UGS PHARMACOLOGY SUMMARY (LEC 1-4)

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Lec 1

Quinolones (fluoroquinolones,floxacin):

- MOA: inhibition of microbial DNA synthesis by inhibiting bacterial gyrase enzyme(type 2 topoisomerase).

- their use has been reduced due to: toxicity, resistance, and introduction of macrolides.

- general features: broad spectrum, cidal, synthetic (chemotherapeutic agents).

-1st generation: effective for gram(-) and weak effect on gram(+).

-2nd generation: additional activity at gram(+)

-3rd and 4th generation: additional activity at gram(+), anaerobes, and pseudomonas.

- Most widely used agents: ciprofloxacin (2nd gen), levofloxacin (3rd gen), moxifloxacin (4th gen).

- Orally effective but absorption affected by food containing iron and ca2+.

- 1st generation: nalidixic acid, pipemidic acid, oxolinic acid.

- 2nd generation: ciprofoxacin, ofloxacin ….(+any other drug ending with the suffix floxacin not mentioned in other generations).

- 3rd generation: levofloxacin, sparfloxacin, gatifloxacin.

- 4th generation: moxifloxacin, prulifloxacin, gemifloxacin.

- Uses: complicated UTIs (cipro&levo), respiratory infections, bacterial prostatitis and cervicitis, bacterial diarrhea (shigella,salmonella,E.coli).

- Mechanisms of bacterial resistance: efflux pumps, production of proteins that protect DNA gyrase, DNA gyrase mutations.

- Side effects: GI irritation, cardiac toxicity (QT prolongation-torsade de pointes), interfere with cartilage development (children, pregnancy), some maybe carcinogens.

Nitrofurantoin:

- Synthetic, cidal, orally effective.
- Gram (+) &gram (-) especially E.coli.
- Called UTI antiseptic (highly effective in UTIs-cystitis).
- Multiple MOAs: damaging bacterial DNA and disrupting RNA and proteins synthesis and many metabolic processes.
- Rare resistance due to multiple MOAs.
- Pulmonary fibrosis is a major side effect.
- Contraindicated in G6PD deficiency.

Fosfomycin:

- Broad spectrum, cidal.
- Uses: UTIs(cystitis), occasionally prostate infections.
- Inhibits cell wall synthesis by inhibiting phosphoenolpyruvate synthetase and thus peptidoglycan synthesis.
- Given only in a single dose due to rapid microbial resistance.
- Well tolerated orally but can cause: metallic taste, stomach upset, dizziness, stuffy nose, back pain, vaginal itching or discharge.

Lec 2

Posterior pituitary hormones:

- **ADH&oxytocin.**
- Nonapeptides (9 A.As), neurohormones.
- Synthesized in the hypothalamus.
- Stored in and released from posterior pituitary.
- V1R in CNS – role as neurotransmitters ?
- Unknown Role of oxytocin in man.
- At the 3rd and 8th positions ADH (phenylalanine,arginine), oxytocin (isoleucine,leucine) respectively.
- **Vasopressin/ADH/AVP**:
- V1aR: vasoconstriction & platelets aggregation, V1bR: increase ACTH release, V2R: increase H2O reabsorption in CD & increase synthesis of factor 8 and vWF.
- Oxytocin like activity.
- Factors increasing ADH sec: hypovolemia, hyperosmolarity, fever, stress, pain, nausea, hypoxia, certain PG, ANG 2, nicotine, beta and cholinergic agonists, TCA, insulin, morphine, vincristine.
- Factors decreasing ADH sec: hypervolemia, hypoosmolarity, alcohol, ANP, phenytoin, cortisol, anticholinergics, alpha agonists, GABA.
- SIADH: excessive ADH secretion causing dilutional hyponatremia, caused by head trauma,encephalitis,meningitis,oat cell carcinoma.
- Treated by water restriction (Rx of choice), hypertonic saline, fludrocortisone (aldosterone like activity to increase Na+), ADH antagonists.
- **ADH antagonists**: **conivaptan** (nonselective blocker at V1R&V2R given IV), **tolvapta-lixivaptan-satavaptan** (selective blockers at V2R given orally), all are used for SIADH, CHF, and liver cirrhosis.
- Deficiency of ADH (diabetes insipidus,DI) causes are: congenital,familial,idiopathic,head trauma,malignancy,gestational DI

is caused by overproduction or decreased clearance of vasopressinase. DI is treated by HRT (hormone replacement therapy)

- Natural human ADH (**pitressin**) – short half life 15 min.
- Porcine synthetic ADH (**lypressin**) – half life of 4 hrs.
- **Desmopressin**(ADH analogue) – half life of 12 hrs, PO/SC/IM/intranasal,most widely used.
- **Felypressin** (synthetic ADH like drug) has strong vasoconstrictor activity so used in dentistry for topical anesthesia.
- Clinical uses of ADH: DI, nocturnal enuresis, hemophilia, bleeding esophageal varices.
- SEs of ADH: allergy, pallor, abdominal pain in females (oxytocin like effect), angina pain, H2O intoxication, gangrene (rare).

Drugs acting on the uterus:

- These are divided into uterine stimulants and relaxants (tocolytics).
- **Uterine stimulants**: oxytocin, prostaglandndins, and ergot alkaloids.
- **Oxytocin**: contracts the myoepithelial cells of the breast → milk letdown (ejection) and contracts the uterus → delivery.
- Major stimuli for oxytocin secretion: baby cry and suckling.
- The uterus is insensitive to oxytocin in early pregnancy but it maximizes upon delivery.
- Slight ADH like activity, and questionable role in men.
- MOA: Surface receptors → stimulation of voltage gated Ca2+ channels → depolarization of uterine muscles → contractions, also increases intracellular calcium and prostaglandins release.
- Clinical uses: induction of labor (drug of choice,IV infusion), postpartum hemorrhage (I.M. ergot alkaloids are better), breast engorgement (intranasally), abortifacient (IV infusion,> 20 weeks of gestation, ineffective in early pregnancy).

- Ergot alkaloids for postpartum hemorrhage: ergonovine, methylergonovine, syntometrine (oxytocin+ergometrine).
- Side effects: rupture of uterus (major), H2O intoxication &HTN (ADH like activity).
- Specific oxytocin antagonist: atosiban (tocolytic), has little vasopressin antagonistic effect (specific), effective in management of premature delivery (IV).
- **Prostaglandins**:
- Dinoprostone (PGE2): abortifacient, induction of labor.
- Dinoprost (PGF2a): same uses as Dinoprostone.
- Carboprost (PGF2a): abortifacient and postpartum hemorrhage.
- Gemeprost (PGE1): prime the cervix and induce uterine contractions.
- **Ergot alkaloids(IM,ORAL)**: ergonovine, methylergonovine.
- Remain the drug of choice for postpartum hemorrhage.
- As compared to oxytocin, they are more potent (prolonged contractions) and less toxic.
- Contraindicated to be used as inducers to delivery (fetal distress and mortality).
- **Uterine relaxants (tocolytics)**:(major contradiction: fetal distress)
- Clinical use:premature delivery(weeks 20-36)→improve fetal survival.
- B-adrenergic agonists: increase cAMP → decrease cytoplasmic Ca2+.
- Ritodrine (B2 agonist): IV infusion, most widely used, highly effective. (writer note: it was withdrawn from US due to toxicity).
- Terbutaline (B2 agonist): oral, SC, IV.
- Side effects: tachycardia, sweating, chest pain …...
- Magnesium sulfate(IV infusion): activates adenylate cyclase and Ca2+ dependent ATPase.
- Uses: premature delivery and convulsions of pre-eclampsia.

- Other tocolytics: dydrogesterone (progesterone), oxytocin competitive antagonists (atosiban), PG synthesis inhibitors (NSAIDs like indomethacin and meloxicam), nifedipine (CCB).
  Lec 3 and 4 (combined for better context):

Antifungal Agents:

Polyenes (polyene macrolide antibiotics): amphotericin B, nystatin, natamycin.

- MOA: Bind to ergosterol in fungal plasma membrane forming pores which allows leakage of intracellular ions especially K+ causing fungal death (cidal). They bind selectively to ergosterol and not cholesterol in mammalian plasma membranes.
- Mechanisms of resistance: decrease ergosterol content, impaired binding to ergosterol.
- **Amphotericin B:**
- Poorly absorbed orally, useful for fungal infection of GI tract.
- Drug of choice for most systemic infections (slow IV infusion).
- Locally used in corneal ulcers, arthritis, and bladder irritation.
- Poor penetration of BBB except in meningitis.
- Excreted by kidneys(some in bile),traces found in urine after months!
- Half life 15 days.
- Side effects: renal toxicity (80%), hypokalemia, hypomagnesaemia, anemia, thrombocytopenia, impaired hepatic function, N&V, anaphylactic shock.
- Liposomal preparations: lipid associated delivery system to reduce its toxicity (more efficacious but expensive).
- Effective in candidiasis and *cutaneous leishmaniasis.*
- **Nystatin:**
- Too toxic for systemic use.
- Not absorbed from GIT, skin, or vagina.

- Administered orally to prevent or treat superficial candidiasis of mouth, esophagus, and GIT.
- For vaginal candidiasis: used as cream or pessaries for 2 weeks.
- For cutaneous infections: cream, ointment, or powder.
- **Natamycin**:
- Used for fungal keratitis (corneal infection).
- Especially effective against Aspergillus & fusarium keratitis.
- Not absorbed orally (applies to all polyenes).
- Available in cream and ophthalmic eye drops.
- **Azoles**:
- Imidazoles (2 nitrogen atoms in the azole ring): ketoconazole, miconazole, clotrimazole.
- Triazoles (3 nitrogen atoms in azole ring): fluconazole, itraconazole, voriconazole, posaconazole.
- They added greatly to treatment of systemic infections.
- MOA: fungistatic, inhibitors of ergosterol synthesis, they inhibit CYT P450 demethylase enzyme.
- Mechanism of resistance: mutation in demethylase's gene.
- **Ketoconazole:**
- Only administered orally, narrow spectrum, used for systemic mycosis.
- Well absorbed orally especially with acidic environment.
- Bioavailability is decreased with H2 blockers, PPIs, food,and Sucralfate.
- Highly bound to plasma proteins (lipophilic) but doesn't cross BBB.
- Metabolized in liver by CYT p450 (CYP3A4) and excreted in bile.
- Active against many fungi but not aspirigillus.
- Shampoo and aerosols foams for seborrheic dermatitis (I know we just said only orally!!).
- Could be used in Cushing's syndrome (inhibits cortisol synthesis) and prostate cancer (inhibits testosterone synthesis).

- Inhibits adrenal and gonadal steroidogenesis (abnormal menses in females, loss of libido, impotency, gynaecomastia in males).
- Other side effects: N&V, hepatotoxic (fatal but rare), hair loss, fluid retention and HTN, as other azoles (contraindicated in pregnancy.
- Drug interactions: it inhibits cyt p450 system so potentiates the toxicity of drugs metabolized by this system like: cyclosporine, phenytoin, tolbutamide, warfarin.
- Cyclosporine and phenytoin inhibit ketoconazole metabolism so increase its toxicity.
- Warfarin and rifampin increase its metabolism so decrease its toxicity and its DOA.
- Ketoconazole decreases ergosterol in fungal plasma membrane thus, it reduces the fungicidal action of amphotericin B (never combine them, contraindicated).
- **Triazoles:** fluconazole, itraconazole, voriconazole, posaconazole.
- Newer antifungals, less toxic (more selective), and more effective.
- Penetrate the CNS (vs ketoconazole).
- Cause less endocrine disturbances (vs ketoconazole).
- Resistant to degradation.
- **Fluconazole**:
- Completely absorbed from GIT (excellent bioavailability orally+CS).
- Same plasma concentration achieved orally or IV.
- Bioavailability not altered by food or acidity.
- Less effect on hepatic microsomal enzymes.
- Drug interactions are less common.
- Easily penetrates CSF and the drug of choice for cryptococcal meningitis and coccidiodomycosis.
- Used prophylactically in bone marrow transplant recipients.
- Resistance isn't a problem except in HIV.
- Renal excretion.
- Uses: candidiasis, cryptococcosis, in AIDS.

- Active against histoplasmosis, blastomycosis, spirotrichosis, ring worm(tinea) but itraconazole is better at the same dose.
- Not effective in aspergillosis.
- Side effects: N&V,rash,diarrhea,reversible alopecia,no endocrine SEs,hepatic failure (maybe fatal), highly teratogenic.
- **Itraconazole:**
- Lack side effects of ketoconazole.
- Broad spectrum of activity(IV&orally).
- Food increases its absorption.(dec in keto, neutral in itra)
- Highly metabolized by CYP3A4.
- Highly lipid soluble, well distributed to bone, sputum, adipose tissue.
- Doesn't penetrate CSF adequately as compared to fluconazole therefore, it's concentration is less to treat fungal meningitis.
- Needs 4 days to reach steady state so loading doses are recommended in deep mycosis.
- IV reserved only for serious infections.
- Side effects: N&V,hypertriglyceridemia,hypokalemia,increased aminotransferase(hepatotoxic),rash(leads to drug discontinuation).
- **Voriconazole:**
- Similar to itraconazole but more potent.
- Less inhibition of cyt p450.
- Reversible visual disturbances.
- **Posaconazole:**
- Similar to itraconazole.
- Prophylactic against candida and aspergillus in immunocompromised.
- Treatment of oropharyngeal candidiasis.
- Treats infections by mucor species and other zygomycetes.
- Given orally and well tolerated.
- Like ketoconazole inhibits cyt p450 system.
- SEs:most commonly GIT disturbances,headache,hepatotoxic.

- Topical azoles: miconazole, clotrimazole, butoconazole, terconazole, are topically active drugs, rarely administered parenterally due to severe toxicity.
- Use of topical azoles is associated with contact dermatitis, vulvar irritation, edema.
- Miconazole is a potent inhibitor of warfarin metabolism (bleeding) even when applied topically.
- Any azole is equal to nystatin in treating vulvar candidiasis.
- Oral azoles for topical infections: fluconazole,itraconazole,ketoconazo.

- **Allylamines (fine)**
- Terbinafine,naftifine,butenafine.
- MOA: Like Azoles they inhibit ergosterol synthesis but they target different enzyme in the pathway which is squalene epoxidase,in contrast to Azoles(static)they are cidal due to squalene accumulation.
- Significantly higher amount of squalene inhibits human squalene(selective).
- **Terbinafine:**
- Synthetic allylamine, drug of choice for treating dermatophytes.
- The most common dermatophytes are tinea organisms(ring worm).
- As compared to griseofulvin(another drug for tinea) it is better tolerated and requires shorter duration of therapy.
- Fungicidal but activity limited to candida and dermatophytes.
- Effectively treats onychomycosis (fungal infection of nails), 250 mg daily for 6 weeks in finger and 12 weeks in toe onychomycosis.
- Well absorbed orally,bioavailability decreases due to first pass metabolism in the liver.
- 99% binding to proteins in plasma and metabolized by p450 system.
- The drug accumulates in skin,nails,and fat.
- Severely hepatotoxic (liver failure,maybe fatal).
- Initial T1/2=12 hrs,terminal T1/2=200-400hrs!, due to slow release from tissue (can be found in plasma after 4-8 weeks).

- Contraindicated in nursing mothers(accumulates in breast milk).
- Not recommended in azotemia and hepatic failure (excreted by both).
- SEs: GIT, taste and visual disturbances, severe allergic reactions.
- Rifampin decreases and cimetidine increases it plasma concentration.
- **Naftifine:**
- Effective in tinea pedis(athlete's foot), tinea cruris(jock itch), and tinea corporis(trunk).

Echinocandins(fungin)

- Caspofungin, micafungin, anidulafungin.
- MOA: interfere with synthesis of fungal cell wall by inhibiting the synthesis of D-glucan, fungicidal.
- **Caspofungin:**
- Especially useful for aspirigillus and candida.
- Not very active orally so given IV.
- Highly bound to serum proteins.
- Slowly metabolized by hydrolysis and N-acetylation.
- Eliminated equally by urinary and fecal route.
- SEs: N&V, flushing, liver dysfunction.
- Very expensive ☺.
- **Antifungals that inhibit mitosis:**
- Griseofulvin.
- MOA: binds to tubulin interfering with microtubule function and spindle formation thus inhibiting fungal mitosis.
- Has been largely replaced by terbinafine for treating onychomycosis due to its toxicity.
- Fungistatic for species of dermatophytes and has narrow spectrum.
- Griseofulvin absorption increases with fatty meal (griseo-greasy)
- Barbiturates decrease its absorption from GIT.

- Not effective topically and must be given orally for hair and nail dermatophytes infections.
- Metabolized by the liver and induces CYT p450 enzymes (so it increases its own metabolism).
- Clinical uses: mycotic diseases of skin, hair (esp.scalp), and nail, also highly effective in athlete's foot (tinea pedis).
- It needs 1 month for scalp, 6-9 months for finger nails and at least a year for toe nails.
- Not effective in subcutaneous or deep mycoses.
- SEs: peripheral neuritis, mental confusion, vertigo, blurred vision.
- **Drugs that inhibit DNA synthesis (antimetabolites):**
- **Flucytocine (5FC-5 fluorocytosine).**
- MOA: enters fungal cells by permease (enzyme not found in mammalian cells) and gets converted to 5-fluorodeoxyuridine-5'-monophosphate, this false nucleotide inhibits thymidylate synthase, thus depriving the fungus of thymidylic acid (an essential DNA component). This mononucleotide is further metabolized to become trinucleotide and incorporated into fungal RNA disturbing nucleic acid and protein synthesis (fungistatic).
- Amphotericin B increases cell permeability, allowing more flucytosine to penetrate the cell, thus amphotericin B and flucytosine are synergistic.
- Has useful activity against candida and cryptococcus.
- Effective in combination with itraconazole for chromoblastomycosis and with amphotericin B for cryptococcosis.
- Highly effective in cryptococcal meningitis in AIDS patients.
- Well absorbed orally and penetrates into CSF.
- SEs: reversible neutropenia and thrombocytopenia and occasional bone marrow depression, severe enterocolitis, diarrhea, N&V.
- **Tolnaftate:**
- Effective in most cutaneous mycosis.
- Ineffective against candida.

- Tinea pedis cure rate is 80%.
- **Ciclopirox olamine**: effective in tinea vesicolor.
- **Antifungals for cutaneous mycotic infections (already discussed before):**
- Topical preparations: amphotericin B,nystatin,topical azoles,tolnaftate,terbinafine.
- Oral preparations: oral azoles,griseofulvin,terbinafine.