a deep breath of N_2O, it diffuses rapidly into the bloodstream from the alveoli, which is almost like it creates negative pressure in the alveoli, which in turn forces oxygen and the anesthetic of choice into the alveoli, accelerating their effect. That is the second gas effect.

Nitrous oxide

- Main disadvantages is that it has a speed movement, which may retard the oxygen uptake during recovery, thus causing diffusion hypoxia.

- It has moderate to no effect on the cardiovascular system and the least hepatotoxic of the inhalation anesthesia.

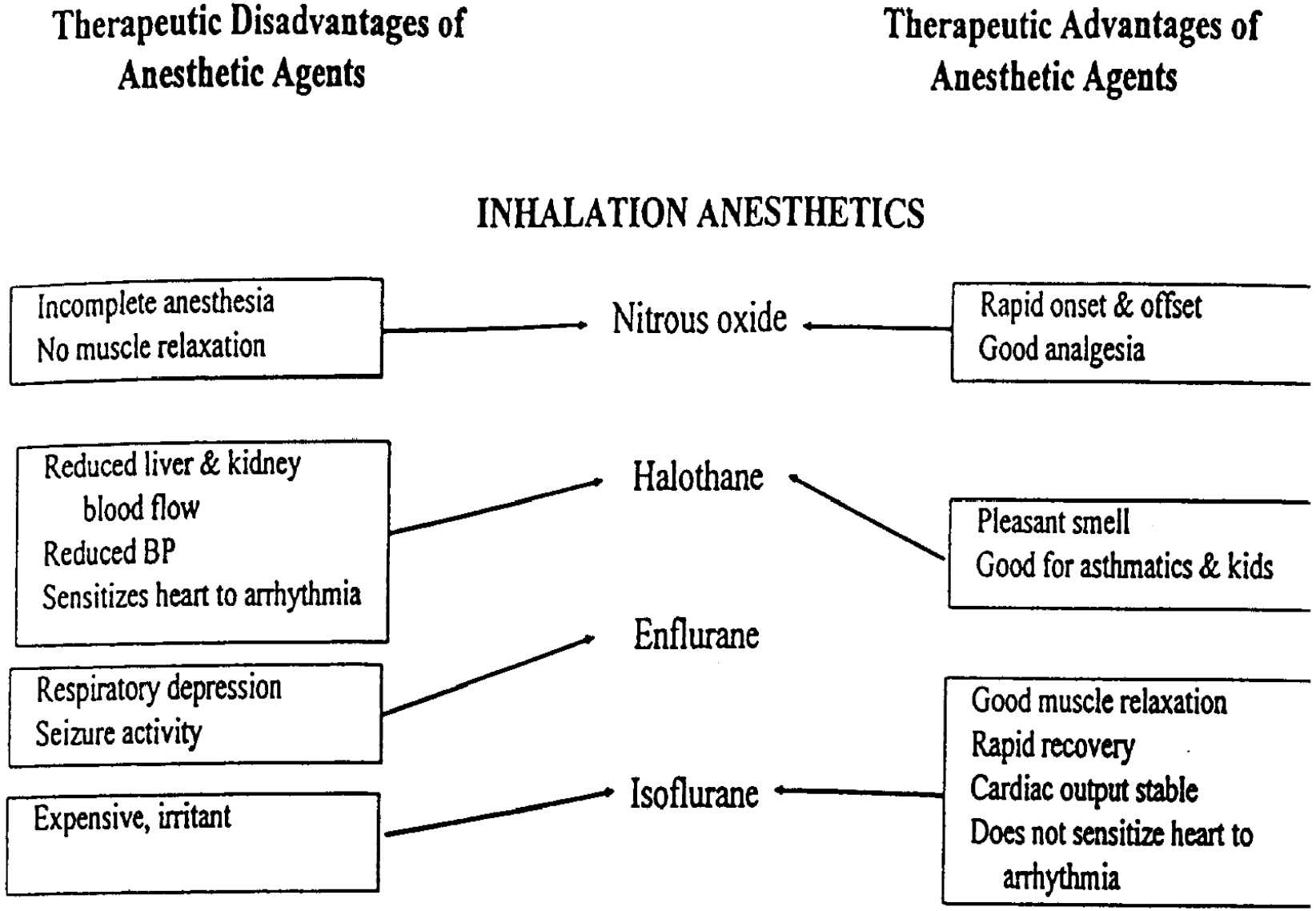
The opposite of the second gas effect:
Since N_2Os diffusion capacity is much higher than oxygen, when it exists it occupies most of the alveoli and dilutes Oxygen, hindering its ability to diffuse, causing Diffusion Hypoxia. So, when the patient exits the OR after N_2O, we administer 100% pure oxygen.

Barbiturates

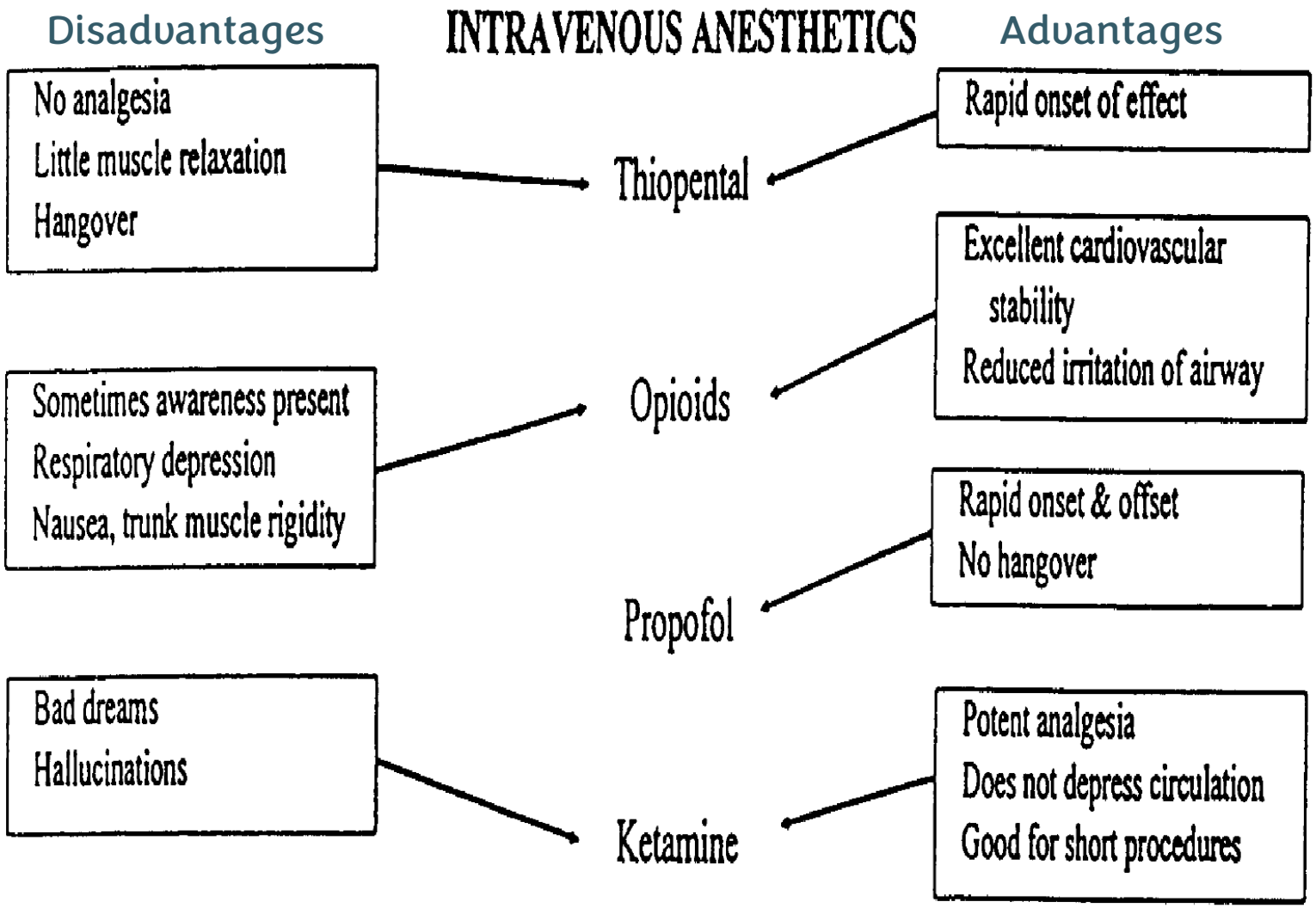
This slide was skipped, but you can read it just in case.

- Thiopental is a potent but weak analgesics. It is an ultra-short-acting Barbiturate and has high lipid solubility.
- Quickly inter the CNS and depress function, often in less than one minute.
- It produces short duration of action because its concentration in the CNS decrease quickly below that necessary to produce anesthesia.
- Main adverse effects are coughing, chest wall spasm, and bronchospasm (asthmatic patient).

SUMMARY


Therapeutic Disadvantages of Anesthetic Agents
Therapeutic Advantages of Anesthetic Agents
INHALATION ANESTHETICS
Incomplete anesthesia
No muscle relaxation
Nitrous oxide
Rapid onset & offset
Good analgesia
Reduced liver & kidney blood flow
Reduced BP
Sensitizes heart to arrhythmia
Halothane
Pleasant smell
Good for asthmatics & kids
Respiratory depression
Seizure activity
Enflurane
Expensive, irritant
Isoflurane
Good muscle relaxation
Rapid recovery
Cardiac output stable
Does not sensitize heart to arrhythmia

Summary


Disadvantages
INTRAVENOUS ANESTHETICS
Advantages
No analgesia
Little muscle relaxation
Hangover
Thiopental
Rapid onset of effect
Excellent cardiovascular stability
Reduced irritation of airway
Sometimes awareness present
Respiratory depression
Nausea, trunk muscle rigidity
Opioids
Rapid onset & offset
No hangover
Propofol
Bad dreams
Hallucinations
Ketamine
Potent analgesia
Does not depress circulation
Good for short procedures

PHARMACOLOGY QUIZ LECTURE 5

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			