Genitourinary System Module

Pharmacology

Drugs acting on the pregnant uterus

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Drugs acting on uterus smooth muscles

A. **Uterine Stimulants (uterotonics):** are used to stimulate the uterus in three main clinical scenarios:

   1. To initiate uterine activity for induction of labor or termination

   2. To augment slowly progressing labors

   3. To stimulate delivery of the placenta and prevent post-partum hemorrhage

B. **Uterine relaxant (tocolytics):** are used to relax the uterus in cases of **preterm labor; to delay preterm (before the aga of 37-week gestation) delivery.**

***Both classes of drugs target the pathways that initiate and produce uterine contractions.**

Uterine Stimulants

These drugs increase **uterine contraction:**

1. **Posterior pituitary hormone :** Oxytocin, Desaminooxytocin
2. **Ergot alkaloids:** Ergometrine, Methylergometrine
3. **Prostaglandins (E2, F2α) analogues:** Dinoprostone, Dinoprost, Misoprostol.

Posterior pituitary hormone uterotonic: Oxytocin

- Oxytocin is a nonapeptide hormone (contains nine amino acid residues).
- It is generated in the hypothalamus but stored and released from the posterior pituitary gland.
- Oxytocin is one of the few that exhibit positive feedback loops, i.e., release of oxytocin stimulates even more of a release of oxytocin.
- Stimulates uterine contractions in the myometrium by causing G-protein coupled receptors to stimulate a rise in intracellular calcium in uterine myofibrils.
- Uterine contractions, cause more oxytocin to be release leading to increase in both the intensity and frequency of contractions and enables a mother to carry out vaginal delivery completely.
- Causes contractions of the myoepithelial cells in the female breasts to enable milk expulsion.
- Oxytocin also has both antidiuretic and vasodilatory effects, increasing cerebral, coronary, and even renal blood flow.

Oxytocin: clinical use

- Oxytocin is indicated and approved by the FDA for two specific time frames: antepartum and postpartum.

- In the antepartum period, exogenous oxytocin used for strengthening uterine contractions with the aim of successful vaginal delivery of the fetus; For mothers who have:

1. inactive uteri that require stimulation to start labor

2. preeclampsia (high blood pressure in late stage of pregnancy), maternal diabetes, premature rupture of the membranes: these conditions require delivery before labor has begun

3. inevitable or incomplete abortions in their second trimester

- Indication in the postpartum period include delivery of the placenta and control postpartum hemorrhage.

- Cervical status must be favorable (soft and dilated) for oxytocin use.

Oxytocin: Administration and side effects

- Oxytocin is inactive orally and is generally administered by i.m. or i.v. routes, rarely by intranasal spray.
- It is rapidly degraded in liver and kidney; **plasma t½ ~6 min.**

Side effects:

1. Inappropriate dosage of oxytocin can cause uterine hyperstimulation, uterine rupture, hemorrhages, maternal death, fetal distress and fetal death.
2. Water intoxication: because of ADH like action of large doses given along with i.v. fluids.

Ergot alkaloids

- Ergometrine and methylergometrine are ergot alkaloids that increase the uterine muscle tone by causing continuous tetanic contractions (contraction lasting more than 90 seconds).

- It causes contractions of both upper and lower segments of uterus i.e.fundus and cervix (tend to compress rather than to expel the fetus).

- **Uses:**

1. Control and prevent postpartum hemorrhage(PPH)

2. After caesarean section to prevent uterine atony (weak uterus muscle, leads to postpartum hemorrhage)

- They are vasoconstrictive and increase the risk of hypertension post partum. Other side effects with ergot alkaloids are pain after birth, nausea and vomiting.

Ergot alkaloids

- **Adverse effects :-**

1.Nausea, vomiting

2.Increase in blood pressure occur occasionally.

3.High doses for many days → ↓ milk secretion (due to inhibition of prolactin release).

- **They are contraindicated during pregnancy and before the delivery of the placenta (3rd stage of labor).**

Prostaglandins (E2, F2α) analogues

- PGE2, PGF2α are potent uterine stimulants and cause ripening of cervix.
- **Dinoprostonw, Dinoprost** and **Misoprostol** are PGs analogues.
- PGs increase tone as well as amplitude of uterine contractions.
- **Uses:**

1. Induction of labour
2. Cervical ripening
3. Therapeutic abortion (proceeded 2 days by Mifepristone (anti-progestin))
4. Postpartum haemorrhage

****Should be stopped before administering oxytocin.**

Uterine relaxant (tocolytics)

- Tocolysis is intended to prolong gestation for two to seven days in case of premature labor
- This allows for transportation to a higher care facility and to administer of corticosteroids (for fetal lung maturity)
- Tocolysis is beneficial in patients having preterm labor before 34 weeks gestation.
- Tocolysis is not intended to increase gestation of the fetus to term but is focused on providing a window of time to support treatments that to improve outcomes for delivery.
- Different medications currently used are:
  - Beta-Adrenergic receptor agonists
  - Calcium channel blockers
  - Nonsteroidal antiinflammatories
  - Oxytocin inhibitors

β Adrenoceptor agonists

- **Ritodrine** and **terbutaline**

- Selective β2 receptor agonist used specifically as a uterine relaxant.

- Mechanism of action: Bind to β adrenoceptors, which increases in level of cAMP reducing intracellular calcium level leading to smooth muscle relaxation.

- Side effects: Cardiac arrhythmias, Tachycardia, Hypotension, Hyperglycemia, Hypokalemia, Sweating,, nausea , vomiting.

Calcium channel blockers

Nifedipine:

- Decrease the influx of Ca2+ ions →↓ uterine contractions
- Adverse effects: Tachycardia, hypotension, Constipation, ankle edema, coughing and wheezing (be careful with asthmatic pts).
- Administration: oral and sublingual. Recent literature has shown sublingual nifedipine achieved faster tocolysis
- Compared to other tocolytic agents, calcium channel blockers significantly delay birth (7 days)

Oxytocin antagonist: Atosiban

- Is a peptide analogue of oxytocin that acts as antagonist at the oxytocin receptors.
- May be less effective as tocolytic than β 2 agonists.
- Postpone preterm labour with fewer cardiovascular and metabolic complications than β2 adrenergic agonists.