Direct-Acting Adrenergic Agonists

د.اسماء الثويني

Asist.Prof./M.B.Ch.B/M.S.C/P.h.D Pharmacology and therapeutics

•***Adrenaline*** (Commonly used catecholamine)

•Adrenaline activates with **both α & β** receptors. (**non-selective**)

•At **low doses**, **β effects (vasodilatation)** on the vascular system predominate, whereas at **high doses**, **α effects (vasoconstriction)** are predominate.

•**Effects of adrenaline:**

•***Cardiovascular (The major effects):***

- **Heart :** ***(β_1 effects)***

- **+ve inotropic effect**
- **+ve chronotropic effect**
- **Increase cardiac output**
- **increased O_2 demands on the myocardium.**
- **Increase A-V conduction velocity (may cause arrhythmia.**

- **Blood vessels :**
  - **constricts** arterioles in the **skin**, **mucous membranes**, and **viscera** ***(α effects)***
  - **dilates** vessels going to the **liver** and **skeletal muscle** ***(β effects)***
  - **Renal** blood flow is **decreased**.
- **Blood pressure :**
  - **increase** in **systolic BP**
  - slight **decrease** in **diastolic BP**
  - **mean BP** is slightly **elevated.**

•Respiratory:

- **powerful bronchodilatation**
- relieves all known **allergic bronchoconstriction**.
- In the case of **anaphylactic shock**, this can be **lifesaving.**
- inhibits the release of **histamines** from **mast cells.**

•

•Hyperglycemia:

- **increase glycogenolysis** in the **liver** and skeletal muscles.
- **increased release** of **glucagon**
- **decreased release** of **insulin** (**α_2** effect)

•

•Lipolysis:

- agonist activity on the **β_3** receptors of adipose tissue

Pharmacokinetics:

rapid onset but a **brief duration of action** (due to rapid degradation).

In **emergency (life threatening)** situations → **i.v.** (for the most rapid onset). Also given **s.c.** , **i.m.,** or **topically to the eye**.

Oral administration is **ineffective** (inactivated by intestinal enzymes, **MAO & COMT**).

s.c. → **vasoconstriction** (**α** effect) → **delay absorption** from skin
i.m. → **vasodilatation** (**β** effect) → **rapid absorption** from muscles
(i.m is better in emergency than s.c.)

Biotransformation:

like other catecholamines, metabolized by **MAO**, and **COMT**. The final metabolites found in the **urine** are **metanephrine** and vanillylmandelic acid (***VMA***).

•Therapeutic uses :

•

•1- Anaphylactic shock: **(Drug of choice)**

•Used **i.m.** for rapid **elevation of BP**, **bronchodilatation**, and **inhibition of histamine release** from mast cells.

•2- Cardiac arrest:

•Restore cardiac rhythm (regardless of the cause)

•Used **i.v.** & in life threatening cases, directly to the heart (**intracardiac**)

•

•3- Bronchospasm:

•Emergency treatment of **acute asthma.** Used **s.c.**

•But, selective β_2 agonists, like ***Salbutamol***, are presently favored

•

•4- Glaucoma:

•reduce **IOP** in **open-angle glaucoma.**

•It **reduces the production of aqueous humor** by vasoconstriction of the ciliary body blood vessels.

•contraindicated in closed-angle glaucoma due to mydriatic effect

•

•5- Local Anesthesia:

•increase the **duration of the local anesthesia** by producing vasoconstriction so delay absorption from the injection site.(dental use)

•

•6- Local Bleeding:

•vasoconstrict mucous membranes to control oozing of capillary blood. (e.g. in ***Epistaxis***)

•Adverse effects:

- ***Cardiac arrhythmias***
- ***Elevation of Bl.Pr and even cerebral Hemorrhage***
- ***Acute Pulmonary edema***

• Tremer

• Gangrene of fingures.

•Interactions:

1. ***Hyperthyroidism*** (**enhanced CVS effects**)
2. ***Cardiac out flow obstruction (HOCM)***
3. ***Diabetes:*** adrenaline cause **hyperglycemia** & **dose of insulin** may have to be **increased**
4. ***β -Blockers:*** **prevent (*β* effects)**, leaving (**α** effects). This may lead to an **increase in BP.**
5. ***Inhalation anesthetics:*** **halothane sensitize the heart** to the effects of adrenaline, which may lead to **arrhythmia.**

•***Noradrenaline***

•

•**predominantly stimulates α adrenoceptors** (Its action on **β** receptors is insignificant)

•

•**Cardiovascular actions:**

•

•**Intense vasoconstriction** □rise in peripheral resistance □ Both systolic and diastolic BP increase.

•

•

•**Therapeutic uses:**

•Noradrenaline is a potent vasoconstrictor and has very brief duration of action, has limited use clinically now a day.(may used in emergency treatment of **Acute hypotensive state in ccu**)

•***Isoproterenol***

•synthetic catecholamine **predominantly stimulates β adrenoceptors**.

•**nonselective** (stimulate **β_1** and **β_2**)

•**Cardiovascular actions:**

•**Intense stimulation of the heart** (**β_1 effect**), (**active as adrenaline** in this action). Increase **heart rate** and **force of contraction** □increased **COP**

•**Dilates the arterioles** of **skeletal muscle** (**β_2** effect) □decrease total peripheral resistance (TPR).

•**Increase systolic BP** slightly, but it greatly **reduces mean** and **diastolic BP**.

•**Pulmonary action:** A profound and rapid **bronchodilatation**.

•Pharmacokinetics:

•can be **absorbed** by the sublingual mucosa but is **more reliable when given parenterally** or as an inhaled aerosol.

•Therapeutic uses:

- **rarely** used as a **bronchodilator in asthma**. (non-selective)
- **stimulate the heart** in **emergency**.(**A-V block or cardiac arrest**)
-

•Dopamine

•Dopamine **can activate both α and β** adrenergic receptors, in addition to **dopaminergic receptors** (**D_1**) that occur in the peripheral **mesenteric** and **renal vascular beds**, where binding of dopamine produces **vasodilatation**.

•Dopamine receptors: (5 subtypes)

- **D_1** like (**D_1** & **D_5**) are **G_s** types more important **peripherally**
- **D_2** like (**D_2** , **D_3** & **D_4**) are **G_i** types more important **centrally**
-

•Cardiovascular effects: (dose-dependant)

- **At dose 2-5 mg/kg/min: D_1 effect (**vasodilatation of mesenteric and renal B.V.**)**
- **At dose 5-15 mg/kg/min: β_1 effect (**positive inotropic and chronotropic effects**)**
- **At dose >15 mg/kg/min: α_1 effect (**vasoconstriction & ↑ TPR**)**

•Renal and visceral:

•Dopamine **dilates renal and splanchnic arterioles** by activating dopaminergic receptors **increasing blood flow to the kidneys and other viscera.**

- **Therapeutic uses:**

- **Drug of choice for treatment of *shock (ex. Septic shock)*** and is given by **i.v. infusion**.
- dopamine is far **superior to noradrenaline,** and **adrenaline** which diminishes the blood supply to the kidney and may cause **renal shutdown.**
- Dopamine is rapidly metabolized by **MAO** (mostly **MAO-B**) or **COMT**,

- **Adverse effects: nausea**, **hypertension**, **arrhythmias**

- ***All discussed drugs (catecholamines) are non-selective (affects α and β adrenoceptors) directly acting sympathomimetic drugs***
-

- **Selective directly acting sympathomimetic agents includes**
- **(Selective α_1 , α_2 , β_1 & β_2 agonists)**

Selective α_1 agonists

•

•**Xylometazoline and Oxymetazoline**

•

•Direct-acting synthetic **α_1** adrenergic agonist that is primarily used as:

- ***nasal decongestant***
- ***eye decongestant*** (to relief redness associated with swimming, colds, or contact lens).

•

•Absorbed to **systemic circulation** produce **nervousness**, **headaches**, and **trouble sleeping**.

•

•**Rebound congestion** is observed with long-term use.

•

•**Phenylephrine**

•

•It is a vasoconstrictor that **raises both systolic and diastolic BP** and produce **reflex bradycardia** when given parenterally.

•

•**Therapeutic uses:**

- **Nasal decongestant** (produces prolonged vasoconstriction)
- Used in ophthalmic solutions for **mydriasis**.

- **Methoxamine**
- It is **non-selective α agonist** (activate both α_1 ,and α_2).
- **Uses:**.
  - as **nasal decongestant**.
  - to **overcome hypotension** during surgery involving **halothane anesthetics (adrenaline cannot be used)**.
- **Nasal decongestant:**
- ***Therapeutic uses:***
  - Common cold
  - Allergy
  - Sinusitis (enhance drainage from sinuses)
  - Prevent otitic barotraumas (open eustachian tubes)
- ***Administration:***
  - Nasal drops
  - Tubes
  - Sprays
  - Oral preparation
- ***Duration of action:***
  - short acting (phenylephrine)
  - intermediate acting (ephedrine & pseudoephedrine)
  - long acting (oxymetazoline & xylometazoline)
- ***Adverse effects:***
  - rebound congestion
  - local ischemia (rhinitis medicamentosa)
  - lipoid pneumonia (oily drops can enter to the lungs)

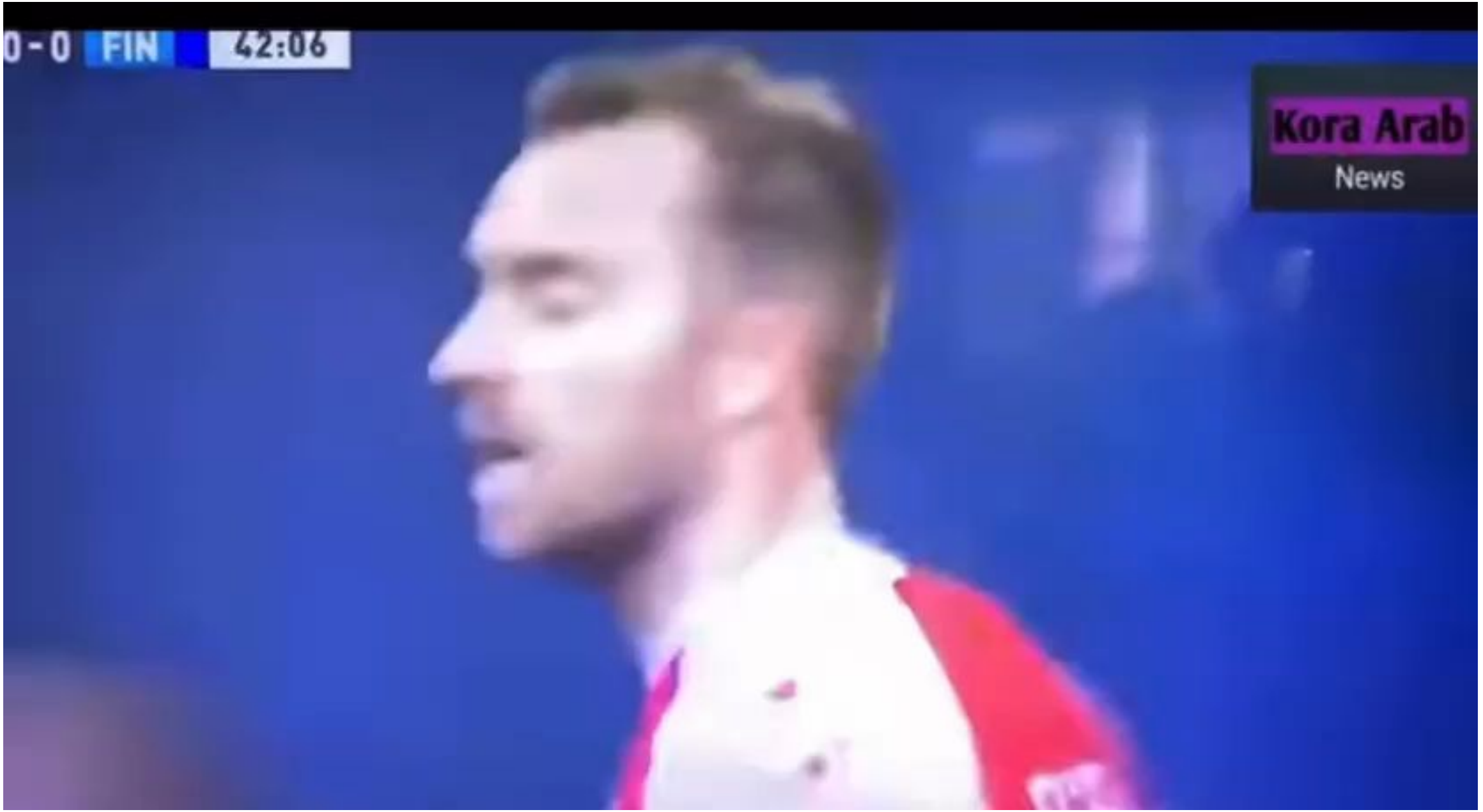
Selective α_2 agonists

- **Clonidine**
- Clonidine is an **α_2** agonist that acts ***centrally*** (on postsynaptic **α_2** receptors) to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery and also acts ***peripherally*** (on presynaptic **α_2** receptors) to inhibit the release of noradrenaline from noradrenergic neurons.
- **Therapeutic uses:**
  - **hypertension** (centrally acting antihypertensive drug)
  - **minimize the symptoms of withdrawal** from **opioids** or **benzodiazepines**
  - reduce frequency of **migraine** attacks
  - can help to quit smoking in women
- **S.E : drowsiness** , **orthostatic hypotension**, **oedema**, **wt. gain** and **rebound HTN** .

- **MethylNoradrenaline**
-

- Produced from ***methyldopa*** (centrally acting antihypertensive drug) that is metabolized in the noradrenergic neurons (**instead of DOPA**) to produce **methyldopamine** (**instead of dopamine**) which converted to **methylnoradrenaline**. (**instead of noradrenaline**)
- It is **stored** and **released** instead of noradrenaline (**false neurotransmitter**) and after release it directly stimulate **α_2** receptors and reduce the noradrenaline release.(also **decreasing sympathetic outflow**)


'ANK YOU!


0 - 0
FIN
42:06
Kora Arab
News