

* Pharma (5) ..
((Cont. Anesthesia ..))

* بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

→ Inhalation Anesthetics :o

Notes :o

[1] Pharmacodynamic: The body's biological response to drug.

← (تأثير الدواء على الجسم)

[2] Pharmacokinetics (Simply): What the body does to the drug.

← (تأثير الجسم على الدواء)

* ملاحظة: لمعرفة تأثير دواء أخذته (Oral / IV) ، فإنني سبب عنده صودا
المريض ، ومن ثم نقوم بالمقارنة بين الـ

Conc. of drug in blood.

Effect of drug (therapeutic effect)

، زيادة على ذلك فإنني زيادة الجرعة ، صودا لـ :

((Desired effect))

[3] Effective dose 50 (ED50): The dose of medication that produces a specific effect in 50% of Population that takes that dose.

[4] lethal dose 50 (LD50): The dose of medication that required to kill 50% of the test animals ((Reaches toxic dose)).

[5] Therapeutic index window: The range of drug dosages which can treat disease effectively without reach or having toxic effects.

← (ملاحظة: ED50 ، LD50)
((unwanted effect)) ((wanted effect))

[6] Therapeutic window of inhalation anesthesia is low, minimal extra-dose could cause lethal toxic dose.

So, It's important to be careful, and using it in lower therapeutic level.

← {
- Sympathetic suppression.
- Respiratory suppression.
- CV suppression

[7] To ~~measure~~ measure the conc. of inhaled anesthetic drug → end tidal volume

↳ Measured by Mechanical ventilator machine.

Alveoli drug concentr. ←
وحتى نستطيع معرفة مقدار الـ
ويزداد لو حسبنا بالقدرة مع (Therapeutic effect) المستطوع
Desired Effect ← For Therapeutic desired dose

[8] MAC (minimum alveolar concentration): The minimum concentration of an inhaled anesthesia, that prevents skeletal muscle movement in response to a surgical incision in 50% of Patients. ⇒ ED 50

كل Gas الـ MAC في الـ Alveoli

↳ To Reach Full therapeutic anesthetic effect to All patients ⇒ ((MAC × 1.3))

MAC of NO₂ is the highest = 105%

[9] MAC - awake: ((Not responds to ^{الأوامر} Commands, but still lower MAC value. Patient able to respond to a noxious stimulus.))

← = المريض لا يستجيب للأوامر، أرفع اليد، حركه جلد...
← = كل شيء يستجيب للـ Painful Stimuli

[10] Partition Coefficient: Describe how a Solute is distributed between 2 immiscible solvents.

Cont. →

→ Inhaled anesthesia is distributed between Air / Blood.
← من مصداق: إذ لو كان (Higher solubility) في الـ Air عن Blood

If solubility is higher in Blood → Recovery Period will be longer

* Partition Coefficient $\Rightarrow \frac{\text{Blood}}{\text{Air}} \Rightarrow < 1$
Fast recovery
higher affinity in Air.

[11] Alveolar-to-Venous Partial Pressure Gradients.

↳ The differences between alveolar and venous Partial Pressure is due to: tissue uptake of inhalation agents.

venous bld ← Brain tissue ← Arterial bld ← Alveoli ← Inhalation Anesthesia
↳ Lung

↳ ∴ Partition Coefficient equal (1) if Partial pressure gradient is persists ((Maintained))

← الداخل = الخارج
← التركيز متساوي في كل من الـ Tissue / Blood
(Partial Pressure) in Alveoli = (PP in Blood) ←
= (in tissue).

⇒ Stop Inhalation Anesthesia ∴
drug concentration will decline downward (backward)
From Brain tissue to blood → Alveoli. ((Redistribution))
* Higher Conc.

* Note: ① At equilibrium Partial Pressure is equal but,
Concentration is equal!!
↳ depends on Partition Coefficient.

(Nitric oxide)

② NO is the highest MAC, Higher dose is needed to reach anesthetic Action.

← لذلك فأنه استسخدم فقط 50-80% من جرعة ^{MAC} وبنسبة متوسطة على
ال sedative action ← (Anesthetic action) (ما بضرته في 1.3) !!

← لا نستخدمه لوحده إنما بجانب (other inhaled anesthesia).

(50%)
③ If Nitric oxide used For example in Combination with Isoflurane, I can't use Isoflurane its original dose: $\rightarrow 70\%$.



Slide (17+18)

Important Nitric oxide is not used in case of Pneumothorax / Skull base Fracture or any other injuries causing Air occupying areas.

← وذلك لأنه لا NO يرتبط بـ Nitrogen receptors، ولا N₂ يحد من انتشاره أو تسريبه خارج الجسم فأنه لا NO / N₂ ينحصر في داخل cavity مما يزيد حجم cavity.

→ 1) Causing : 1) Compression on surrounding structures.
2) ↑ herniation.

lower MAC → more potent

Isoflurane Lower MAC than NO ⇒ ∴ Isoflurane is more potent drug (with lower dose, reach therapeutic effect)

Highest MAC → NO / # Lowest MAC → Halothane

أيضًا يجب الأخذ بعين الاعتبار $\leftarrow$ (Partition Coefficient)

2.3
1) Halothane $\rightarrow$ high Partition coefficient & high affinity to blood $\rightarrow$ (Slow/Long recovery)

$\rightarrow$ High Potent $\rightarrow$ long recovery Period.

$\rightarrow$ Contact time between Brain / blood (High).

$\rightarrow$ Accumulation in Peripheral tissue

$\rightarrow$ As Anesthetic agent :-

$\rightarrow$ suppress COP ✓

$\rightarrow$ suppress Respiratory ✓

$\rightarrow$ Vasodilation. ✓

$\rightarrow$ Excretion :-

• Expiration $\rightarrow$ خروج الدواء من الجسم $\rightarrow$ excretion $\rightarrow$ خروج الدواء من الجسم =

$\rightarrow$ but, Halothane

$\rightarrow$ 80-60% $\rightarrow$ expiration

$\rightarrow$ 20-40%

$\rightarrow$ Metabolism Pathway:

Producing:

(Bromide + Floride + trifluoro-acetic acid)

= Hepatotoxic agents :

$\rightarrow$ may cause fulminant hepatitis.

((Stages of Anesthesia))

Induction

* High dose of drug.
(stage I $\rightarrow$ III)

Maintenance

* Maintained dose of drug till the end of operation.

Recovery

* Withdraw of drug by cessation administration.

→ According to the Above...

↳ can I use Inhalation Anesthesia in induction dose? (knowing, it has Low Therapeutic window.)

↳ NO^{I can't}, instead of it I use IV drugs as: Profol or bentothale

↓
Exception → (Nitric oxide + Sevoflurane) can be used in induction phase.

↳ Also, Not cause Bronchocon. : use (Asthmatic patient / ^{children} / ^{pts})

Anesthetic drugs not give Analgesic effect except Ketamine.

① ↳ In Induction dose: I Look for drug, ~~not~~ give higher effect with Lower dose.

↳ Anesthesia
↳ Immobilization
↳ Amnesia

[- IV drugs or
- NO + Sevoflurane]

↳ Anesthetic drugs will given in combination with Analgesic agents (Narcotic), (Fentanyl).

② ↳ Maintenance; with inhaled Anesthesia.

(Isoflurane / Halothane) ← الوارد على

→ CVD ← لا يوجد على

↳ High recovery.

Anesthetics (2)

Study slide (1/2/3)
4

① Isoflurane $\Rightarrow$ (1.4) Partition Coefficient.

- $\hookrightarrow$ High $\rightarrow \therefore$ high solubility in blood.
- $\hookrightarrow$ long recovery duration.
- $\hookrightarrow$ Not used for induction.

Note :

Soda lime : Cause entraption to CO₂ (Expired) ^(only), in close circuit of inhalation.

$\hookrightarrow$ SevoFlurane activate with soda lime causing toxic material $\Rightarrow$ cause nephrotoxicity.

② SevoFlurane $\Rightarrow$ (0.65)

$\hookrightarrow$ used in induction phase.

$\hookrightarrow$ Cause minimal suppression to CVS / Respiratory.

$\hookrightarrow$ Still cause vasodilatation.

$\rightarrow$ (Malignant hyperthermia : 0)

(Malignant Hyper.) تقریباً كل ادوية Anesthesia تب inhaled

② $\hookrightarrow$ succinylcholine the lonely NMj blocker that cause Malignant hyperthermia.

$\hookrightarrow$ Cause : uncontrolled released to Ca²⁺ (Ca²⁺ channels on ER)

$\hookrightarrow$ ↓ metabolism

$\hookrightarrow$ ↑ thermoregulator centers $\rightarrow$ ↑ heat

$\hookrightarrow$ Irregular loss of temperature that produce from metabolic reactions.

$\hookrightarrow$ ↑ production / ↓ loss of heat

① (Stop Anesthesia) : وقف الدواء *

② Fluids (cold).

③ Dantrolene $\rightarrow$ block Ca²⁺ channels.

Contr. $\rightarrow$

Burn victims & Patients with muscular dystrophy & myopathy
& Myotonia & Osteogenesis imperfecta.

↳ They are susceptible to Malignant Hyperthermia.

1

Propofol (ON-OFF mechanism) →

1) Iv sedative / hypotonic

2) Used for induction + maintenance anesthesia.

3) Highly irritants. (Alkaline) & lipid emulsion (milk like) infusion.

off: anesthetic

Sedative Phase

30 min

تقریباً

(Iv drugs & Inhalation & (Recovery)) : في غالبية الأحوال
(Induction) (Maintenance)

↳ Bolus Iv

↳ Lipophilic

↳ Reach to rich

blood vasculature organ
(Brain) (High amount)

(Poor blood supply)

Low blood

vasculature.

(Low amount)

(Faster)

(Drug distribution)

= In Induction From high Con. (Blood) → low Con. (Brain)
= In Recovery From high (Brain) → low (Blood) (More slowly)

بمجرد ↓ ال Con. في ال Brain ال dose تصبح شيئاً فشيئاً أقل

Sedation Anesthetic effect

↳ (Accumulated dose in) brain ..

So Dentothale → more lipophilicity → More accumulation in brain → ↑ Recovery time.

Expired air.

Note : Recovery of inhaled anesthesia is faster than Iv dose.

⇒ Hiccup :-

= بدأت مع الحرقنة (induction) (IV) وبعدها (Maintenance) الحرقنة
inhalated anesthesia ، رغم سيقول IV Conc. هنا ، لكنه لا بأس ، لأنه لا يتم تقويض
الفاقة بال inhaled dose ، وكذلك بعد ذلك لما توقف ال dose
أدخل في ال Recovery وصار كل شيء عاد إلى طبيعته .

- ② Barbiturates :- Fast onset مقارنة others / Long onset ^{مقارنة} Propofol.
(Thiopental / Benthothal.)
↳ long acting , more lipophilic than Propofol
(higher Recovery Period) ..

③ Benzodiazepine :-

.. Used in Conjugate with Anesthesia agents for (Sedation + Amnesia)

Sedative dose ^(ICU)
of drug is
lower than
anesthetic dose.
^(surgery)

⇓

Example: midazolam / Diazepam / Lorazepam .

⇒ It Cause:

- 1) enhancing inhibitory effect to NT (GABA)
- 2) Minimal CV depressant.
- 3) Still Cause Potential respiratory depression .

④ Opioids :- (Narcotics)

- Used in combination with anesthetic drugs , because their analgesic Property .

- The most commonly used opioids are fentanyl

(Fast onset)
(low duration)
(100x potent than morphine)

⑤ Etomidate :

↳ Used in Cushing syndrome to suppress Pituitary and adrenal to decrease Cortisol.

↳ So, ↓ CORTISOL (maintain BP during stress)

← لذلك ~~هو~~ لا يُستخدم Etomidate هنا

⑥ Ketamine $\rightarrow$ minimal Hypotension.

↳ Short acting Anti-NMDA receptor.

- ↳ Have anesthetic and analgesic properties

↳ NOT cause VD but it stimulates central sympathetic outflow cause stimulation to heart + increase BP + CO. (maintain vascular tone) → in unshocked patients.

← في حالات ال (severe hemorrhage) ← وعنه الحاجة لإجراء Surgery فإنتيم

اعطاء جرعات low dose of ketamine ← وذلك حتى يتم طرد السم
وتنفي الا Adrenaline ، وذلك ان ketamine له اي فزونه يحفز ال
VC وذلك بسبب VD.

⑦ Dexmedetomidine :-

↳ α_2 agonist and have sedative effect

↳ Higher Affinity on $\alpha_2 \Rightarrow > 1000$ than clonidine.

↳ More Potent than Clonidine.

↳ has sedative, analgesic, sympatholytic and anxiolytic effect that blunt CV response.

(α_2):
Clonidine
Refractory
HTN
crisis

slide
(17 + 18 + 19)
• $\hat{\mu} = 18.5$

Anesthetics (3)

(** study the chapter)

- 1) = General anesthesia is not suitable in all cases, especially (HF, IHD, CVD), in which Anesthetic drugs (All) may cause Hypotension / $\downarrow$ CO.
- 2) = Hypotension can be controlled by vasopressors.
- 3) = Anesthesia increase the arrhythmogenicity to All vasopressor.

(Hypotension $\leftrightarrow$ arrhythmia) $\rightarrow$ أقل خطورة $\rightarrow$ أقل خطورة

$\leftarrow$ local anesthesia $\rightarrow$ أقل خطورة $\rightarrow$ أقل خطورة (More safer)

[1] Cocaine :

- Is a naturally occurring cpd. / ester cpd $\rightarrow$ degraded by esterase.
- Is the First anesthetic to be discovered and is the only naturally occurring local anesthetic.

$\Downarrow$ $\Downarrow$

* However, It not used clinically it's adverse effects and abuse Potential.

= Cocaine is not stable in blood, so they derived more stable form (Amide).

= All other Anesthetic drugs are synthetically derived.

= Procaine, The 1st synthetic derivative of Cocaine.

ester $\Rightarrow$ إستر

Notes :

[1] local Anesthetics are weak bases in its chemical form, So, in Physiological pH it presents in 2 Forms :

• Not Absorbed $\leftarrow$ Ionized. ✓

• Absorbed $\leftarrow$ un ionized. ✓

Cont. $\rightarrow$

2) local Anesthesia cause blocking to Na⁺ channels. to block AP in Afferent + Efferent neurons.

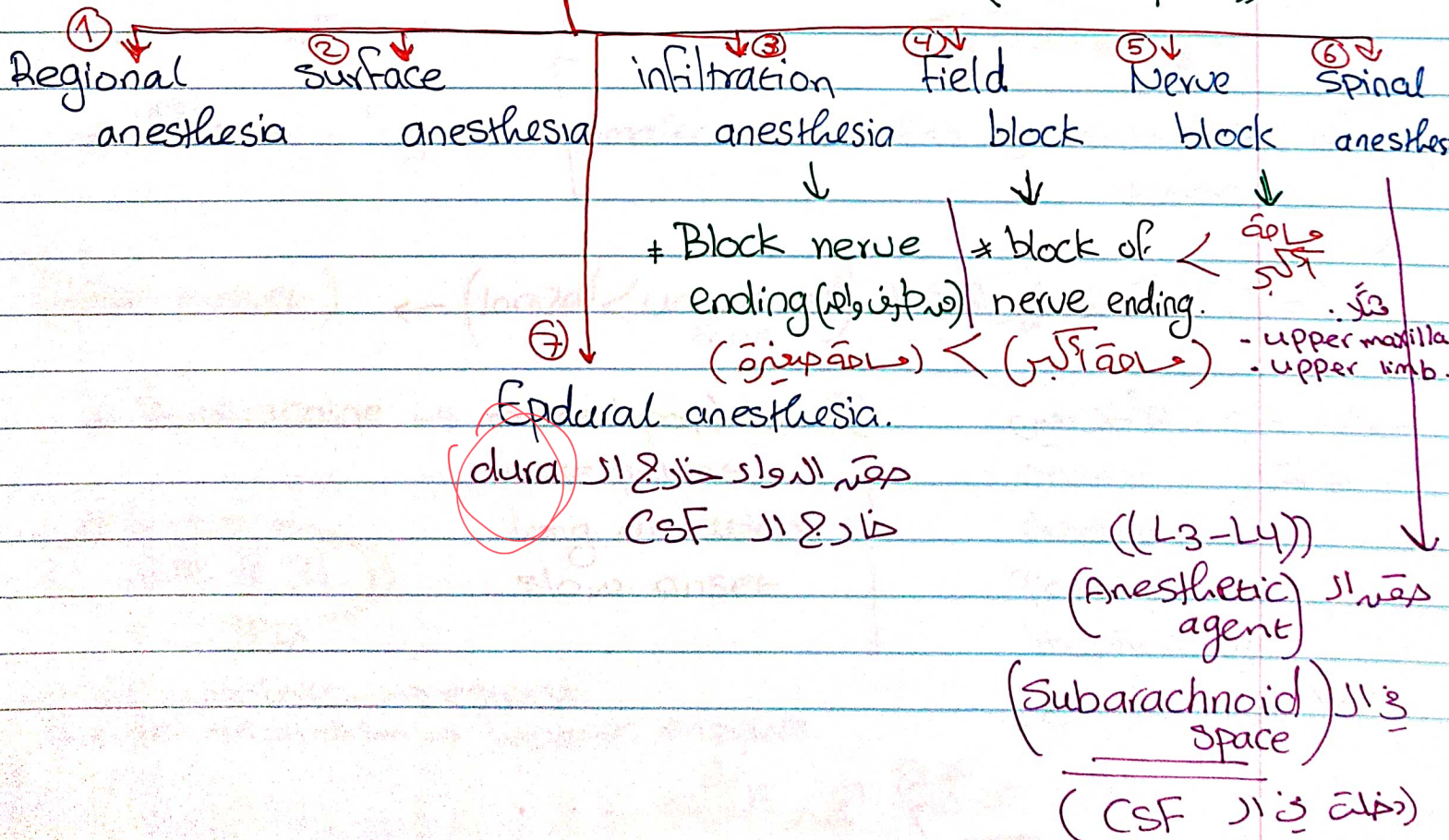
3) local anesthesia must being in unionized form to ~~being~~ be able to diffuse through cell membrane.

4) In cytoplasm it must transformed into ionized form which. responsible for blocking to Na⁺ channels.

5) For Onset of action unionized form must being higher level.

→ Local Anesthesia (Amide / Ester)
↳ Bupivacaine / Lidocaine / mepivacaine
Ropivacaine / Tetracaine.

→ Application of Local Anesthesia 80 ((Techniques)) :-



* Note: 0

Spinal anesthesia cause hypotention + sympathetic depression (headache).

Direct effect of local anesthesia on vessels is vasodilation. Cause:

$\left. \begin{array}{l} \rightarrow \uparrow \text{ Conc. Systemically.} \\ \rightarrow \downarrow \text{ Conc. locally.} \end{array} \right\} \text{Not wanted: } \rightarrow \text{ effect.}$

3. زنگنه حاص

لذلك هناك 3 Forms جاهزة تكون عبارة عن خليط من الـ (Adrenaline + Tidocaine).

↳ vasoconstriction =

↓ For : ↑ localization of local anesthesia

- Prevent ↓ distribution to systemic circulation
- Prevent toxicity.

What is P_{ka} in chemistry??

= Local anesthesia ~~is~~ are in 2 forms (ionized / unionized)

= Dissociation Constant $\Rightarrow$ (each weak base has specific constant).

(K_a)

slide # 28.

⇒ $pK_a = -\log K_a$ [Smaller value of pK_a → Faster onset of action]

(Fast onset) ← (ionized $\leftarrow$ un-ionized form) جیت کلا کلاؤ ~~پھر کھاتے~~ ال

Bupivacaine $\rightarrow$ more lipophilic

more potent

Long duration

slow onset

لذلك يجب الأخذ بعين

onset : جہاز

dehydration

Potency

lipophilicity

عناختار دواي حسين

11/25/20

slide # 31

.. فظ

ester metabolism $\rightarrow$ esterase.

Amide metabolism $\rightarrow$ hepatic enzymes.

line ✓ . . . الحمد لله