Pharmacology/Therapeutics I Block V & VI Handouts – 2013-14

49. Pharmacotherapy of Anemia & Heme Growth Factors – Kini

50. Immunomodulation Therapy – Robinson

51. Anti-Mycobacterials – Pachucki

52. Drugs Used in the Treatment of Allergies & Asthma – Patel

53. Antifungal Agents - Clipstone

Pharmacotherapy of Anemias and Hematopoietic Growth Factors

Date: Monday, November 11, 2013 – 8:30 am
Reading Assignment: Basic & Clinical Pharmacology, Twelfth Edition, BG Katzung (ed), 2012, Chapter 33, Agents Used in Anemias; Hematopoietic Growth Factors, Pages 581-599

KEY CONCEPTS & LEARNING OBJECTIVES

1. To discuss the basic pharmacology, clinical indications for use, and toxicity of the following agents used in the therapy of anemia:

    a. Iron

    b. Vitamin B_{12}

    c. Folic Acid

2. To discuss the basic pharmacology, clinical indications for use, and toxicity of the following growth factors used in the therapy of cytopenias:

    a. Erythropoietin

    b. G-CSF

    c. GM-CSF

    d. IL-11

    e. Romiplostim

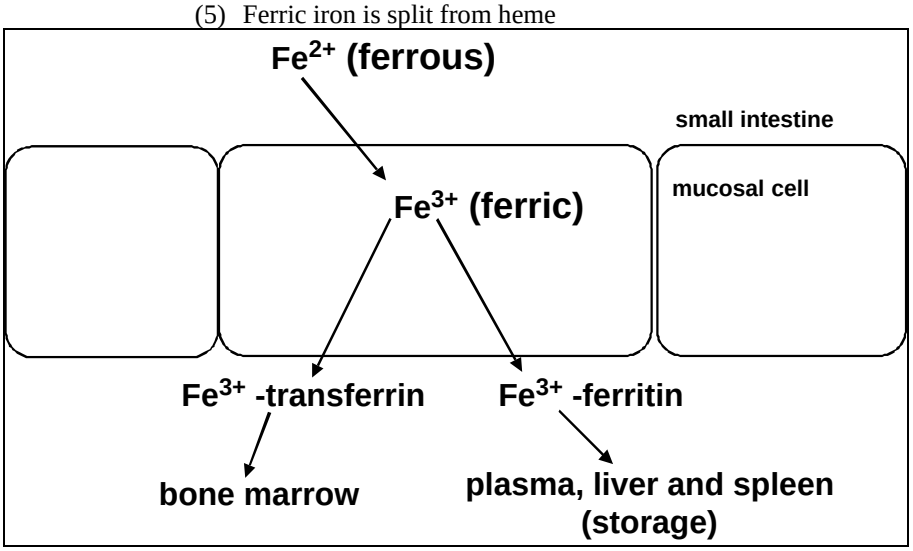
    f. Eltrombopag

Pharmacotherapy of Anemias and Hematopoietic Growth Factors

I. Agents used in anemias

A. Iron

1. Basic pharmacology
   a) Approximate distribution
      (1) 70% in hemoglobin
      (2) 10% in myoglobin
      (3) 10-20% stored as ferritin and hemosiderin
      (4) <1% in enzymes (e.g. cytochromes), and transferrin
   b) Intake
      -Average US diet contains 10-15 mg of which 0.5-1 mg is absorbed.
   c) Absorption
      (1) Heme iron is absorbed intact from duodenum and jejunum
      (2) Non-heme iron must be converted to ferrous iron (Fe^{2+})
      (3) Absorption is by active transport
      (4) Within mucosal cell, ferrous iron is converted to ferric (Fe^{3+})
      (5) Ferric iron is split from heme



   d) Fate
      (1) In case of demand, ferric iron is bound to transferrin for immediate transport via the blood to bone marrow
      (2) Stored as ferritin or hemosiderin in liver and spleen
      (3) Ferritin in plasma is in equilibrium with body storage and can be used to estimate total body stores
   e) Iron balance
      (1) Maintained by changes in absorption regulated by the concentrations of transferrin and ferritin in mucosal cells
      (2) In iron deficiency transferrin goes up, ferritin goes down
      (3) In iron overload transferrin goes down, ferritin goes up

2. Indication for iron therapy-Prevention or treatment of iron deficiency anemia (microcytic hypochromic anemia)
   a) Increased requirements
      (1) Frequently present in premature infants
      (2) Children during rapid growth period

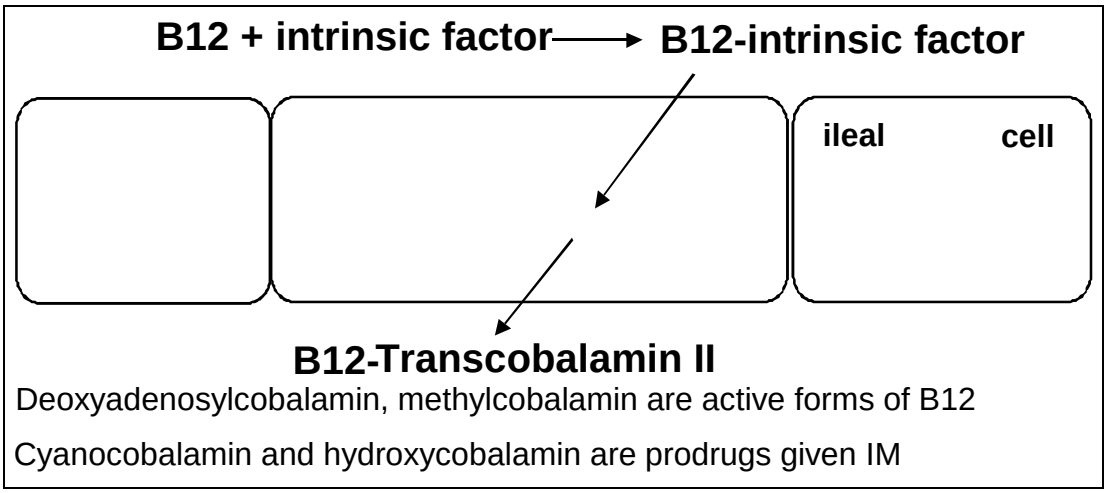
(3) Pregnant and lactating women
b) Inadequate absorption: postgastrectomy or severe small bowel disease
c) Blood loss
(1) Menstruation
(2) Occult gastrointestinal bleeding

3. Iron therapy
a) Oral preparations
(1) Only ferrous salts (sulfate, gluconate, fumarate)
(2) Response within a week, normal in 1-3 months
(3) Adverse effects: GI distress (take with or after meals); black stool may obscure recognition of GI bleeding
b) Parenteral iron therapy
(1) Usually iron dextran, deep i.m. or i.v. infusion (also iron-sucrose and iron sodium gluconate)
(2) Indicated post-gastrectomy/small bowel resection, malabsorption syndromes, intolerance of oral preps
(3) Adverse effects: local pain and tissue staining with i.m., headache, fever, nausea, vomiting, back pain, arthralgias, urticaria, bronchospasm, anaphylaxis/death (rare)

4. Clinical toxicity
a) Acute: accidental ingestion of iron tablets
(1) May be fatal in small children
(2) Necrotizing gastroenteritis
(3) After short improvement, metabolic acidosis, coma and death
(4) Treatment:
(a) Gastric aspiration, lavage with phosphate or carbonate solution
(b) Activated charcoal is ineffective
(c) Deferoxamine, a potent iron chelating substance i.m. or i.v.
b) Chronic (iron overload)
(1) Seen in an inherited disorder, hemochromatosis
(2) Patients receiving repeated red cell transfusions
(3) Excess iron deposited in heart, liver pancreas leading to organ failure
(4) Treatment:
(a) Intermittent phlebotomy
(b) Iron chelation

B. Vitamin B_{12} and folic acid

1. Basic pharmacology
a) Chemistry and pharmacokinetics of vitamin B_{12}
(1) Deoxyadenosylcobalamin and methylcobalamin are the active forms
(2) Cyanocobalamin and hydroxycobalamin (therapeutic drugs) are converted to the active forms
(3) Absorption
(a) Vitamin B_{12} is absorbed only after complexing with “intrinsic factor”
(b) Absorption (1-5 µg/day) occurs in the distal ileum by a specific transport system
(c) Deficiency often caused by lack of intrinsic factor or bowel disease (transport)
(d) Absorbed vitamin B_{12} is bound to plasma transcobalamin II for distribution



(4) Storage: liver is major storage site containing 3-5 mg of vitamin B_{12}

b) Chemistry and pharmacokinetics of folic acid
   (1) Richest sources are yeast, liver, kidney, and green vegetables
   (2) Absorption
      (a) Average diet contains 500-700 µg
      (b) Polyglutamate forms must be hydrolyzed to monoglutamate
      (c) Monoglutamate form inters bloodstream by active and passive transport
   (3) Storage
      (a) 5-20 mg of folates are stored in liver and other tissues
      (b) Folates are excreted and destroyed by catabolism
      (c) Since normal daily requirements are ~ 50 µg, diminished intake will result in deficiency and anemia within 1-6 months

2. Clinical pharmacology: treatment of macrocytic or megaloblastic anemias
   a) Vitamin B_{12} and folic acid used only for prevention or treatment of deficiencies
   b) Important to determine whether vitamin B_{12} or folic acid deficiency is the cause since folic acid will not prevent the irreversible neurological damage
   c) Vitamin B_{12} deficiency caused by malabsorption usually requires lifelong parenteral injection of cyanocobalamin or hydroxocobalamin
   d) Response is rapid and return to normal in 1-2 months
   e) Folic acid deficiency due to inadequate intake or diminished storage is treated with oral doses of folic acid

II. Hematopoietic growth factors

A. Erythropoietin

1. Basic pharmacology
   a) 34-39 kDa glycoprotein
   b) Functions:
      (1) Stimulates proliferation and differentiation of erythroid cells
      (2) Promotes release of reticulocytes from bone marrow
   c) Produced by the kidney
   d) Usually inverse relationship between hemoglobin level and serum erythropoietin level, but not in chronic renal failure

e) Recombinant human erythropoietin (Epoetin alfa, Epogen) is produced in a mammalian cell expression system

2. Indication for erythropoietin therapy
   a) Chronic renal failure
   b) Some patients with aplastic anemia, hematologic malignancies, anemias associated with AIDS, cancer
      (1) In these patients, erythropoietin is most effective if endogenous erythropoietin levels are disproportionately low
      (2) Higher does required than in chronic renal failure, but responses are still incomplete
   c) Treatment of anemia of prematurity
   d) Post phlebotomy

3. Erythropoietin therapy
   a) Given IV or subcutaneously
   b) Increase in reticulocyte count seen in about 10 days
   c) Increase in hemoglobin seen in 2-6 weeks

4. Clinical toxicity
   a) Hypertension
   b) Thrombotic complications
   c) Allergic reactions
   d) Increased risk of tumor progression in cancer patients

B. G-CSF and GM-CSF

1. Basic pharmacology
   a) G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte-macrophage colony stimulating factor) are myeloid growth factors
   b) Recombinant human G-CSF (filgrastim, Neupogen) is produced in a bacterial expression system
   c) Recombinant human GM-CSF (sargramostim, Leukine) is produced in a yeast expression system
   d) Pegfilgrastim (Neulasta): Filgrastim conjugated to polyethylene glycol-longer half-life
   e) Functions:
      (1) Both G-CSF and GM-CSF stimulate proliferation and differentiation of myeloid cells
      (2) G-CSF promotes release of hematopoietic stem cells from bone marrow (GM-CSF is less efficient)
      (3) GM-CSF also stimulates proliferation and differentiation of erythroid and megakaryocytic precursors

2. Indication for G-CSF/GM-CSF therapy
   a) After intensive myelosuppressive chemotherapy
      (1) Accelerates rate of neutrophil recovery
      (2) Reduces duration of neutropenia
      (3) Reduces febrile neutropenia, antibiotic use, days of hospitalization
   b) Can also be used after chemotherapy for acute myeloid leukemia (AML)
      (1) Accelerates neutrophil recovery, reduce infection
      (2) No evidence for increased relapse rate
   c) Treatment of congenital neutropenia, cyclic neutropenia, neutropenia associated with myelodysplasia and aplastic anemia
   d) High dose chemotherapy with autologous stem cell transplant
   e) Mobilization of peripheral blood stem cells for autologous transplant

3. Clinical toxicity
   a) G-CSF preferred since it is better tolerated in general

b) G-CSF can cause bone pain, splenic rupture (very rare)
c) GM-CSF can cause fever, arthralgia, myalgia, peripheral edema, pleural/pericardial effusion
d) Allergic reactions

C. Interleukin-11

1. Basic pharmacology
   a) IL-11 is produced by stromal cells in the bone marrow
   b) Recombinant human IL-11 (Oprelvekin, Neumega) is produced in a bacterial expression system
   c) Stimulates growth of megakaryocytic progenitors
   d) Increases peripheral platelets

2. Indication for IL-11 therapy
   a) Patients with thrombocytopenia after cytotoxic chemotherapy
      (1) Can be used if platelet transfusions are refractory, or to prevent adverse reactions of transfusions
      (2) Usually given for 14-21 days after chemotherapy, or until the platelet count rises above 50,000/uL

3. Clinical toxicity
   a) Fatigue
   b) Headache
   c) Dizziness
   d) Cardiovascular effects (dyspnea, atrial arrhythmia)
   e) Hypokalemia

D. New agents for thrombocytopenia

a) Romiplostim (AMG 531)- A novel protein known as a “peptibody” with two domains; a peptide domain that binds the thrombopoietin receptor (Mpl), and an antibody Fc domain that increases half-life

b) Eltrombopag-A small molecule thrombopoietin receptor agonist

IMMUNOMODULATION THERAPY

Date: November 12, 2013 – 9:30 am

Reading Assignment: Katzung 11th edition: p. 970-984 **(NOT INCLUDING CYTOKINES)**

KEY CONCEPTS

1. The specific type of immune response implicated in a specific autoimmune disease or organ transplant rejection must be identified prior to rational use of any form of immunomodulatory therapy

2. Therapeutic immunomodulation therapy always requires a risk/benefit ratio calculation (risk of infection versus risk of autoimmune attack or organ rejection).

LEARNING OBJECTIVES

1. Recall key steps in the immune response
2. Identify points of vulnerability in the immune response that lend themselves to modification with immunopharmacologic therapy
3. Differentiate immunomodulation agents by their ability to interfere in specific steps of the immune response sequence
4. Identify the specific risks associated with each class of drugs.
5. Identify critical drug interactions that change the risk/benefit ratio for the patient

Key Words:

Immunomodulation [E02.095.465]
Transplantation Immunology [G12.425.901+]
Immunocompromised Host [G12.476]

DRUGS COVERED IN THE LECTURE

1. Corticosteroids
2. Cyclophosphamide
3. Azathioprine
4. Methotrexate
5. Mycophenolate Mofetil
6. Leflunomide
7. Cyclosporine
8. Tacrolimus
9. Rapamycin
10. Monomurab
11. Monomurab
12. Basiliximab
13. Daclizumab
14. Rituximab
15. Intravenous Imunoglobulins
16. Tofacitinib

#51 - IMMUNOMODULATION THERAPY

I. Overview

A. The classical term for therapeutic strategies used to inhibit immune responses **is immunosuppression**. However this is an imprecise term that doesn't reflect the reality of the clinical situation because, in almost all instances, the entire immune system is not suppressed. Indeed this would be a very bad scenario for the patient since global suppression would greatly enhance the risk of serious infection. **Thus, the use of any immunomodulator is a double-edged sword that involves careful calculation of a risk/benefit ratio.**

B. The goal of "immunosuppressive" therapy is to modify a component of the immune response that is either doing what it is supposed to do: reject an allograft, or re-regulate/inhibit an arm of the immune system that is inappropriately causing a disease state.

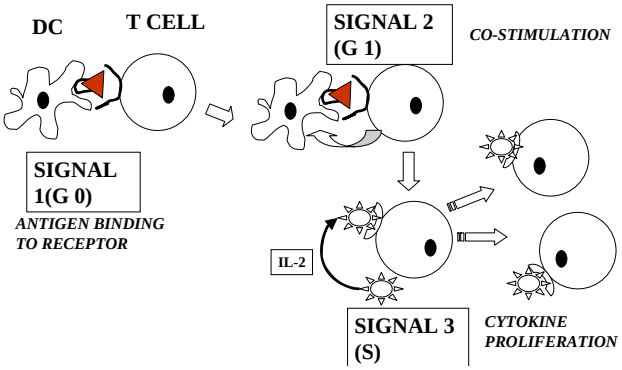
C. In light of the above, a better term for "immunosuppressive therapy" **is immunomodulation therapy.**

D. Understanding and predicting outcomes of immunomodulation is directly linked to understanding how the immune system works and the availability of drugs and biologic agents available to modify the component of the immune response that is causing the disease state. **There is increasing availability of selective agents specifically developed to inhibit lymphocyte and cytokine actions.**

E. As a general disclaimer, there are **NO herbal or alternative therapies** available to substitute for the medications to be discussed and in fact many have the potential to increase the side effects of efficacy of immunosuppression strategies.

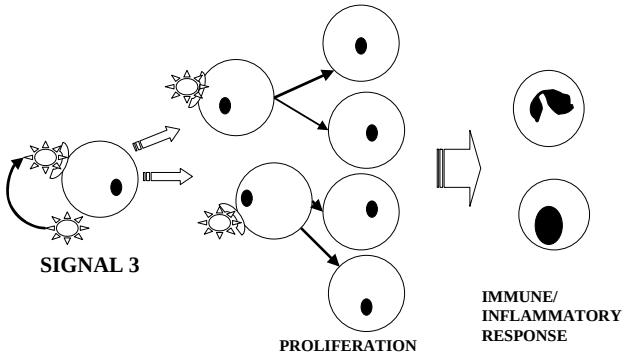
II. Quick overview of the immune system.

WHAT SHOULD HAPPEN



BOTH FIGURES BY JOHN A ROBINSON

THE END GAME



Take Home Message: The more signals you understand, the more chances you have of rationally blocking an immune reaction.

III. **Pharmacology of Currently Available non-selective to quasi-selective immunomodulators**

A. Adrenocorticosteroids (CS)- the first class of drugs available to clinicians for the suppression of inflammatory responses- no matter what the cause. They are widely used because of their rapid onset of action and their extremely broad spectrum of suppression. The latter quality is exploited when the clinician cannot determine the specific mechanism of the immunologically driven disease in a critically ill patient.

1. **Mechanism(s)/Sites of action.** A general principle of immunomodulation by CS is that they inhibit gene transcription **directly by competing for NF-κB and other nuclear activating factors in promoter regions of inflammatory cells**. They should be considered very non-specific in their immunomodulatory effects. The major immune system effects are:

    a. Inhibition of macrophage production of pro-inflammatory cytokines, especially IL-1, 6 and TNF-α.
    b. Suppression (partial) of antigen presentation
    c. Alteration in neutrophil and lymphocyte traffic patterns that reduce their availability at inflammatory sites
    d. Impaired chemotaxis of neutrophils

CORTICOSTEROIDS

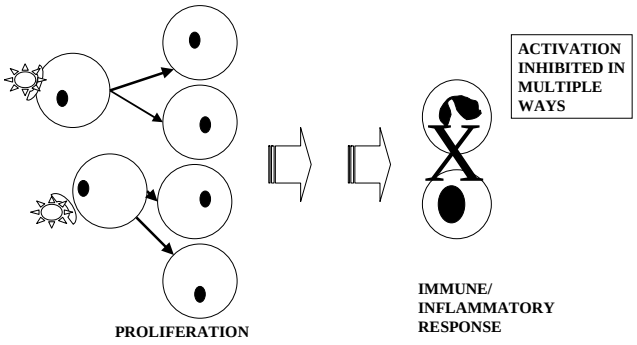


Fig. By John A Robinson

2. **Clinical uses. CS** are extensively used in any disease with poorly regulated inflammation and inflammatory cytokine imbalance. Examples range from rheumatoid arthritis and systemic lupus to inflammatory bowel disease and asthma.
    a. human circadian rhythm dictates early pro-inflammatory cytokine peaks (AM joint stiffness is the clinical expression), so CS most effective when given in the AM (in theory- about 2AM!)
3. **Pharmacokinetics.**
    a. Oral (prednisone, methylprednisolone, dexamethasone)
    b. Intravenous
    c. "Depo" formulations for intraarticular and other space use
    d. Lotion, creams and ointments in varying potency
    e. There will soon be a delayed release form to exploit the circadian timing of pro-inflammatory cytokine release.
4. **Side effects.**
    a. The promiscuous binding to many nuclear activation sites on neutrophils and macrophages creates **impaired T cell responses and poor neutrophil function and a high risk of infection with almost all classes of organisms.**
    b. Non-immunologic effects include acceleration of **osteoporosis** because of decreased calcium uptake, altered bone cytokine balance and impaired bone formation
    c. **Diabetes mellitus**- secondary to increased insulin resistance
    d. Multiple **CNS** effects that range from insomnia to psychosis and severe depression and emotional lability
    e. Obesity and stria
    f. **Hypertension**- interference with the renin/angiotensin axis

B. Anti-Proliferative Immunomodulators. Most of the anti-proliferative drugs commonly used for immunomodulation have been hijacked from

oncology. The rationale for their use derives from the observation that an active immune response is associated with lymphocyte proliferation and anti-cancer drugs should be effective at inhibiting cellular division. The early anti-proliferative drugs have broad effects and inhibit almost all actively dividing cells. Two systems with large populations of rapidly dividing cells are the bone marrow and hair follicles **and severe bone marrow depression and alopecia** are common side effects in patients being treated with them. These drugs are considered non-selective because of their lack of precisely targeting a step in the immune response.

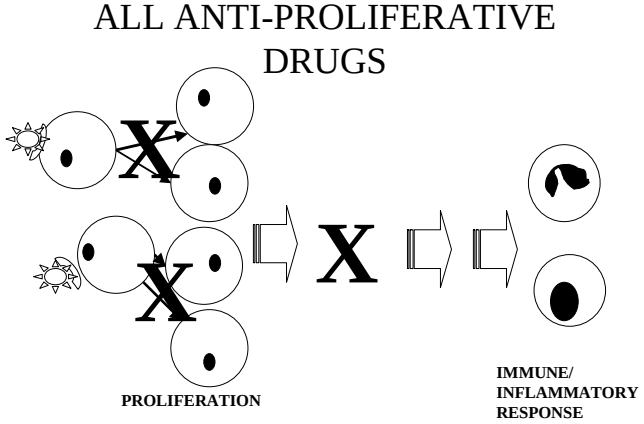


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1. **Cyclophosphamide (Cytoxan)**
    a. An alkylating agent that is inactive until metabolized by the liver. Has potent effects on B and T cells but the precise sites of action are unknown
    b. Main clinical use is systemic lupus and vasculitis. The use of this drug is decreasing as better agents are now available
    c. Can be given intravenously as pulse dose or daily in oral form. Dosage for immunosuppression is much lower then for cancer chemotherapy
    d. Has several severe side effects that limit its use;
        i. Significant **bone marrow depression**
        ii. **Hemorrhagic cystitis** and cancer of the bladder
        iii. **Infertility.** Female more common than male but arrangements must be made where possible to bank sperm and ova prior to therapy
2. **Azathioprine (Imuran)**
    a. Prodrug that is metabolized to 6-mercaptopurine which is a purine antimetabolite.
    b. Genetic polymorphisms of thiopurine S-methyl transferase-TMPT- (deactivates the active drug) can influence blood levels.
        i. Measure TPMT prior to starting the drug

c. Considered a "weak" immunomodulator and its precise mechanism of action is not known. Decreasing use in transplantation and autoimmune diseases as more effective therapy becomes available.

d. Side effects are mainly bone marrow depression and hepatotoxicity. The **COADMINISTRATION OF ALLOPURINOL MARKEDLY INCREASES AZATHIOPRINE HALF LIFE BECAUSE BOTH DRUGS COMPETE FOR THE SAME CATABOLIC ENZYME. THE END RESULT IS SEVERE BONE MARROW DEPRESSION.**

e. Available in oral and intravenous forms. Bimodal (fast and slow) metabolizers

3. Methotrexate

a. Folate antagonist that inhibits dihydrofolate reductase and interferes with de novo synthesis of purines and pyrimidines. This mechanism is operative at high doses for the treatment of cancer but is NOT the mechanism active during its low dose, once a week use in immunologic diseases. At low doses the drug is thought to increase extracellular adenosine which is anti-inflammatory

b. **Clinical uses**: Extensively used in rheumatoid arthritis and a few other inflammatory arthritides.

c. **Pharmacokinetics**: Can be given IM, IV and orally

d. **Side Effects:** leucopenia, mouth ulcers and hypersensitivity pneumonitis.

4. **Mycophenolate mofetil (Cellcept**)

a. **Mechanism of action:** a prodrug that is rapidly converted by plasma esterases to mycophenolic acid which inhibits T and B cell proliferation by blocking the de novo pathway of nucleotide synthesis. Proliferating lymphocytes are highly dependent on the de novo pathway.

b. **Pharmacokinetics:**

i. Oral and intravenous forms

ii. Prodrug

iii. Serum peak after oral dose is about 1.5 hours and must be given twice a day.

c. Clinical uses: is rapidly replacing azathioprine in transplantation and autoimmune diseases. Previously considered a "steroid sparing" immunomodulator that can be used to reduce corticosteroid requirements in patients with lupus and other autoimmune diseases but is now the standard of care for SLE

d. Side Effects: mild bone marrow depression and GI side effects. Expensive.

5. Leflunomide (Arava)

a. **Mechanism of action**: Prodrug that is metabolized to a selective inhibitor of de novo pyrimidine synthesis. Rapidly dividing lymphocytes require 2 pathways for pyrimidine synthesis in order to meet the demand for new cell membranes. Inhibition of the de novo pathway is an effective inhibitor of proliferation.

b. Pharmacokinetics: Oral prodrug that is metabolized to an active metabolite with a very long half-life of 15-18 days and an extensive entero-hepatic circulation.

c. Clinical uses: Used in rheumatoid arthritis and increasing application in transplantation and autoimmune diseases

d. Side Effects:

i. Diarrhea that can be significant

ii. Rare bone marrow suppression

iii. Hepatotoxicity-including liver failure

iv. Teratogenic – a woman trying to get pregnant must go through a long wash-out period because of its long half-life. Elimination can be accelerated by using cholestyramine

C. Calcineurin inhibitors (CNI) - cyclosporine and tacrolimus are the two are currently in use. Both are first generation quasi-selective in their immunomodulatory effects and can be discussed together.

1. Mechanism(s)/ Sites of action.

a. Both act primarily on T- Lymphocytes

b. Block signal #1 by binding to cyclophilin A (cyclosporin) and FKBP (tacrolimus). The complexes bind to calcineurin and prevent activation of multiple nuclear activation factors that should be turned on at the time of antigen binding to the TCR.

c. G1 phase cannot begin without Signal #1 acting in concert with Signal #2

CALCINEURIN INHIBITION

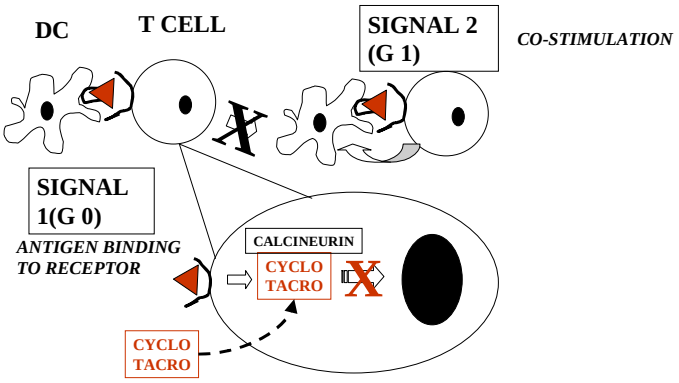


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2. Clinical uses

a. Critical component of anti-rejection protocols for solid and stem cell transplantation

b. Also can be used in diseases where there is evidence that T-cells are a primary mediator –examples include ulcerative colitis, uveitis and other auto-immune diseases

3. Pharmacokinetics. Both are difficult drugs to use clinically because:

a. narrow therapeutic window.

b. wide **interindividual and intraindividual** variability in adsorption and metabolism

c. multiple significant drug interactions

i. any drug that activates (induces) the hepatic cytochrome P450 enzyme system will **decrease** both cyclosporine and tacrolimus blood concentrations. Phenytoin (dilantin, barbiturates, rifampin can rapidly reduce blood levels. **THIS IS AN EXTREMELY SIGNIFICANT PROBLEM BECAUSE AN ALLOGRAFT CAN BE LOST IF CALCINEURIN INHIBITOR LEVELS ARE NOT MAINTAINED.**

ii. Concomitant use of non- steroidal anti-inflammatory drugs will increase the risk of nephrotoxicity.

iii. Any drug that suppresses hepatic metabolism of CNI will **increase** the level of the drug. Common examples include erythromycin, clarithromycin, the anti-fungal –conazoles, danazol and diltiazem. There are multiple others. **THIS IS ALSO**

AN EXTREMELY SIGNIFICANT PROBLEM BECAUSE PROTRACTED HIGH BLOOD LEVELS OF CNI CAN LEAD TO NEPHROTOXICITY (ESP. CYCLO) AND NEUROTOXICITY AND DIABETES (TACRO). Local suppression of P450 at the gut level by grapefruit juice can also elevate serum levels.

iv. Drugs that Increase the level of CNI can be exploited to reduce the dose of daily CNI as a cost benefit strategy

v. a, b &c mandate a need for patient monitoring of blood levels

vi. preparations: oral, intravenous and topical

4. Side Effects. Calcineurin is a widespread nuclear factor activator found in multiple tissues and the CNI have multiple side effects, most of which are dose dependent and can be managed by careful blood level monitoring

a. Important cyclosporine effects are: hypertension, hypercholesterolemia and nephrotoxicity

.

b. Important tacrolimus effects are: neurotoxicity, diabetes mellitus.

D. Inhibitors of mammalian target of rapamicin (mTOR). This is a second-generation quasi-selective immunomodulator designated rapamycin (RAP). Also called **sirolimus** and there is a closely related newer formulation called **everolimus**

1. **Mechanism(s) /Sites of action.** Whereas the CNI act by blocking TCR activation by antigen, RAP targets signal transduction and cytokine cascade activation that prevents the activated lymphocyte from progressing through the G1 phase to the S phase. Specifically, Rapamycin:
   - **a.** Blocks co-stimulation signal #2 and…
   - **b.** cytokine receptor signaling pathways (#3)-**especially IL-2/IL-2R mediated** events
   - **c.** Rap also inhibits expression of bcl and is pro-apoptotic
   - **d.** Rap is anti-fibrogenic- hence its use on coronary artery stents to prevent re-stenosis.

MAMMALIAN TARGET OF RAPAMYCIN

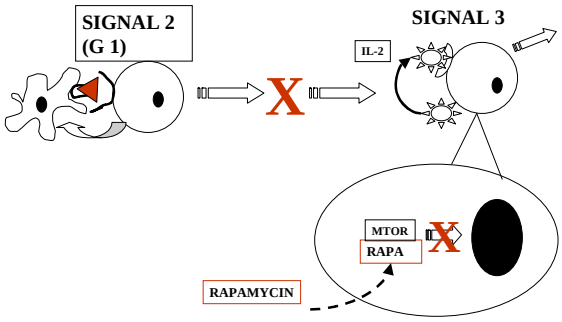


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2. Clinical uses.
   - **a.** Has gained wide acceptance in solid organ transplantation
   - **b.** **Since RAP acts at different sites than the CNI, it is synergistic with CNI and this may be a major improvement is treatment of transplant recipients**
   - **c.** Also in theory can be used in any auto-immune disease that is T-cell mediated.
   - **d.** There is some evidence that T-cell dependent B cell activation is suppressed by RAP and this expands the list of potential diseases that could be treated with RAP

3. Side Effects. mTOR is present in non-lymphoid tissues also and so RAP side effects include:
   - **a.** Decreased lipoprotein lipase and insulin growth factors cause hypertriglyceridemia which can be severe and exacerbate the hypercholesterolemia caused by CNI
   - **b.** Mild bone marrow suppression
   - **c.** Interaction with CNI may increase its nephrotoxicity but RAP is not nephrotoxic.
   - **d.** Bilateral pulmonary infiltrates that can be confused with infection

IV. BIOLOGIC RESPONSE MODIFIERS (BRM)

A. The development of BRM is linked to the availability of technologies that can generate monoclonal antibodies and fusion chemistry to create hybrid molecules. Two general rules apply.

1. There is constant drive to create molecules with exquisite specificity for a cell receptor that, if blocked, will modulate the immune response thought to be producing the disease in question.
2. There is a constant drive to create molecules that are as “human” as possible. Early BRM were usually mouse molecules that patients over time would develop antibodies to (called HAMA-human anti mouse antibodies). HAMA usually blunts the effect of the

monoclonal by causing its rapid elimination by antigen-antibody complexing. Most current BRMs are fusion or chimeric proteins with human Fc fragments attached to mouse antigen binding fragments. This reduces their antigenicity and increases their half-life because patients treat the Ig Fc as a native molecule.

B. Monoclonal antibodies/fusion proteins directed at cell receptors.

1. **T cell receptor- OKT3 or monomurab**:
   a. the first murine (mouse) antibody generated with hybridoma technology to be used clinically. It has specificity for the CD3 portion of the T cell receptor and broad suppressive activity of many T cell functions.
   b. It is an effective BRM for use in preventing transplant rejection but its generalized T-cell suppression is associated with severe viral infection, especially CMV and EBV. The latter, either as a reactivated infection or de novo, is associated with post transplant lymphoproliferative disease and lymphoma.

2. **Basiliximab (Simulect) and Daclizumab (Zenapax).**
   a. Chimeric murine/human monoclonal antibodies that bind to the IL- 2R of **ACTIVATED T cells** and prevent further activation.
   b. Major indication is prevention of allograft rejection
   c. Side effects of both are those related to T-cell suppression. Intravenous administration and saturation of the receptor sites are dose related and may last for up to 12 weeks

3. **Rituximab (Rituxan). Very effective depleter of B cells, NOT plasma cells, because it is specific for CD20 on the B cell surface. Used in the treatment of lymphoma and increasingly used in autoimmune diseases mediated by B cells.**
   a. May also block antigen presentation by B cells
4. **Abatacept (Orencia**) is CTLA IgG. Binds to CD80/86 on APC and prevents CD28 activation. Important biodrug in transplant and patients that have failed TNF inhibition. Cannot be use with Anti-TNF monoclonals.
5. **Omalizumab** is monoclonal against the high affinity receptor on IgE. Once bound, IgE cannot activate the FcReceptor on mast cels and basophils. Useful in asthma
6. **Mepolizumab** is monoclonal against IL-5. Useful in hyper-esosinophilc syndromes
7. **Tocilizumab** is humanized monoclonal against IL-6. Useful in Rheumatoid arthritis

C. Replacement of IgG antibodies.

1. Pooled Intravenous Immunoglobulins (IVIG). Used in the absence of normal antibodies. The major indications are all genetically transmitted B cell defects, e.g., X linked agammaglobulinemia

D. Modulation of the Fc receptor.

1. Pooled Intravenous Immunoglobulins (IVIG). Major indications are multiple autoimmune diseases
2. Many commercial sources available with little significant difference between preparations. Must be given intravenously and half-life variable and dependent on serum level.

E. **Modulation of TNF-α.** Discussed in Rheumatoid Arthritis Lecture. Principle applies however to ANY disease where TNF if a primary mediator-Hint: the list is endless!

F. Kinase inhibition. Newest strategy and will be mentioned in treatment of rheumatoid arthritis

1. tofacitinib inhibits JAK 1/3

2. Trade name is Xeljanz

V. SUMMARY TABLE: Do NOT memorize trade names, half lives or elimination unless something specific to them was mentioned in the lecture or powerpoint.

Generic	Trade	Half-Life	Action	Elimination	Benefit
Corticosteroids	Many	Variable	Suppress nuclear Promoters	Liver	Blanket immunosupression
Cyclophosamide	Cytoxan	~6 hrs IV	Alkylating, Antiproliferative	Liver Minor renal	B-cell suppressor
Azathioprine	Imuran	4-6 hrs	Antimetabolite	Liver	Mild antiproliferative
Methotrexate	Same	3-10 hrs	Adenosine increase	Renal	Anti-inflammatory
Mycophenolate Mofetil	Cellcept	8-10 hrs	Block de novo nucleotide synthesis	Kidney	Anti-proliferative
Leflunomide	Arava	15-18 days	Block de novo pyrimidine synthesis	Liver	Anti-proliferative
Cyclosporine	IV same, Neoral	Variable	Calcineurin inhibitor	Kidney	Blocks signal #1
Tacrolimus	Prograf	Variable	Calcineurin inhibitor	Kidney	Blocks signal #1
Rapamycin	Sirolimus	Variable	mTOR inhibition	Kidney	Blocks Signal #2, 3
Monomurab	OKT3	Variable	Blocks CD3 activation	Liver	Prevent rejection
Basiliximab	Simulect	Variable	Blocks IL-2R	Liver	Prevent rejection
Daclizumab	Zenapax	Variable	Blocks IL-2R	Liver	Prevent rejection
Omalizumab	Xolair	Variable	Prevent IgE binding to Fcε Receptor	Liver	Asthma
Mepolizumab	Bosatria	Variable	Neutralizes IL-5	Liver	Eosinophilic mediated pathology
Tocilizumab	Actemra	Variable	Blocks IL-6 effects	Liver	Rheumatoid Arthritis
Pooled IVIg	Many	Dependent on Serum C	Replacement	Multiple	Antibody immunity

ANTIMYCOBACTERIALS

Date: November 21, 2013 – 10:30 AM

Reading Assignment: **Basic & Clinical Pharmacology, B.G. Katzung, 12th Edition.** Chapter 47

LEARNING OBJECTIVES:

1. To be able to list first line antituberculosis agents.

2. To be able to list major toxicities of first line anti-mycobacterial agents.

4. To be able to discuss all the therapeutic indications of rifampin.

5. To be able to discuss the mechanism of primary and secondary resistance in *M. tuberculosis* infections.

6. To be able to describe the rationale for multi-drug therapy

LIST OF DRUGS COVERED IN LECTURE

Isoniazid, Isonicotinic Acid Hydrazide, INH
Rifampin, Rifampicin
Ethambutol
Pyrazinamide
Streptomycin

ANTIMYCOBACTERIALS
Isoniazid, Ethambutol, Rifampin, Pyrazinamide, Streptomycin

I Principles of anti-tuberculous therapy
- A. Multiple drugs which organisms are susceptible
- B. Drugs must be taken regularly
- C. Drug therapy must continue for a sufficient period of time
  - i.

II. ISONIAZID, ISONICOTINIC ACID HYDRAZIDE, INH

A. Clinical use - never alone for active infection
1. First line drug for active pulmonary TB
2. Always used in combination with other Anti-TB drug
3.. Treatment for latent infection

B. Mechanism of action
1. Isoniazid is a prodrug
2. active form inhibits the synthesis of mycolic acid in the mycobacterial cell wall
3. drug must be activated by catalase peroxidase which is regulated by the *katG* gene
4. Bactericidal on actively replicating organisms
5. Bacteriostatic on "resting organisms"
6. Active against *M. kansasii* but not other non-tuberculous mycobacteria
7. Active against intracellular and extracellular organisms

C. Resistance
1. Many mutations in *katG* gene result in inactivation of catalase-peroxidase
2. Mutation in regulatory region of inhA gene which is involved in mycolic acid synthesis
   a.Also results in resistance to ethionamide (cross resistance)

C. Pharmacokinetics
1. Reduce dosage by half in severe hepatic insufficiency
2. Metabolism - acetylation in liver by N-acetyltransferase
   a. Non-acetylated INH is excreted in urine
   b. Rate of acetylation in humans is genetically controlled-
      - rapid or slow acetylators
      - Slow acetylators 6 hours after a 4mg/kg dose plasma INH level more than 0.8 µg/ml and
      - Rapid acetylators INH level less than 0.2 µg/ml
      - Acetylator status has no effect on the outcome of daily therapy because the plasma levels are maintained well above inhibitory concentrations

5. Distribution wide including CSF, CSF levels 20% plasma levels but may equal plasma in meningeal inflammation.

D. Toxicity

1. Hepatotoxicity- Asymptomatic elevation of transaminases seen within the first month of therapy in 10-20% of reciepients
   a.Rate of clinical symptomatic hepatitis patients given INH alone 0.6%
   b. Occurs after weeks to months of therapy
   c. Hepatotoxicity correlated with age older more likely to occur
   d. Increased in alcoholics, preexisting liver damage, pregnant women, women up to 3 months post-partum, in combination with acetaminophen, patients receiving other hepatotoxic drugs such as rifampin, patients with active Hepatitis B,
2. Neurotoxicity
   a. Peripheral neuritis more frequent in slow acetylators who have higher plasma levels of unaltered drug
   b. Use pyridoxine to prevent neuritis

3. Hypersensitivity reaction- fever, maculopapular rash
   lupus like syndrome, positive ANA,

E. Significant Drug Interactions
1. Dilantin toxicity,
2. INH and rifampin increases occurrence of hepatitis
3. Decreases itraconazole
4. Decreases levodopa

III. <u>RIFAMPIN, RIFAMPICIN</u> - semisynthetic derivative of a complex macrocyclic antibiotic rifamycin B produced by *Streptomyces mediterranei*.
Rifabutin and rifapentine same class different pharmacokinetics

A. Clinical use

1. First line drug for TB always in combination with other drugs
2. Gram positive organisms, <u>*Staph aureus* always in combination</u>

B. *N. meningitidis*, prophylaxis meningococcal meningitis

1. Cannot be used alone in therapy as an antibacterial agent because of rapid development of resistance.

C. Mechanisms of action and resistance

1. Inhibits DNA dependent RNA polymerase
2. *rpoB* gene produces RNA polymerase ß subunit
2. *rpoB* mutations lead to rifampin resistance
    a. Frequency 10^8
    b. RNA polymerase can no longer bind the drug
3. Bactericidal to all population of organisms

D. Pharmacokinetics
1. Metabolized in the liver
2. Meningococcal meningitis chemoprophylaxis
3. Distribution penetrates well into most tissues, CSF levels 0.5 µg normal meninges, 4-8 x increase inflamed meninges

E. Toxicity

1. Most common- GI upset
2. Hepatotoxicity enhanced with use of other hepatotoxic drugs including INH
3. Red discoloration urine, tears, pleural fluid- permanent discoloration of soft contacts
4. Acute renal failure, interstitial nephritis
5. Influenza syndrome- more common with intermittent dosing
6. Thrombocytopenia
7. Cholestatic jaundice

F. Drug interactions

1. Induces hepatic microsomal enzymes reacts with 100 drugs.
2. Accelerates clearance of: methadone, coumadin derivatives, glucocorticoids, estrogen, oral hypoglycemic agents, digitoxin, anti-arrhythmic agents (quinidine, verapamil, mexiletine), theophylline anticonvulsants, ketoconazole, cyclosporin, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors
3. Impairs effectiveness of oral contraceptives.
4. should not be used with protease inhibitors and non-nucleoside reverse transcriptase inhibitors because it induces metabolism of the drug

IV. <u>ETHAMBUTOL</u> - active only against mycobacteria

A. Clinical use –
a. first line tuberculosis therapy
b. always used in combination with other anti-TB drugs
c. Used to inhibit the development of resistance to other agents

B. Mechanism of action

1. inhibits synthesis mycobacterial arabinosyl transferase encoded by *embB*
2. Effects biosynthesis within cell wall
3. Bacteriostatic

C. Pharmacokinetics

1. Reduce dose in renal failure
2. Distributed throughout the body. Cerebrospinal levels low even in inflamed meninges.

D. Toxicity

1. Ocular - retrobulbar neuritis- symptoms: blurred vision, central scotomata, red-green color blindness, dose related, < 1%
2. Don't use in children who are too young for assessment of visual acuity and color blindness
3. Peripheral neuropathy less common

V. PYRAZINAMIDE

A. Clinical use

1. Antituberculous therapy first line for initial therapy, always in combination

B. Mechanism of action and resistance
1. Bactericidal
2. Mutation in gene *pncA* encoding pyrazinamidase
3. Results in loss of pyrazinamidase
Which converts drug to active form of pyrazinoic acid

C. Pharmacokinetics
1. Best avoided in renal failure because metabolic products excreted largely in urine
2. Distribution good, CSF in tuberculous meningitis

D. Toxicity

1. Hepatitis, worse in patients with preexisting liver disease
2. Skin rash and gastrointestinal intolerance
3. Arthralgia, increased serum uric acid levels, but acute gout is uncommon

E. Drug interactions

1. Cyclosporine
2. Ethionamide
3. Rifampin
4. Zidovudine

VI. STREPTOMYCIN - used as an antituberculous agent, first line agent bactericidal for extracellular organisms

A. Clinical use: second line antituberculous agent

B. Mechanism of action and resistance

1. Bactericidal
2. Inhibits protein synthesis by binding to ribosome
3. Resistance mutational changes ribosomal binding protein or ribosomal binding site
4. Isolates resistant to streptomycin are **not** cross resistant to amikacin, kanamycin or capreomycin

C. Pharmacokinetics

1. Excretion renal- use in reduced dose in renal failure
2. Enters CSF only in the presence of meningeal inflammation

D. Toxicity

1. Ototoxicity
2. Nephrotoxicity

VII. Treatment Regimens

A. Initial phase: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months
B. Followed by 2 drugs for 4-6 months
C. Use of single drug will result in development of antimicrobial resistance

VIII. Types of antimicrobial resistance

A. Primary resistance
1. Organism is resistant to the antimicrobial at the time that the patient acquires the organism
2. Wild strains of *Mycobacterium tuberculosis* have intrinsic resistance to the antituberculous drugs.

3. One organism in 10^6 is resistant to INH..

B. Secondary resistance
1. Develops in patients who have been treated.
2. Develops in patients who are taking only one drug or taking meds erratically
3. Rationale for treatment with multiple anti-tuberculous drugs
   a. Cavitary lesions contain 10^7 –10^9 organism
   b. In a population of M. TB 1 organism in 10^6 may mutate by chance and become reisistant to anti-tb drug
   c. If only one anti-tb med is taken then all sensitive organisms will be killed but 10^1-10^3 resistant organisms will survive and grow
   d. Chance mutation to two drugs is 10^6 X 10^6 = 10^{12}
   e. There are only 10^7 - 10^9 organisms in a cavitary lesion
4. May also develop in patients with HIV infection
5. Or patients who have poor absorption of meds

C. Cross resistance
1. Cross resistance- presence of resistance to one drug is accompanied by resistance to another anti-TB med.
Example viomycin and capreomycin (second line agents) are cross resistant
2. Some INH resistant mutants are also resistant to ethionamide

D. Multi-drug resistance
1. MDR TB- resistant to both INH and rifampin
2. More common in HIV infected patients
3. Associated with nosocomial transmission and a high mortality in HIV infected patients

E. Extensive Drug Resistant (XDR) TB
1. Resistant to all of the following:
Both INH and Rifampin,
Resistant to any fluoroquinolone and
Resistant to at least one of the 3 injectable second-line drugs-
Streptomycin, Capreomycin, kanamycin, amikacin

IX. Treatment outcomes
1. Must take meds
2. Outcome of not taking meds is relapse
3. Directly observed therapy ensures

X. Treatment of Latent Infection
1. single drug isoniazid
2. a single drug may be administered because the number of organisms in the body is low

XI. Treatment of non-tuberculous infections.

1. *Mycobacterium avium-intracellular* infections
    a. Resistant to all first line agents
    b. Treat with combinations of ethambutol, clarithromycin, clofazamine, rifabutin
2. *Mycobacterium kansasii*
    a. Rifampin, ethambutol and isoniazid for 18 months.

XII. Dapsone

A. Clinical use
    i. Leprosy
    ii. Second line TB
    iii. Treatment of pneumocystis jiroveci(PJP) pneumonia in combination with trimethoprim
    iv. Prophylaxis for PJP

B. Pharmacology
    1. Distributed throughout the body
    2. Reduce dose in renal failure

C. Toxicity
    1. Minor hemolysis in patients with G6PD deficiency
    2. Anorexia, nausea, vomiting
    3. Hematuria, fever, pruritis
    4. Sulfone syndrome
    5. Erythema nodosum leprosum

XIII Clofazamine

A. Clinical use
    a. Lepprosy
    b. multidrug resistant TB,
    c. *M. avium intracellulare* infections

B. Mechanism of action
    1. Weakly bactericidal

D. Toxicity
    1. GI intolerance
    2. Skin pigmentation

XV LIST OF DRUGS COVERED IN LECTURE

Isoniazid, Isonicotinic Acid Hydrazide, INH
Rifampin, Rifampicin
Ethambutol
Pyrazinamide
Streptomycin
Dapsone
Clofazamine

Tarun B. Patel, Ph.D.

TREATMENT OF ASTHMA

Date: November 26, 2013
Reading Assignment: Katzung, Basic and Clinical Pharmacology 11th Ed., pp. 339-356

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To realize the importance of the airway constrictory and inflammatory components in asthma.

2. To know the pharmacology, mechanism of action and therapeutic uses of the different groups of clinically used anti-asthma drugs.

3. To learn the pharmacology and therapeutic uses of the adrenal corticosteroids for asthma.

4. To know the contra-indications of certain drugs used in the treatment of asthma.

5. To understand the pharmacokinetics of drugs used to treat asthma when administered via different routes – and the importance of this in emergency situations.

LIST OF IMPORTANT ANTI-ASTHMATIC DRUGS COVERED IN LECTURE

1. $Beta_2$-adrenergic agonists
    a. Metaproterenol (Metaprel®)
    b. Albuterol (Proventil®)
    c. Terbutaline (Brethaire®)
    d. Bitolterol (Tornalate®)
    e. Salmeterol (Serevent®)
2. Methylxanthines
    a. Theophylline (Theo-Dur®)
3. Muscarinic Receptor Antagonists
    a. Ipratropium bromide (Atrovent®)
4. Adrenal Corticosteroids
    a. Beclomethasone (Vanceril®)
    b. Flunisolide (AeroBid®)
    c. Triamcinolone (Azmacort®)
5. Cromolyn sodium (Intal®)
6. Leukotreine inhibitors
    a. Zafirlukast (Accolate®)
    b. Montelukast sodium (Singulair®)
    c. Zileuton (Zyflo®)
7. Monoclonal antibodies
    a. Omalizumab (Xolair®)

TREATMENT OF ASTHMA

A) Incidence of Asthma:

- Large population in the US suffers from Asthma – approx. 8.7% children/adolescents.
- Prevalence has increased in the last couple of decades – higher among children and African Americans
- One of the leading causes of hospitalization in children.

B) Characteristics of Asthma:

Airway obstruction or narrowing: Reversible, either spontaneously or with treatment.

Airway inflammation consisting of:

1) Bronchial infiltration with inflammatory cells
2) Mucosal edema of the bronchial wall
3) Hypertrophy of bronchial smooth muscle cells
4) Epithelial injury with loss of ciliated cells
5) Subepithelial fibrosis
6) Mucous gland hypertrophy causing mucus plugs in airway

Airway hyperresponsiveness consisting of an exaggerated bronchoconstrictor response to:

1) Allergens
2) Environmental pollutants
3) Viral infections
4) Cold air
5) Exercise
6) Drugs (e.g. aspirin)

C. PATHOPHYSIOLOGY OF ASTHMA

1. Exacerbations of asthma are due to decrease in expiratory airflow

Difficulty in breathing out is due to air being trapped behind occluded or narrowed small airways

2. Asthma was previously thought to be purely a hypersensitivity reaction occurring in a sensitized individual whenever:

An allergen interacted with IgE antibodies on mast cells, leading to the release of histamine causing bronchoconstriction.

3. It is now known that only 30% of asthma is due to allergies

It is currently recognized that airway hyperresponsiveness in asthma is due to multiple mechanisms that have complex interactions.

a) Immediate phase: Inhalation of either an allergen or a non-specific stimulus activates mast cells, platelets and macrophages to cause the release of spasmogens such as histamine,

platelet-activating factor (PAF) and leukotrienes C_4 and D_4 which cause an immediate bronchospasm.

b) Late phase: Mast cells, platelets and macrophages also release chemotaxins such as leukotriene B_4 and platelet-activating factor (PAF) which causes a delayed, late phase consisting of the infiltration of inflammatory cells which release mediators that also cause bronchospasm, as well as epithelial damage.

4. Two main categories of anti-asthmatic drugs

a. Bronchodilator drugs
b. Anti-inflammatory drugs

D. DIAGNOSIS OF ASTHMA

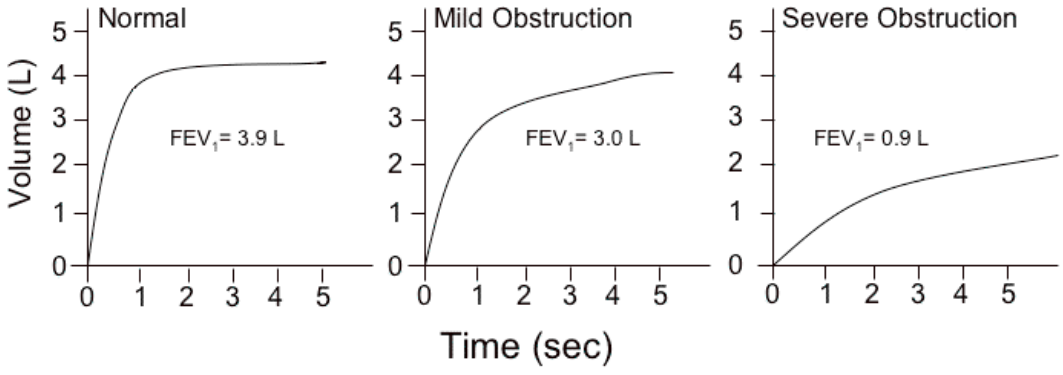
1. History: Wheezing, Cough, Shortness of breath, Chest Tightness, Sputum production

2. Physical Examination:

a. Wheezing with a prolonged phase of forced expiration
b. Reduced intensity of the breath sounds
c. Rhinitis
d. Sinusitis
e. Nasal polyps

3. Laboratory Tests

a) Spirometry
1) FEV_1 (forced respiratory volume in 1 second)



E. BRONCHODILATOR THERAPY FOR ASTHMA

1. Beta$_2$-adrenergic agonists

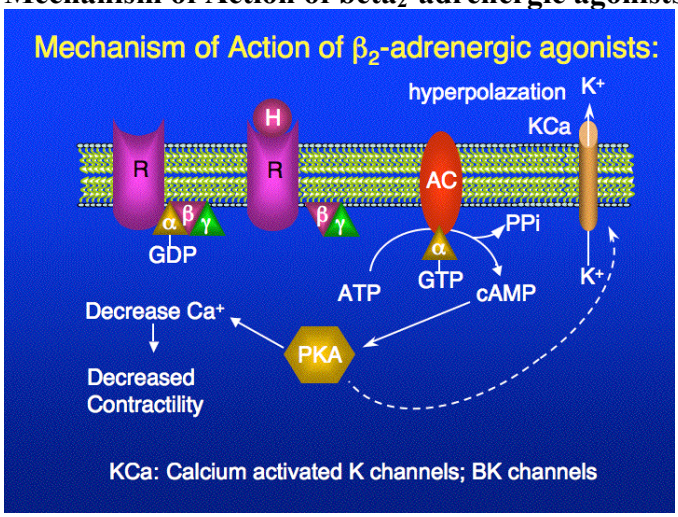
a. General considerations of beta$_2$-adrenergic agonists

1) Medication of choice for the treatment of bronchospasm in asthmatics

b. Selective beta$_2$-adrenergic agonists used for asthma:

1) Metaproterenol (Metaprel®)
2) Albuterol (Proventil ®)
3) Terbutaline (Brethaire®)
4) Bitolterol (Tornalate®)

c. Mechanism of Action of beta$_2$-adrenergic agonists:



d. Routes of administration of beta$_2$-adrenergic agonists for asthma:

1) Inhalation route

a) Metered dose inhaler

Inhaled therapy delivered directly to the lungs is preferable to systemic oral therapy for the following reasons:

(1) Inhaled therapy produces more bronchodilation than systemic oral therapy for asthma
(2) Inhaled therapy causes fewer systemic side effects than systemic oral therapy for asthma.
(3) Inhaled therapy has a faster onset of action that systemic oral therapy for asthma.
(4) Inhaled therapy achieves desired results at lower doses than systemic oral therapy for asthma.

b) Compressor-driven nebulizer

(1) Expensive, no portability, and bacterial contamination are disadvantages.
(2) Advantage: delivers consistent doses without the patient's coordination in cases of severe asthma.

2) Oral route

1) Larger doses are required compared to inhalation route.

2) Has more adverse effects than inhalation route.

3) Onset of action is slower than inhalation route.

3) Parental route: Terbutaline can be injected subcutaneously without the necessity of the patient's cooperation.

e. Pharmacokinetics of β_2-adrenergic agonists in asthma

	Inhalation Route		Oral Route	
	Onset of Action (min)	Duration of Action (hr)	Onset of Action (min)	Duration of Action (hr)
metaproterenol	<1	1-3	15-30	4
Bitolterol	3-4	5-8		
Albuterol	5-15	3-6	15-30	8
terbutaline	15-30	3-6	60-120	4-8
salmeterol	10-20	12		

1) Inhalation Route
   a) Fastest onset of bronchodilator action: metaproterenol.
   b) Shortest duration of bronchodilator action: metaproterenol.
   c) Longest duration of bronchodilator action: salmeterol

2) Unique metabolism of bitolterol
   a) Lung esterases hydrolyze bitolterol to terbutylnorepinephrine which is the active form of the drug, therefore bitolterol is a prodrug.
   b) Bitolterol is a beta$_2$-selective drug because esterases that hydrolyze the drug are present in higher concentration in the lung compared to the heart.

f. Therapeutic uses of beta$_2$-adrenergic agonists for asthma

1) Albuterol: Standard of inhaled beta$_2$-agonists for bronchospasm in:
2) Terbutaline: Only beta$_2$-agonists that can be used by subcutaneous injection for emergency treatment of status asthmaticus.
3) Metaproterenol: Quickest onset of action of any beta$_2$-agonist for asthma when inhaled.
4) Bitolterol: Long duration of action (8 hours) when inhaled.
5) Salmeterol: Has the longest duration of action of any beta$_2$-agonist. Should be used only for the maintenance treatment of asthma and not for treatment of acute attacks of asthma.

g. Side effects of beta$_2$-adrenergic agonists used for asthma

1) **Skeletal muscle tremor**: Most common. Occurs as fine finger tremors. Tolerance develops therefore start with low dose and progressively increase dose.
2) **Anxiety, restlessness and apprehension**: May limit therapy.
3) **Tachycardia**: A result of direct stimulation of heart rate by β_1-receptors and the reflex stimulation of heart rate from β_2-receptor-mediated peripheral vasodilatation.

2. Methylxanthines
Theophylline (Theo-Dur®)

a. Chemical structure of theophylline

1) Theophylline is 1,3-dimethylxanthine

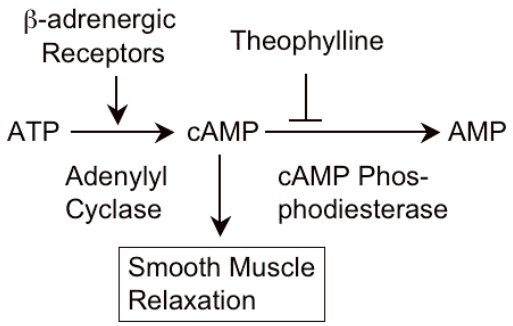
2) Solubility of theophylline has been increased by the formation of a complex between theophylline and ethylenediamine known as aminophylline

b. Mechanisms of anti-asthmatic actions of theophylline

1) Inhibition of smooth muscle phosphodiesterase

a) Theophylline increases intracellular levels of cAMP by inhibiting phosphodiesterase, which slows down the degradation of:

b) An accumulation of cAMP could explain the bronchodilatation and vasodilatation caused by theophylline.



2) Antagonism of smooth muscle cell surface receptors for adenosine

a) Because inhaled adenosine causes bronchoconstriction in patients with asthma but does not affect people without asthma, the action of theophylline as a competitive antagonist at adenosine receptors may be important in the treatment of asthma.

3) Interference with the uptake and sequestration storage of Ca^{2+} ions by the sarcoplasmic reticulum in striated muscle, with a resulting increase in the cytoplasmic concentration of Ca^{2+} ions

a) Explains the action of theophylline to increase the strength of contraction of cardiac and skeletal muscle.

c. Routes of administration of theophylline for asthma (cannot be inhaled)

1) **Standard (short-acting) oral preparations**: Onset of action is 45-60 minutes. Duration of action is 4-6 hours.
2) **Prolonged-release (sustained-release) oral preparations**: Duration of action is 8, 12 or 24 hours, therefore useful in nocturnal asthma.
3) **Intravenous route**: Aminophylline (ethylenediamine complex with theophylline) is administered as a slow infusion for acute, severe asthma.

d. Pharmacokinetics of theophylline in asthma

1) Hydroxylated and demethylated in liver and excreted by kidneys

2) Any slight alteration in the percentage of theophylline that is metabolized will produce large differences in its clearance.

a) The mean half-life of theophylline is shortened by cigarette smoking.

(1) Smoking induces hepatic enzymes that degrade theophylline
(2) Half-life of theophylline in non-smoking adults is 9 hours
(3) Half-life of theophylline in smoking adults is only 5 hours

b) The mean half-life of theophylline is prolonged in patients with:

(1) A decrease in hepatic blood flow from congestive heart failure
(2) A decrease in hepatic function such as in cirrhosis
(3) Obesity
(4) Oral contraceptives
(5) Viral upper respiratory infection

3) Monitoring of serum concentrations of theophylline is important because:

a) Range of safe therapeutic serum concentrations of theophylline is very narrow, being between: 5-15 micrograms/ml.
b) Inter-individual variability of theophylline clearance is very large
c) Theophylline has significant dose-related toxicities

e. Therapeutic uses of theophylline for asthma

1) Theophylline is used in two ways

a) To treat acute asthmatic episodes
b) As maintenance therapy for chronic asthma in order to prevent attacks and to minimize signs and symptoms during periods of remission.

2) Goals for using theophylline in the treatment of asthma

a) Reverse bronchospasm by relaxing bronchial smooth muscle
b) Improve respiratory function by increasing the contractility and reducing the fatigue of the diaphragm skeletal muscle
c) Increase ventricular ejection fraction by a positive inotropic effect on cardiac muscle

f. Side effects of theophylline

1) Therapeutically effective serum theophylline level of 5-15 micrograms/ml

a) Close to the toxic concentration of theophylline, therefore periodic monitoring of drug levels is strongly recommended

2) If serum theophylline levels remain below 15 micrograms/ml

a) Adverse effects are rare

3) At serum theophylline levels from 20-35 micrograms/ml

a) Headache
b) Dizziness
c) Nervousness and insomnia
d) Nausea and vomiting
e) Epigastric pain due to theophylline relaxing the gastroesophageal sphincter, which leads to reflux into the esophagus and heartburn since theophylline can also increase gastric acid secretion.

4) At serum theophylline levels above 35 micrograms/ml

a) Serious central nervous system effects
   (1) Agitation
   (2) Hyperreflexia
   (3) Fasciculations
   (4) Generalized convulsions
      (a) Especially dangerous because they can occur without warning signs
      (b) May be refractory to standard anticonvulsant therapy, with death or severe residual effects being possible
b) Serious cardiac toxicity
   (1) Tachycardia
   (2) Arrhythmias
   (3) Circulatory collapse
c) Pronounced elevation in body temperature in children
d) Relaxation of the bladder muscle
   (1) May cause urinary retention in older men with enlarged prostate

5) Side effects of theophylline can be avoided by:

a) Starting with low doses and gradually increasing the dose of theophylline to the desired plasma level.
b) Order periodic blood levels of theophylline

6) Rapid intravenous administration of therapeutic doses of aminophylline

a) Can occasionally result in sudden death due to cardiac arrhythmias
b) Always perform IV administration of theophylline slowly over a longer time.

3. Muscarinic Receptor Antagonists

Ipratropium bromide

a. General considerations of ipratropium bromide: Anticholinergic drug that is a muscarinic antagonist because asthma can be associated with vagal-mediated stimulation of bronchial smooth muscle causing bronchospasm and mucus

hypersecretion. Unlike atropine, ipratropium bromide has no systemic toxicity when administered as an aerosol.

b. **Ipratropium bromide (Atrovent®)**: A quaternary isopropyl derivative of atropine

c. **Biochemical mechanism of anti-asthmatic action of ipratropium bromide**

1) Ipratropium bromide inhibits the effect of acetylcholine released from airway vagal nerves by antagonizing muscarinic receptors in bronchial smooth muscle cells, resulting in:

a) A decreased concentration of inositol triphosphate, which leads to:
(1) a decreased release of Ca^{2+} ions from the endoplasmic reticulum, causing
(2) relaxation of bronchial smooth muscle

d. **Routes of administration of ipratropium bromide for asthma**

1) Available in a metered-dose inhaler or a nebulized solution, with an onset of action 30-90 minutes and a duration of action of 5 hours

e. **Therapeutics uses of ipratropium bromide**

1) In combination with $beta_2$-adrenergic agonists if additional bronchodilitation is needed in severe acute asthma.
2) When inhaled $beta_2$-adrenergic agonist and/or theophylline is not adequate or it is not well tolerated in asthmatic patients
3) When a coexisting chronic bronchitis or cough is predominant symptom is asthmatic patients
4) Drug of choice for treatment of chronic bronchitis or emphysema in non-asthmatic patients (chronic obstructive pulmonary disease, COPD).

f. **Side effects of ipratropium bromide used for asthma**

1) Very safe because poorly absorbed when inhaled, resulting in very low blood levels of drug
2) Local drying in the mouth following inhalation
3) Inform patients to close their eyes to avoid accidental contact of the spray with their eyes, or else they will have blurred vision for near objects due to dilatation of the pupils.

F. ANTI-INFLAMMATORY THERAPY FOR ASTHMA

1. Adrenal corticosteriods

a. General considerations of adrenal corticosteroids

1) Asthma is a chronic inflammatory disease with allergy being a frequent component of asthma
2) Physicians must not only treat the symptoms of asthma but:
a) must also treat the underlying inflammation of asthma
3) Adrenal corticosteriods do not relax airway smooth muscle directly but they do produce marked increases in airway diameter by decreasing

inflammation.

4) Adrenal corticosteroids can reduce the frequency and severity of chronic asthma attacks

b. Adrenal corticosteroids used for asthma:

a) Beclomethasone (Venceril®)
b) Flunisolide (Aerobid®)
c) Triamcinolone (Azmacort®)
d) Prednisone (Meticorten®)

c. Routes of administration of adrenal corticosteroids for asthma

1) Oral administration

a) Prednisone (Meticorten®)

2) Intravenous administration

a) Methylprednisolone (Solu-Medrol®)

Used for the emergency treatment of status asthmaticus

3) Inhalation administration

a) Beclomethasone (Vanceril®): A chlorinated analogue of betamethasone taken four times a day
b) Flunisolide (AeroBid®): A fluorinated steroid taken twice a day.
c) Triamcinolone (Azmacort®): A fluorinated steroid.

d. Pharmacokinetics of adrenal corticosteroids in asthma

1) Oral and inhaled adrenal corticosteroids

a) Onset of action: 3 hours
b) Duration of action: 6 or 12 hours
c) Adrenal corticosteroids do not cause their effects rapidly in asthma

e. Biochemical mechanism of anti-asthmatic action of adrenal corticosteroids

1) Adrenal corticosteroids prevent the synthesis or action of inflammatory mediators during late phase asthmatic reactions:

a) Adrenal corticosteroids increase the synthesis of lipomodulin, which
b) inhibits phospholipase A_2 activity, thereby
c) suppressing the release of arachidonic acid, which
d) leads to an inhibition of the synthesis and release of leukotrienes B_4, C_4 and D_4 as well as prostaglandins, resulting in reductions in leukocyte chemotaxis, bronchiolar smooth muscle contraction, vascular permeability and airway mucus secretion.

f. Therapeutics uses of adrenal corticosteroids for asthma

1) Because of the importance of the inflammatory component in asthma, adrenal corticosteroids must now be considered as part of the first line prophylactic therapy for all cases of asthma.

a) A short course of oral adrenal corticosteroid should always be combined with an inhaled steroid in order to reduce the amount of the oral dose.

g. Side Effects of Adrenal Corticosteroids used in treatment of Asthma:

1) <u>Systemic adverse effects from short-term oral adrenal corticosteroids</u>

a) Hyperglycemia
b) Edema
c) Rounding of facial contour

2) <u>Systemic adverse effects from long-term oral adrenal corticosteroids</u>

a) Osteoporosis
b) Cataracts
c) Myopathy
d) Hypothalamic-pituitary-adrenal axis suppression
e) Psychological depression

3) <u>Inhaled adrenal corticosteroids</u>

a) Do not produce systemic side effects (adrenal insufficiency)
b) Local adverse effects
   (1) Oropharyngeal candidiasis (can be minimized by rinsing the mouth and gargling with water immediately after inhalation)
   (2) Dysphonia (hoarseness)
   (3) Dryness of mouth and throat
   (4) Occasional coughing due to upper airway irritation (can be minimized by using a spacer attached to the metered-dose inhaler, which decreases the oropharyngeal deposition while increasing the lower airway deposition of the adrenal corticosteroid)

Combination Therapy: Symbicort® - mixture of glucocorticoid (Butenoside & formoterol fumarate – long acting β-AR anatagonist)

2. <u>Cromolyn sodium</u>

a. <u>General considerations of cromolyn sodium (Intal®)</u>

1) Nonsteroidal anti-inflammatory drug used only for prevention of asthmatic attacks

b. <u>Routes of administration of cromolyn sodium for asthma</u>

1) Inhaled as an aerosol by a compressed metered inhaler

c. Pharmacokinetics of cromolyn sodium

1) When used prior to a challenge such as exercise or cold air:

a) Onset of action: 10-15 minutes

b) Duration of action: 4-6 hours

d. Mechanism of anti-asthmatic action of cromolyn sodium

1) Cromolyn sodium inhibits the degranulation of mast cells, preventing the release of histamine and other mediators of bronchospasm:

a) Cromolyn sodium reduces the transmembrane influx of Ca^{2+} ions induced by IgE antibody-antigen interactions on the sensitized mast cell surface

2) Cromolyn sodium inhibits the recruitment of neutrophils and eosinophils to the pulmonary epithelium:

a) Cromolyn sodium inhibits neutrophil chemotactic factor (NCF)

3) Cromolyn attenuates the ability of platelet activating factor (PAF) to cause airway hyperreactivity

e. Therapeutic uses of cromolyn sodium for asthma

1) Cromolyn sodium, when used prophylactically before exposure will inhibit:

a) Immediate allergen-induced airway narrowing
b) Late phase allergen-induced airway narrowing

2) Pretreatment with cromolyn sodium will block:

a) Exercise-induced bronchoconstriction
b) Cold, dry air-induced bronchoconstriction

3) Cromolyn sodium is not capable of reversing asthmatic bronchospasm

a) Cromolyn sodium cannot be used to treat an acute episode of asthma.

b) The only use of cromolyn sodium is in the prevention of bronchospasm

4) There is no way to reliably predict whether a patient will respond to cromolyn sodium

a) A 4-6 week trial may be required to determine the efficacy of cromolyn in asthmatic patients

5) In patients with severe asthma who respond poorly to individual drugs, therapeutic benefits may be enhanced by combining cromolyn sodium with an adrenal corticosteroid and/or a bronchodilator such as a beta$_2$-adrenergic agonist or theophylline

a) If combined therapy is prescribed, then one must individualize the dose of each drug in order to obtain maximal benefit with minimal adverse reactions

f. Side effects of cromolyn sodium used for asthma

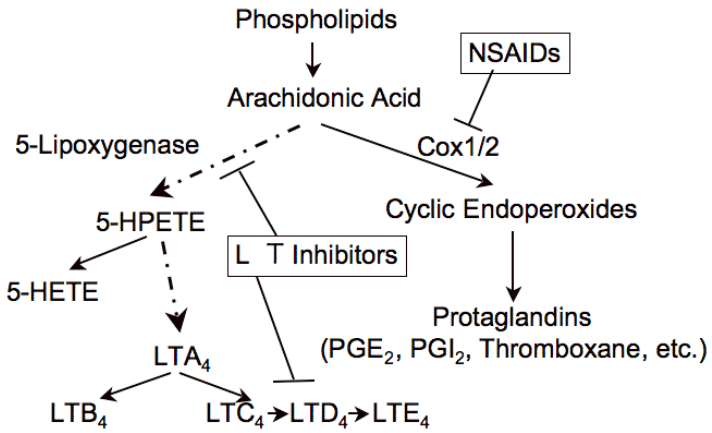
1) Reversible hypersensitivity reactions such as dermatitis (rare)

g. Drug related to cromolyn sodium

1) Nedocromil sodium (Tilade®). Same pharmacological effects as cromolyn sodium – indicated in individuals>12yrs old.

3. Leukotreine inhibitors

a. General Considerations



b. Biochemical mechanisms of action of leukotreine inhibitors

1) Two types: Inhibitors of Synthesis (Zileuton) and antagonists of LT receptors (Zafirlukast, Montelukast)

1) Preventing actions of leukotreines

2) Properties of leukotreines:

a) Previously known as slow reacting substances of anaphylaxix – may be overproduced when Cox1/2 are inhibited.

b) Contribute to bronchoconstriction, inflammation, edema and mucus secretion, thereby obstructing airways in asthma.

c) Cysteinyl leukotreines such as LTD_4 are the most potent bronchoconstrictors

c. Representative leukotreine inhibitors

1) Zafirlukast (Accolate®)

a) Mechanism of action

A cysteinyl-leukotreine$_1$ receptor antagonist that competes with LTD_4 at its cysteinyl LT_1 receptor site on airway target cells, resulting in blocking the bronchoconstrictive effect of LTD_4 in both the early and late-phase asthmatic response, as well as also blocking the inflammatory response of LTD_4 in the late asthmatic phase.

b) Pharmacokinetics of zafirlukast

1) Take 20 mg tablet either 1 hour before or 2 hours after breakfast and dinner since food reduces the bioavailability of zafirlukast

c) Therapeutics uses of zafirlukast

(1) Prevention of asthmatic attacks in patients 12 years and older, with a therapeutic trial being the only way to determine which asthma patients will show a clinical improvement

a) Not a rescue medication itself during an acute asthmatic attack because it does not act quickly enough. However, does reduce the need for a rescue beta$_2$ -agonist in chronic asthma patients.

(2) Improves pulmonary function in mild-to-moderate asthma

(3) Effective in aspirin-induced asthma that is caused by an overproduction of leukotreines resulting from the inhibition of prostaglandin synthesis by aspirin.

(4) Effective in prevention of cold-air-induced bronchoconstriction in patients with mild-to-moderate asthma.

d) Contraindications of zafirlukast

(1) Breast-feeding

e) Side effects of zafirlukast

f) Drug interactions of zafirlukast

(1) zafirlukast plus warfarin produces an increased prothrombin time with possible bleeding because zafirlukast inhibits the cytochrome P450 enzymatic degradation of warfarin

2) Montelukast sodium (Singulair®)

a) Mechanism of action:
Another cysteinyl-leukotreine$_1$ receptor blocker that prevents the bronchoconstriction, mucus secretion and vascular leaks caused by LTD_4

b) Therapeutic uses of montelukast

(1) Effective in adults 15 years and older (10 mg tablet daily) and in pediatric patients 6-14 years (5 mg chewable tablet daily)
(2) Effective in preventing exercise-induced bronchospasm
(3) Should not be used as a rescue medication for acute asthma episodes

c) Side effects of montelukast

3) Zileuton (Zyflo®)

a) Mechanism of action
A 5-lipoxygenase inhibitor - therefore, also inhibits actions of LTB_4

b) Therapeutic uses of zileuton

(1) Administered orally four times a day

(2) Effective in preventing exercise-induced asthma, cold-air-induced asthma and aspirin-induced asthma

(3) Reduces nocturnal symptoms and bronchial obstruction in nocturnal asthma

c) Side effects of zileuton

(1) Increases alanine transaminase to more than 3-fold in 3% of treated patients. However, will revert back to normal when drug is discontinued. FDA recommends measurement of alanine transaminase before therapy with periodic monitoring thereafter. Contraindicated in patients with hepatic diseases.

(2) Occasional dyspepsia

4) Monoclonal antibodies

a. Omalizumab (Xolair®)

1) Biochemical mechanism of action of omalizumab

a) An allergic component mediated by antigen-specific IgE attached to receptors on mast cells causes the release of

histamine and leukotrienes that increase mucosal inflammation producing spasm of airway smooth muscle.

b) Omalizumab forms a complex with circulating free IgE which lowers free IgE serum concentrations to undetectable levels. This prevents IgE from binding to mast cells preventing the release of histamine and leukotrienes from mast cells.

2) Route of administration of omalizumab

a) Subcutaneous injection every 2-4 weeks

b) Patient cost is $12,000 per year

3) Adverse effects of omalizumab

a) It is currently not known whether long-term lowering of free IgE serum concentrations could increase the risk of malignancy…since in a completed study for less than 1 year, malignant neoplasms occurred in 0.4% of 4,127 patients exposed to omalizumab as compared to 0.1% of 2,236 controls.

4) Present status of omalizumab

a) The high cost, the need for subcutaneous injections, and the concern about its long-term safety restricts the use of omalizumab to patients with severe asthma that cannot be controlled by other drug

SUMMARY REVIEW TABLE FOR LECTURE

Anti-asthmatic Drug	Classification	Biochemical mechanism of anti-asthmatic action	Routes of administration	Type of therapeutic use	Unique therapeutic use	Major side effects
$Beta_2$ adrenergic Agonists	Bronchodilator	1. Stimulate adenylyl cyclase causing increase of cAMP resulting in bronchodilatation 2. Inhibits release of mediators from mast cells that causeBronchospasm	1. Inhalation 2. Oral 3. Subcutaneous (Terbutaline only)	Symptomatic relief of bronchospasm in acute asthma attacks	1. Subcutaneous terbutaline for status asthmaticus 2. Bitolterol for Nocturnal asthma	1. Skeletal muscle tremor 2. Anxiety 3. Tachycardia
Theophylline	Bronchodilator	1. Inhibits cAMP phosphodiesterases causing increase of cAMP resulting in bronchodilation 2. Competitive antagonist at adenosine receptors resulting in bronchodilation	1. Oral 2. Slow IV over 40 min.	Maintenance therapy for chronic asthma	1. Sustained-release oral therapy for nocternal asthma	**Narow Therp. Index** 1. Fasciculations 2. Generalized Convulsions 3. Tachycardia 4. Circulatory collapse
Ipratropium Bromide	Bronchodilator	1. Antagonist at muscarinic,receptors leading to decreased inositol triphosphate,causing decreased release of Ca^{2+} ions from endoplasmic reticulum resulting in Bronchodilatation	1. Inhalation	Alone or in combination with $beta_2$- adrenergic agonist in acute asthma attacks	1. When a coexisting chronic bronchitis or cough is the predominant symptom in asthmatic patients	1. Local drying of mouth
Adrenal corticosteroids	Anti-inflammatory Agent	1. Increases synthesis of lipomodulin, which inhibits phospholipase A_2 which suppresses release of arachidonic acid, which inhibits release of leukotrienes and prostaglandins, resulting in bronchodilatation	1. Inhalation 2. Oral 3. IV	Maintenance therapy for chronic asthma	1. Treats the underlying inflammation of asthma, reducing frequency and severity of attacks	1. Systemic from oral therapy 2. Local such as oropharyngeal candidiasis, dysphonia, dry mouth and cough from inhalation therapy
Cromolyn Sodium	Anti-inflammatory Agent	1. Decreases Ca^{2+} influx by IgE Ab and thereby Inhibits release of mediators from mast cells that cause Bronchospasm	1. Inhalation	Prophylactic therapy for preventing bronchospasm	1. Prior to exercise challenge 2. Prior to cold air challenge	1. Occasional coughing
Zafirlukast	Leukotriene Inhibitor	1. Complete with LTD_4 at its receptor site on airway cells to block bronchoconstriction and inflammation	1. Oral (on an empty stomach)	Prophylactic therapy for preventing bronchospasm	1. Aspirin – induced asthma 2. Prior to cold-air challenge	1. Headache 2. Nausea
Zileuton	Leukotriene Inhibitor	1. Inhibits 5'-lipooxygenase to decrease production of leukotrienes	1. Oral	Prophylactic therapy for preventing bronchospasm	1. exercise/aspirin-induced asthma 2. nocturnal symptoms/ nocturnal asthma	1. contraindicated in patients with hepatic disease.
Omalizumab	Monoclonal antibody	1. Forms a complex with IgE which lowers serum free IgE preventing release of histamine and leukotrienes from mast cells	1. Subcutaneous	Prophylactic therapy for chronic asthma		1. Possible long-term risk for malignancy

DRUGS USED TO TREAT ALLERGIRES
(HISTAMINE AND ITS ANTAGONISTS)

Date: November 26, 2013
Reading Assignment: Katzung, *Basic and Clinical Pharmacology*, 11th. Ed., pp.271-280

KEY CONCEPTS AND LEARNING OBJECTIVES

Histamine via its different receptors produces a number of physiological and pathological actions. Therefore, anti-histaminergic drugs may be used to treat different conditions.

1. To know the physiological functions of histamine.

2. To understand which histamine receptors mediate the different effects of histamine.

3. To know what stimuli cause the release of histamine.

4. To know the types of histamine antagonists that are available clinically.

5. To know the clinical uses of H_1 receptor antagonists.

6. To know the drug interactions associated with the use of anti-histaminergic drugs.

Drug List

See Summary Table at the end of handout

I. Histamine biology

An ethylamine endogenously formed by the decarboxylation of the amino acid histidine by histidine decarboxylase. Histamine is located in the central (hypothalamic neurons) and enteric (GI tract) nervous systems; tissue (mast cells – skin, bronchial mucosa, intestinal mucose); and, blood (basophils).

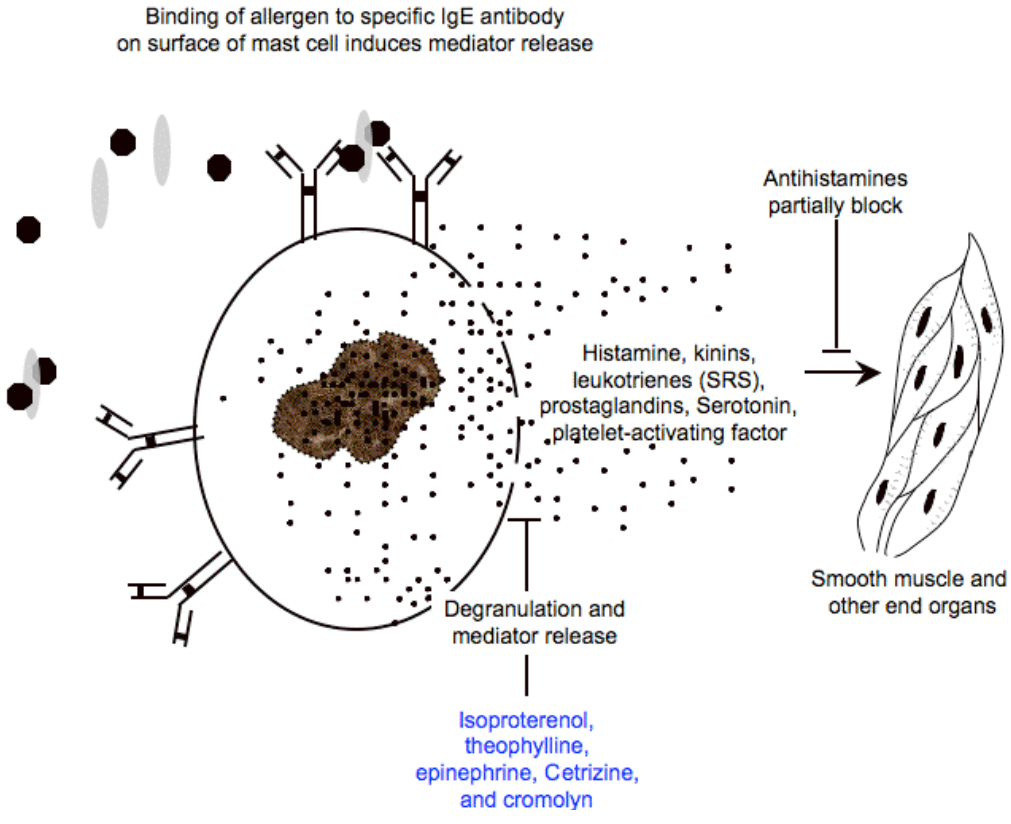
Histamine is released by neural and immunologic (see figure from Katzung, reproduced below) stimulation.

Other methods of Histamine release: certain therapeutic agents –antibiotics, vancomycin, bradykinin, substance P, non-specific cell damage – urticaria associated with scratching

Metabolized by two different pathways and the metabolite N-methylhistamine in urine is a more accurate index of endogenous histamine levels.

There are four types of histamine receptors. H_1 and H_2 receptors are located post-synaptically; H_3 presynaptically. All are found in the brain. In the periphery H_1 and H_2 receptors have a distinct distribution:

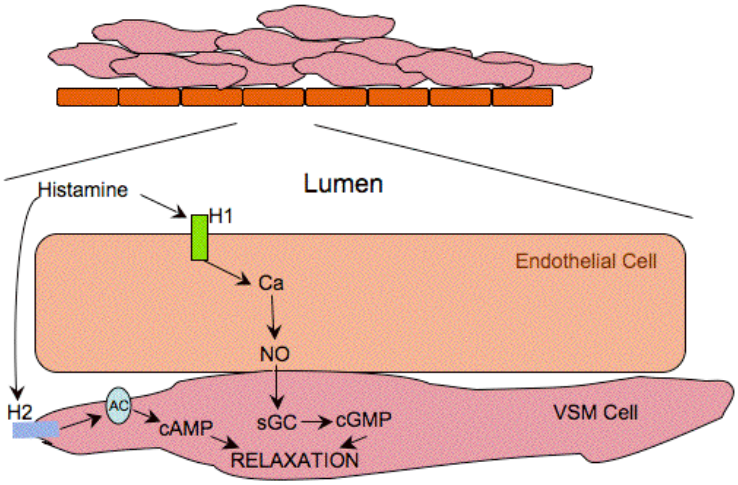
H_1 - Smooth muscle, endothelium.
H_2 - Gastric mucosa, cardiac muscle, vascular smooth muscle.
H_3 – Presynaptic
H_4 – Blood Cells in bone marrow & circulation – mediate chemotaxi of eosinophils and mast cells.



II. Physiological Effects of Histamine

A. Cardiovascular (H_1 and/or H_2 receptor mediated)

1. vasodilation of arterioles and precapillary sphincters – **IMP to know Mechanism.**
2. hypotension and reflex tachycardia
3. increased permeability of postcapillary vessels; transudation (H_1 receptors)
4. flushing, sense of warmth and headache result



B. Gastrointestinal Tract

1. gastric acid secretion by activation of H_2 receptors on parietal cells
2. contraction of GI smooth muscle (H_1 receptors)

C. Bronchoconstriction (H_1 receptor mediated)

D. Stimulation of peripheral nerve endings (H_1 receptor mediated): itching and red flares

E. The "triple response" to histamine in skin (predominantly H_1 mediated)

1. Reddening: dilation of small vessels
2. Red irregular flare with itching; stimulation of nerve endings.
3. Edematous wheal: separation of endothelial cells permitting transudation.

III. Treatment of Allergy: H_1 Histamine Antagonists

A. Three types of drugs are used clinically to block histamine actions.

1. Physiological antagonists, especially epinephrine, have smooth muscle actions opposite to those of histamine but act at different receptors β2-adrenergic receptors. **REM:** Also blocks histamine release.

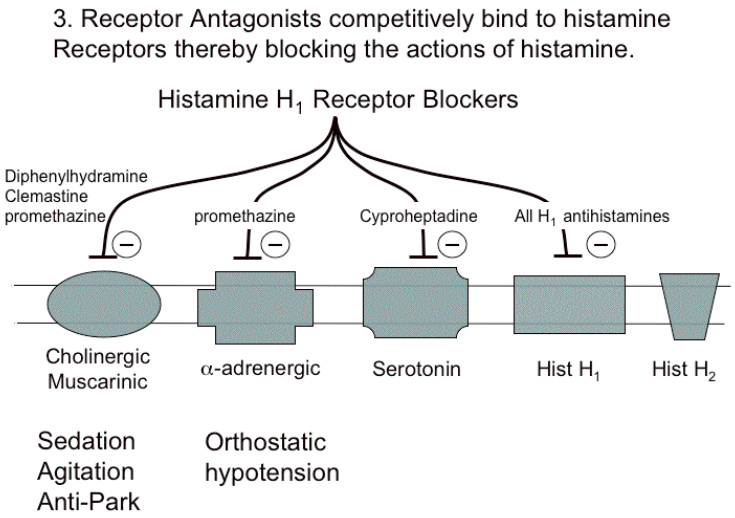
2. Release inhibitors, such as cromolyn sodium and nedocromil, reduce the

degranulation of mast cells resulting from antigen-IgE interaction.

β_2-adrenergic agonists, such as metaproterenol, appear to reduce histamine release while producing bronchodilation.

Cetrizine (Zyrtec) also inhibits histamine release

3. Receptor Antagonists competitively bind to histamine receptors thereby blocking the actions of histamine.



B. H_1 Antagonists are used primarily in the treatment of allergic rhinitis and urticaria (hives) and motion sickness. These drugs are not useful in the therapy of bronchial asthma. Because many of the H_1 antagonists are not selective they have other applications. A large number of the 20 plus H_1 blockers are available OTC either alone or formulated with other drugs as "cold pills" and sleep aids. **NEW FDA Recommendation** (Oct 2008) Cold medications containing H_1 receptor antagonists –NOT to be used in children <4 yr of age.

H_1 antagonists are readily absorbed from the GI tract and are widely distributed throughout the body. Most are extensively metabolized in the liver, and form active metabolites. The H_1 blockers have a duration of action of 4-6 hours.

The newer drugs have longer durations of action (12-24 hrs) and are less lipid soluble. Thus, they do not cross the blood brain barrier to any large degree and are less sedating. The newer drugs, however, are more expensive.

Contraindications for newer drugs:

Fexofenadine (Allegra®): Glaucoma, Urinary retention, MAO inhibitors
Loratadine (Claritine®): Pregnancy, Lactation

Other H1 Antagonists:

Doxepin (Sinequin®): Tricyclic Anti-depressant – most potent anti-histamine available (800X > potent than diphenhydramine). Used in Rx of chronic urticaria not responsive to other H1 antagonists.

Anti-cholinergic – best tolerated by patients who have depression. Disorientation and confusion in non-depressed patients.

Table 16-2. Some H_1 antihistaminic drugs in past or current clinical use.

Drugs	Usual Adult Dose	Anti-cholinergic Activity	Comments
First Generation Antihistamines			
Ethanolamines Carbinoxamine (Clistin)	4-8 mg	+++	Slight to moderate sedation
Dimenhydrinate (salt of diphenhydramine) (Dramamine)	50 mg	+++	Marked sedation; anti-motion sickness activity
Diphenhydramine (Benadryl, etc)	25-50 mg	+++	Marked sedation; anti motion sickness activity
Doxylamine	1.25 – 25 mg	nd	Marked sedation; now available only in OTC "sleep aids"
Ethylaminediamines Pyrilamine (Neo-Antergan)	25 – 50 mg	+	Moderate sedation; component of OTC "sleep aids"
Tripelennamine (PBZ, etc)	25 – 50 mg	+	Moderate sedation
Piperazine derivatives Hydroxvzine (Atarax, etc)	15 – 100 mg	nd	Marked sedation
Cyclizine (Marezine)	25 – 50 mg	-	Slight sedation; anti-motion sickness activity
Meclizine (Bonine, etc)	25 – 50 mg	-	Slight sedation; anti-motion sickness activity
Alkylamines Brompheniramine (Dimetane, etc)	4 – 8 mg	+	Slight sedation
Chlorpheniramine (Chlor-Trimeton, etc)	4 – 8 mg	+	Slight sedation; common component of OTC "cold medication"
Phenothiazine derivatives Promethazine (Phenergan, etc)	10 – 25 mg	+++	Marked sedation; antiemetic
Miscellaneous Cyproheptadine (Periactin, etc)	4 mg	+	Moderate sedation; also has antiserotonin activity
SECOND GENERATION ANTIHISTAMINES			
Piperidines Fexofenadine (Allegra)	60 mg	-	Lower risk of arrhythmia
Miscellaneous Loratadine (Claritin)	10 mg	-	Longer action
Cetirizine (Zyrtec)	5 – 10 mg	-	

Nd, no data found

From Katzung, 9th ed. p. 265

Undesirable side effects and toxicity of the H_1 blockers are very uncommon; they include anorexia, nausea, vomiting, constipation, diarrhea, epigastric distress, decreased alertness, impaired ability to concentrate, drowsiness, and muscular weakness. Blood dyscrasias (eg, leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia) occur rarely. Overdosage is accompanied by anticholinergic effects: dry mouth, palpitations, chest tightness, urinary retention, visual disturbances, convulsions, hallucinations, and, later, respiratory depression, fever, hypotension, and mydriasis. These are often most problematic in the elderly.

Diphenhydramine and other anti-histamines with strong anti-cholinergic action are relatively contraindicated in patients with asthma and chronic obstructive pulmonary disease (COPD), especially during acute attacks, because anticholinergic actions may thicken secretions and reduce expectoration.

Treatment of Anaphylaxis:

For mild reactions (eg, generalized pruritus, urticaria, angioedema, mild wheezing, nausea, and vomiting), epinephrine. If an antigen injected into an extremity caused the anaphylaxis, a tourniquet should be applied above the injection site and 1/2 of the above dose of epinephrine also injected into the site to reduce systemic absorption of the antigen. A second injection of epinephrine subcutaneously may be needed. After symptoms resolve, an oral antihistamine should be given for 24 h.

For more severe reactions, with massive angioedema but without evidence of cardiovascular involvement, adult patients should be given diphenhydramine 50 to 100 mg IV in addition to the above treatment to forestall laryngeal edema and to block the effect of further histamine release. When the edema responds, long-acting epinephrine can be given for its 6- to 8-h effect; an oral antihistamine should be given for the next 24 h.

The most severe reactions usually involve the cardiovascular system, causing severe hypotension and vasomotor collapse. IV fluids should be rapidly infused and the patient should be recumbent with legs elevated. Epinephrine should be given slowly with close observation for development of side effects, including headache, tremulousness, nausea, and arrhythmias. The underlying severe hypotension may be due to vasodilation, hypovolemia from loss of fluid, myocardial insufficiency (rarely), or a combination of these. When all the above measures have been instituted, anti-histamines may then be given for treatment of slow-onset urticaria, asthma, laryngeal edema, or hypotension.

Generic Name	Trade Name	Mechanism	T½ hrs	Elimination	Benefit
Diphenhydramine	Benedryl	H1 antagonist – 1st generation	4-6	hepatic	OTC
Chlorpheniramine	Chlor-trimeton	H1 antagonist – 1st generation	4-6	hepatic	OTC
Fexofenadine	Allegra	H1 antag. – 2nd generation	12	hepatic	BBB/hrs
Loratidine	Claritin	H1 antag. – 2nd generation	24	hepatic	BBB/hrs
Citirizine	Zyrtec	H1 antag. – 2nd generation	12-24	hepatic	BBB/hrs

OTC = over the counter medication
BBB = reduced transfer across the blood brain barrier

SUMMARY REVIEW TABLE FOR LECTURE

Drug	Classification	Biochemical mechanism of anti-asthmatic action	Routes of administration	Type of therapeutic use	Contraindications	Major side effects	Comments
Diphenhydramine (Benedryl®)	Histamine H1 receptor antagonist – **1st generation**	Blocks histamine H1 receptors	1. Oral 2. Intravenous	1. Allergic rhinitis, 2. Urticaria 3. adjunctive therapy in anaphylactic reaction. 4. Anti-motion sickness activity (muscarinic receptor blocker) but **Dimenhydrinate (Dramamine®) preferred**		1. Marked sedation or agitation due to mucarinic receptor blockade.	All H1 antagonists are relatively contraindicate in COPD during acute attacks – anticholinergic activity thickens secretion and decreases expectoration **New FDA Recommendation: Not to be used in "cold medicines" for children <4yrs**
Chlorpheniramine (Chlor-trimeton®)	Histamine H1 receptor antagonist – **1st generation**	Blocks histamine H1 receptors	1. Oral	1. Allergic rhinitis, 2. Common ingredient in OTC "cold medications".	1. Glaucoma 2. bladder neck obstruction 3. symptomatic prostate hypertrophy 4. during acute asthma attack	1. Slight sedation or agitation due to mucarinic receptor blockade.	See above
Fexofenadine (Allegra®)	Histamine H1 receptor antagonist – **2nd generation**	Blocks histamine H1 receptors	1. Oral	1. Allergic rhinitis, 2. Idiopathic chronic urticaria	1. Glaucoma 2. urinary retention 3. in conjunction with MAO therapy		1. Erythromycin and ketoconazole increase plasma fexofenadine concentrations 2. Antacids and fruit juices decrease bioavailability
Loratidine (Claritin®)	Histamine H1 receptor antagonist – **2nd generation**	Blocks histamine H1 receptors	1. Oral	1. allergic rhinitis 2. allergic reactions to blood or plasma 3. Dermatographism 4. adjunctive therapy in anaphylactic reaction.	1. Hypersensitivity to anti-histamines 2. Pregnancy 3. Lactation	1. Nausea 2. Fatigue 3. Headache	Non-sedating – does not cross BBB
Citrizine (Zyrtec®)	Histamine H1 receptor antagonist – **2nd generation**	Blocks histamine H1 receptors Also blocks histamine release	1. Oral	1. Allergic rhinitis, 2. Idiopathic chronic urticaria	1. Hypersensitivity to hydroxyzine	1. Sedation 2. Faitgue 3. Dry mouth	
Doxepin (Sinequan®)	Tricyclic Anti-depressant	Potent H1 receptor antagonist	Oral	Chronic Urticaria not responding to other H1 antagonists	Those for tricyclic anti-depressants	Disorientation, confusion in non-depressed patients	

ANTIFUNGAL DRUGS

Date: Thursday, December 5th, 2013 8:30-9:30am

Optional Reading Assignment: Basic and Clinical Pharmacology
Katzung, 12th Edition
Chapter 48 pp 849-857

Key Concepts and Learning Objectives.

1. List the indications and contraindications for the major classes of antifungal agents

2. Describe the spectrum of activity and principal clinical uses for the major classes of antifungal agents.

3. Describe the mechanism of action for the major classes of antifungal agents.

4. List the major adverse effects associated with the use of the major classes of antifungal agents.

5. Discuss the principal pharmacokinetic parameters (e.g. absorption, distribution & elimination) of the major classes of antifungal agents and the effects that these have on the clinical use of these drugs.

6. Distinguish the major differences between the members of the azole class of antifungals based upon their spectrum of activity, pharmacokinetic parameters and major adverse effects.

7. Identify those antifungal drugs that pose significant risk of major drug interactions and describe the likely effects on the serum concentration of any co-administered drug

8. Apply your knowledge of the pharmacology of the major classes of antifungal drug agents to select the most appropriate medication for a specific patient based upon the presence of both a specific fungal pathogen and patient-specific criteria.

9. Identify the recommended antifungal agents used in the treatment of specific systemic, localized and cutaneous fungal pathogens

Drugs covered in this lecture

I. Systemic antifungal drugs for systemic infections

A. Polyene Antifungal agents
Amphotericin B*

B. Fluorinated pyrimidine
5-Flucytosine

C. Azole antifungal agents
Imidazoles: Ketoconazole
Triazoles: Fluconazole*, Itraconazole*, Voriconazole*, Posaconazole*

D. Echinocandins
Caspofungin*, Micafungin* & Anidulofungin*

II Systemic antifungal drugs for cutaneous fungal infections

Griseofulvin*
Terbinafine*

III Topical antifungal drugs for cutaneous fungal infections

Polyene: Nystatin
Azoles: Miconazole, Clotrimazole & Terconazole
Allylamines and Benzylamines: Terbinafine, Naftifine & Butenafine

Note: The most important antifungal drugs are highlighted in bold with an asteric.

I. Systemic antifungal drugs for systemic infections

A. AMPHOTERICIN B

Overview

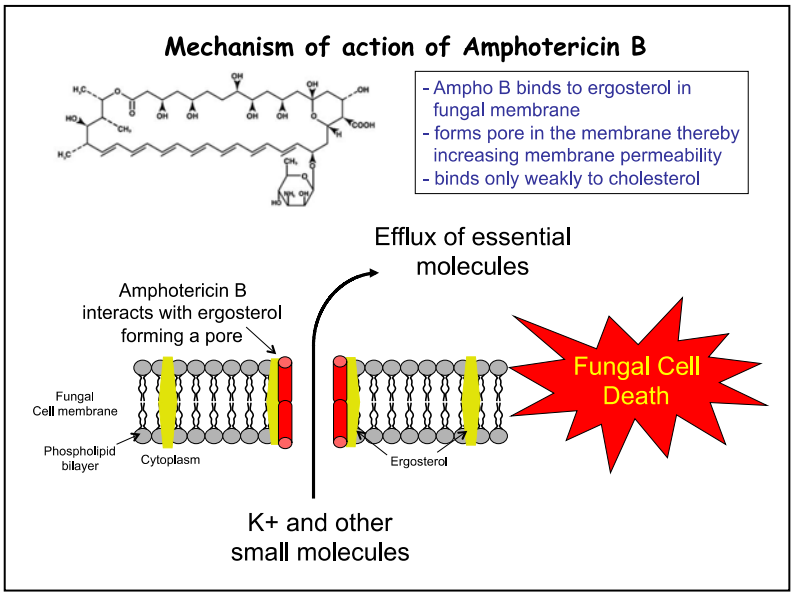
a) Naturally occurring polyene macrolide antibiotic from Streptococcus nodosus
b) Broadest spectrum of all antifungal agents
c) Associated with significant toxicities
    - alternative liposomal formulations reduce side effects
d) Despite the presence of newer drugs, Ampho B remains the standard therapy for treatment of life-threatening mycoses

Mechanism of Action

a) Primarily <u>fungicidal</u>

b) Binds to ergosterol in the plasma membrane of sensitive fungal cells causing pores to form that disrupt membrane function allowing electrolytes (K+) and small molecules to leak out causing cell death.

c) Binds ergosterol with much greater affinity than to cholesterol present in the plasma membrane of mammalian cells



Spectrum of Activity

Amphotericin B has the broadest spectrum of all antifungal agents

Effective against:	*Candida sp (except C. lusitaniae)*
	Cryptococcus
	Histoplasmosis
	Blastomycosis
	Coccidioidomycosis
	Aspergillus sp
	Fusarium
	Zygomycosis/Mucormycosis
Not active against:	*Pseudallescheria boydii (Scedosporium apiospermum)*

Resistance is infrequent and is usually associated with decreased ergosterol content of fungal membranes

Pharmacokinetics

a) Not orally absorbed from GI tract
b) Administration is via IV infusion
c) Oral Ampho B is only effective against fungi within the lumen of the GI tract
d) Drug is highly hydrophobic. The standard formulation is a colloidal suspension with sodium deoxycholate (C-AMB). Alternative liposomal formulations are associated with increased efficacy and decreased toxicity (L-AMB, ABLC & ABCD), although are considerably more expensive (~ $600-1000/day vs ~ $25/day for C-AMB)
e) Drug is widely distributed throughout the body
f) Long serum half-life ~ 15hrs
g) 2-3% of drug distributes to CNS, although drug is effective in treatment of meningitis
h) Intrathecal injection can be used to treat fungal meningitis in severely ill patients, but is poorly tolerated (seizures/neurological sequelae)
i) No dosage adjustment required in Renal/hepatic impairment

Clinical Uses

a) All life-threatening mycotic infections:
   - fungal infections in immunosuppressed patients
   - severe fungal pneumonia
   - severe cryptococcal meningitis
   - disseminated infections of endemic mycoses
   - Patients not responding to AZOLE-treatment of invasive *Aspergillus*

b) Used as initial induction therapy to reduce initial fungal burden and is then replaced by one of the newer/less toxic AZOLE drugs for chronic therapy and prevention of relapse
c) Often given as prophylatic therapy to patients with profound neutropenia and fever who have not responded to broad spectrum antibacterial agents over 5-7 days
d) Treatment of choice for Zygomycosis/Mucormycosis
e) Topical and localized administration:
   - Mycotic corneal ulcers
   - Fungal arthritis (local injection)
   - Candiduria- bladder irrigation (no systemic toxicity)

******NOTE: Only antifungal agents that is approved for use in the treatment of pregnant and/or breast feeding women.

Adverse Effects (Low therapeutic index)

Infusion-related toxicities (Ampho-terrible):

nearly universal

Fever, chills, muscle spasms, vomiting, headache and hypotension

- Slow infusion rate/decrease daily dose
- Pre-emptive medication: antipyretic, anti-histamine, corticosteroids

Cumulative toxicities:

a) Nephrotoxicity (common)

Reversible- ↓Renal perfusion via vasoconstriction

Maybe reduced with Na+ loading

Irreversible- Renal tubule injury (with prolonged administration)
- Tubular acidosis and severe K+ and Mg++ wasting
- More common in presence of diuretic volume depletion or other nephrotoxic medications
e.g. aminoglycosides or cyclosporin

b) Hepatoxicity (occasional)- increase in liver enzymes

c) Anemia– reversible suppression of erythrocyte production due to ↓erythropoietin

Drug Interactions:
Ampho B should not be given concurrently with other nephrotoxic agents e.g. aminoglycosides or cyclosporin

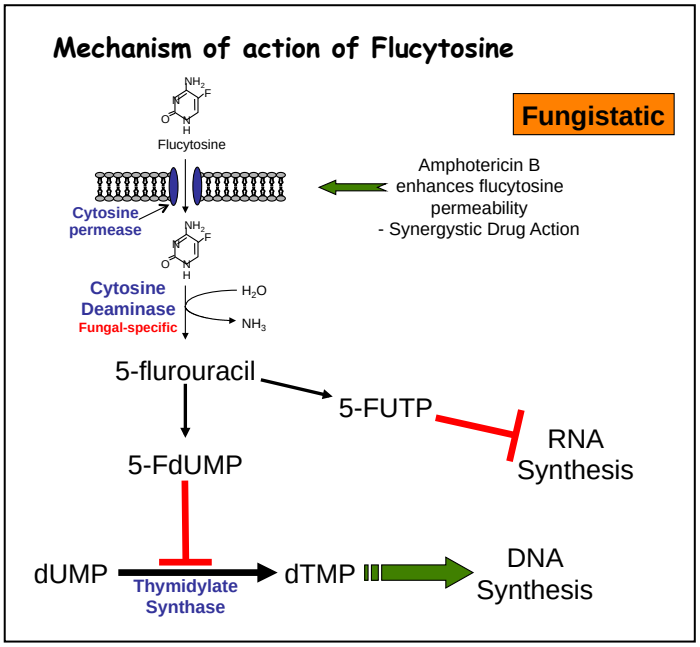
B. FLUCYTOSINE

Overview

a) 5-flurocytosine is a synthetic pyrimidine (originally developed as an anti-metabolite chemotherapy agent, although not effective)
b) Use is restricted due to high incidence of primary and acquired resistance
c) Typically used in combination with other antifungal drugs (Ampho B)

Mechanism of Action

a) Fungistatic
b) Enters the cell via a specific cytosine-specific permease not found in mammalian cells
c) Within the cell it is sequentially converted to 5-flurouracil by the enzyme cytosine deaminase and then to 5-flurodeoxyuridine monophosphate (5-FdUMP) and 5-flurouridine trisphosphate (5-FUTP)
   - 5-FdUMP inhibits thymidylate synthase a key enzyme in nucleotide/DNA synthesis
   - 5-FUTP inhibits RNA synthesis
d) Note: Mammalian cells do not express cytosine deaminase
e) Ampho B increases cell permeability to Flucytosine



Spectrum of Activity and Clinical use

a) Narrow spectrum: *Cryptococcus neoformans,*
Candida sp
Agents of chromoblastomycosis
e.g. *Fonsecaea pedrosol, Fonsecaea compacta, Phialophora verrucosa and Cladosporium carrionii*
b) Use is restricted due to high incidence of primary and acquired resistance
c) Resistance due to mutations in cytosine permease, cytosine deaminase, uracil phosphoribosyl transferase (5-FU to 5-FUMP), or ↑production of endogenous cytosine
d) Emergence of resistance is reduced with combination therapy
e) Typically used in combination with either Amphotericin B or itraconazole

Flucytosine + Ampho B ⇒ Candidiasis or Cryptococcosis

Flucytosine + itraconazole ⇒ Chromblastomycosis

Pharmacokinetics

a) Good oral absorption
b) Wide distribution
c) Penetrates well into the CSF (useful for Cryptococcal meningitis)
d) Renal elimination
e) t1/2 ~ 6 hrs, but > 200 hrs in renal failure
f) Dosage adjustment required with renal impairment

Adverse effects

a) Is metabolized by gut microflora to 5-flurouracil (Toxic anti-metabolite)
- GI (frequent): nausea, vomiting, diarrhea
- Bone marrow toxicity (anemia, leukopenia & thrombocytopenia)
- More common in those with underlying hematological disorder or receiving radiation or chemotherapy

b) Should not be used in PREGNANCY

C. AZOLE ANTIFUNGAL AGENTS

General overview of Drug Class

a) New class of antifungals
b) Widely used clinically
c) Generally broad spectrum of activity
d) Less serious side effects compared to Ampho B
e) Major inhibitors of CYP450 enzymes make drug interactions a significant problem

Two major chemical classes:

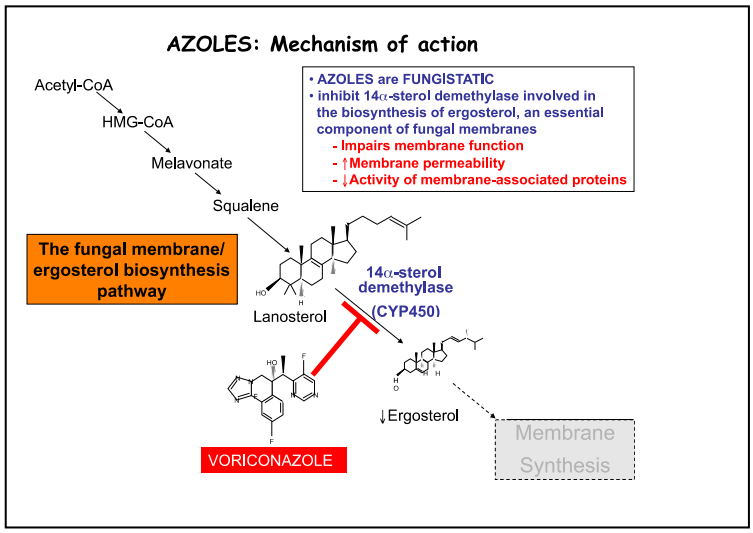
Imidazoles Ketoconazole (Oral, systemic fungal infections)
Clotrimazole, miconazole (Topical, superficial fungal infections)

Triazoles Fluconazole (Oral, systemic fungal infections)
Itraconazole (Oral, systemic fungal infections)
Voriconazole (Oral, systemic fungal infections)
Posaconazole (Oral, systemic fungal infections)

Mechanism of action

a) Azoles are primarily fungistatic

b) All azoles inhibit the enzyme 14a-sterol demethylase, a fungal CYP450 enzyme involved in the conversion of lanesterol into ergosterol



Results in ↓ergosterol and ↑14α-methylsterol content of fungal membranes, which affects the biophysical structure of the phospholipids bilayer causing increased membrane permeability and reduced activity of critical membrane-associated proteins such as those involved in electron transport.

Spectrum of activity

Each specific drug exhibits a unique spectrum of activity, although all exhibit activity against most Candida species and Cryptoccoccus neoformans.

Common Adverse effects of Azole antifungals

a) GI distress,
b) Hepatotoxicity –requires hepatic enzyme monitoring
c) Should not be used in pregnancy

Azole-drug interactions

a) All azoles are either substrates or inhibitors of CYP450 enzymes. Therefore many potential drug interactions

	Ketoconazole	Fluconazole	Itraconazole	Voriconazole	Posaconazole
MOA	Inhibition of 14α-sterol demethylaseinvolved in the synthesis of ergosterol, an essential component of fungal membranes				
Spectrum of Activity	*Dermatophytes* *Candida sp* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces*	*Dermatophytes* *Candida sp* *C. Glabrata (+/-);C.krusei (-)* *Cryptococcus* *Coccidioides* *Histoplasma (+/-)* *Blastomyces (+/-)*	*Dermatophytes* *Candida sp* *C. glabrata (+/-)/C.krusei (+/-)* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces* *Pseudoallerischeri Boydii/Scedosporium (+/-)* *Aspergillus* (+)	*Dermatophytes* *Candida sp* *Inc C. glabrata/C.krusei* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces* *Pseudoallerischeri Boydii/Scedosporium* *Aspergillus (+++)* *Fusarium*	*Dermatophytes* *Candida sp* *Inc C. glabrata/C.kruseii* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces* *Pseudoallerischeri Boydii/Scedosporium* *Aspergillus (+++)* *Fusarium* *Mucor*
CSF Penetration	No	**YES**	No	**YES**	No
Renal Dose Adjustment	No	**YES**	No	No	No
Drug interactions	**+++++**	**++**	**+++**	**+++**	**+++**
Adverse Effects	**Endocrine effects**	Minor adv effects Alopecia	**Hypertension/Hypokalemia/ Peripheral edema** **Contraindicated in Ventricular Dysfunction/CHF**	Photosensitivity/ Rash/Periostitis/ **Visual changes/ Hallucination/ Seizures**	Well tolerated
Clinical Uses	Largely replaced by itraconazole Cheap 2nd line agent Mucocutaneous Candidiasis/ Dermatophytes	Candida **TOC: Cryptococcal meningitis** **DOC: Coccidioidal meningitis**	TOC: Dermatophytes TOC: Onchomycosis Non-meningeal Blastomyces/Histoplasma/ Coccidioides **NOT FOR Cryptococcal meningitis**	**TOC: Invasive Apsergillus/Fusarium** Treatment of Pseudoallerischeri boydii	**Treatment of invasive Fungal infections Candida/Aspergillus** Antifungal prophylaxis in neutropenia **Salvage therapy for mucormycosis**

SPECIFIC AZOLE ANTIFUNGAL AGENTS

C1. KETOCONAZOLE (Prototype)

Overview

a) 1st oral azole antifungal introduced (also available as topical formulation)

b) Broad spectrum of activity includes: *Candida, Coccidioides, C. neoformans*, *H. capsulatum, B. dermatitids and dermatophytes*

c) However, poor PK and Adverse effect profile limit its clinical use
- Oral ketoconazole requires acidic environment for absorption
- drug penetrates poorly into CSF and urine

d) Many adverse effects due to inhibition of mammalian CYP450 enzymes involved in adrenal and gonadal steroid synthesis-
- ↓cortisol and ↓testosterone
- gynecomastia, ↓libido, impotence,
- menstrual irregularties,
- Orthostatic hypotension & fatigue

e) Many drug interactions due to inhibition of CYP450 enzymes

f) Oral ketoconazole now largely replaced by itraconazole (broader spectrum, greater potency, fewer adverse effects)

g) Topical ketoconazole used to treat common dermatophyte infections

C2. FLUCONAZOLE

Overview

a) Available as ORAL or IV
b) Well absorbed
c) Cheap, well-tolerated, high therapeutic index
d) Excellent penetration into CSF
e) Fewest drug interactions of all azoles
f) >80% of drug eliminated unchanged in the urine
    - Dosage adjustment required in renal insufficiency

Spectrum of activity and Clinical Uses:

a) Equivalent to Ampho B for Candida albicans
b) Antifungal agent most commonly used for mucocutaneous candidiasis
c) Poor activity towards C. glabrata and no activity towards C.krusei
d) Treatment of choice for Cryptococcal meningitis (Ampho B induction and maintenance therapy)
e) Drug of choice for Coccoidioidial meningitis (good CSF penetration/less morbidity than intrathecal Ampho B)
f) Limited activity against dermatophytes
g) Limited activity against endemic fungi (EXCEPT Coccidoidies)
    i.e. limited activity against Histoplasmosis, Blastamycosis, Sporotrichosis
    less potent than itraconazole
    Can be used if itraconazole contraindicated, although high dose required
h) NOT EFFECTIVE for treatment of: Aspergillosis or Zygomycosis/Mucormycosis

Adverse effects

a) Well tolerated with only minor adverse effects
    - nausea, headache, skin rash, GI
    - Alopecia (reversible) has been associated with long duration high dose therapy

C3. ITRACONAZOLE

Overview

a) Oral solution/Capsules- requires acidic environment for absorption
b) Broader spectrum of activity than fluconazole
c) Has now largely replaced ketoconazole
d) Long half-life/once daily dosing
e) Extensively metabolized in the liver/inactive metabolites eliminated in urine/feces
f) Poor penetration of CSF and the eye
g) Strong inhibitor of CYP3A4 – many drug interactions

Spectrum of activity and Clinical Uses:

a) Treatment of choice for dermatophytes/onchomycosis
b) Preferred agent for non-meningeal Blastomyces, Histoplasmisis, Sporothrix and Coccidioidomycosis
c) Active against Ampho B-resistant *Pseudallerischeriasis*
d) Effective against *Candida*, although more side effects than fluconazole
e) Active against *Aspergillus*, although less effective than Voriconazole (DOC)
f) Not recommended as maintenance/salvage therapy of Cryptococcal meningitis due to poor penetration of CSF and frequent relapse
g) NOT ACTIVE against either Fusarium or Mucor

Adverse Effects

a) Typical Azole Adverse effects: GI distress, hepatotoxicity
b) Should not be used in pregnancy
c) Itraconazole-specific effects:
    - Triad of hypertension, hypokalemia and peripheral edem
    - Can cause congestive heart failure in patients with ventricular dysfunction
    - Should not be used for the treatment of simple fungal infections in patients with a history of ventricular dysfunction or CHF

C4. VORICONAZOLE

Overview

a) Newer Azole
b) Extended spectrum anti-fungal
c) Oral and IV formulations
d) Absorption inhibited by fatty meal
e) Well absorbed, broadly distributes into tissues including CSF
f) Inhibitor of CYP 2C19, 2C9 and 3A4- many drug interactions
g) Less toxic than Ampho B
h) Undergoes extensive hepatic metbolism- no active metabolites
i) <2% excreted in urine unchanged No need for dosage reduction in renal insufficiency
j) Exhibits non-linear metabolism 50% increase in dose can result in 150% increase in serum concentration (important since some adverse effects are dose dependent)

Spectrum of activity and Clinical Uses:

a) Similar to Itraconazole in spectrum
b) Excellent activity against Candida sp. including fluconazole-resistant C. glabrata and C. krusei
c) Good activity against dimorphic fungi:
    Blastomyces, Histoplasmosis, Coccidioides & Paracoccidioides
d) Enanced activity against Apergillus and Fusarium
e) Treatment of choice for invasive *Aspergillus* (less toxic than Ampho B)
f) Treatment of Pseudoallescheria boydii
g) NOT ACTIVE against Mucor

Adverse Effects

a) Generally well tolerated- Occasional GI distress and Hepatoxicity
b) Tetratogenic and should not be used in pregnancy
c) Unique side effects

Minor

(i) Periostitis (Bone Pain) – inflammation of the periosteum
(ii) Transient vision changes (Visual blurring/changes in color vision)
    Affects ~ 30% of patients
    Occurs within 30 mins of dose/lasts 30-60 mins
    Observed after first dose- symptoms diminish with time
(iii) Photosensitivity/Rash- rarely Steven's Johnson's Syndrome

More Serious (Associated with high serum concentration > 5.5 mcg/ml))

(i) Visual/Auditory hallucinations

(ii) Seizures

C5. POSACONAZOLE

Overview

a) Newest Azole
b) Broadest spectrum of azole family
c) Oral formulation only (lack of IV formulation limits use in severely ill patients)
d) Requires acidity for absorption
e) Readily distributes to tissues, but POOR penetration of CSF and urine
f) Unchanged drug eliminated in the feces – not necessary to reduce dosage in renal insufficiency
g) Inhibitor of CYP3A4 therefore many potential drug interactions

Spectrum of activity and Clinical Uses:

a) Broadest spectrum of azole family similar to voriconazole
b) Primarily used in treatment and prophylaxis of invasive fungal infections (e.g. Candida/Aspergillus)
c) Used for antifungal prophylaxis in patients with:
   - prolonged neutropenia due to chemotherapy
   - severe Graft-versus-host-disease
d) ONLY azole active against Zygomycosis/Mucormycosis (used as a salvage agent)

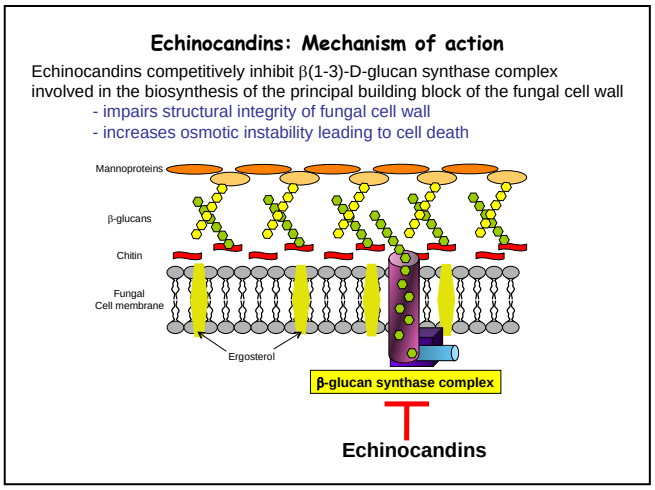
Adverse Effects

a) Good safety profile
b) Nausea, vomiting, diarrhea- most common
c) Fetal abnormalities- Not to be used in pregnancy

D. ECHINOCANDINS: Caspofungin, Micafungin & Anidulafungin

Overview

a) Newest class of antifungal agents
b) First agents to target the fungal cell wall
c) Large lipopetides/Poor oral availability
d) Must be administered IV
e) Long half-lives
f) Poor penetration of CSF
g) Very expensive compared to other agents
h) Echinocandins are not significant substrates or inhibitors of CYP450 therefore few drug interaction



Mechanism of Action

a) Echinocandins non-competitively inhibit β(1-3)-D-glucan synthase complex involved in the synthesis of β(1-3) glucan- the principal building block of the fungal cell wall.

b) Inhibiting glucan synthesis impairs structural integrity of the cell wall resulting in osmotic instability and cell death.

Spectrum of activity and Clinical Uses:
a) *Candida sp* (Fungicidal) including *C. glabrata* and *C. krusei*
- Frequently used as first line treatment for invasive Candida
(especially critically ill/neutropenic patients)
- Major advantage fungicidal with minimal associated adverse effects

b) *Aspergillus sp.* (Fungistatic)
- Salvage therapy for invasive *Aspergillus* infections that fail Ampho B treatment

c) NO SIGNIFICANT ACTIVITY towards *Cryptococcus* or dimorphic fungi

Adverse effects
a) Well tolerated, few adverse effects, safest antifungals available
b) Histamine-like effects (skin itching) with rapid infusion

II Systemic antifungal drugs for cutaneous fungal infections

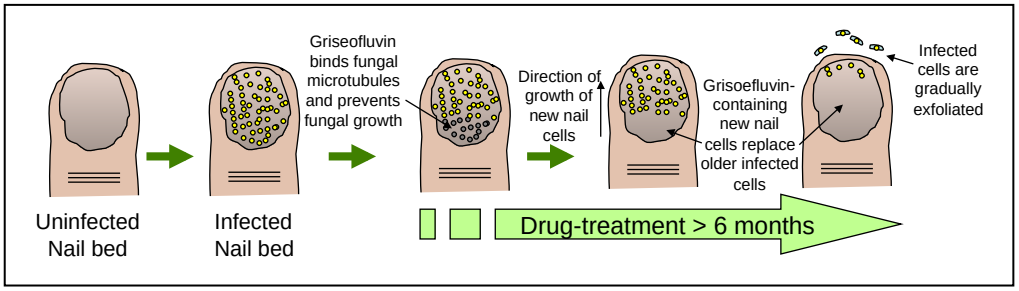
For treatment of superficial skin and nail infections with dermatophytes:
Microsporum, Epidermophyton & Trichophyton
Tinea pedis (foot)
Tinea cruris (groin)
Tinea corpora (body)
Tinea captis (scalp)
Onchomycosis (nail)

II. E. GRISEOFULVIN (ORAL)

Overview
a) Very insoluble fungistatic drug
b) Administered in a microcrystalline form
c) Absorption is improved with a fatty meal
d) Only used for mycotics infection of the skin, nails and hair due to Microsporum, Epidermophyton & Trichophyton
e) No activity against other fungi
f) Therapeutic use is limited by the availability of topical/oral antifungal agents with fewer side effects
g) Now largely replaced by terbinafine for treatment of onchomycosis

Mechanism of Action

a) The drug is fungistatic and binds to fungal tubulin thereby inhibiting fungal microtubule function, preventing the formation of the mitotic spindle and blocking fungal mitosis
b) Griseofulvin accumulates in keratin-producing precursor cells when these cells first differentiate and binds tightly to keratin making these newly differentiated cells resistant to fungal infection
c) This allows the new growth of hair, nails and skin to be free of dermatophyte infection



d) Infected skin, nail and hair cells are gradually exfoliated and replaced by uninfected new cells
e) Successful treatment with Griseofulvin typically requires longterm treatment (nails- 6-12 months; skin, 2-6 weeks)

Adverse effects
a) A large number of adverse effects, although serious side effects are rare

(i) Headache common
(ii) Nervous system- lethargy, vertigo, blurred vision
(iii) Hepatotoxicity (rare)
(iv) Augments effects of alcohol
(v) Leukopenia, neutropenia and monocytosis have been reported
(vi) Skin- urticaria, photosensitivity, rash and skin eruptions
(vii) Should not be taken during pregnancy due to fetal abnormalities

Drug Interactions
Griseofulvin induces hepatic CYP450 enzymes – can increase the metabolism of certain drugs e.g. warfarin and oral contraceptives

II.F. TERBINAFINE (ORAL)

Overview
a) An Allylamine antifungal agent
b) Low oral bioavailability due to significant 1st pass effect
c) Deposits in skin, nails, hair and fat
d) Long half-life (200-400 hrs)
e) Extensively hepatically metabolized and renally-excreted- not recommended for patients with hepatic/renal insufficiency

Spectrum of activity and Clinical use
a) Limited to dermatophytes and *Candida albicans*

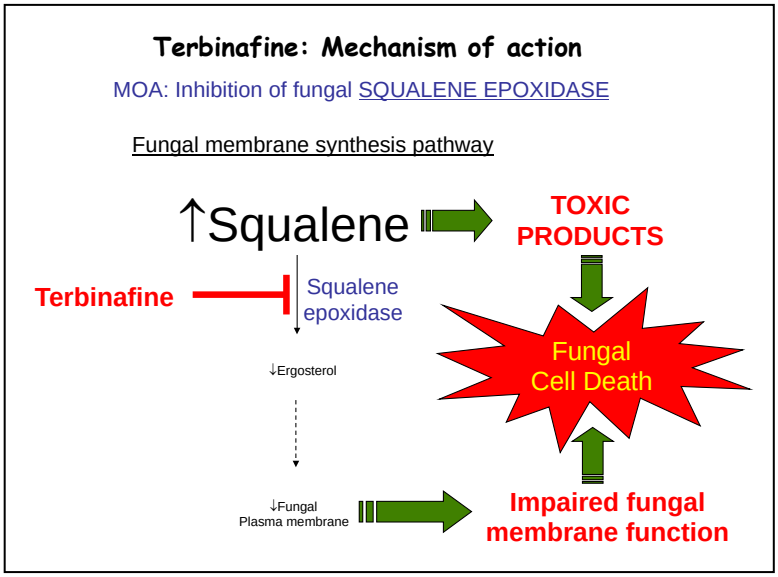
b) Used in the treatment of tinea captis, tinea corpis, tinea cruris, tinea pedis and Onchomycosis
c) Cure rate is ~90%- more effective then either griseofulvin or itraconazole

Mechanism of action

a) The drug is fungicidal
b) It inhibits fungal squalene epoxidase, an enzyme involved in the synthesis of ergosterol

- decreased ergosterol synthesis impairs fungal membrane function

- Causes accumulation of squalene, which is toxic resulting in fungal cell death



Adverse effects

a) Well tolerated
b) Low incidence of GI distress, headache or rash
c) Rarely terbinafine may cause hepatotocity, neutropenia or Stevens-Johnson syndrome
d) Few significant drug interactions

III Topical antifungal drugs for cutaneous fungal infections

III.G. NYSTATIN

a) Similar structure and mechanism of action to Ampho B
b) Too toxic for IV administration
c) Available in gels, creams ointments and suppositories
d) Not significantly absorbed from skin, mucus membranes or GI tract
   - little toxicity when given topically
e) Used for the treatment of oral Candidiasis (swish and swallow)
   - drug is not absorbed and is quantitatively excreted in the feces
f) Not effective against dermatophytes
g) Few adverse effects as drug is not absorbed

III.H. TOPICAL AZOLES: Clotrimazole, Miconazole and Terconazole

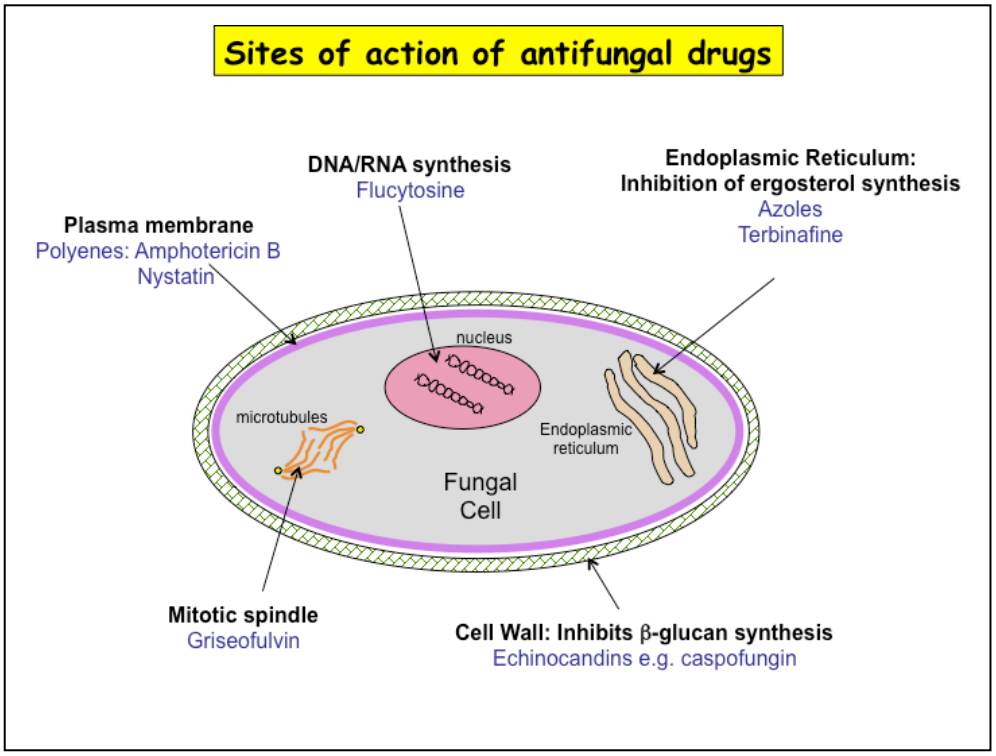
a) Available as creams, lozenges and suppositories
b) Clinical uses: Oral and Vulvovaginal candidiasis & Dermatophyte infections
c) Absorption negligible- Adverse effects rare

III.I TOPICAL ALLYAMINES AND BENZYLAMINES

Allylamines: Terbinafine & Naftifine
Benzylamines: Butenafine

a) All drugs act to inhibit squalene epoxidase and are fungicidal
b) Spectrum of activity limited to *Candida albicans* and dermatophytes
c) Used in the treatment of Tinea cruris, Tinea corporis and Tinea pedis

SUMMARY MATERIAL



Summary of major antifungal drug classes

	Indications	MOA	Adverse Effects	Misc.
Amph B	• Broad Spectrum • All life-threatening mycotic infections Candida, Cryptococcus Histoplasma, Blastomyces, Coccidioides, Aspergilus, Fusarium, Mucor **Not *C. lusitaniae*** **Not *Pseudallerischeri boydii*** • TOC Mucormycosis	Binds to ergosterol in fungal plasma membrane and forms pores causing increased membrane permeability and loss of cytoplasmic K+	Infusion related (Ampho-terrible) Fever, Chills, spasms, vomiting Cumulative Nephrotoxicity/Hepatoxicity/Anemia	• **Only Antifungal drug approved for use in pregnancy** • **Used for initial induction therapy followed by consolidation therapy with less toxic Azole**
Flucytosine	• Narrow spectrum *Cryptococcus neoformans* -especially cryptococcal meningitis *Candida sp* Agents of chromblastomycosis	Taken up via cytosine permease and converted by fungal-specific cytosine deaminase to 5-FU analogs that inhibit thymidylate synthase and RNA synthesis	• GI (frequent) nausea/vomiting/diarrhea • BM toxicity- more common in those with blood disorder • Tetratogenic	• **Good CSF penetration** • **Used in combination with Amph B** • Frequent resistance • Dosage adjustment in Renal failure • Not to be used in pregnancy
Echinocandins Caspofungin Micafungin Anidulafungin	• *Candida* inc *C. glabrata/C. kruseii* • Treatment of invasive *Candida* • Treatment of Invasive *Aspergillus* • No activity for Cryptococcus or Dimorphic fungi	• Acts on fungal cell wall • Inhibits β(1-3) D glucan synthase complex - Impairs membrane structure - Increases osmotic instability	• Well tolerated • Histamine-like effect with Rapid infusion	• Poor CSF penetration • Not to be used in pregnancy
Griseofulvin	• Treatment of mycotic infections of Skin, nail and hair due to dermatophytes	• Fungistatic • Binds fungal microtubules and inhibits mitotic spindle • Accumulates in newly differentiated Keratin producing cells preventing fungal growth	• Many adverse effects - Headache, lethargy, vertigo, blurred vision - Urticuria, photosensitivity, rash - Hepatotoxicity - Leukopenia, neutropenia, monocytosis - Fetal abnormalities	• Very insoluble • Strong CYP450 inducer - many drug interactions • Not to be used during pregnancy
Terbinafine	Treatment of onchomycosis and superficial skin infections • *Candida Albicans* • *Dermatophytes* Treatment of *tinea captis, tinea carpis, tinea cruis & tinea pedis*	Inhibits fungal squalene epoxidase resulting in formation of toxic products and inhibition of ergosterol synthesis	• Well tolerated • Adverse effects rare Hepatotoxicity neutropenia Stevens Johnson	• Long half life (> 200 hrs) • Not recommended in hepatic/renal insufficiency

	Ketoconazole	Fluconazole	Itraconazole	Voriconazole	Posaconazole
MOA	Inhibition of 14α-sterol demethylaseinvolved in the synthesis of ergosterol, an essential component of fungal membranes				
Spectrum of Activity	*Dermatophytes* *Candida sp* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces*	*Dermatophytes* *Candida sp* *C. Glabrata (+/-);C.krusei (-)* *Cryptococcus* *Coccidioides* *Histoplasma (+/-)* *Blastomyces (+/-)*	*Dermatophytes* *Candida sp* *C. glabrata (+/-)/C.krusei (+/-)* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces* *Pseudoallerischeri Boydii/Scedosporium (+/-)* *Aspergillus* (+)	*Dermatophytes* *Candida sp* *Inc C. glabrata/C.krusei* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces* *Pseudoallerischeri Boydii/Scedosporium* *Aspergillus* *(+++)* *Fusarium*	*Dermatophytes* *Candida sp* *Inc C. glabrata/C.kruseii* *Cryptococcus* *Coccidioides* *Histoplasma* *Blastomyces* *Pseudoallerischeri Boydii/Scedosporium* *Aspergillus* *(+++)* *Fusarium* *Mucor*
CSF Penetration	No	**YES**	No	**YES**	No
Renal Dose Adjustment	No	**YES**	No	No	No
Drug interactions	+++++	**++**	+++	+++	+++
Adverse Effects	**Endocrine effects**	Minor adv effects Alopecia	**Hypertension/Hypokalemia/ Peripheral edema** **Contraindicated in Ventricular Dysfunction/CHF**	Photosensitivity/ Rash/Periostitis/ **Visual changes/ Hallucination/ Seizures**	Well tolerated
Clinical Uses	Largely replaced by itraconazole Cheap 2nd line agent Mucocutaneous Candidiasis/ Dermatophytes	Candida **TOC: Cryptococcal meningitis** **DOC: Coccidioidal meningitis**	Dermatophytes Onchomycosis Non-meningeal Blastomyces/Histoplasma/ Coccidioides **NOT FOR Cryptococcal meningitis**	**TOC: Invasive Apsergillus/Fusarium** Treatment of Pseudoallerischeri boydii	**Treatment of invasive Fungal infections Candida/Aspergillus** Antifungal prophylaxis in neutropenia **Salvage therapy for mucormycosis**

Summary of Spectrum of activity of Antifungal agents for Systemic Infections

Organism	Antifungal agent						
			AZOLES				
	AmB	Flucytosine	Flu	Itra	Vori	Pos	Echocandins
Candida sp	+	+	+	+	+	+	+
C. glabrata	+	+	+/-	+/-	+	+	+
C.krusei	+	+/-	-	+/-	+	+	+
C. lusitaniae	-	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	+	+	-
Coccidioides sp	+	-	+	+	+	+	-
Blastomyces sp	+	-	+/-	+	+	+	-
Histoplasma sp	+	-	+/-	+	+	+	-
Aspergillus sp	+	-	-	+	+	+	+
Fusarium sp	+	-	-	-	+	+	-
Pseudallerischeri boydii/ Scedosporium apiospermum	-	-	-	+/-	+	+	-
Zygomyces/Mucor	+	-	-	-	-	+	-

Treatment of Dermatophyte infections and Onchomycosis

Tinea captis (ringworm of the scalp)	Oral Griseofulvin (long safety history) Oral Terbinafine Oral fluconazole/Itraconazole Note: Topical antifungals are ineffective
Tinea pedis **Tinea corporis** **Tinea cruris**	Topical antifungals e.g. AZOLES or Terbinafine **NOT NYSTATIN** (not active against dermatophytes)
Chronic/extensive disease **Immunocompromized patient**	Oral terbinafine/Itraconazole/fluconazole
Onchomycosis	Oral terbinafine or Itraconazole 2nd line: Oral fluconazole or griseofluvin Note: Topical antifungals are ineffective

Fungal Disease	Type	Recommended treatment
Endemic Mycoses Histoplasmosis Blastomycosis Coccidioidmycosis	Mild/moderate	An Azole-e.g. Itraconazole (preferred)
	Severely ill/ disseminated	Amph B (induction) An Azole (consolidation/maintenance)
		Note: Fluconazole can be used to treat Coccidioidmycosis and is DOC for Disseminated disease/meningitis
Candidiasis	Mucocutaneous Oral/vaginal/rash	Initially a topical Agent: Nystatin or an azole OR oral Fluconazole if topical treatment is unsuccessful
	Mild/moderate	Fluconazole OR another Azole
	Severe disease	Amph B OR an Azole OR an Echinocandin
	Meningitis	Amph B +/- Flucytosine (induction) Fluconazole (consolidation/maintenance) NOT AN ECHINOCANDIN- poor CNS penetration
Cryptococcosis	Pulmonary/skin	Fluconazole OR Amph B
	Meningitis	Amph B +/- Flucytosine (induction) Fluconazole (consolidation/maintenance)
Aspergillosis	Pulmonary/skin	Itraconazole
	Invasive	Voriconazole OR Amph B Itraconazole- maintenance/Alt. agent Echinocandins/posaconazole- salvage
Mucormycosis		Amph B OR Posaconazole (salvage)
Fusariosis		Amph B OR Voriconazole/Posaconazole (salvage)