Reproductive System

PHARMACOLOGY 432 TEAM

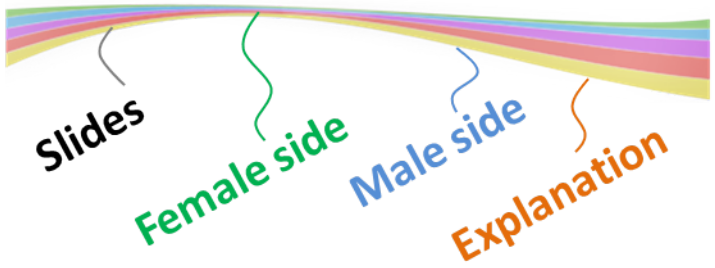
TOCOLYTICS&OXYTOCIN

This lecture was done by:

Ibrahim AlQasir &
Hossam Alshehri

And reviewed by:

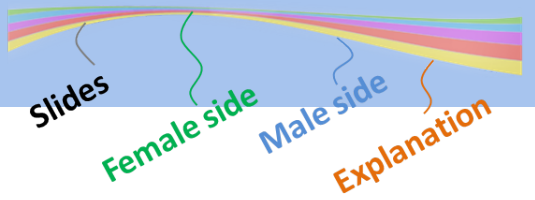
Ahlam Almutairi



Learning Objectives:

1. Drugs used to induce & augment labor.
2. Drugs used to control post partum haemorrhage.
3. Drugs used to induce pathological abortion.
4. Drugs used to arrest premature labor.
5. The mechanism of action and adverse effects of each drug.

NOTE: Regarding 'Prostaglandins' the female doctor had much more details than the males, so it's up to you to choose the source you want to study from, both are here.



Mind Map

- Oxytocins (uterine contraction)
  - Oxytocin
  - Ergot Alkaloids
  - Prostaglandins
  - Differences between Oxytocic Drugs
- Tocolytics (uterine relaxation)
  - β-ADRENOCEPTOR AGONISTS
  - CALCIUM CHANNEL BLOCKERS
  - **Oxytocic Antagonist** e.g. Atosiban
  - **-Prostaglandin synthetase inhibitors**
    -Magnesium sulphate
    -COX inhibitors (indomethacin)

Oxytocin(Synthetic is preferred) ➡ syntocinon

Pharmacokinatics	M.O.A	USES
Not effective orally (Destroyed in GIT) Administered i.v. (LABOR!) Also as nasal spray (Milk Ejection!) Not bound to plasma proteins Catabolized by liver & kidneys Half life = 5 minutes	promoting Ca+ influx from extracellular fluid & sarcoplasmic.R into cell , ↑↑ in cytoplasmic calcium ◊ uterine contraction!	1-Facilitation of labor at term IV-infusion (Reinforcement of labor) 2- Induction of labor for conditions requiring early vaginal delivery (I.V infusion) e.g. a) Mild pre-eclampsia b) Uterine inertia (no contraction) c) Incomplete abortion d) Post maturity e) Maternal diabetes f) Premature rupture membranes 2- Post partum uterine hemorrhage (ergometrine replaced it) 3- Impaired milk ejection: One puff in each nostril 2-3 min before nursing

Oxytocin(Synthetic is preferred) ➡ syntocinon

CONRAINDICATIONS	Precautions	Side Effects
Basically when we don't want a vaginal delivery because of: a) Hypersensitivity b) Prematurity c) Abnormal fetal position d) Evidence of fetal distress e) Cephalopelvic disproportion f) Incompletely dilated cervix	a) Multiple pregnancy (afraid of uterine rapture due to weakness of muscles) b) Previous c- section c) Hypertension	1. Maternal death due to hypertension due to Fluid retention,(always keep your eye on the monitors) 2. Uterine rupture (Cervix is not dialated enough!!!) 3. Fetal Distress,death (ischaemia) 4. Water intoxication 5. Hyponatremia, heart failure, Seizures

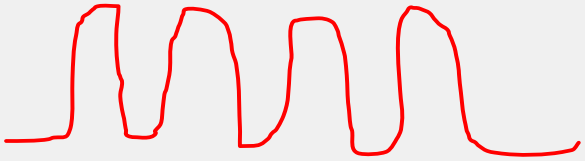
Pharmacological actions of oxytocin

Uterus

Small doses

stimulates both the frequency and force of uterine contractility particularly of the fundus segment of the uterus.

These contractions resemble the normal physiological contractions of uterus (contractions followed by relaxation)



Large doses

1. causes sustained contractions
2. Immature uterus is resistant to oxytocin. (it's taken only in full-term because it's naturally produced during labor (full-term).
3. Contract uterine smooth muscle only at term
4. Sensitivity increases to 8 fold in last 9 weeks and 30 times in early labor.
5. Clinically oxytocin is given only when uterine cervix is soft and dilated.

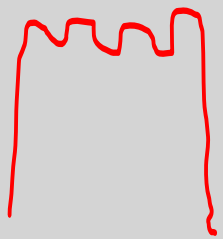
Mammary glands

suckling stimulate the production of oxytocine

Oxytocin Stimulate myoepithelial cells surrounding mammary alveoli produce milk production

Without oxytocin induced contraction lactation can not occur.

Ergot Alkaloids ➡ Ergometrine

Action	Pharmacokinetics	CONRAINDICATIONS
Alkaloid derivatives induce TETANIC CONTRACTION of uterus without relaxation in between (not like normal physiological contractions) it causes contractions of uterus as a whole (tend to compress rather than to expel the fetus) 	*Absorbed orally from GIT (tablets) *Usually given I.M *Extensively metabolized in liver. *90% of metabolites are excreted in bile	**INDUCTION OF LABOR IN :** a) 1st and 2nd stage of labor b) Vascular disease. c) Severe hepatic and renal impairment. b) Severe hypertension

Ergot Alkaloids ➡ Ergometrine

USES	Side effects	PREPARATIONS
***Post partum hemorrhage (3rd stage of labor)** (very strong contraction of smooth muscles and closure of blood vessels) *The delivery of placenta *Hastens involution of the uterus	**a) Nausea, vomiting, diarrhea** **b) Hypertension** **c) Vasoconstriction of peripheral blood vessels (toes & fingers)** **d) Gangrene**	**Syntometrine** (ergometrine 0.5 m + oxytocin 5.0 I.U), **I.M.** **Natural** **Ergonovine** **Synthetic** Methyl ergometrine Methyl ergonovine

(MALE SLIDES) Prostaglandins

Drugs&Pharmacokinetics	USES
PGE2 – Dinoprostone: Extra-amniotic and vaginal route PGF2α- Dinoprost, Carboprost: intra-amniotic injection Misoprostol(synthetic PGE1): intravaginally as a gel or tablets **found in some NSAIDS and could cause an ABORTION!**	1.Induction of abortion 2.Induction of labor (in case of fetal death in uterus). 3.Postpartum hemorrhage.

Side Effects	Precautions	Contraindications:
a) Nausea , vomiting b) Abdominal pain. c) Diarrhea. d) Bronchospasm (PGF2α). e) Flushing (PGE2)	1- Asthma 2- Glaucoma 3-Multiple pregenency 4- Uterine rapture	a)Mechanical obstruction of delivery b)Fetal distress c)Predisposition to uterine rupture

Prostaglandins (FEMALE SLIDES)

dinoprostone:	Effects of dinoprostone
Uses: -Facilitation of labor at term -Induction of labor -Medical Abortifacient -Used as vaginal suppositories alone or with oral Misoprostol **S/ E** Nausea, vomiting, diarrhea Incomplete abortion, Increase blood loss, Flushing (PGE2)	*Stimulation of G protein coupled PGE2 receptors ➔ contraction of myometrium *Ripening of cervix due to direct effect on cervical collagenase resulting in softening *Has natriuretic effect (no diuretic effect =no Salt and water retention) -Superior to oxytocin for women with pre-eclampsia , as no fluid retention

Carboprost: 15 methyl PGF2α Analog
Uses: -Induction of labor -To control PPH IMI -For 2nd trimester abortion , single intra-amniotic Injection **S/ E** Vomiting, diarrhea,Transient rise of temperature, Bronchoconstriction, Fetal toxicity uncommon

Differences between Oxytocic Drugs

Drugs	Oxytocin	Prostaglandins
Contraction	At term	All pregnancy
Cervix	Doesn't soften it	Soften it
Duration of action	Shorter	Longer
Uses	induce and augment labor and post partum Hemorrhage	-Induce abortion in 2nd trimester -Used as vaginal suppository forinduction of labor -Post partum hemorrhage.

Drugs	Oxytocin	Ergot Alkaloids
Contraction	Physiological	Titanic
Uses	-To induce &augment labor. *Post partum hemorrhage.	Post partum hemorhhage
Duration and Onset	-Rapid onset . -Shorter duration of action.	-Moderate onset. -Long duration of action.

Summary of Tocolytics

Drugs	MOA and USES		Side Effects
B-Agonists (retodrine) i.v. drip	increase in the level of cAMP reducing intracellular calcium level.	Premature labor & threatened Abortion Selective β_2 receptor agonist used specifically as uterine relaxant.	➢ Tremor ➢ Nausea , vomiting ➢ Flushing ➢ Sweating ➢ Tachycardia (high dose) ➢ Hypotension ➢ Hyperglycemia ➢ Hypokalaemia ➢ Anxiety, Restlessness, Headache ➢ Pulmonary edema
Ca-channel blockers (nifedipine)	Causes relaxation of myometrium by inhibiting the amplitude of spontaneous contractions and oxytocin-induced contractions		➢ Constipation ➢ Ankle edema ➢ Coughing ➢ Wheezing ➢ Tachycardia ➢ Headache, dizziness ➢ Hypotension ➢ Flushing

Summary of Tocolytics

Drugs	MOA and USES	Side Effects
Atosiban (Oxytocic Antagonist).	Compete with oxytocin at its receptors on the uterus. **(Antagonizes the effects of oxytocin at its receptors)** **Used as tocolytic in premature labor** **Given by IV infusion for 48 hrs.**	
Prostagland-ins synthase Inhibitors (NSAID,s e.g. Indomethacin, Aspirin, Ibuprofen)	depletion of prostaglandins prevents stimulation of uterus	Ulceration premature closure of ductus arterious

(Tocolytic Drugs).

DRUGS PRODUCING UTERINE RELAXATION

Uses:

1. To arrest premature labor
2. Delay delivery for 48 hrs , this time can be used to administer glucocorticoids (Injection betamethasone) to mother for maturation of the fetal lung.

1. **Question: 30 year pregnant lady came to the clinic with vaginal bleeding, fetal death was diagnosed, which drug is the best to induce abortion in this case?**
   A. Oxytocin
   B. Dinoprostone
   C. Ergometrine

2. **Question: Pregnant lady admitted for labor, she has been pregnant for 9 months and 2 weeks, the best drug to initiate the delivery would be:**
   A. Oxytocin
   B. Dinoprostone
   C. Ergometrine

3. **Question: Syntocinon induces it's action by:**
   A. Inhibiting the uptake of Ca
   B. Promote Ca Efflux
   C. Promote Ca Influx

Answers: B, A, C

Questions

1. **Question: 28 year old female came to the clinic complaining of spontaneous uterine contractions which of the following is the best drug for treatment ?**

   A. Oxytocin
   B. aspirin
   C. Atosiban
   D. Nifedipine

2. **Question: which one of the following is the action of Atosiban :**

   A. depletion of prostaglandins
   B. Compete with oxytocin at its receptors on the uterus
   C. Bind to β-adrenoceptors

Answers: D, B

Reproductive System

PHARMACOLOGY 432 TEAM

Pharmacology Leaders

Tuqa Al-Kaff & Abdullah Al-Anzi

Pharmacologyteam1@gmail.com