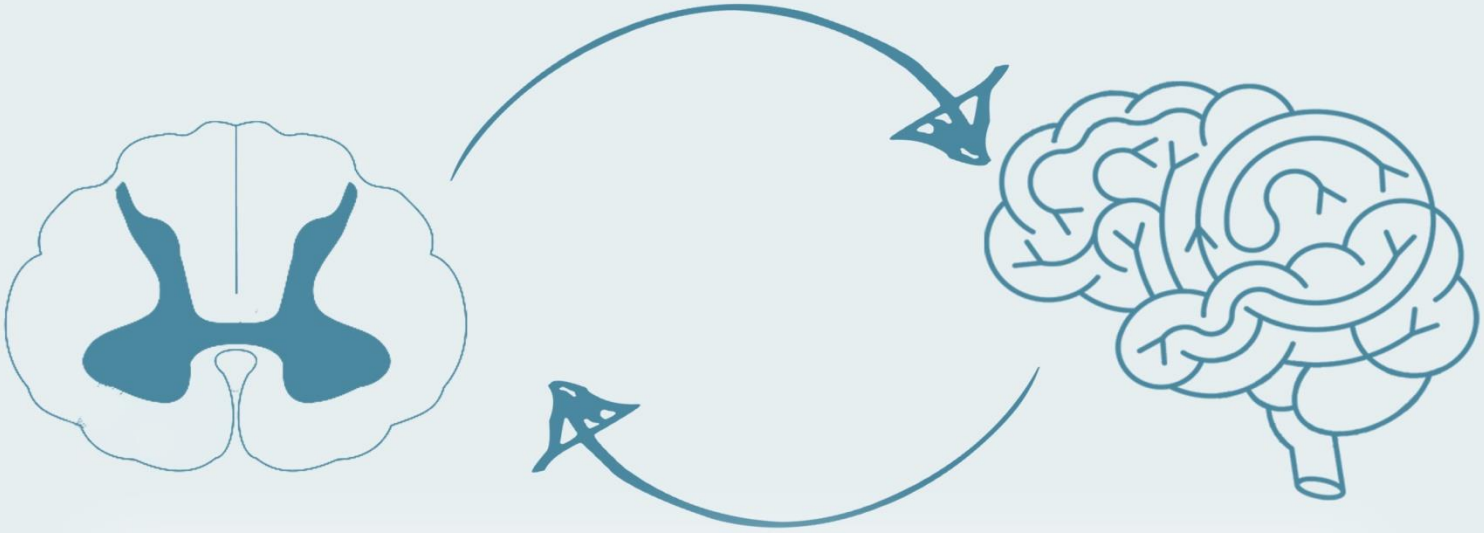


CNS

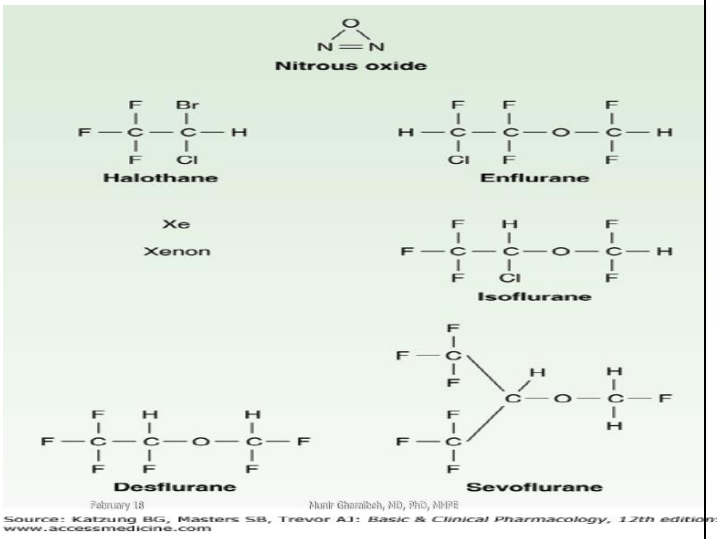
pharmacology

0 slides 0 sheets

number	4
Done by	Kamal Nasir
Correction	Dr. Munir
Doctor	Munir Gharaibeh

Inhalational Anesthesia:

The doctor continued talking about inhalational anesthetics; he talked about the structure of those agents. As you can notice from the figure and from the names of those agents (flu), most of them consist of fluoride ions, and this is the main reason for them being nephrotoxic. Xenon, although is an inert gas, but can be used as an anesthetic.



Mechanism of action of those drugs is more related to a physical interaction than a chemical one with brain tissue, so it depends on the agent's ability to interact with the neuronal fluid membrane, and this interaction will result in decreased levels of alertness and consciousness.

Table 31-2. Summary of Major Characteristics of Important Anesthetics

	Analgesia	Blood pressure	Respiration	Muscle relaxation	Prominent adverse effects	MAC	Blood-gas partition coefficient at 37°C	Vapor pressure at 20°C (torr)
Ether	4+	↑	↑	3+	Flammable; slow action	1.9	12	425
Halothane	2+	↓	↓↓	+	Myocardial depression; hepatotoxicity?	0.77	2.3	243
Methoxyflurane	3+	↓	↓↓	+	Renal toxicity	0.16	12	23
Enflurane	2+	↓	↓↓	2+	Respiratory and cardiovascular depression	1.68	1.8	175
Isoflurane	2+	↓	↓↓	2+	Respiratory and cardiovascular depression	1.15	1.4	239
Chloroform	2+	↓	↓↓	+	Hepatotoxicity; narrow margin of safety	0.77 In dogs		160
Nitrous oxide	4+	Little change	Little change	None	Weak anesthetic—need other agents as well	105%	0.47	Gas
Cyclopropane	2+	↑	↓	2+	Flammable; expensive	9.2%	0.4	Gas

Regarding the figure above, doctor mentioned the following:

- Ether and nitrous oxide both have the highest level of analgesia so they are used in cases of more painful procedures.
- Most of them decrease blood pressure, except for cyclopropane and ether.
- Ether is not used clinically nowadays.
- All of them are muscle relaxants, with Ether being the strongest, except for Nitrous oxide which lacks this characteristic.

Halogenated Anesthetics:

Most of the available general anesthetics belong to this family.

1) **Halothane**
    - It is the prototype for halogenated anesthetics. It decreases respiration rate, blood pressure, and is a good muscle relaxant.
    - Nonflammable, Nontoxic, has a sweet odor.
    - Complete anesthetic in high doses, has a high MAC.
    - Cardiorespiratory depressant, sensitizes the heart to NE.
    - It may cause Hepatic Necrosis (1/35.000), which is an allergic reaction to halothane. This reaction needs sensitization, meaning that it occurs with second exposure to the agent not the first one, and antibodies can be detected in serum.
    - It causes abortion in animals, but not in humans.
    - It is not commonly used nowadays.

2) **Enflurane**
    - Has a stronger activity in neuromuscular blocking, in addition to rapid induction and emergence. On the other hand, this drug sensitizes heart to catecholamines, is associated with seizures like EEG changes, and releases fluoride ions causing nephrotoxicity.

3) **Isoflurane**

- This drug is similar to Enflurane but it maintains the cardiac output and has minimal effect on it. It is also less metabolized so less hepatotoxic.

4) **Desflurane**
    - It has low solubility, and rapid induction and emergence.
    - Used in outpatient procedures. (Receiving medical treatment without being admitted to the hospital e.g dentistry)

5) **Methoxyflurane**
    - Sweet smelling
    - Slow induction & emergence due to high solubility.
    - It causes intense analgesia, and the blood pressure is maintained.
    - Causes renal toxicity.

6) Sevoflurane

Nonhaloganetd anesthetics:

Nitrous Oxide:

- It is an old gaseous chemical compound that was used in circus as the "laughing gas".
- It is a cardiac depressant, but stimulates the sympathetic system.
- It lowers tidal volume but increases respiratory rate, so it has a minimal effect on respiration.
- Very weak, MAC = 105%.
- Very easy to use, it is given through a mask, and is very safe.
- We give this gas under hyperbaric conditions (more than atmospheric pressure).
- Analgesic (25% of Morphine power)

- Used in dentistry and labor, but epidural analgesia is nowadays more preferable in labor.
- Mainly used in the induction phase and then a halogenated anesthetic must be administered.
- It can also be combined with other agents if there is pain.

Ether:

It is the oldest anesthetic agent; action was first demonstrated in 1846, and was first used in dentistry. Ether is flammable and explosive, and also irritant for both the patient and the doctor. This drug has a long duration of action, and has a slow induction. It is eliminated through exhalation over a period of few days. It is a complete anesthetic but with poor activity. The drug is safe but has few side effects represented by postoperative nausea and vomiting.

Cyclopropane

Chloroform

Antiparkinsonian Drugs

Parkinson, also known as paralysis agitans, is a disease described by a scientist named James Parkinson in 1817. It is characterized by peculiar gate, bradykinesia, and resting tremor. Patients usually have poor facial expressions (Mask like face), and they suffer from depression and dementia. The type of rigidity involved with this disease is Cog-wheel, in comparison with clasp knife spasticity associated with stroke. Patients usually have reduced arm swinging while walking, and they also suffer from cognitive decline.

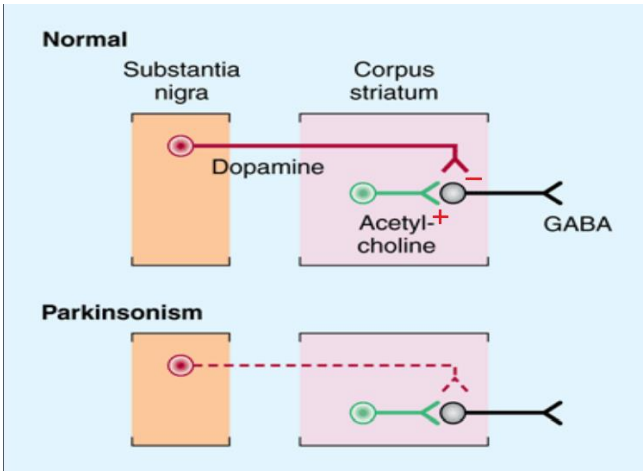
**Huntington's chorea is a different disorder characterized by loss of cholinergic neurons.

Etiology:

- Postencephalitic (viral infection)

- Arteriosclertoric
- Autoimmune
- Poisoning: Co, Mn++, Mercury, Copper (Wilson disease). **MTPT** which is a synthetic byproduct of meperidine drug (similar to morphine), and it is a protoxin that gets converted to the toxin MPP+ leading to cell death and premature Parkinsonism.

- Drugs (iatrogenic):
    - Reserpine and α-Methyl Dopa which are used for hypertension as they can cause depletion of norepinephrine and dopamine.
    - Anti-psychotics can cause conditions similar to Parkinson but not the disease itself.
- Aging
- Genetic factors
- Multi-factorial



Parkinson is mainly due to an abnormality in dopamine secreting neurons in the four nuclei of basal ganglia. Voluntary motor function is initiated in the cerebrum which contacts the basal ganglia to initiate voluntary muscle movements. Dopamine is an *inhibitory* neurotransmitter secreted from Substantia Nigra and it inhibits GABAergic activity (inhibits the main inhibitory neurotransmitter of CNS), so it is important for proper motor function. On the other hand, cholinergic system is the excitatory neurotransmitter for GABAergic activity, so any loss in the inhibitory dopaminergic system will cause over excitation of the cholinergic and hence the GABA causing **inhibition of CNS.**

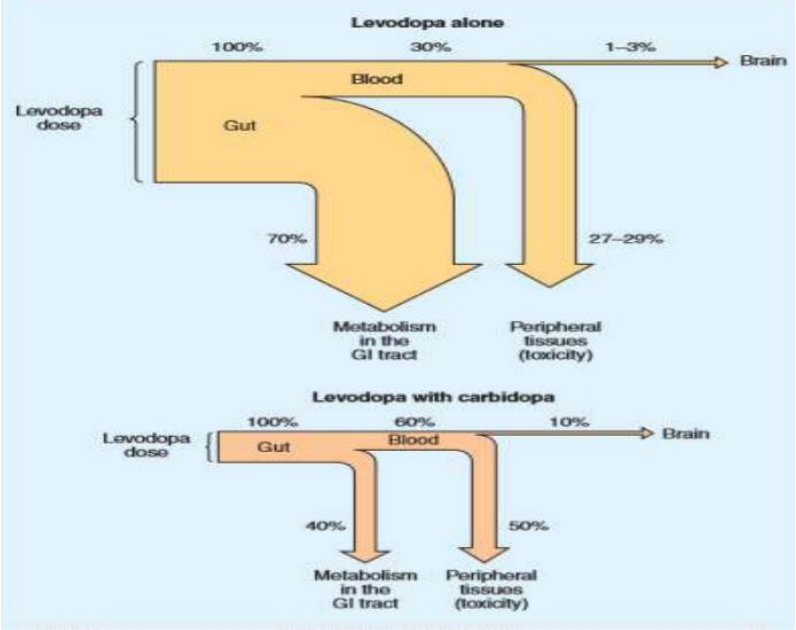
It is given as L-DOPA which is derived from tyrosine; they bind to dopamine receptors found in basal ganglia.

Dopamine does not cross BBB, it should be given intravenously, so it is given as L-DOPA (which can cross BBB, and in brain converted to dopamine).

1) **L-DOPA or Levodopa**
    - This drug is given instead of Dopamine because the latter is not absorbed well from the GIT and doesn't cross BBB. L-DOPA is given orally as it is well absorbed and can reach the systemic circulation; it also reaches the brain. It is derived from tyrosine, and binds to dopamine receptors found in basal ganglia.

When we administer Levodopa part of it is converted to dopamine in the systemic circulation, so if we can inhibit this peripheral conversion, higher levels of Levodopa will be available to reach the brain. This also lowers the availability of dopamine peripherally, and consequently the peripheral effects of dopamine (mainly cardiovascular effects) will be avoided. Drugs targeting LAAD enzyme (L-dopa decarboxylase) like **Carbidopa and Benserazid** are always combined with L-dopa to reduce the dose of L-dopa and its corresponding side effects. The combination of Levodopa with the Carbidopa is named "**Sinement**" and it is given in different doses 10/100mg, 25/100mg, 25/250mg (dose of Carbidopa/ dose of Levodopa).

The figure below compares administering Levodopa with Carbidopa and without, pay attention to the percentage reaching brain.



- Most effective drug.
- Rapidly absorbed but delayed by some types of food.
- Should be used for years to observe the fruitful outcomes (will not completely cure the disease).
- Does not stop the progression of the disease, but lowers mortality.
- One third of the patients respond very well and one third less well, and the remainder either are unable to tolerate the drug or do not respond at all.
- Responsiveness may be lost completely, perhaps because of the disappearance of dopaminergic nigrostriatal nerve terminals, or some direct pathologic process of the receptors.

- Side effects: (doctor said read them without memorization, but take a look at the important point)

I. GI symptoms→ Anorexia, Nausea, Vomiting.
II. Cardiovascular effects→ Postural Hypotension, tachycardia, extrasystoles,
III. Dyskinesias→ Choreoathetosis of the face and distal extremities is the most common. Variable among patients. (Choreaathetosis is nonrhythmic, rapid, nonsuppressible involuntary movement)

IV. Behavioral effects→ Depression, anxiety, agitation, delusions, hallucinations, confusion.

V. Fluctuations in response→ (important)

I. Wearing off reaction and also known as End of Dose Akinesia; is the emergence of symptoms when we reduce concentration of the drug.

II. On-off Phenomenon: marked dyskinesia alternating over the course of a few hours with on-periods of improved mobility. It is treated with **Apomorphin** injection, which is a strong dopamine agonist starting to work within 10 minutes of injection and lasts for up to 2 hours.

VI. Miscellaneous Effects: Mydriasis, glaucoma, hot flushes, and gout.

Contraindications**:**

- Psychotic patients → can lead patients having Schizophrenia to Parkinson
- Glaucoma
- Active peptic ulcer disease
- Bleeding
- History of melanoma or undiagnosed skin lesions

2) **<u>Dopamine receptor agonists</u>**

- Directly stimulate receptors
- Not superior to other drugs.
- Variable response for patients
- Lower incidence of dyskinesia and fluctuations.
- Have a long duration of action.
- Used as first line therapy.
- Less effective but can be used instead of Levodopa to prevent the side effects.
- Can be used as adjunct to Levodopa.

- **Bromocriptin→** D2 agonist which suppresses lactation and is an ergot plant derivative.
- **Pergoride→** Also an ergot plant derivative
- **Praminepixol**
- **Ropinirol→** has a neuroprotective activity by scavenging hydrogen peroxide.

  They have side effects like Levodopa but they are less severe and without the on and off phenomena

3) **<u>Drugs Inhibiting MAO and COMT enzymes:</u>**

   These drugs inhibit metabolism of dopamine in brain and peripheral nervous system.
- **Selegilline→** inhibits MOA increasing level of dopamine centrally and peripherally.
- **Rasagiline→** inhibits MOA increasing level of dopamine centrally and peripherally.
- **Entacapone→** inhibits COMT
- **Tolcapone→** inhibits COMT.

4) **<u>Amantadine (Antiviral drug)</u>→** it is used for Influenza and it's helpful for Parkinson patients as it enhances synthesis, release and uptake of dopamine.

5) **Amorphin→** used for on and off phenomena.

6) Anti-cholinergic drug:
- **Atropine→** natural alkaloid
- **Scopolamine→** natural alkaloid

   Synthetic alkaloids:
- **Trihexylphenidyl**

- **Benztropine**
- **Biperiden**
- **Orphenadrine**
    - These drugs are used in mild and early stages.
    - They are helpful in blocking Sialorrhea, which is a consequence of Parkinson disease defined as an incoordination of muscles causing drooling of saliva, so those agents cause dryness.

7) Antihistamines→
- **Diphenhydramine**
- **Orphenadrine**
- **Chlorphenoxamine**.

Other agents used in neuroprotective therapy:

- Antioxidants
- Anti-apoptotic agents
- Glutamate antagonists
- Glial derived neurotropic factors.
- Coenzyme Q10
- Creatine
- Antiinflammatory agents
- Gene therapy
- Surgery:
  - Ablation of the ventral intermediate nucleus of the thalamus for tremor.
  - Ablation of the posteroventral portion of globus pallidus for dyskinesia.