521 DENS-Clinical Dental Therapeutics

Lecture 4

Pharmacology of Metronidazole and Antifungal Agents

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Resistance to Penicillins

I. Production of β-lactamases
   - This family of enzymes can inactivate penicillins by hydrolyzing the β-lactam ring
   - The production of β-lactamases is considered the principal cause of bacterial resistance to β-lactam antibiotics
   - Examples of bacteria that produce β-lactamases are *Staphylococcus aureus* and many strains of *H. influenzae*, *Neisseria*, and *Pseudomonas*

II. The occurrence of modified penicillin-binding sites
   - Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect its bactericidal activity
   - Example: penicillin resistance in *Streptococcus pneumoniae* (pneumococcus) is caused by altered PBPs

III. Decreased permeability to the drug
   - Decreased penetration through the outer membrane prevents the drug from reaching the target PBP
   - This occurs with G-ve organisms, which have an outer membrane that limits penetration of hydrophilic antibiotics. This is of particular relevance in determining the extraordinary resistance of *Pseudomonas aeruginosa* to most antibiotics
Metronidazole

**Metronidazole, Overview**

- Metronidazole is a synthetic, nitroimidazole-derivative antibacterial and antiprotozoal agent.
- Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided.

**The Chemistry & Pharmacokinetics**

- Oral metronidazole is readily absorbed and permeates all tissues by simple diffusion.
- Intracellular concentrations rapidly approach extracellular levels. Peak plasma concentrations are reached in 1–3 hours.
- Protein binding is low (< 20%), and the half-life of the unchanged drug is 7.5 hours.
- The drug and its metabolites are excreted mainly in the urine. Plasma clearance of metronidazole is decreased in patients with impaired liver function.
**Mechanism of Action:**

- Metronidazole is activated (reduced) by the microbial proteins flavodoxins and ferredoxins found in anaerobic bacteria and certain protozoans.
  - Mammalian cells are unharmed because they lack flavodoxins and ferredoxins that reduce the nitro group of metronidazole.
  - Flavodoxins and ferredoxins electron-transfer proteins that serve as electron donors in the reductive activation of anaerobic ribonucleotide reductase, biotin synthase, etc.
- Once activated, the drug (a short-lived reduction product, most probably the protonated one electron nitro radical anion) oxidizes DNA causing strand breaks and subsequent cell death.

**Clinical Uses**

- **Amebiasis**
  - Metronidazole is the drug of choice for the treatment of all tissue infections with *Entamoeba histolytica*.
  - It is not reliably effective against luminal parasites and so must be used with a luminal amebicide to ensure eradication of the infection.
  - Tinidazole, a related nitroimidazole, appears to have similar activity and a better toxicity profile than metronidazole.

- **Giardiasis**
  - Metronidazole is the treatment of choice for giardiasis.
  - The dosage for giardiasis is much lower—and the drug thus better tolerated—than that for amebiasis.
  - Efficacy after a single treatment is about 90%.
  - Tinidazole is equally effective.

- **Trichomoniasis**
  - Metronidazole is the treatment of choice. A single dose of 2 g is effective.
  - Metronidazole-resistant organisms may lead to treatment failures.
  - Tinidazole may be effective against some of these infections.
  - *T. vaginalis* infection is a venereal disease. Therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism has been found to be present, in order to prevent re-infection of the partner.
**Metronidazole, Clinical Uses, contd.**

- **Bacterial Infections**
  - Metronidazole has potent antibacterial activity against anaerobes, including bacteroides and clostridium species
  - Metronidazole is indicated for treatment of anaerobic or mixed intra-abdominal infections, vaginitis (bacterial vaginosis), antibiotic-associated enterocolitis, acute gingivitis and other dental infections
  - Metronidazole is indicated for treatment of vaginitis due to bacterial Gardnerella or Mycoplasma hominis infection in symptomatic patients
  - Helicobacter pylori eradication therapy, as part of a multi-drug regimen in peptic ulcer disease

**Metronidazole, Adverse Effects**

- **Adverse Effects**
  - Convulsive seizures and peripheral neuropathy (with prolonged use) are serious adverse effects, however they are rare
  - Nausea, vomiting, diarrhea, epigastric distress, abdominal cramping and constipation. *Taking the drug with meals lessens gastrointestinal irritation.*
  - A sharp, unpleasant metallic taste, furry tongue, glossitis, dry mouth and stomatitis. *These may be associated with a sudden overgrowth of Candida which may occur during therapy*
  - Proliferation of Candida in the vagina, dysuria, polyuria, dark urine, cystitis, incontinence and proctitis
  - Reversible neutropenia (leukopenia) and reversible thrombocytopenia
  - Metronidazole has a disulfiram-like effect
  - Although teratogenic in some animals, metronidazole has not been associated with this effect in humans
  - Metronidazole and its metabolites are mutagenic in bacteria. Chronic administration of large doses led to tumorigenicity in mice and rats
Antifungal Agents

Antifungal Agents, Overview

- Fungi are plant-like non-photosynthetic Eukaryotes that may exist in colonies of single cells (yeast) or filamentous multicellular aggregates (molds or hyphae)
- Human fungal infections have increased dramatically in incidence and severity in recent years, due mainly to:
  - cancer treatment and the HIV epidemic (why? Is immune system involved?)
  - critical care accompanied by increases in the use of broad-spectrum antimicrobials
- Fungal infections can be divided into:
  1. superficial infections (affecting skin, nails, scalp or mucous membranes)
  2. systemic infections (affecting deeper tissues and organs)
- The treatment of superficial fungal infections caused by dermatophytic fungi may be accomplished with:
  1. topical antifungal agents, e.g., clotrimazole, miconazole, terbinafine, ketoconazole, or
  2. orally administered agents, e.g., griseofulvin, fluconazole, terbinafine, ketoconazole
- Superficial infections caused by candida species may be treated with topical applications of clotrimazole, miconazole, ketoconazole, nystatin, or amphotericin B
- Chronic generalized mucocutaneous candidiasis is responsive to long-term therapy with oral ketoconazole
Antifungal Agents, Examples

Amphotericin B

- Amphotericin B is an antifungal antibiotic produced by Streptomyces nodosus.
- It is poorly absorbed from the GIT. Oral amphotericin B is thus effective only on fungi within the lumen of the GIT and cannot be used for treatment of systemic disease.
- For systemic infections, it can be given by slow i.v. injection.
- It can also be given topically.

Mechanism of Action of Amphotericin B

- Amphotericin B is selective in its fungicidal effect because it exploits the difference in lipid composition of fungal and mammalian cell membranes.
- Amphotericin B binds to ergosterol (a fungal cell membrane sterol) and alters the permeability of the cell by forming amphotericin B-associated pores in the cell membrane. 
  - How?
    - Amphotericin B combines avidly with ergosterol along the double bond-rich side of its structure and associates with water molecules along the hydroxyl-rich side.
    - This amphipathic characteristic facilitates pore formation by multiple amphotericin molecules, with the lipophilic portions around the outside of the pore and the hydrophilic regions lining the inside.
  - The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death.

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Antifungal Agents, Amphotericin B

- Antifungal Activity
  - Amphotericin B remains the antifungal agent with the broadest spectrum of action.
  - It has activity against the clinically significant yeasts, including *Candida albicans*, but ineffective against dermatophytes.
  - It is used intravenously in the treatment of many systemic mycoses.

- Adverse Effects: The toxicity of amphotericin B can be divided into two broad categories: immediate reactions, related to the infusion of the drug, and those occurring more slowly.
  - Infusion-Related Toxicity: These reactions consist of fever, chills, muscle spasms, vomiting, headache, and hypotension.
    - They can be ameliorated by slowing the infusion rate or decreasing the daily dose.
  - Slower Toxicity:
    - Renal damage is the most significant toxic reaction.
    - A varying degree of anemia due to reduced erythropoietin production by damaged renal tubular cells is occasionally seen.
    - Abnormalities of liver function tests are occasionally seen.
Antifungal Agents, Azoles

- Azoles are synthetic compounds that can be classified as either imidazoles or triazoles according to the number of nitrogen atoms in the five-membered azole ring.
- The imidazoles consist of ketoconazole, miconazole, and clotrimazole. The latter two drugs are now used only in topical therapy.
- The triazoles include itraconazole and fluconazole.

Mechanism of Action

- The antifungal activity of azole drugs results from the reduction of ergosterol synthesis by inhibition of fungal cytochrome P450 enzymes.
- The specificity of azole drugs results from their greater affinity for fungal than for human cytochrome P450 enzymes.
- Imidazoles exhibit a lesser degree of specificity than the triazoles, accounting for their higher incidence of drug interactions and side effects.

Clinical Use

- The spectrum of action of these medications is quite broad, ranging from many candida species, the dermatophytes, to the endemic mycoses.
- They are also useful in the treatment of intrinsically amphotericin-resistant organisms.

Adverse Effects

- As a group, the azoles are relatively nontoxic. The most common adverse reaction is relatively minor gastrointestinal upset.
- All azoles have been reported to cause abnormalities in liver enzymes and, very rarely, clinical hepatitis.
Antifungal Agents, Nystatin

- Nystatin is too toxic for parenteral administration and is only used topically.
- It is currently available in creams, ointments, suppositories, and other forms for application to skin and mucous membranes.
- Nystatin is not absorbed to a significant degree from skin, mucous membranes, or the gastrointestinal tract. As a result, it has little toxicity.
- Nystatin is active against most candida species and is most commonly used for suppression of local candidal infections.
- Some common indications include oropharyngeal thrush, vaginal candidiasis.