

* Pharma (3)

* NMJ blocking agents + Anesthetics (1)

1) NMJ blockers agents:

* Drug agents that cause blocking to Cholinergic transmission between motor nerve endings and nicotinic receptors on skeletal muscles.

* Note:

1) D-Tubocurarine: is the 1st agent that derived from Curarines and have clinical use.

2) NMJ blockers are classified into:

= Depolarizing agents. (as: succinylcholine).

= Non-depolarizing agents.

Competitive



long acting

. D-Tubocurarine.

. Pancronium.

. Doxacurium.

. Pipecuronium.

Intermediate

. Atracurium.

. Vecuronium.

. Rocuronium.

. Rapacuronium.

. Cisatracurium.

short acting.

. Mivacurium.

3) Non-depolarizing agents: *Competitive NB*

(a) Degraded by: ACh reductase ^{but more stable} → longer 1/2 life than ACh.

(b) ACh-antagonist → block nicotinic receptors.

(c) ~~irreversible~~ Reversible or Competitive relation with ACh,

(In which, higher Concentration with ACh overcomes the agent binding)

(d) Paralytic action is limited with specific time,

(كلما موجود antagonizing agent قبل كافي على motor end plate فانه لا)

Paralytic action موجود وبيجود انكافى Conc. يقل التأثير.

نقطة !!

عدم طرد في

البرانية كانت

ستة اناطيا

الغائر، ثم

تم الاستفادة

من خصائصها في

علاج الربو...

* للمقارنة بين الأدوية أو لاختيار الدواء المناسب للحالة المرضية يجب الأخذ بعين الاعتبار :-

- 1] Onset of action.
- 2] Duration.
- 3] Histamin release. → cause: (VD, Bronchoconstriction)
- 4] Ganglionic blocker.
- 5] Muscarinic blocker. → cause: Tachycardia.

espically; blockade of adrenal medulla → cause decrease the Production of adrenaline (cause, sustained blood pressure), So, Blood Pressure will drop + Blood vessels will dilate. (decrease Sympathetic tone).

Indications of use:

1] Intubation:

ex: exacerbation asthma (cyanosis, silent chest, complete B.C) .. (Status asthmaticus) وهذا ما يسمى أيضاً بـ (urgent intubation) وهذا يتركز في التدخل العاجل

↳ Hypoxia: low O₂ level in blood. (Respiratory Failure type 1) ..

↳ COPD Patient: Hypercapnia (CO₂ = 75-90) → (Respiratory Failure type 2) N CO₂ = 35-45 if CO₂ become ≈ 50

↳ Covid 19 Patient: High respiratory rate, with low O₂ Concentration ≈ ≤ 92%. Patient may become unconscious.

↓ Tissue Hypoxia على مستوى الأنسجة

ولذلك:

* (I have to monitor respiratory rate)

Tachypnea.

Bradypnea.

يعني لو كانت ABG ووجدت الـ CO₂ = 40 و O₂ conc. = 90 هـل اعتبر هذا مستوى الـ CO₂ طبيعي؟

لا، وذلك بسبب الـ Tachypnea، كونه الـ R.R = 60، هذا يجب يكون الـ CO₂

low، بسبب الـ wash out السريع لـ CO₂ يعني فترتها الأقلية = 20

Cont.

وهذا ينذر بحدوثه وضع المريض ، بحيث إنو ال (High respiratory) ، هيب
لـ Respiratory m. ، وذلك لـ يصبح قادراً على Wash ال CO_2 ..
لـ ولو اسحق الوضع هكذا المريض يكون على عتبة ال
Respiratory arrest + Death.

→ Need very Urgent intubation.

↳ Intubation during Surgery.
(endotracheal tube + mechanical ventilation)

= Respiratory cycle
- Inspiration
- Plateau
- Expiration

↳ ARDS : (Acute respiratory distress syndrom) ;

↳ Most Cause, is pneumonia.

↳ line of treatment depends on monitor Plateau pressure
which must be < 30 to keep the synchronization between
the mechanical ventilation machine and Patient respiration,
to ensure that patient takes the wanted tidal volume,
(according to patient's weight.)

لـ وذلك طالما ان (P.P) < 30 معناه المريض يقاوم الجوز ، لا زرع اعطي
المريض skeletal m. relaxant ، لتحسين ال Oxygenation على قوت ال lung
وال ABG.

* Note :

= Does most cases of intubation need drug infusion for muscle relaxation ?

→ No, Because ~~the~~ in most cases wanted drugs being with
(Fast onset + Short duration), Paralytic effect is needed
during intubation only.

↳ But.

+ ARDS : Needs Fusion dose of drug → to increase
the Compliance + Oxygenation.

→ (بعض النظرة نوع ال drug أو ال Duration.)

① Non-depolarizing agents : (Competitive antagonist)

① D-Tubocurarine:

- = Cause histamine release.
- = Hypotension → Blockade of ganglia.
- = Tachycardia → Muscarinic blockade.
- = long duration of action.
- = slow onset of action.
- = 1st discovered drug.

② Pancuronium :

- = No Histamine release. (CVD due to hypotension / chest pain / HF / IHD) ^{ممنوعة}
- = No Ganglionic blockade.
- = Still blockade muscarinic receptors → Tachycardia.
- = long duration. approx x 120 min
- = accumulating with infusion dose.

(Antidote) ← (Neostigmine) ^{أنتيدوت}
 ↳ Neuromuscular reductase inhibitor (↑ ACh conc.)

= excreted unchanged in urine, so dose adjustment is needed in case of renal problems.

③ Atracurium :

- = Intermediate duration (30-60 min).
- = Not Fast onset
- = Minimal action on: Muscarinic blockade → (Tachycardia) ^{* But still cause}
Ganglionic blockade ^{↓ BB}
- = ((Still cause: Histamine release.)) ^{VD / BC}
- = break down by AChE reductase, Hoffman metabolism.
- occur in plasma (Atracurium deactivated in plasma)
- ↳ No Risk on: Kidney liver diseases.

spontaneously
degraded

4) Rocuronium:

- Fast onset of action $\approx 1-2$ min. $\rightarrow$ succinylcholine
 - Intermediate duration of action $\approx 30-60$ min.
 - No Ganglionic effect.
 - Not cause histamine release.
 - Occasionally cause Tachycardia.
 - mild - No muscarinic action.
 - Best safety Profile.
 - degraded by reductase enzyme in plasma.
 - Doubling of dose is needed for increase onset of action.
- [also, $\uparrow$ duration of action]

↳ Sometimes, with some cases as:

(Short neck, difficult intubation) → intubation Failed.

(nicotinic R. ← Nicotinic R.)

Emergency: (Specific)

So, Segamedex is needed in this case as Antidote to antagonise the Paralytic effect of Rocuronium.

5) Mivacuronium:

- = Short duration of action.
- = Onset $\approx$ 2-4 min.

[2] Depolarizing agent :- (not competitive antagonist)
succinylcholine:

Succinylcholine :

بصری اکثر دواس $\xrightarrow{\text{H}^+}$ ACH نه قابله Structure

= Firstly, it acts as agonist, causing Persistent depolarization and open Na^+ channel, Prolonged Action Potential (Prevent resting period to occur). ← Phase (1) of depolarizing agent.
(Desensatization phase) ↓ I can see.

(Desensatization phase) $\downarrow$ I can see.

← لذلك المرض عندما يَتَفَيَّقُ

Intubation/ Surgery 11 vs

مِنْهُ مَنْ أَلْفٌ فِي عِلَالَتِ

حسنه ۱۲۰۳

* Fasciculation Contraction in :

- Trunk
- Face
- Neck

Persist
For:
(15 sec)
maxi.

After (15 sec) of succinylcholine dose:

→ Phase (2)

(Antagonizing phase)

(Competative antag.) ← Succinylcholine

Note:

• Neostigmine will have no action in phase (1) ⇒ 1st 15 sec,
And in phase (2) it will give it own action as antidote
to Succinylcholine.

→ And muscle power will recover and return
to its Normal Condition.

⇒ Succinylcholine:

- Fast onset of action ≈ 1-1.5 min.

- Short duration of action ≈ 5-8 min

No rule to Neostigmine → Phase (1) : 1st 15 sec ↓

✓ Neostigmine. ← Phase (2) : Last ↓

= Act as agonist on:

↳ Nicotinic receptor in muscular end plate.

• Ganglionic effect : (1st dose)

↳ on therapeutic dose: It act as agonist causing (Brady-Cardia)

↳ with Continual dose:

Persistent → It could cause Tachycardia, because it become in
Phase (2) → causing antagonist effect.

= No histamine release.

= Maintain Blood Pressure : (No hypotension).

= Cause K⁺ efflux → may cause hyperkalemia →
arrhythmia.

إذا حصلنا آثاراً عن
4 دقائق فسنستعمل
فهم الدواء تقريباً
ولم نثبت ال
Brady-/tachy-
قد حياة المريض
كله مع اد

Continual use
Tachycardia + persist Phase (2)

Note: as:

= Aminoglycosides (Amikacin / Gentamycin) have synergistic Paralytic effect with NMJ blockers.

= Aminoglycosides, Tetracycline, Clindamycin, Lincomycin, Polymyxin B, Colistin.

↳ They all have synergistic effect with Paralytic action with NMJ blockers.

un Controlled excitation that cause by Succinylcholine + excessive Ca^{2+} movement (influx).

↳ Which may cause: Malignant refractory hyperthermia

in this case:-
* Dantrolene (drug of choice)

TOF (Train of Four): Refers to Peripheral nerve stimulation Using 4 electrical impulses, usually applied to Fascial and or ulnar nerves.

* Notes:

= Paralytic dose of NMJ blocker is differ from Patient to another.
= ARDS Patient is given the lowest therapeutic dose of NMJ blocker (as: infusion dose), that to Prevent Complete Paralysis and avoid the aspiration and lethal consequences as: pneumonia.

ولذلك قبل بدء عمل الـ infusion لـ (ARDS Patient)، اعمل TOF test

بـ 4 electrical impulses (4 muscles)، فانتج اختيار Muscle twitching هذه العضلات.

و نكتب اد [base line] الاستجابة العضلات الاربعة ونضع تقييم لـ

لأنه المريض مستقر يكون يعني أنه Hemiplegia
وبذلك لو أخذ المريض (4/4) يعني انجمله الـ infusion حتى اقبل (2/4)

لا يعني كما سبق، لا ازيد انه اقبله (Complete Paralysis)
ولو (3/4) قبل ← يعني اقبل (1/4)

(Holiday) $\approx$ (2-1 hours)

(Stop drug infusion to ARDS patient) أنقيا يوميا كل صباح أقود

وذلك لنعوض:

- * Stimulation.
 - * movement.
 - * HR.
 - * R.R of him self.
- وهذه الآلية أيضا قد تساهم في
على الحس والتخلص من ان intubation
ومساعدة الجسم للتقليل من حجم الدواء
المتركز في الجسم على مدار الـ 24h.

* 2nd part of the lecture :

Anesthetics (1)

Anesthetics: Agents that cause reversible loss of sensation and Consciousness (depression to CNS).

↳ divided into: General and local anesthesia ..

↳ These drugs are used to provide safe and efficient Sedation based on the type / duration of the procedure and Patient characteristics, Immobilization, unconsciousness or unawareness, and analgesia / amnesia.

* Types of Anesthesia, Inhalation: (Gas, liquids) (من خلال الجهاز التنفسي)

* ketamine: also IV drug.

- mechanism of action: separate signals (we don't use it) (Dissociative drug) between Cortical + medulla.
... لا يربط بين نفس في عوالم متداخلة

- Halothane.
- Methoxyflurane.
- Enflurane.
- Isoflurane.
- Desoflurane.

Anesthetics agents:

low dose

High dose.

sedative effect

Anesthetic effect

Anesthesia من أجل أنقيا
: من أجل

* Inhibition to Cortico medullary tract + inhibition to Hippocampus.
(amnesia) (Immobilization)

IV anaesthesia

1] Propofol : (onset of action 30-40 sec)

= IV anesthetic drug.

= Intralipid emulsion (as: chylomicron (surround by surfactant))

= Cause (ON-off) action.

Bolus : ON → anesthetic patient.

Holding : off → Patient wake up.

→ once stop infusion, manifestations stop and redistribution from brain to blood.

= Very Painful (alkaline drug) → Irritant.

= accumulation in brain. → lead to tissue necrosis

→ gangrene.

2] Thiopentone : See IV

= More accumulation and binding power to brain + Fat tissue than Propofol.

= Higher lipophilicity → Fast brain accumulation.

= initiation of anaesthesia is fast → (1-2 min)

= → long period of recovery ≈ 24 h.

3] Ketamine : 0

for children

= Could be used in surgery and urgent cases in emergency department. ((followed by in need))

= Fast onset & Dose = 50 mg → 50 mg.

= Not Cause air way blockade (keep air way adequacy)

= Duration of action = approx. (30 min).

Cause → Anesthetic + Analgesic + Patent air way effect.

= used in Damage open surgery or Complex surgery in ICU for recheck the surgery

emergency

Fat
لوانفط طريق

قد ييب

Coagulation

لناوي

ان يكو على

شال

emulsion

Notes :

= Anesthetics Cause :

- + direct CVS depressant.
- + Cardiac muscle depressant $\Rightarrow$ (IHD , HF , $\dots$)
- + Sympathetic depression.
- + Hypotension.

Status of Organ Systems with anesthetics :

① CVS :

- Suppress CVS function to varying degree.
- Its important to Consideration :
 - HF.
 - Coronary artery disease.
 - Valvular disease.
- Hypotension may be worsen or develop during anesthesia.
 - $\hookrightarrow$ Causing decrease of ejection fraction or perfusion pressure $\Rightarrow$ (So, waste products + drugs metabolites wash out will decrease, causing prolonged recovery period).
 - $\hookrightarrow$ Also, ischemic injury to tissue may occur.

General anesthesia $\leftarrow$ قد تكون كثير خطورة على حياة المريض
المريض ، لذلك يجب ان يكون حذر او اختيار انواع اخرى من (Anesthesia)
(Epidural anesthesia) : على

$\hookrightarrow$ Vasoactive agents may be necessary in case of hypotension.

$\hookrightarrow$ Also, Fluid is important (1-2 L)

If I give this amount to Cardiac patient-
he may have Pulmonary edema.
(decompensated HF) $\dots \rightarrow$ لذلك (0.5L) يجب ان يكون حذر

Medical history is important to any elective surgery.
المعرفة :
نوع الأدوية =
الاضرابات =
الحل / علاج =

* Anesthesia increase the arrhythmogenicity to all vasopressor.

↑ لا يرفع لو الـ vasopressor يا آخه

← General Anesthesia

مريض في (Unstable angina) ولا الـ

(Heart Complications)

(except)

↓
norepinephrine

Adrenaline

Noradrenaline.

Dopamine

Phenylephrine.

* Note ...

study slide

* (5+6+7)

* Mechanism of action of anesthetic agents :-

- 1] Dissolved in cellular biphospholipid Layer.
- 2] Desensatization + Isolation to any stimulus
- 3] Increase inhibition.
- 4] decrease activation.
- 5] Prevent Action Potential Propagation + generation.

↓

↓

* That's Caused by :-

Slide # 8

1] GABA action. (open chloride channels)

↳ increase Cl^- influx → Hyperpolarization.

↳ Except, (Ketamine)

2] Glycine action → increase inhibition → open chloride channels. ↳ Except, (Ketamine)

⇒ Ketamine: ~~NMDA~~ action (blocking glutamate)

↓

↓

(Inhibit excitation)

3] Works also on K^+ channels (two pore domain channels)

↳ open K^+ channels.

• تكون أسهل معرفة (Patient history) في معرفة :
- الأدوية التي يعانى منها المريض .

• Drugs ✓

↳ Because there , drugs increase analgesic + Anesthetic effect
↳ Drugs decrease Anesthetic effect

• Pregnancy . -

↳ Highly teratogenic .

[2] Respiratory syst. affection .

= Anesthetic agents cause respiratory depress except Ketamine .

[3] Hypothermia :

= NMT blockers cause vasodilation + Anesthetic effect cause direct vasodilation also indirect depression to Sympathetic nervous syst. (cold)

↳ During Surgery ; Fluids are used to maintain blood Pressure and Room temperature being Low (cold.)

↳ Hypothermia تسبب انخفاض حرارة الجسم

↳ Also , in Damage Control Surgery or Complex surgery , high amount of temperature will lost .
(decrease / lost of Core temperature set point)

↳ Thermoregulation Center won't sense the temperature and lose of heat , so It won't cause V.C to decrease the amount of lose .

↳ Also ; vasodilatation of blood vessels ↑ loss of heat by transferring it from Core to Periphery .

↳ Complication : Coagulopathy , increase risk of bleeding which increase the mortality rate .

↳ Fluids تسبب انخفاض حرارة الجسم قبل إعطاء المريض حقوقاً أو أكسجيناً .
↳ إعطاؤها ببطء .

Stages of general anesthesia ≈ # (Slide # 11)

Induction



① adults:

= NMJ blocker with anesthetic effect (IV)
 ↳ To facilitate Endotracheal intubation by muscle relaxation.

② Children:-

= volatile agents as SevoFlurane inhalation
 ↳ To induce general anesthesia.

Maintenance

= Commonly provide with volatile anesthesia also IV as Propofol can be used.

= Opioids (Fentanyl) are used for analgesic effect with inhaled agents because Propofol alter consciousness but not perception to pain.

Recovery

= After cessation of the maintenance anesthetic drugs,
 ↓

The patient is evaluated to return of consciousness.

Depth of anesthesia ≈

Slide # 14

• Four sequential stages characterized by increasing CNS depression as the anesthetic accumulates in the brain.

① Stage 1: loss of Pain Sensation. (Analgesia)

↳ Sensation interfere with sensory transmission in spinothalamic tract.

↳ Amnesia and awareness of pain occur.

② Stage 2: (Excitement) ≈ The patient displays delirium and possible combative behaviours.

↑ = factor 1

③ Stage 3: (Surgical anesthesia) ≈ Gradual loss of muscle tone + reflexes as CNS is further suppressed.

(Ideal stage of surgery) .. patient respiration.

↳ Careful monitoring to prevent undesired progression to stage (IV)

منه
 ↓
 stage 4

④ Stage (4) : (Medullary Paralysis) :

↳ Severe depression to Respiratory + Vasomotor Centers occurs..

↳ Support the ventilation + circulation to prevent death..

Note :-

①# Induction phase is ~~is~~ Fast, So anesthetic effect become from 1 to 3 quickly (directly), without symptoms of 2nd (excitation) stage occur. That because;

②* In Recovery phase, I'll see all stages from (3 to 1). Because it ~~is~~ Prolonged phase, I'll see phase (2).

⇒ the rapid-acting (IV) agents are given before inhalation of anesthetic agent.

﴿وقفا عند الـ Phenomena الـ لا زلنا على...﴾

... مَوْءِدُكَ اللَّهُ ✖