



PT 431 Team Pharmacology

Reproductive Block

Lecture 3

Tocolytics and oxytocin

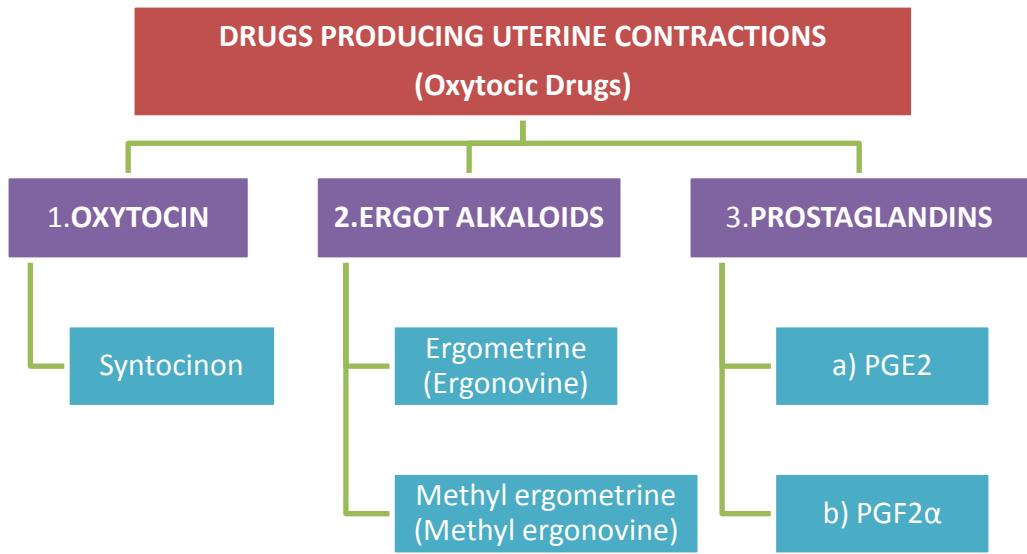


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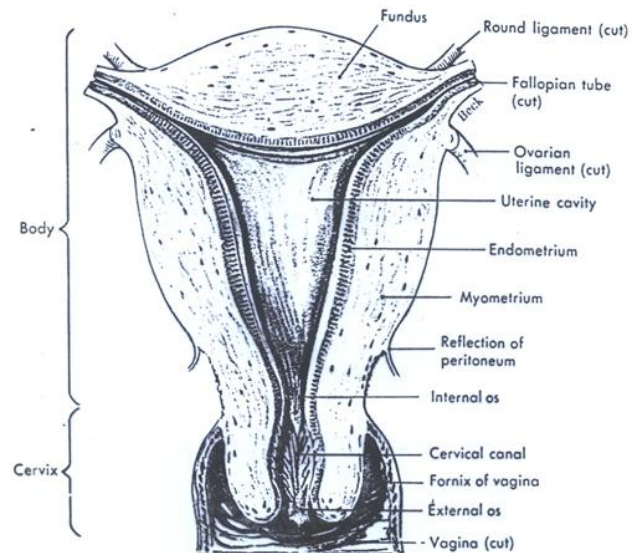
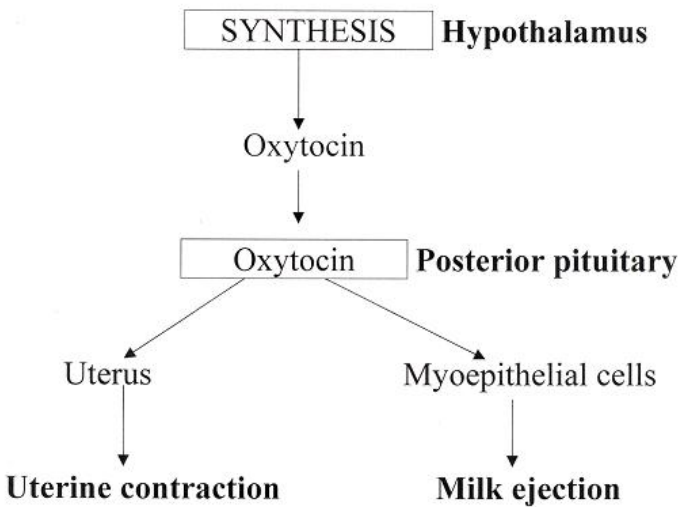
DRUGS AFFECTING UTERINE MUSCLE CONTRACTILITY



1. Oxytocin (Syntocinon):

◆ **Synthesis:**

OXYTOCIN



Oxytocin secretion occurs by sensory stimulation from **cervix, vagina**, and from **suckling at breast**.

◆ **Pharmacokinetics:**

- Not effective orally “peptide”.
- Administered intravenously.
- Also as nasal spray (we use it in patient with impaired milk ejection to stimulate milk secretion)
- Not bound to plasma proteins.
- Catabolized by liver & kidneys.
- Half life = 5 minutes.

◆ Role of action:

- 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).
- Immature uterus is **resistant** “not responding” to oxytocin
- Contract uterine smooth muscle only at term
- Sensitivity increases to 8 fold in last 9 weeks and 30 times in early labor
- Clinically oxytocin is given only when uterine cervix is soft and dilated



We can't give oxytocin if the cervix is not softened or dilated; we must give her prostaglandin first to dilate it

◆ MOA:

Oxytocin → myometrial cell membrane receptor → promoting Ca⁺ influx from extracellular fluid & sarcoplasmic.R into cell → ↑↑ in cytoplasmic calcium → uterine contraction!

◆ Therapeutic Uses of Oxytocin

1- Induction & augmentation of labor (slow I.V infusion):

- a) **Mild pre-eclampsia**
- b) **Uterine inertia** (absence of effective uterine contractions during labor)
- c) **Incomplete abortion**
- d) **Post maturity** “if the pregnant complete the full term without delivering”
- e) **Maternal diabetes**

Pre-eclampsia: A pregnancy disorder in which the pregnant woman develops hypertension and proteinuria in late pregnancy, if not controlled it will lead to eclampsia.

Eclampsia: is an acute and life-threatening complication of pregnancy, characterized by the appearance of tonic-clonic seizures, usually in a patient who has developed pre-eclampsia.

2- Post partum uterine hemorrhage (I.V drip) (ergometrine replaced it)

3- Impaired milk ejection:

One puff in each nostril 2-3 min before nursing

◆ Side Effects of Oxytocin

1. Maternal death due to hypertension
2. Uterine rupture (like when cervix wasn't dilated)
3. Fetal death (ischaemia)
4. Water intoxication

◆ Contraindications:

- a) Hypersensitivity
- b) Prematurity
- c) Abnormal fetal position
- d) Evidence of fetal distress
- e) **Cephalopelvic disproportion** "when the capacity of the pelvis is inadequate to allow the fetus to negotiate the birth canal"

◆ Precautions

- a) Multiple pregnancies
- b) Previous c- section
- c) Hypertension

2. Ergot alkaloids

- Ergometrine (Ergonovine)
- Methyl ergometrine (Methylergonovine)

◆ Role of action:

- Alkaloid derivatives induce **TETANIC CONTRACTION** of uterus without relaxation in between (not like normal physiological contractions)
- It causes contractions of uterus as a whole i.e. **fundus and cervix** (tend to compress rather than to expel the fetus)



◆ Pharmacokinetics:

- Absorbed orally from GIT (tablets).
- Usually given I.M.
- Extensively metabolized in liver.
- 90% of metabolites are excreted in bile.

◆ Therapeutic uses of ergots:

- Post partum hemorrhage (3rd stage of labor = placental delivery)

◆ Preparations

Syntometrine (ergometrine 0.5 mg + oxytocin 5.0 I.U), I.M

◆ Side effect of ergots:

- a) Nausea, vomiting, diarrhea
- b) Hypertension
- c) **Vasoconstriction of peripheral blood vessels (toes & fingers)**
- d) **Gangrene**

◆ Contraindications:

-Induction of labor in these situations:

- a) 1st and 2nd stage of labor.
- b) Vascular disease.
- c) Severe hepatic and renal impairment.
- b) Severe hypertension

3. Prostaglandins (PgE2, Pgf2):

◆ Therapeutic uses

1. Induction of abortion (pathological).
2. Induction of labor (in case of fetal death in uterus).
3. Postpartum hemorrhage.

◆ Side effect of prostaglandins:

- | | |
|-----------------------|-----------------------------------|
| a) Nausea , vomiting. | b) Abdominal pain. |
| c) Diarrhea. | d) Bronchospasm (PGF2 α). |
| e) Flushing (PGE2) | |

◆ Contraindications:

- a) Mechanical obstruction of delivery.
- b) Fetal distress.
- c) Predisposition to uterine rupture.

◆ Precautions:

- | | |
|-------------|-------------------------|
| a) Asthma | b) Multiple pregnancies |
| c) Glaucoma | d) Uterine rupture |

UTERINE RELAXANTS DRUGS PRODUCING UTERINE RELAXATION (Tocolytic Drugs):

◆ Action and Uses:

Relax the uterus and **arrest threatened abortion or delay premature labor.**

Threatened abortion: a condition in pregnancy before the twentieth week of gestation characterized by uterine bleeding and cramping sufficient to suggest that miscarriage may result.

1. β -ADRENOCEPTOR AGONISTS

Ritodrine, i.v. drip

Selective β_2 receptor agonist used specifically as a uterine relaxant.

◆ Mechanism of action:

Bind to β -adrenoceptors \rightarrow activates enzyme Adenylate cyclase \rightarrow $\uparrow\uparrow$ cAMP
 \rightarrow reducing intracellular calcium level (cAMP will sequester Ca $^{+}$ & inactivate myosin kinas)

◆ Side effect of Ritodrine (β -agonist):

- Tremor.
- Nausea , vomiting.
- Flushing.
- Sweating.
- Tachycardia (high dose)
- Hypotension (dilate skeletal and hepatic arteries)
- Hyperglycemia ($\uparrow\uparrow$ gluconeogenesis in skeletal and liver)
- Hypokalaemia (a reflex because of $\uparrow\uparrow$ insulin because of gluconeogenesis and that will lead to the uptake of K from blood by cells)

2. CALCIUM CHANNEL BLOCKERS

e.g., Nifedipine

- Causes relaxation of myometrium.
- Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions.

◆ Side effect of Nifedipine (Ca blocker):

- Headache, dizziness
- Hypotension
- Flushing
- Constipation
- Ankle edema
- Coughing
- Wheezing
- Tachycardia

3. Prostaglandin synthetase inhibitors

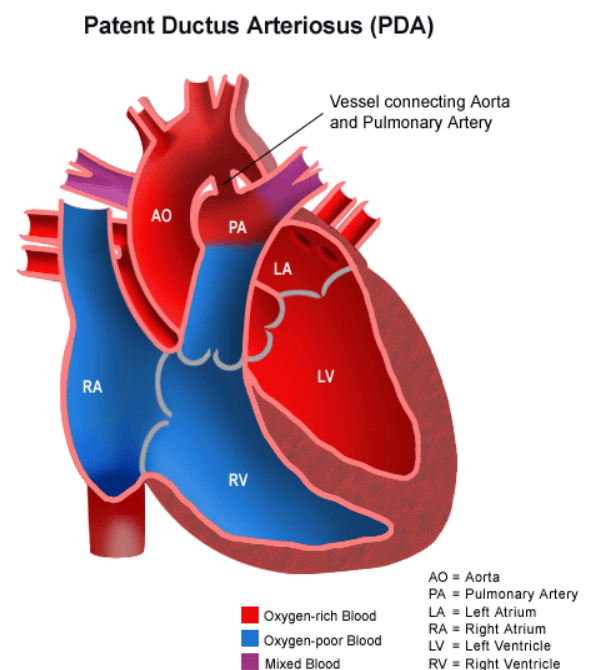
- The depletion of prostaglandins prevents stimulation of uterus.

1. NSAIDs:

e.g: Indomethacin
Aspirin
Ibuprofen

◆ Side effect of NSAIDs:

Ulceration
Premature closure of ductus arterious



Summery

Difference B/w Oxytocin and Prostaglandins

Character	Oxytocin	Prostaglandins
Contraction	Only at term	Contraction through out pregnancy
Cervix	Does not soften the cervix	Soften the cervix
Duration of action	Shorter	Longer
Uses	Induce and augment labor and post partum hemorrhage	-Induce abortion in 2 nd trimester of pregnancy. -Used as vaginal suppository for induction of labor -Post partum hemorrhage.

Difference B/w Oxytocin and Ergometrine

Character	Oxytocin	Ergometrine
Contraction	Resembles normal physiological contractions	Tetanic contraction; doesn't resemble normal physiological contractions
Uses	-To induce & augment labor. *Post partum hemorrhage.	Only in post partum hemorrhage
Onset and Duration	-Rapid onset . -Shorter duration of action.	-Moderate onset. -Long duration of action.

◆ Oxytocin :

- Stimulates uterine contractility; particularly that of the **fundus segment**.
- **contracts myoepithelial cells** in the mammary gland and have a **Weak antidiuretic** action.
- Taken in the form of Nasal spray in case of Impaired milk ejection.

◆ Ergots:

- **ADRs include:** Vasoconstriction of peripheral blood vessels (toes & fingers).
- **Ergots are not used if the fetus is still in the uterus .**

◆ PROSTAGLANDIS :

- promote a series of coordinated contraction of body of uterus along with relaxation of cervix

◆ Tocolytics are used to To delay or prevent preterm labor. They include:

1. β -ADRENOCEPTOR AGONISTSE.g. Ritodrine & terbutaline
2. CALCIUM CHANNEL BLOCKERS e.g., Nifedipine
3. Prostaglandin synthesis inhibitors (Aspirin, indomethacin, ibuprofen)

430 team notes:

Remember the first choice in:

- Induction of labor in pregnant woman (with soft and dilated cervix):
Oxytocin
- Induction of abortion:
Prostaglandin
- Postpartum hemorrhage:
Ergotamine

Question

- 1. Which one of the following drugs produces tetanic contraction:**
 - a. Oxytocin
 - b. Ergot Alkaloids
 - c. Prostaglandis
 - d. Beta-adrenoceptor agonist

- 2. Which one of the following drugs is clinically used to delay preterm labor?**
 - a. Syntocinon
 - b. Ritodrine
 - c. Prostaglandin E2
 - d. Ergonovine

- 3. A healthy pregnant woman admitted to the hospital for labor and she was about 10 days post term. After examination, the uterine cervix was soft. Which one of the following drugs is to be selected to induce labor?**
 - a. Ergonovine
 - b. Prostaglandin E2
 - c. Oxytocin
 - d. Prostaglandin F2 alpha

Answers: B, B, C