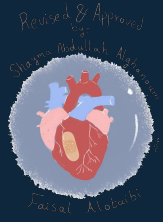


PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Drugs Used in Anaphylaxis

Objectives:

- Perceive the differences between anaphylactic shock and other types of shock.
- Recognize its nature, causes & characteristics
- Specify its diagnostic features.
- Identify its standard emergency management protocol.
- protocol Justify the mechanism of action and method of administration of each of the different used drugs to limit its morbid outcomes.

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

Editing file

Anaphylaxis

Anaphylaxis Is a sudden, severe hypersensitivity reaction affecting the whole body (generalized or systemic) in response to allergen.

Symptoms

- **Rash**
- **Mucosal swelling**
- **Difficulty in breathing**
- **Hypotension** (reduced blood pressure)

SHOCK

Generalized circulatory derangement causing multiple organ HYPOPERFUSION [Inadequate oxygen delivery to meet metabolic demands] & strong sympathetic activation

- If the shock is intense or sustained enough, it will lead to irreversible derangements sets then to permanent functional deficit or death

Dr's note :It's also a protective mechanism since the body can't maintain its posture, it will fall down making it easy for the blood to reach the brain (circulation and gravity)

What type of shock is the anaphylactic shock?

Video

Types of shock

Hypovolemic	Obstructive	Cardiogenic	Distributive
• Hemorrhage • Fluid loss (plasma,EFC)	• Extra-cardiac obstruction. E.g.Cardiac tamponade ,Pulmonary embolism	• Inability to contract & pump. E.g. myocardial infarction.	• Decreased Peripheral Resistance E.g. septic shock ,Neurogenic shock, **Anaphylactic shock**

ANAPHYLACTIC SHOCK

A life-threatening allergic reaction that causes shock (hypoperfusion) and airway swelling.
"Anaphylactic shock" is a term that specifically refers to an episode of anaphylaxis.
Perfusion means delivery of oxygen to the tissues , Hypoperfusion : decreased O2 delivery to the tissues.

The Nature of anaphylactic shock

Non-Immunologic Anaphylaxis (ANAPHYLACTOID)

- Directly act on mast cells (Not IgE-mediated)
- Exogenous substances directly degranulate mast cells.
- E.g. Radiocontrast dye (enhance the visibility of internal structures in X-ray-based imaging techniques), Opiates(such as heroin and morphine, binds to the brain's opioid receptors that is responsible for controlling pain) , Depolarizing drugs, Dextrans (plasma volume expander made from glucose, restore blood plasma lost through severe bleeding)

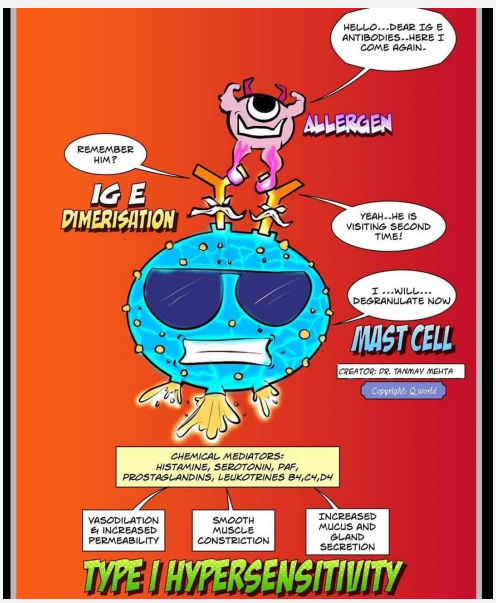
Immunologic Anaphylaxis (known as ANAPHYLAXIS)

- It belongs to type I hypersensitivity reaction
- Occurs after exposure to foreign substances (antigen) such as food, insect or animal venom, drugs, blood products
- The immune system will then develop antibodies for this antigen and it will remain in the body for a while
- After a 2nd exposure to the same antigen in previously sensitized persons (antigen-specific IgE are present), IgE binds with mast cell causing its degranulation.

Because anaphylactic and anaphylactoid reactions produce the same clinical manifestations and are treated exactly the same way. we use the term anaphylaxis to refer to both conditions.

characters of anaphylactic shock:

- Rapidly developing [5/30 min. → can be hours]
- Severe, life-threatening
- Multisystem involvement
- Mortality: due to respiratory (70%) or cardiovascular deficits (25%)



The degranulation of the **mast cells** will release **Histamine**, **Leukotrienes** and other inflammatory substances and will lead to :

blood vessels
-vasodilation
-leakiness
-Hypo-perfusion

skin
-pruritus
-urticaria
-edema

Mucous Swelling
-Rhinitis 16%
-Airway 56%
-Angioedema 88%
-GIT 30%

Lungs
-bronchospasm
-vasoconstriction
-shortness in breath

Heart
-decreased output
-decreased coronary flow -Circulatory Collapse

Anaphylactic Shock Therapy

Rescue

When the diagnosis is made as an anaphylactic shock
(after calling the ambulance), emergency treatment should be immediately start as follows:

Life Threatening Problems:	Management
Airway: swelling, hoarseness, stridor Breathing: rapid breathing, wheezing, cyanosis, fatigue, confusion, oxygenated Hb (SpO2) < 92%	Respiratory support ▪ Open airway for O2 inhalation
Circulation: pale, clammy, low BP, faintness, drowsy /coma	Circulatory support ▪ Lay down and raise legs up ▪ Fluid replacement

1st Line Therapy

- Adrenaline (give IM by Auto injector or by syringe, unless there is a specialist to give IV)
- IV fluid challenge Crystalloid is given for children to increase the blood plasma level.

2nd line Therapy

- Chlorpheniramine (first generation H1 blocker) (IM or slow IV).
- Hydrocortisone (Glucocorticoids) (IM or slow IV)

Adjuvant to 2nd line

- **Bronchodilators**: -Salbutamol (nebulizer), -Ipratropium (nebulizer), -Aminophylline (IV).

- **Glucagon**:
"to increase cardiac output" For patients taking beta-blockers & with refractory hypotension .

- **H2 blocker**: "we mainly want to block H1 so we give H2 blocker to support the action of H1 antagonist "
- Ranitidine: I.V
- Cimetidine: contraindicated in elderly renal/hepatic failure, or if on beta-blockers.

Why do we use the 2nd line adjuvants?

Objective of Therapy:
- To support the respiratory & circulatory deficits.
- To halt the existing hyper-reaction.
- To prevent further hyper-reaction of immune system (prevent biphasic phenomenon).

Biphasic Phenomenon:
- 2nd release of mediators without re-exposure to antigen *leukotrienes and histamines are still active* (in up to 20%)
- Clinically evident 3-4h after the initial manifestations clear.

First line therapy

Adrenaline (epinephrine) (A **Sympathomimetic**)

Mechanism	A nonselective adrenergic agonist [a1, a2, b1, b2]
Indication	★ **Drug of choice for anaphylactic shock.**
Actions	**1-As an α-Adrenergic agonist:** Reverses peripheral vasodilation(vasoconstriction), thus maintains BP & directs blood flow to major organs. Vasoconstriction leads to decreasing edema → reverse hives(urticaria),swelling around face & lips & angioedema (a swelling of the area beneath the skin) in nasopharynx & larynx. **2-As a β-Adrenergic agonist:** **β□1 effect:**↑ force of myocardial contraction. **β□2 effect:** Dilates bronchial airways +↓ histamine & leukotriene release from mast cells . **3-As histamine antagonist:** *Adrenaline is the physiological antagonist of histamine: Attenuates(reduce)the severity of IgE-mediated allergic reactions. ***Explanation:** There are several substances that have antihistaminergic action despite not being ligands for the **histamine** receptor. .Thus, despite not being true **antihistamines** because they do not bind to and block the **histamine** receptor, **epinephrine**(adrenaline) and other such substances are **physiological antagonists to histamine**
ADRs	Causes dysrhythmias if given IV.

Contraindications

-Rare in a setting of anaphylaxis

-Not given for cardiac patient who are older than 40 years

★ -Patients taking **β-blockers** either are:

- **Refractory(not responding);** as it may antagonize β effects of adrenaline.(β□ receptors won't be stimulated since they're blocked, no ↑ cAMP, no effect)

- **Rebound hypertension(**severe increase in blood pressure) *: (unopposed **α** effect), specially when adrenaline is repeated.

* if a patient on a nonselective beta-blocker receives a systemic dose of epinephrine, ,the beta-blocker prevents the vasodilation, leaving unopposed alpha vasoconstriction. The resulting hypertensive reaction(rebound hypertension) can be large.

Administration

-IM: why?

- 1-Easily accessible by using **Auto-injectors Kits**, they are disposable prefilled devices,automatically administer a single dose of epinephrine in emergency.
- 2-Greater margin of safety → no dysrhythmias as with IV.
- 3-No need to wait for IV line, if present, it should be given by **physician** under monitoring.

-Repeat every 5 □-□□10 min as needed.

-Patient should be observed for □4-□6 hours **Why ?**

(fear of biphasic anaphylaxis)

NOTE THAT:If hypotension persists, start Dopamine Why not noradrenaline ?

From pharmacology team 438;
We use dopamine to protect the kidney. Why not noradrenaline? *Noradrenaline is nonselective on (α1, α2, β1). It has no effect on β2 stimulation of α1 (vasoconstriction) causes hypertension, but this vasoconstriction is not opposed by the stimulation of β2 (vasodilatation) Therefore, noradrenaline will cause a very severe vasoconstriction, much more than what is required in the case of anaphylactic shock.

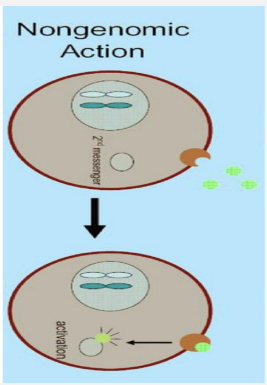
Second line therapy

Corticosteroids (anti- inflammatory)

Mechanism

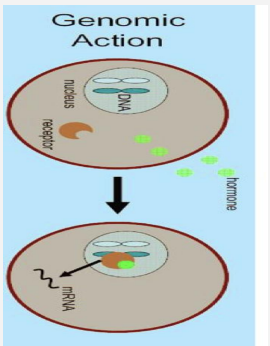
Non-genomic action:

- Immediate Glucocorticoids actions on **Membrane-bound receptors**,which leads to modulating 2nd messengers levels.
- Rapid onset of action (seconds or minutes).*That's why we use it in anaphylactic shock.



genomic action:

- Takes hours to days to be activated.
- Intracellular receptors (cytosol or nucleus)



Action

Non-genomic action in anaphylactic shock:

- Reverse hypotension & bronchoconstriction.
- ↓ release of inflammatory and allergic mediators (anti-chemotactic & mast cell stabilizing effects.)
- ↓ mucosal swelling and skin reaction.
- May help to limit biphasic reactions by **decreasing allergic mediators.**

Administration

- Given slowly IV or IM.
- Not used alone **(not life saving).**

Second line therapy

H1 Blockers

Drug	**Pheniramine (first generation antihistamine,** similar to chlorpheniramine)
Action	• Though mast cells have already de-granulated, yet these drugs can still help to counteract (prevent) histamine-mediated vasodilation & bronchoconstriction. • May help to limit biphasic reactions by **blocking histamine receptors.**
Administration	• Given slowly I.V or I.M • It can not be used alone **(not life saving).**

Adjuvant to second line therapy

H2 Blockers AND Proton pump inhibitors (PPIs)*

*PPIs are only in girls slides

Drugs	**Ranitidine ,Cimetidine (H2 blockers)** **Pantoprazole (proton pump inhibitors)** All PPIs are named using the suffix " prazole" كلهم عندهم B2 blockers and PPIs بس الأفضل اننا stomach في receptor نستعمل PPIs بسبب drug interactions of B2 blockers
Action	• The significance of H□ blockers is not established, these drugs are associated with **serious adverse drug interactions.** ★ **Pantoprazole is a Proton pump inhibitor it is safer and given once. (decrease stomach acidity)**
Contraindications	**Cimetidine** shouldn't be given to **elderly**, **renal/ hepatic** failure, or if on **b-blockers.** Why? Because it inhibits **cytochrome P450 (CYP450)** which controls drug-drug interactions. So when given it may **increase the toxicity** of other drugs , therefore it's replaced by ranitidine.

Adjuvant to second line therapy

Bronchodilators

Drugs	Salbutamol nebulizer	Ipratropium nebulizer	Aminophylline IV
Administration	*If there is respiratory obstruction bronchodilators given in IV(Aminophylline) If not given inhaled (salbutamol or ipratropium)		
	Inhalation		Parenteral IV
action	β□2 agonist : • Relaxation of bronchial smooth muscle.(Bronchodilation) • Decrease mediators released from mast cell and basophils. • inhibit airway microvascular leakage.(part of inflammation) • Not effective in Patients taking β2 blockers,	Anticholinergic (Antimuscarinic) • Decrease secretion of mucus • Bronchodilator • An extra important action: Decreases c**G**MP, therefore decreases the contractility of smooth muscles.	• may be useful in the treatment of anaphylaxis when inhaled bronchodilators are not effective & bronchospasm is persistent. • Given in hospital setting as levels of drug should be therapeutically monitored because it has narrow therapeutic index. • Increase c**A**MP • Smooth muscle relaxation
P.K	• Short acting. • Rapid onset of acting.	• Longer acting • Less rapid in action	

Adjuvant to second line therapy
Glucagon

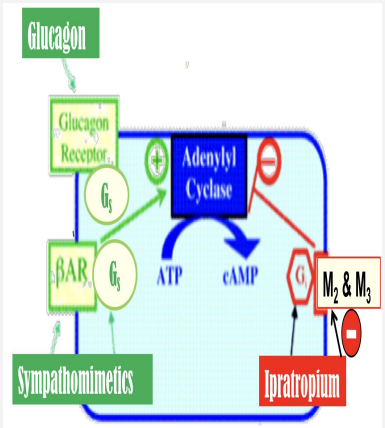
Mechanism

Main action: act on glucagon receptors in the heart.

(Glucagon is naturally occurring hormone in our body produced by the alpha cells of the pancreas -**rising the level of BP**-)

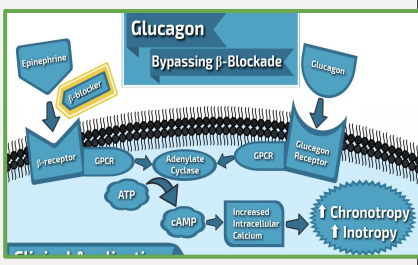
Action

- Has both positive inotropic(forced contraction of heart) & chronotropic(heart rate) effect on heart→ increase cardiac cyclic AMP.



- This effect is completely **independent of Adrenergic Receptors**, That is why effective in spite of β-adrenergic blockade.

- Efficacy of acting on bronchi is less prominent than that of the heart → **no evident bronchodilation (glucagon receptors only exist on the heart)**



* Patients with anaphylaxis who are taking a beta-adrenergic blocking agent (eg, for hypertension, migraine prophylaxis) can have refractory anaphylaxis that is poorly responsive to standard measures. But Glucagon activates adenylate cyclase at a site independent from beta-adrenergic agents, causing an increase in (cAMP). باختصار له مستقبلات خاصة على السل ممبرين فما راح يتأثر بسببه البيتا بلوكر عكس الادرينالين.

Clinical uses

Drug of choice for severe anaphylaxis in patients taking β-blockers.

Boys Doctor notes :

- Bee stings can directly cause Anaphylaxis even if it was the first time for patients to get stinged by the bee because that the bee's have Histamine on there sting thus, will stimulate mast cells degranulation .

- Difference between anaphylaxis and asthma is that in anaphylaxis Alpha1 (vasoconstriction) beta1 (increase heart output) and beta2 (Bronchodilation) is required because we need to restore the blood pressure also, so adrenaline is the drug of choice while in Astma beta1 is not desirable, so we only want Bronchodilation hence the use of selective beta2 agonists.

- Patient in emergency he developed severe anaphylactic shock what is the best to Give him ?

1. Adrenaline + Hydrocortisone(glucocorticoids)
2. Adrenaline +Chlorpheniramine(H1 Blocker)
3. Adrenaline + Salbutamol (B2 Agonist)

The answer will be Adrenaline + Hydrocortisone

- Pharmacological antagonist is when both of the drugs work on the same receptor while physiological antagonist is when drugs reverse each other actions but not on the same receptor .

MCQ

1-If a patient has a severe anaphylactic shock and he is taking a B-blocker, what is the proper drug in this case ?			
A- Corticosteroid	B- Glucagon	C-Salbutamol	D-Oxybutynin

2-If hypotension persist with anaphylactic shock, what should we prescribe :			
A-Adrenaline	B-Dopamine	C-Glucagon	D-Atropine

3-Symptoms of anaphylaxis can occur:			
A-Shortly after coming in contact with an allergen	B-Hours after coming in contact with an allergen	C-All of above	D-neither

4-Your patient is having a sudden and severe anaphylactic reaction to a medication. You immediately stop the medication and call a rapid response. The patient's blood pressure is 80/52, heart rate 120, and oxygen saturation 87%. Audible wheezing is noted along with facial redness and swelling. As the nurse you know that the first initial treatment for this patient's condition is?			
A-IM Epinephrine	Nebulized salbutamol	C-IV Diphenhydramine	D-IV Epinephrine

5-Which of the following patients is most likely to be treated with intravenous glucagon?			
A-An 18-year-old woman who took an overdose of cocaine and now has a blood pressure of 190/110 mm Hg	B-A 27-year-old woman with severe diarrhea caused by a flare in her inflammatory bowel disease	C- A 57-year-old woman with type 2 diabetes who has not taken her glyburide for the last 3 d	D- A 62-year-old man with severe bradycardia and hypotension resulting from ingestion of an overdose of cimetidine

Answers

1	2	3	4	5
B	B	C	A	D

SAQ

Q1)a patient develop what we called Biphasic Phenomenon what does that mean?

Q2)List some drugs we can use to prevent Biphasic Phenomenon ?

Q3) List some of the bronchodilators that can be used as Adjuvant to 2nd line therapy?

Q4) What is the role of corticosteroids in the treatment of anaphylaxis?

Q5) While playing in the garden, a 7-year-old boy is stung by 3 bees. Because he has a previous history of bee sting allergy, he is brought to the emergency department by his mother who is very concerned about a possible anaphylactic reaction.

1- What are probable signs of an anaphylactic reaction to bee stings?

2-If this child has signs of anaphylaxis, what is the treatment of choice?

3- what is the drug mechanism of action ?

A1) It is a second episode of anaphylaxis with 2nd release of mediators without re-exposure to antigen.

A2) 2nd line anaphylaxix's drugs. Such as

1\ Glucocorticoids : Hydrocortisone

2 \ First generation H1 blocker : Chlorophenamine

A3) Salbutamol as β2 Agonist. Ipratropium as Anti-muscarinic. Aminophylline as Methyl-xanthine.

A4) slide 7

A5) 1- Bronchospasm, tachycardia, hypotension, laryngeal edema

2-Epinephrine

3-slide 5

GOOD LUCK!

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