1st semester Lectures

سلام ..

هذي الملزمة اجتهاد شخصي

عبارة عن تجميعه لأهم الأدوية بالترم الأول +أسئلة الميد تيرم

اتمنى تكون مفيدة واتمنى ما تطلع الأسئلة منها :)

والقروب يخلي مسؤوليته في حالة خروج أي سؤال عن الملزمة ☺

1) Mid year pharma exam 2007-2008
2) Immunosuppressive drugs
3) Anti- amebic drugs
4) Anti-viraldrugs
5) Anti-fungal drugs
6) Cancer chemotherapy
7) Anti-helminthic drugs
8) Antileshmaniasis
9) Anti-malaria drugs (last version)
10) Antischistosomiasis drugs

Ur SiStErs:

425 Pharma Girls

هذا اللي قدرت أتذكره من الأسئلة أتمنى تكون مفيدة وطبعاً فيه بنات ساعدوني الله يجزاهم خير

و عَ حسب معلوماتي الاختبار كان 40 سؤال

3 ماتش

17 صح وخطأ

20 mcq

Match

1- AE of Anti-malarial drugs :

chloroquine retinopathy
quinine cinchonism
primaquine methaemoglobinemia
mefloquine psychiatric disorders

proguanil ☒

2- according to mechanism of action :
inhibit cell wall synthesis ceftriaxone
inhibit ptn. synthesis via binding to 50s ribosomal subunit clindamycine
inhibit ptn. synthesis via binding to 30s ribosomal subunit doxycycline
inhibit topoisomerase 2 (DNA gyrase) & topopisomerase 4 ciprofloxacine

Sulphonamides→ ☒

3- AE of immunosuppressant :

cyclosporin --- hirsutism
tacrolimus --- hyperglycemia
corticosteroids--- osteoprosis
ATG--- anaphylactic reaction
azathioprine

True & False

1- drugs used in Rx. of HBV infection :
a- alpha interferon (T)
b- amantidine (F)
c- didanosine (F)
d- lamivudine (T)

2- Ribavirin :
a- inhibit viral mRNA (T)
b-effective as monotherapy for Rx. of HCV infec. (F)
c- lead to hemolysis (T)
d- is # in pts. with heart dis. (T)

3- grisofulvin:
a- is fungicidal (F)
b- absorption is increased with fatty meal (T)
c- is enz. inhibitor (F)
d- selectively taken by newely synthesied skin (T)

4-amphotericin B:
a- is not effective for fungal infec. of GIT (F)
b- is the drug of choice for all life threatening mycotic infections (T)
c- it can not be used topically (F)

5- as compared with vinblastin , vincristine is :
a- less myelosuppressant (T)
b- cause constipation (T)
c- can not be given orally (T)
d- cause peripheral neuropathy (T)

6- bleomycine :
a- cause breaking of DNA strand (T)
b- given orally (F)
c- used for Rx. of hodgkin's lymphoma (T)
d- lead to pulmonary fibrosis (T)

7- metronidazole :
a- act on trophozoites & cyst (F)
b- can laed to disulfiram like effects if it's taken with alcohol (T)
c- potentiate anticoagulant effect of warfarin (T)

8- emetine & dehydroemetine :
a- given Iv (F)
b- depress cardiac contraction & conduction (T)

9- cyclosporine:
a- given orally (T)
b- lead to HTN (T)
c- phenytoin lead to decrease its clearance (F)

10- drugs for schistosomiasis :
a- metrifonate (T)
b- oxamniquine (T)

11- sodium stibogluconate :
a- not absorbed orally (T)
b- used in cutaneous & visceral leishmaniasis (T)
c- lead to arrhythmia (T)
d- renal & hepatic fun. are affected (T)

12- pentamidine :
a- not absorbed oraly (T)
b- lead to hypoglycemia (T)
c- used in visceral & cutaneous leishmaniasis (T)
d- causes irreversible renal insufficiency (F)

13- primaquine :
a- has gametocidal action aganist the 4 malaria species (T)
b- has no effect aganist erythrocytic stage (T)

14- pyrimethamine :
a- inhibit plasmodial DHF reductase thus inhibit folate syn. required for purine & pyrimidine syn. (T)
b- slow acting blood schizontocides (T)
c- resisrance is found worldwide(T)
d- can be combinated with sulfodoxine (T)/

15- ciprofloxacine can be used for Rx. of :
a- syphilis (F)
b- UTI caused by multidrug resistance organisms (T)
c- soft tissue , bone , joints , intra abdominal infec. (T)
d- TB (T)
e- Legoneusis (T)

16- pyrazinamide :
hepatotoxic (T)
is a prodrug (T)
Effective as mono therapy (F)
Poorly adsorbed from GIT . (F)

Best answer

1- AE of ketokonazole all true EXCEPT :
a- menstrual irregularity
b- kidney damage
c- gynecomastia
d- hepatotoxic

2- polyene antifunal drugs act via :
a- inhibtion of human cytochrome p450
b- binding to ergosterol & alter permeability of cell memb. leading to leakage of intracellular ions

3- Methotrexate all true EXCEPT:
a- inhibit folate syn. through inhibtion of dihydrofolate reductase enz.
b- can lead to renal damage
c- it's heamatological effects can be reversed by leucovorin
d- is s phase specific

4- amoxicillin :
a- used in Rx. of shigellosis
b- penicillinase resistant
c- it's absorption is better than ampicillin

5- AE of cidofovir :
a- metabolic alkalosis
b- nephrotoxic
c- hepatotoxic
d- increase IOP

6- cephaclor used in Rx. of all the following EXCEPT:
a- meningitis
7- clarithromycin :
a- destroyed by stomach acidity
b- effective aganist atypical mycobacterial infec.

8- which one of the following used for Rx. of chloroquine resistant P.falciparum :
a- mefloquine

9- which one of the following antiviral drugs may lead to pancreatitis :
a- didanosine

10- luminal amebicides all true EXCEPT:
a- iodoquinol
b- chloroquine
c- diloxanide furoate
d- paromomycin

11- which one of the following can be used for Rx. of ambeic liver abscess :
a- metronidazole

12- which one of the following immunosuppressant drugs inhibit IL2 production :
a- tacrolimus

13- sirolimus act via :
a- binding to FK-binding ptn., then binds to mTOR leading to blocking response of Tcell to cytolines

14- regarding the mebendazole all true EXCEPT:
a- more safer than albendazole
b- do not preclude fasting
c- has no activity aganist hook worm

15- ivermectin is the drug of choice for all the following EXCEPT:
a- strongyloids
b- cutaneous larva migrans
c- filariasis
d- ascaris

16- praziquantel all true EXCEPT:
a- its bioavailability increased by phenytoin
b- act via increases cell memb. permeability to ca resulting in paralysis
c- not safe for pregnancy
d- its clearance is reduced in case of liver impairment

17- neomycine :
a- used topically for bacterial eye infection

18- clofazimine all true EXCEPT:
a- has brode spectrum antibacterial activity
b- stored in skeletal muscles
c- used for Rx. of dapson resistant bacilli

Done by :
أشجان الحجي
نشكر كل من ساعد في جمع الاسئلة ،،
ونخص بالشكر نجود العمري ☺

❶ Immunosuppressive drugs

◎ مهم جداً : معرفة كل دوا تبع أي قروب ☺

Immunosuppressive drugs:

1- IL_2 cytokine inhibitors:
a)**calcineurine** inhibitors :
- cyclosporine (CSA).
- Tacrolimus (TAC)

b) **sirolimus** (rapamycine).

2-gene expression inhibitors:
corticosteroids

3-cytotoxic drugs :
Cyclophosphamide
Methotrexete
Also used as anticancer drugs .

4- purine & pyrimidine synthesis inhibitors :
- **Azathioprine**
- **Myclopheolate mofetil.**
- **Lefunomide**

5-Ab blocks T-cell surface molecule involved in signaling immune reaction :
- **A**nti**l**ymphocyte globulins (ALG).
- **A**nti**th**ymocyte globulins(ATG).
- **Rh_0** (D) immunoglobulin
- **Basiximab** & **Daclizumab. (**IL_2 receptor antagonist).
- Muromonab –CD_3

N.B: ((mab)) suffex means :- monoclonal antibody.
The letters ((Zu)) mean humanized Ab , ((Xi)) mean chimerized Ab

6- interferon.

7-thamlidomide (sedative drug)

⇒ By using the genetic engineering, most murine amino acids of Muromonab have been replaced by human ones; producing monoclonal antibody designated humanized (e.g. Daclizumab; Transtuzumab). While the chimeric (Mixed) antibodies contain XI in their name (e.g. Abciximab; Infliximab; Rutuximab

Other Classification of Immunosuppressant (Based on Mechanism of Action)

A) Antiprolifirative Agents

1) Selective Inhibitors of Cytokine production and function (Antibiotics) (e.g. Cyclosporine; Tacrolimus; Sirolimus).

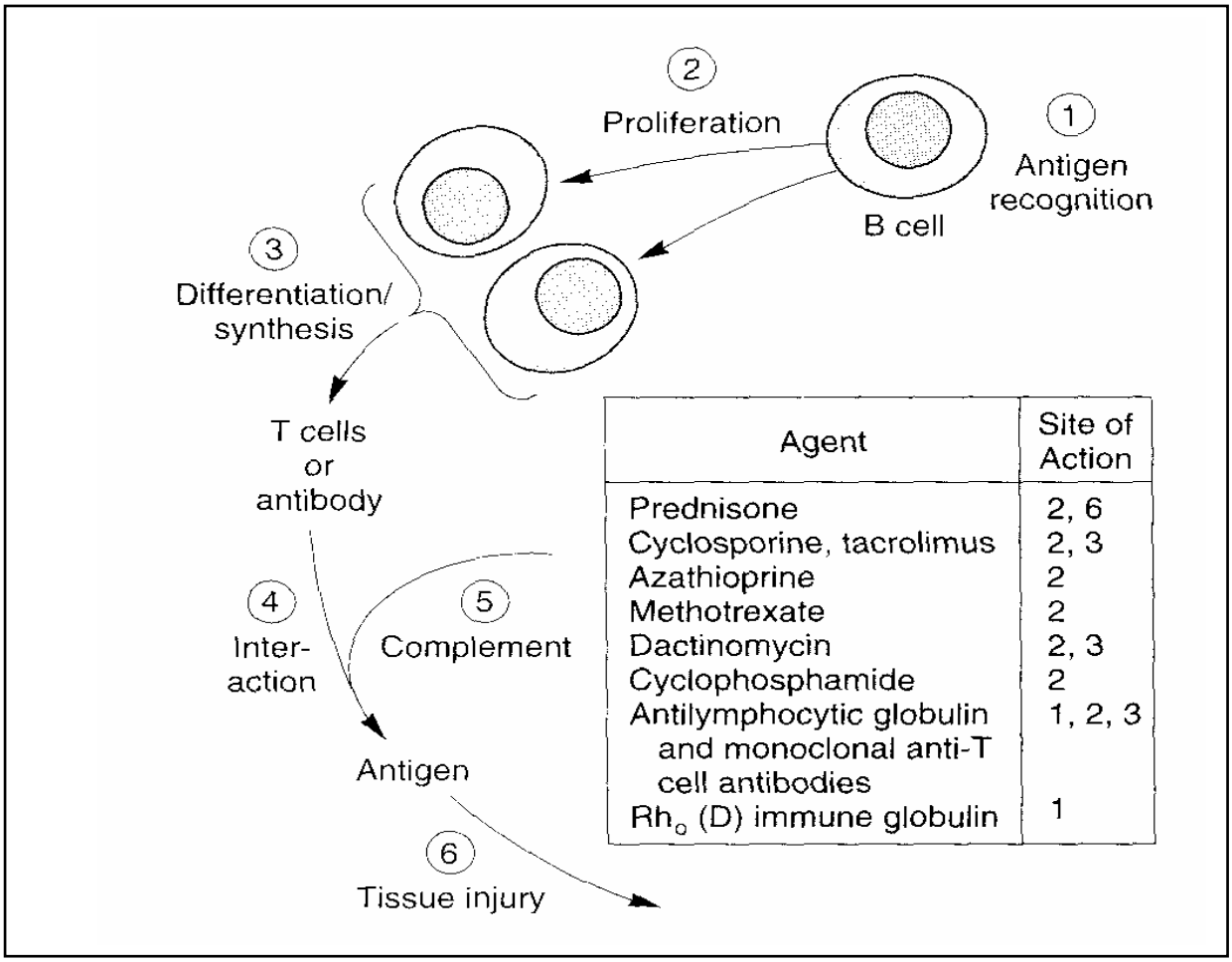
2) Antimetabolites (Azathioprine; Mycophenolate Mofetil)

3) Alkylating Agents (Cyclophosphamide)

B) Lymphocyte Depletion Agents

1) Polyclonal Antibodies (Antilymphocyte Globulin)
2) Monoclonal Antibodies (e.g: Muromonab; Basiliximab; Daclizumab et al)

3) Corticosteroids



Agent	Site of Action
Prednisone	2, 6
Cyclosporine, tacrolimus	2, 3
Azathioprine	2
Methotrexate	2
Dactinomycin	2, 3
Cyclophosphamide	2
Antilymphocytic globulin and monoclonal anti-T cell antibodies	1, 2, 3
Rh_o (D) immune globulin	1

❖ IL_2 cytokine inhibitors

Cyclosporine (T&F , Mx)

- ✓ Peptide from soil fungus .(11 amino acid)

Mechanism of action :

- It inhibits proliferation and differentiation of T-cells by inhibiting IL_2 production .
- Cyclosporine will bind to cyclophillin (interacellular binding protein).. this complex will inhibit (calcinurin) calcinurin is aphosphate necessary for dephosphorilation of transcripting factor (nuclear factor of activated T-cell) promote synthesis of IL_2.

Pharmacokinetics :

- Orally or parenterally(I.V).
- Oral absorption is variable :
  - Gelatin capsule
  - Microemulsion → has higher bioavailability .
- Orally :
  - Slowly and incompletely absorbed
  - Peak levels are reached after 1-4 hrs
  - Elimination T½ = 24hrs.
  - **Its absorption is delayed by fatty meal** (gelatin capsule).
  - 50-60% accumulates in blood cells (erythrocytes, lymphocytes)
- Excreted through **biliary** rout mainly through **feces** and only 6% in urine .

Side effects : (dose dependent)

- Nephrotoxicity . (check drug –drug interaction please :))
- Hepatotoxicity (liver dysfunction)
- Hypertension
- Viral infections.
- Hyperkalemia.
- Lymphoma.
- Glucose intolerance (hyper glycemia).
- Anaphylactic reaction .
- Neurotoxicity (tremors).
- **Hirsutism** .(Mx)
- **Gingival hyperplasia , teratogenicity**

Indications **:**

- Prevents rejection of kidney, liver and cardiac allogenic transplants :
    - Alone or
    - Combined with corticosteroid
- Grafet –versus-host disease in BM transplant (lymphocyte response in the graft to host antigen .
- Autoimmune disorders (e.g: endogenous uveitis ,rheumatoid arthritis ,active …. disease , psoriasis , nephrotic syndrome ,severe corticosteroid –dependent asthma ,early type I DM

Drug interaction:

- ✓ **Additive nephrotoxicity**: other nephrotoxic drugs as
    - aminoglycosides,
    - amphotericin B,
    - NSAIDs: as
        - diclofenac,
        - naproxen and
        - sulindax.
- ✓ **Drugs that increase cyclosporine blood level** –enzyme inhibitors:
    - amidazole containing drugs e.g.cimetidine
    - ketoconazole
    - erythromycin
    - amphotracin B
    - ethinylestradiol (estrogen),
    - spironolactone,
    - allobarbitol.
    - Gentamycin
    - Grape freuit.
- ✓ **Drugs that <u>decrease cyclosporine blood level</u>** –enzyme inducers-:
    - chronic alcoholism
    - glucocorticoids
    - tobacco
    - rifampicin
    - phenobarbitone
    - <u>phenytoin</u>
    - carbenzepine.

Tacrolimus (Mx , MCQ)

(inhibit IL2 production)

- ✓ From fungal origin: mocrolides antibiotic, chemically not related to cyclosprin
- ✓ More potent than cyclosporine.
- ✓ Used with low doses of glucocorticoids.
- ✓ Used now for non-responding atopic dermatitis.

Mechanism of action:

- As cyclosporine (calcineurine antagonist),**EXEPT** it binds to different immunophillin **(FKBP).**

Pharmacokinetics:

- Taken **orally** or **intravenously** or **topically**.
- 10:100 more potent than cyclosporine.
- Oral absorption is variable and is decreased if taken with high fat or high carbohydrate meals.
- Metabolized in the liver by P450 (CYP3A4).
- T½ after I.V = 9-12 hrs.
- **Highly** bound by plasma .
- Excreted mainly in the **bile**.
- Few metabolites are excreted in urine.

Side effects:

- More nephrotoxic, neurotoxic (manifests as aphasia and seizures –dose dependent), and anaphylactoid reaction than cyclosporine , GI disturbance
- **Post-transplant insulin dependent diabetes mellitus** (Mx –hypoglycemia) is a problem.(metabolic disturbance) .
- Other side effects are like those of cyclosporine ***except*** it doesn't cause hirsutism or gingival hyperplasia.

Indications:

- Prevention of rejection of liver and kidney transplants and is given with glucocorticoids.
- It is better than cyclosporine as it decreases the episodes of rejection and lower doses of glucocorticoids can be used to reduce the likelihood of infections.
- It is used for **moderate** to **severe atopic dermatitis** that doesn't respond to conventional therapy.
- An alternative drug of choice for organ transplantation for women.***Why? (because it doesn't cause hirsutism)*** and it is an ointment for psoriasis.

Differences b/w CSA and TAC :-

i. TAC is 10-100 times more potent than CSA in inhibiting immune responses
ii. TAC is better than CSAas it decrease episodes of rejection and lower doses of glucocorticoids can be used to reduce the likelihood of infections.
iii. TAC is more nephro and neurotoxic.
iv. TAC doesn't cause hirsutism .

Sirolimus **(rapamycine)** (MCQ)

- ✓ From fungal source (soil mold).
- ✓ It was called rapamycin maclolides .
- ✓ As potent as cyclosporine .

Mechanism of action :

mTOR : serin-therionin kinase essential for cell cycle progression

- sirolimus and tacrolimus bind to the same cytoplasmic FK-binding protein but instead of forming a complex with calcineurin, sirolimus binds to mTOR (mammalian target of rapamycin) leading to block the progression of activated T-cells from G1 to S phase of the cell cycle and, consequently, the proliferation of these cells .
- As tacrolimus, but it **doesn't block IL production** by activated T-cell but instead **it blocks the response of T-cell to cytokines** .
- Potent inhibitor of **B-cell proliferation** and **immunoglobulin production** (humoral immunity).
- Inhibits **mononuclear cell proliferation** response to **colony stimulating factor** in mice .

Pharmacodynamics:

- ◈ **immunosuppressive** effect
- ◈ **Antiproliferative** effect .

Pharmacokinetics:

- Taken orally- **readily absorbed**- & topically
- Although it is readily absorbed, **high fat meals can decrease its absorption .**
- **Extensively** bound to plasma proteins (remain for 6 months after therapy).
- Metabolized by **CYP3A4** .
- Parent drug and its metabolites are eliminated **mainly** in **feces** –by bile- .

Indications :

- The antiproliferative action of sirolimus is used in cardiology (cardiac catheter stent to prevent stenosis) .
- As replacement of cyclosporine if transplanted patient developed cancer of skin or lips.

- ✓ **Preservation** of rejection of organ transplant alone or combined with CSA or SRL or glucocorticoids (combination with Cyclosporine and sirolimus is synergistic).
- ✓ **Hematopoietic stem cell** transplant recipients .
- ✓ **Topical** use for **dermatological disorders** (atopic dermatitis and psoriasis), with cyclosporine in the management of uveoretinitis .

☠Toxicity :

- ♣ Hyperlipidemia .(cholesterol & trigleceryl).
- ♣ Hepatoxicity .
- ♣ Diarrhea .
- ♣ Hypertension .
- ♣ Headache .
- ♣ Nausea .
- ♣ Thrombocytopenia

❖Inhibitors of cytokine gene expression

Corticosteroids (Mx)

- ✓ Prednisone
- ✓ Prednisolone
- ✓ Methylprednisolone.
- ✓ Dexamethasone .
- ✓ They have both antiinfection & immuno-supp effects .

Mechanism of action :-

- Inhibit the **synthesis & relase** of **inflammatory mediators** by binding to **Glucocorticoids receptors** & complex interacts with **DNA** to inhibit gene transcription of inflammatory gene
- **Decrease production of cytokines** IL1,IL2,interferon ,TNF & adhesion factors .
- **Decrease production of prostanoid** ,due to ↓ expression of cyclo-oxygenase-2
- **degeneration** of IgG ,NO & histamine
- **Inhibit antigen processing** by macrophages .
- **supressT-cell helper** function .
- **T-lymphocyte prolifération**
- **Stabilize lysosomal membrane** .

pharmacokinetics :-

- Orally or paranterally .
- Enter cells by diffusion .
- Metabolized **by liver** .

Pharmacodynamics :

- Suppression of response of infection .
- Suppression of endogenous Glococorticoid synthesis.
- Metabolic effects .

interaction :-

- ☒ solid organ allograft (prednisone & methylprednisolone)
- ☒ haematopoietic stem cell transplantation .
- ☒ autoimmune disease as refractory rheumatoid arthritis , systemic lupus erythematosus , asthma , (prednisone & methylprednisolone)
- ☒ orally prednisone is employed for the prophylaxis rejection .
- ☒ high dose I.V methyl is used as 1st line therapy for treatment of rejection .

💣adverse effects :

- ♣ <u>osteoprosis (Mx)</u>
- ♣ hypercholesterolemia.
- ♣ hyperglycemia .
- ♣ HTN.
- ♣ Cataract .

Antithymocyte globulins (Mx)

- ✓ ***Polyclonal*** prepared by immunization of rabbits or horses with human lymphoid cells.

Note: *humoral antibodies formation remains active.*

Mechanism of action:

- The antibodies bind to the surface of circulating T-lymphocytes.
- The antibodies-bound cells are phagocytosed in the liver and spleen → lymphopenia and impaired T-cells responses.

Indications:

- ✓ Combined with cyclosporine for bone marrow transplant
- ✓ Steroid resistance rejection .
- ✓ Hyperacute phase of allograft rejection. (initial allograft rejection .
- ✓ To prepare the recipient to the transplantation of bone marrow. (7 days prior to transplantation).

Pharmacokinetics:

- IM, IV infusion.
- $T_{1/2}$ = 3-9 days.

Side effects:

- Mainly result from the introduction of foreign proteins obtained from heterogeneous serum (Anaphylactic (Mx) and serum sickness reactions, Local pain and erythema at site of injection).
- Antigenicity .(Abs formed against ATG & ALG)
- Chill.
- Fever.
- Flue –like syndrome .
- Leucopenia.
- Thrombocytopenia.
- Infections and hypersensitivity.
- Lymphoma and cancer.

Methotrexate

- ✓ Folic acid antagonist that inhibit dihydrophalate reductase that interfere with DNA&RNA .
- ✓ Orally ,IV,IM .
- ✓ Execrated in urine
- ✓ Rheumatoid arthritis, psorisis .

Side effects :

- Bone marrow suppression .

جا عليه سؤال بس ما اذكر ايش بالضبط :/

❷Anti-Amebic drugs

Life cycle:

1. Cysts (infective):

- Can survive outside the human body
- Transform to trophozoites

2. Trophozoites (non-infective, invasive):

- Reproduce
- Invade wall of larg intestine, causing ulceration and may migrate to other tissues especially the liver.
- Transform to cyst which are excreted in faeces.

Presence of bacterial flora will help E.histolytica.

clinical presentation:

- Asymptomatic intestinal infection (carrier, passing cysts).
- Mild to moderate intestinal disease (non-dysentric colitis).
- Severe intestinal infection (dysentry).
- Hepatic abscess.
- Ameboma (localized granulomatous lesion of colon).
- Extraintestinal disease (other than hepayic abscess).

Anti-amebic drugs:

1.luminal amebicides:

- Act on the parasites in the lumen of the bowel.
- Should be used for treatment of asymptomatic amebiasis.
- After treatment of systemic or mixed amebiasis for complete eradication.
- Include: iodoquinol, diloxanide furoate, paromomycin.

2.tissue or systemic amebicides:

- Act principally in the intestinal wall and liver (or any other extraintestinal tissue).
- Used for treatment of systemic form of the disease (liver abscess or intestinal wall infection).
- Include: emetine, dehydroemetine, chloroquine(liver only).

3.mixed amebicides:

- Effective against both luminal and systemic form of the disease, although luminal concentration is too low for single drug treatment of luminal amebiasis.
- Include: metronidazole, tinidazole.

Metronidazole (T&F(1-4), MCQ)

Can be used for Rx of amebic liver abcess (MCQ)

- ✓ mixed amoebicide .
- ✓ drug of choice 4 intestinal& extra intestinal amoebiasis.
- ✓ acts on trophozoites 1
- ✓ has no effect on cysts . 2
- ✓ nitro group of metronidazole is reduced by protozoan leading to a reactive product that binds to DNA & proteins resulting into parasite death .

pharmacoKinetics:-

- G orally or IV .
- absorption is rapid & complete.
- Due to rapid absorption from GIT, less effective against parasites in ! lumen.
- wide distribution to all tissues & body fluids (CSF, saliva ,milk) .
- plasma protein binding is low (<20%).
- Plasma ½ life is 8hrs.
- metabolized in liver by mixed function oxidaes (drug-drug interaction).
- Excreted in urine as unchanged drug plus metabolites.
- clearance is ↓ in liver impairment

Clinical uses :-

- anaerobic infections .
- amobiasis
- giardiasis (giardia intistinalis).
- trichomoniasis(trichomonase vaginalis).
- broad spectrum of an aerobic bacteria eg:-
  - H pylori infection
  - pseudo membranous colitis (clostridium defficile) * drug of choice

Adverse effects :-

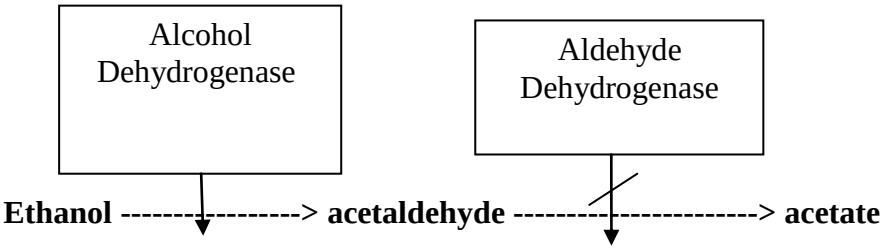
Tinidazol has better toxicity of profile than metronidazole, but equally active.

GIT :-

- NVD .
- dry mouth .
- metallic test .
- oral thrush (monliasis),yeast infection).

-CNS

- peripheral neuropathy .
- ataxia, encephalopathy convulsion (rare).
- dizziness.
- dysuria ,dark urine.
- neutropenia.
- disulifram-like effect if taken w alcohol. 3
- insomnia .



Drug interactions:-

- inhibits CYP 2C9 & 3A4 (subclasses of CYP450).
- potentiate anticoagulant effect of warfarin. 4
- potentiates lithium toxicity.
- Enzyme inhibitors (cimetidine ,ketocanazole).
- Enzyme inducers (phenytoin & phenobabitone ,rifampin).
- disulfiram → confusion & psychotic states

Contraindication:-

1) pregnancy & nursing women.
2) alcohol intake .
3) CNS dizs .
4) severe hepatic diz
5) severe renal diz .

Dehydroemetine and Emetine

(Comparison T&F)

Chemistry:

- ✓ It is a plant alkaloid drived from ipeca, dehydroemetine is a synthetic analogue

Kinetics:

-Erratic oral absorption
-given SC but could be given IM but never IV
-plasma T1/2 = 5 DAYS*

Emetine

- ✓ concentrated in liver, lungs, spleen, kidney, cardiac muscle, and intestinal wall
- ✓ excreted slowly via kidney so it has a cumulative effect
- ✓ Trace amounts could be detected in urine 1-2 months after last does
- ✓ shouldn't be used for more than 10 days (usually 3-5 days)

Pharmacological actions:

- acts on trophzoites causing irreversible block of protein synthesis
- depress cardiac contraction and conduction causing arrhythmia heart failure and death
- anti-adrenergic action may lead to hypotension
- Nausea and vomiting of central origin
- hypokalemia

Clinical uses:

- severe forms of acute amebic dysentery
- Dehydroemetine and tetracycline for a short period followed by metronidazole
- seconce drug of choice in amebic liver abcess along with choloroquine
- (1st drug of choice is metronidazole)

Adverse effects:

- ♣ dehydroemetine is less toxic than emetine
- ♣ local irritation at site of injection, abcesses
- ♣ GIT upset leading to Nausea ,vomiting ,diarrhea
- ♣ neuromuscular weakness
- ♣ minor ECG changes
- ♣ serious toxicities: cardiac arrhythmia ,hypotension, congestive heart failure

***Contraindications*:**

- Heart disease
- Pregnancy
- Children kidney disease
- Chloroquine (antimalarial drug)
- Anti amebic drugs (systemic*liver)
- antimalarial drug
- used in combination w/ metronidazol & diloxanide fluroate for amebic liver diz

luminal amoebicides

MCQ all except ☺ الأدوية تعداد

- ✓ acts on ! parasite in! lumen of !bowl
- ✓ used 4 treatment of asymptomatic amebiasis

Include :-

- diloxanide furoate
- halogenated hydroxyquinoline
- idoquinol

antibiotic :-

- tetracycline
- erythromycin
- paramoycin

❸ Anti-viral Drugs

Major site of anti viral drug action :

1. absorption to & penetration into susceptible host cell.
2. uncoating of viral nucleic acid .
3. synthesis of early regulatory proteins.
4. synthesis of RNA or DNA.
5. synthesis of late structural proteins.
6. maturation of viral particles.
7. release from the cell.

** most antiviral act on step 4&5.*

Antiviral drugs :

1) DNA polymerase inhibitor:

a) agent used to treat HSV & VSV.

- ✓ Acyclovir
  - Encephalitis (I.V acyclovir drug of choice).
    → reversible renal dysfunction
  - Valacyclovir → prodrug of acyclovir
    - Has
      - × higher O. bioavailability
      - × long duration of action

b) agent used to Rx cytomegalovirus infection (MCV)

1) Gancyclovir :

- Given I.V ,orally or intraocular implant →Vitros hemorrhage &retinal detachment .
- Activated to Triphosphate & competes w/ Guanosin for incorporation into Viral DNA .
- D.O.C for MCV inf. Mainly in Pnts w/ AIDS .

2) valGancyclovir :
   prodrug of Gan.
3) Cidofovir

Cidofovir

(MCQ)

- ✓ cytosine nucleotide analog.
- ✓ Its phosphrelation to the active diphosphate is independent of viral enzymes.
- ✓ Acts as a potent inhibitor & alternative substrate for viral DNA polymerase.
- ✓ Inhibit DNA synthesis & incorporated into viral DNA chain .

Pharmacokinetics:

- ✓ half life 2 – 6 hours.
- ✓ The active metabolite (cidofovir diphosphate) has prolonged intracellular half life 17 – 65 hours.
- ✓ Cidofovir phosphocholine has a half life 87 hours serve as an intracellular reservoir of active drug .
- ✓ CSF penetration is poor.
- ✓ Excreted through kidney.

Clinical uses:

- ✓ I.V cidofovir is effective for CMV retinitis.
- ✓ Polyomavirus associated progressive multifocal leuko-encephalopathy syndrome in AIDS patient.

Adverse effects:

- ✓ I.V cidofovir may cause nephrotoxicity (dose dependent).
- ✓ Uveitis, decreased I.O.P.
- ✓ Neutropenia & metabolic acidosis are rare.
- ✓ Hypersensitivity reaction.
- ✓ Adenocarcinoma in rats & embryotoxic.

c) Anti-retroviral Agent

A- Neocluside reverse transcriptase inhibitors: (NRTIs)

- ✓ all are phosphorylated by host cell enzyme to give 5-triphosphate which compete with host cellular triphosphate that are essential substrates for the formation of pro viral DNA by viral transcriptase(viral RNA dependent DNA polymerase)

1) ZIDOVUDINE
2) DIDANOSINE
3) LAMIVUDINE
4) STAVUDINE

B- Non neocluside reverse transcriptase inhibitors (NNRTI)

- ✓ They are highly selective non competitive inhibitors of HIV1 reverse transcriptase.
- ✓ They bind to the enzyme @the site adjacent to the active site .

1) NEVIRAPINE
2) EFAVIRENZ
3) DELAVIRDINE

C- Protease inhibitors:

- ✓ reversible inhibitors of HIV as partly protease enzyme that is responsible for cleavage of viral poly protein in to a number of essential enzymes ,reverse transcriptase ,protease, integrase and several structural proteins. The inhibition prevents maturation of the viral particles and resulting in non infectious virions .

1) Saquinavir
2) Nelfinavir
3) Indinavir
4) Ritonavir

D- Fusion inhibitors (new class of antiretroviral drugs):

1) Enfuvirtide

2-DIDANOSINE : *(analogue of deoxyadenosine)*

(MCQ)

- ✓ orally taken and it is absorption is affected by meals
- ✓ excreted via kidney
- ✓ CSF 20%of plasma concentration
- ✓ plasma T½=30 min , intracellular T½ more than 12 hour
- ✓ Formulation: powder, enteric coated tab, chewable

Adverse effects:

- ✓ *dose related pain and sensory loss in feet**
- ✓ *dose related pancreatitis (major clinical toxicity)**
- ✓ GIT disturbances
- ✓ headache
- ✓ insomnia ,skin rashes , bone marrow depression(*less common*)
- ✓ alteration of liver function
- ✓ hyperuricemia

3-LAMIVUDINE:

(T&F)

Drugs used in HBV:

Lamivudine & α interferon

- ✓ used for HIV-1,HBV infections
- ✓ with HBV is more effective so reduce and less side effects
- ✓ No significant side effects as it doesn't affect mitochondria DNA synthesis or Bone marrow cells
- ✓ has high oral bioavailability
- ✓ *has high rate of mutation if given alone**
- ✓ it is synergistic with a variety of antiretroviral nucleoside analogue.

d)) Anti-hepatitis agents (like in AIDS they are suppresive

1.Alfa-interferon:

- ✓ Endohenous protiens, exerts a variety of actions: antiviral, immunomodulatory & antiproliferative.
- ✓ They bind to specific membrane receptors on the cell surface, initiating a number of intracellular actions.
- ✓ Is produced by B & T-lymphocytes, macrophages & fibroblasts in response to the presence of viruses & cytokines.

➲ Mechanism of action:

- ✓ In the ribosomes of the host cell it induce the production of enzymes that inhibit the translation of viral mRNA into viral proteins, thus stop the production of viruses (degradation of viral mRNA & tRNA)

1) Treatment of viral hepatitis B&C
2) Prevent reactivation of HSV after trigeminal root resection
3) Prevent spread of herpes zoster in cancer patients
4) Cancer leukemia
5) Multiple sclerosis
6) Genital warts

➲ Pharmacokinetics:

- Given SC, IM, IV
- Half life 2-4 hours (variable)
- Don't cross BBB

➲ Contraindications:

- × Psychosis
- × Neutropenia & thrombocytopenia
- × Heart disease
- × Decompensated cirrhosis
- × Uncontrolled seizures
- × Organ transplantation
- × Pregnancy

➲ Clinical uses:

➲ Adverse effects:

a) Flu-like syndrome(as rifampicine)*
b) Thrombocytopenia
c) Granulocytopenia
d) Increase liver enzymes
e) Nausea, fatigue, rash, anorexia, alopecia, hypotension, edema
f) Severe neuropsychiatric side effects

2.Ribavirin:

(T&F)

- Mechanism of action:
  - ✓ Interferes with the synthesis of guanosine triphosphate, so inhibit viral mRNA
  - ✓ It inhibits the replication of a wide range of DNA & RNA including influenza A, parainfluenza, paramyxovirus, HIV, hepatitis.
- Pharmacokinetics:
  - ✓ Oral bioavailability increased with fatty meals & decrease with antacids.
  - ✓ Excreted through urine.
- Clinical uses:
  - ✓ Ribavirin capsules in combination with SC interferon are effective for treatment of chronic hepatitis C.
  - ✓ Monotherapy is not effective in hepatitis C.

- Adverse effects:
  - ✓ 10-20 % hemolytic anemia.
  - ✓ Depression, fatigue, rash, cough, insomnia, nausea, pruritis.
- Contraindications:

✓ Anemia
✓ Renal failure
✓ Heart disease
✓ pregnancy

e) Anti-influenza agents

1) Amantadine & Rimantadine
2) Zanamivir
3) Oseltamivir

৩Amantadine & Rimantadine

- ✓ Prevent replication of the viral RNA of influenza A within the host cells through blocking a viral membrane protein M2 (an ion channel).
- ✓ Rimantadine the ά- methyl derivative of amantadine is more active.

✹ Pharmacokinetics:

- Amantadine is excreted unmetabolized in the urine.
- Rimantadine undergoes extensive metabolism & eliminated by liver.
- Dose adjustment is needed in old ,renal insufficiency for amantadine.
- For rimantadine in hepatic insufficiency.
- Both of them cross BBB.

✹ Clinical uses:

- Prevention of clinical symptoms of influenza A.
- Reduce the duration of fever & systemic complains.
- Amantadine is used for management of Parkinson disease.

✹ Adverse effect:

- ✘ Gastrointestinal intolerance.
- ✘ CNS.
- ✘ Teratogenic.
- ✘ Over dose leads to anti-cholinergic effects.

❹Anti-fungal drugs

figures → ?? مهمه كل دوا وين يشتغل

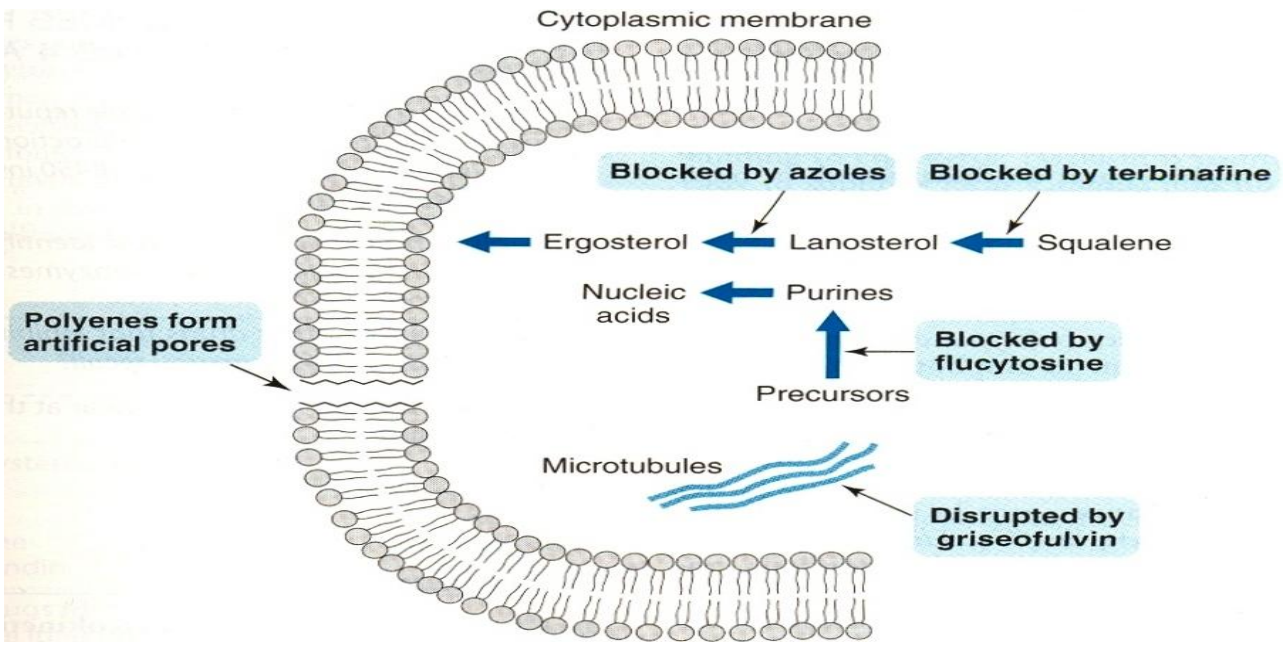
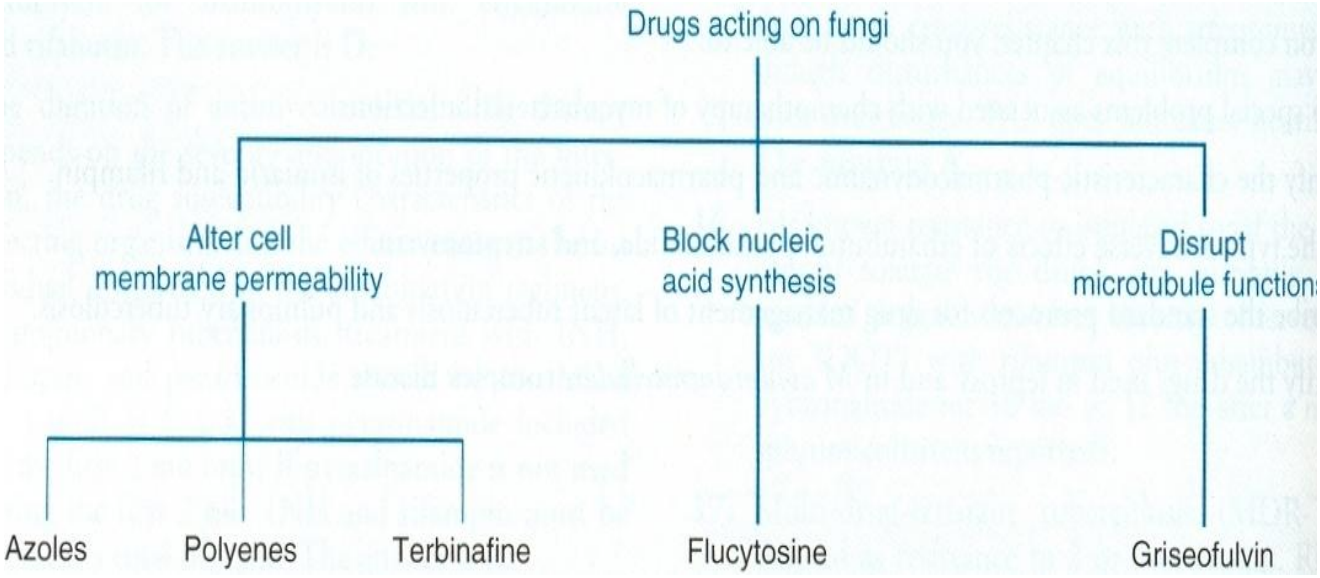


Figure 48-1. Sites of action of some antifungal drugs.The cell cytoplasmic membrane shown is that of a typical fungus. Because ergosterol is not a component of mammalian membranes, significant selective toxicity is achieved with the azole drugs.



Fungal infections are difficult to treat, particularly in the immunocompronused or neutropenic patient. Most fungi are resistant to conventional antimicrobial agents, and only a few drugs are available for the treatment of systemic fungal diseases. Amphotericin B and the azoles (fluconazole, itraconazole, ketoconazole, and voriconazole) are the primary drugs ~~used in~~ systemic infections. They are selectively toxic to fungi because they interact with or inhibit the synthesis of ergosterol, a sterol unique to fungal cell membranes.

◎Classification of antifungal drugs:-

1. **Systemic antifungal drugs for systemic deep infections:**
    - Polyene macrolide: Amphotericin B
    - Flucytocine
    - Azoles:
        - Imidazole → ketoconazole
        - Triazole → fluconazole, itraconazole
        - Newer azoles → voriconazole
    - Caspofungin

2. **Systemic antifungal drugs for mucocutaneous infections:**
    - Grisofulvin
    - Terbinafine

3. **Topical:**
    - Nystatin
    - Topical azoles: clotrimazole & miconazole
    - Topical AllylAmines. e.g: naftifine, terbinafine
    - White field ointment: 12% Benzoic acid & 6% Salicylic acid
    - Castellani paint

Amphotericin B

(T&F)

- Amphotericin A&B are antifungal antibiotic
- Amphotericin A is not used clinically
- It is a plyene macrolide
- (polyene = many double bonds)
- (macrolide = containing a large lactone ring)

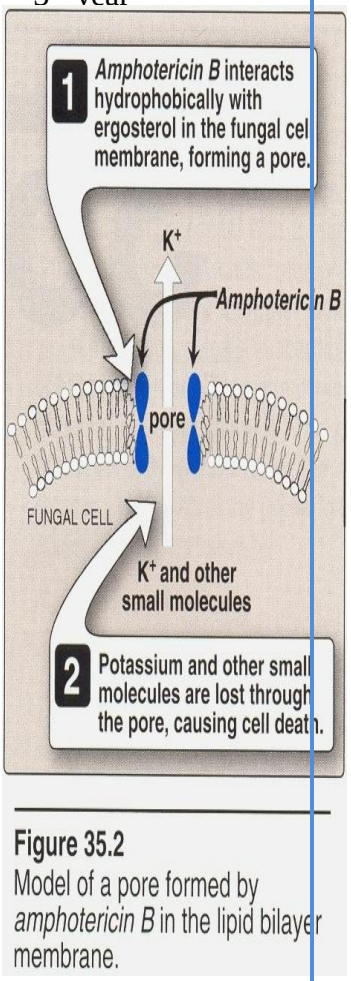


Figure 35.2
Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.

Pharmacokinetics:

- poorly absorbed orally (given orally coz it is effective for fungal infection of GIT)
- for systemic infection given as slow IV infusion
- intrathecal route
- highly bound to plasma protein
- poorly crossing BBB
- metabolized in liver
- excreted slowly in urine over a period of several days & bile (coz of 2 route for excretion no need for dose adjustment)
- T½ life =15 days

Mechanism of action:

- it is a selective fungicidal drug
- disrupt fungal cell membrane by binding to ergosterol, so alters the permeability of cell membrane leading to leakage of intracellular ions & small molecules → cell death

Resistance to Amphotericin B:

- If ergosterol binding is impaired either by:
  1. Decreasing the membrane concentration of ergosterol
  2. Or by modifying the sterol target molecule

Adverse effects:

1. **Immediate reactions (infusion-related toxicity):**
   - Fever, muscle spasm, vomiting, headache, hypotension
   - Can be avoided by:
     - Slowing the infusion
     - Decreasing the daily dose
     - Premedication with antipyretic, antihistaminic or steroids
   - Small dose is usually given to avoid anaphylaxis or convulsions

2. **Slower toxicity:**
    - Most serious is renal toxicity (nearly in all patients)
    - Hypokalaemia
    - Hypomagnesaemia
    - Impaired liver function
    - Thrombocytopenia
    - Anemia (normochromic, normocytic)

Clinical uses:

- Has a broad spectrum of activity & fungicidal action
- **The drug of choice for a life-threatening mycotic infection**
- For induction regimen for serious fungal infection
- Also for chronic therapy & prevention therapy of relapse
- In cancer patients with neutropenia who remain febrile on broad-spectrum antibiotics

Local uses:

- Topical drops & direct subconjuctival injection for mycotic corneal ulcer & keratitis
- Local injection into the joint for fungal arthritis
- Bladder irrigation for candiduria

♣ Liposomal preparations of Amphotericin B:

- Amphotericin B is packaged in a lipid-associated delivery system to reduce binding to human cell membrane, so reducing:
    1. Nephrotoxicity
    2. Infusion toxicity
- it is more effective but more expensive.

➲ It can be used topically (T)

✹Ketoconazole: (MCQ all true except)

- Given only orally
- Absorption is decreased with
  - acid H2 blocker ,proton pump inhibitors
  - and food.
  - Cola drinks improve its absorption
  - in patient with achy hydria؟؟؟
- T½ life increases with dose it is = 7 – 8 hr
- Metabolized in liver, excreted in bile (mainly) urine (low)
- Poorly penetrates BBB

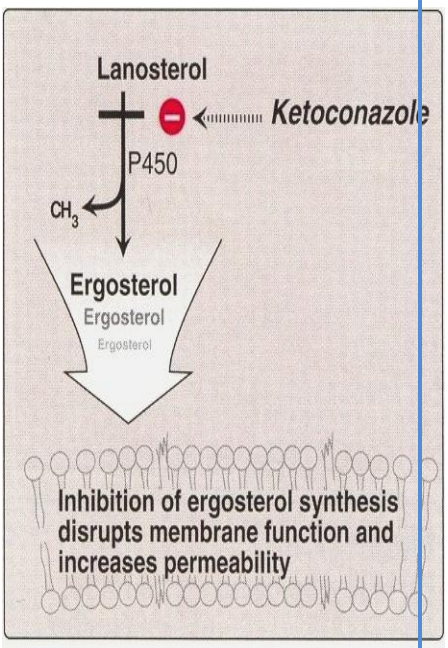


Figure 35.8
Mode of action of *ketoconazole*.

➲ Uses :

used for topical and systimec fungal infections to treat:

1. oral and vaginal candida
2. Dermatophytes
3. systemic mycoses –mucocautaneous candida
4. Topical and shampoo form are useful in treatment of seborrheic dermataitis

➲ Adverse effects :

- ✘ NVD and anorexia
- ✘ hepato toxic
- ✘ Inhibits humen P450
- ✘ Inhibit the adrenal and gonadal steroids leading to (menstruation irregularity ,loss of libido, impotence, gynecomastia).
- ✘ It is efficacy is poor in immune-compromised patient and meningitis
  **(Kidney damage (F))

➲ Contraindications and drug interactions:

5. Pregnancy ,lactation And hepatic dysfunction
6. Interacts with enzyme inhibitors and enzyme inducers
7. H2 blocker and antacid decrease its absorption
8. Ketoconazole and amphotericine shouldnot be given together (important) l2nh yl'3i 3ml el amphotericine m3 el ergosterole.

✹Flucytosin

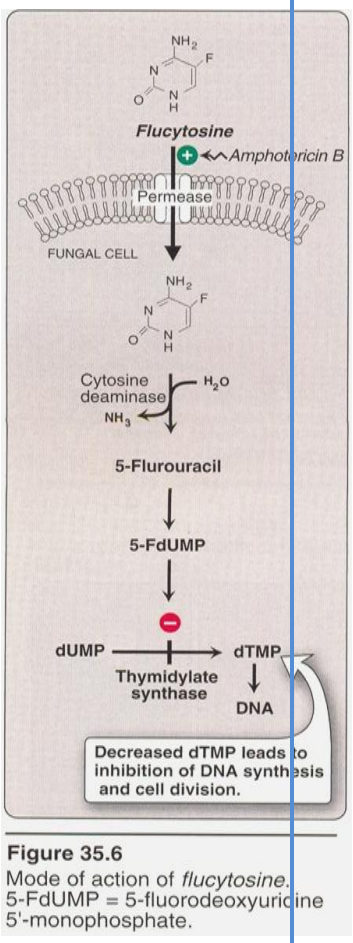


Figure 35.6
Mode of action of *flucytosine*. 5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate.

- ✓ Synthetic pyrimidine antimetabolite.
- ✓ Often given in combination with amphotericine B & itraonazole.
- ✓ For the treatment of systemic mycoses & meningitis.
- ✓ It's a systemic fungistatic drug.

☙ Mechanism of action: (DNA & RNA).

- Taken up by fungal cells via the enzyme cytosine permease.
- Converted intracellularly to 5-FU.
- Then to 5-flurodeoxy uridine monophosphate inhibits DNA synthesis via inhibition of thymidlyate synthase.
- & flurouridine triphosphate inhibits RNA synthesis.

☙ Pharmacokinetics:

- Rapidly & well absorbed orally.
- Widely distributed including CSF.
- Mainly excreted unchanged through kidney .(dose adjustment)
- T½ life = 3-6 hours.

☙ Clinical uses:

- Sever deep fungal infection as in meningitis.
- Generally given with amphotericin B.
- For cryptococcal meningitis in AIDS patients .

☙ Adverse effects:

- Nausea , vomiting ,diarrhea ,sever ∗enterocolitis.
- Reversible neutropenia ,thrombocytopenia , bone marrow depression.
- Alopecia.

Elevation in hepatic enzymes.

✹Griseofulvin

(T&F)

- Fungistatic
- has narrow spectrum.
- Given orally (absorption increases with fatty meal).
- T½life =24 hrs.
- Taken selectively by newly formed skin & concentrated in the keratin.
- Induces CYT P-450 enzymes.
- Should be given for 2-6 weeks for skin & hair infection to allow replacement of infected keratin by resistant structure.
- Inhibits fungal mitosis by interfering with microtubule function.
- Used to treat dermatophyte infection (ring worm of skin,hair,nails).
- Highly effective in athletes foot.
- Ineffective topically.
- Not effective in subcutaneous or deep mycosis.

◈ Adverse effects:

- Peripheral neuritis
- mental confusion
- fatigue
- vertigo
- GIT upset
- enz. Inducer
- blurred vision .

✹ Antifungal drug used for topical fungal infection :

1. topical azole derivatives (clotrimazole, miconazole).
2. Nustatin & amphotericin B.
3. Allyl amines (terbiafine, nafitifine).

Oral antifungal agent used for topical infection:

1) Griseofulvin.
2) Oral azoles.
3) Terbinafine.

Topical antifungal agent

- ✓ Used in superficial fungal infection such as: Dermatophytosis (ring worm, candidiasis, fungal kertitis).
- ✓ They are not effective in mycosis of the nails & hair or subcutaneous mycosis.
- ✓ The preferred formulation for cutaneous application is cream or solution.

Terbinafine:

- Synthetic allyl amine.
- Drug of choice for treating dermatophytes.
- Better tolerated needs shorter duration of therapy
- Decrease the synthesis of ergosterol through inhibition of squalene epoxidase,The accumulation of squalene causing death of fungal cell.
- Fungicidal, its activity is limited to candida albicans & dermatophytes
- Effective for treatment of onchomycosis 6 weeks for finger nails infection & 12 weeks for toe nails infections.
- Well absorbed orally, bioavailability ↓ due to first pass metabolism in the liver.
- Highly protein binding.

Adverse effects :

- Accumulates in skin, nails, fat.
- Hepatotoxic, liver failure even death.
- GIT upset.
- Taste & visual disturbance.

MCQ s:

♠Wich one of !following antifungal drugs produce its effect by inhibiting DNA synthesis in fungal cell?:
1-Ketoconazole
2-Flucytosine
3-Amphotericine B
4-griseofulvin.

T&F

♠Griseofulvin:

Acts by distrupting microtubule function.√
May reduce ! efficacy of oral contraceptive .?
Oral absorption may be ↑with faty foods.√
Is effective topically against many dermatophytes.√

♠As compared to Ketoconazole , fluconazole:

Has a higher oral bioavailability.
Readily enters !CNS.
Has less inhibitory action on hepatic CYT-P54 isoenzyme .
Is eliminated as unchanged drug by ! kidney .

♠Amphotericin B:

Highly protein bound .
Safe to be used in renal impairment .
Has aT½ life of more than one week .
Used in ® of cryptococal meningitis .

♠ Adverse effects of Ketoconazole may include :

Gynaecomastia .
Menstrual irregularities .
Bone marrow suppression .
Hirsutism .
♠ Qs of (cat 2) 2005 by : pharma stars

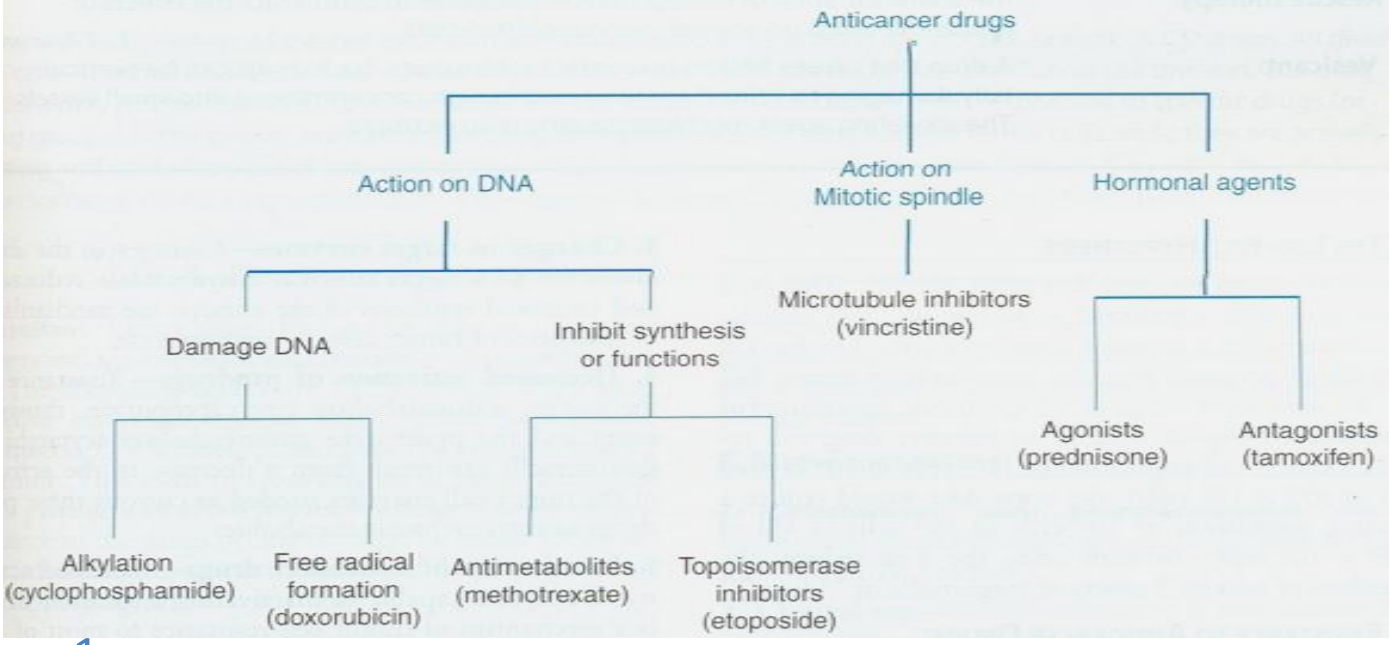
❺Cancer Chemotherapy

- Antimetabolites:
    1. Methotrexate.
    2. Purine antagonist:
        - 6-mercaptopurine.
        - 6-thioguanine.
    3. Pyrimidine antagonist:
        - 5-flurouracil.
        - Cytarabine.
- Antibiotics:
    1. Dactinomycin.
    2. Anthracyclines:
        - Doxorubicin.
        - Daunorubicin.
    - Bleomycin.
- Alkylating agents:
    1. Nitrosaureas.
    2. Mechlorethamine.

  Related drugs:
    1. Cyclophosphamide and ifosfamide.
    2. Dacarbazine.
    3. Cisplatin and carboplatin.
- Plant alkaloid:
    1. Vinblastine.
    2. Vincristine.
    3. Taxanes → paclitaxel.
    4. Podophyllotoxins → etoposide.
    5. Comptothecin: topotecan and irinotecan.

- Steroid hormone antagonist:
  1. Estrogen and prednisone.
  2. Tamoxifen.
  3. Flutamide.
  4. GnRH agonist (leuprolide and goserelin).
  5. Aromatase inhibitors, aminoglutethinuide.
- Miscellaneous:
  1. L-asparaginase.
  2. Interferons.
- Monoclonal antibodies:
  1. Trastuzumab.
  2. Retuximab.
  3. Bevacizumab.
  4. Cetuximab.

Cancer chemotherapy remains an intriguing area of pharmacology. On the one hand, use of anticancer drugs produces high rates of cure of diseases that, without chemotherapy, result in extremely high mortality rates (eg, acute lymphocytic leukemia in children, testicular cancer, Hodgkin's lymphoma). On the other hand, some types of cancer are barely affected by currently available drugs. Furthermore, as a group, the anticancer drugs are more toxic than any other pharmaceutic agents, and thus their benefit must be carefully weighed against their risks. Many of the available drugs are cytotoxic agents that act on all dividing cells, cancerous or normal. The ultimate goal in cancer chemotherapy is to use advances in cell biology to develop drugs that selectively target specific cancer cells. A few such agents are in clinical use, and many more are in development.



◎Antimetabolites

Mechanism of action:

- ✓ Inhibits purine or pyrimidine synthesis.

Methotrexate:

- ✪ Inhibits folate synthesis through inhibition of dihydrofolate reductase step in the formation of purines & nucleic acids DNA & RNA.

Resistance:

1- decreased drug transport into the cell.
2- decreased reductase enzymes.

Route of administration:

- I.V, intrathecal, oral-.
- Excreted in urine-.
- Does not penetrate BBB-.
- Excretion mainly kidney & less extent in feces-.

Adverse effects:

1) N.,V.,D.
2) Renal damage.
3) Hepatic fibrosis or cirrhosis.
4) Pulmonary (cough,dysnea,cyanosis).
5) Neurologic (intrathecal route).
6) Headache,fever seizures.
7) Bone marrow depression

☒ Contraindicated in pregnancy.

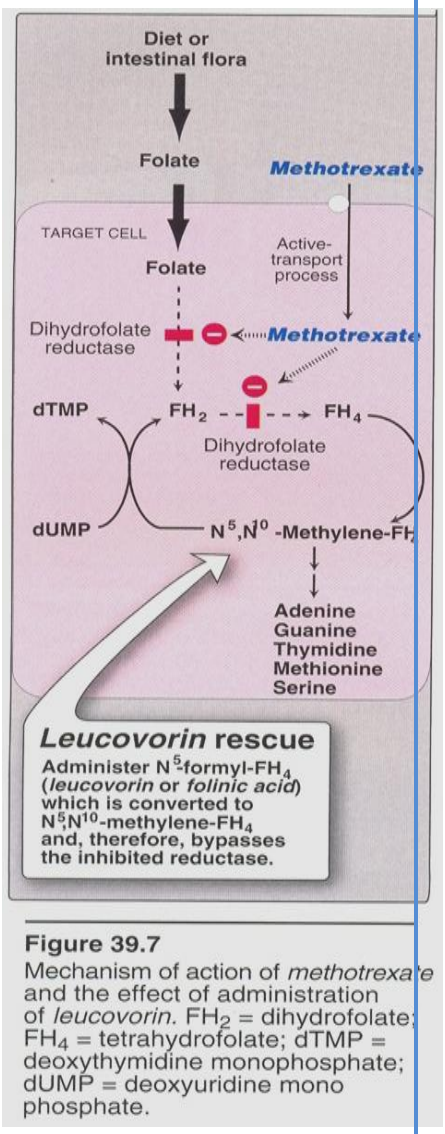


Figure 39.7
Mechanism of action of *methotrexate* and the effect of administration of *leucovorin*. FH_2 = dihydrofolate; FH_4 = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine mono phosphate.

<u>The heamatological toxic effects of methotrexate can be reversed by leucovorin.</u>

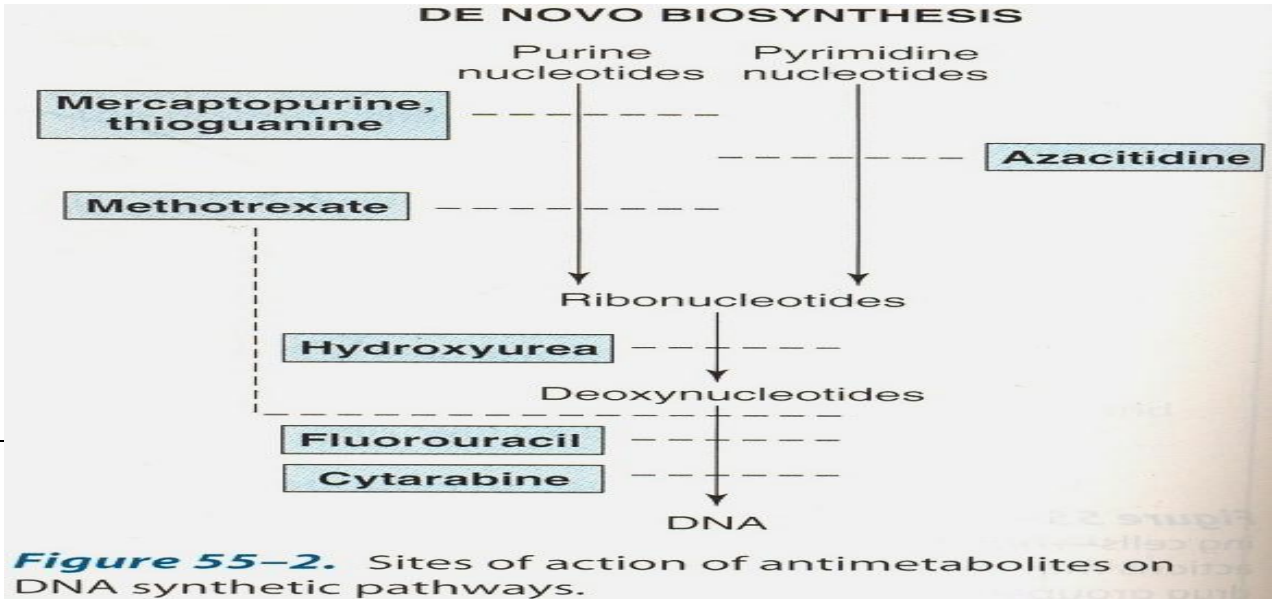


Figure 55–2. Sites of action of antimetabolites on DNA synthetic pathways.

Plant alkaloids microtubule inhibitors:

Vincristine and vinblastine

- ✓ They are derived from vinca rosea .

Mechanism of action :

- Both are cell cycle-specific and phase specific, because they block mitosis in metaphase. They bind to tubulin (GTP-dependent) and block tubulin polymerization to form microtubules .

Resistance :

- Resistant cells have been shown to have an enhanced efflux of vincristine and vinblastine via P-glycoprotein in the cell membrane .
- Alteration in tubulin structure may also affect the binding of the vinca alkaloids.

Pharmacokinetics :

- Intravenous injection of these agents leads to rapid cytotoxic effects and cell destruction. This in turn can cause hyperuricemia (this can be ameliorated by administration of allopurinol).

- Metabolized in the liver by cytochrome P450 .
- Excreted in bile and feces .

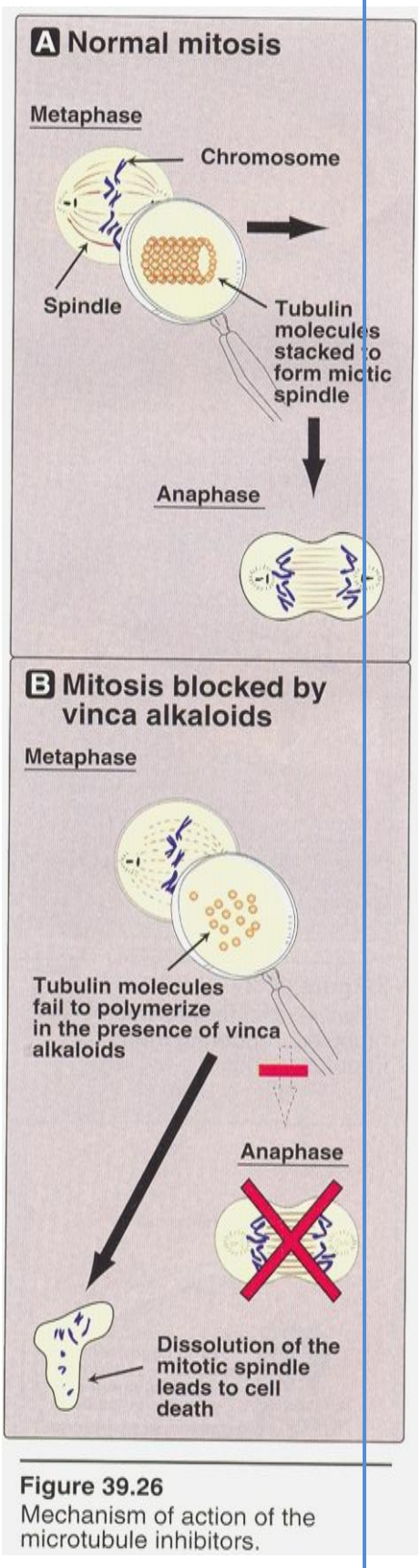


Figure 39.26
Mechanism of action of the microtubule inhibitors.

Therapeutic applications :

1) Vincristine is used in treatment of acute lymphoblastic leukemia, Wilm's tumor, Ewing's soft-tissue sarcoma and Hodgkin's and non-Hodgkin's lymphomas (POMP).
2) Vinblastin is used in: testicular carcinoma, systemic Hodgkin's and non-Hodgkin's lymphomas .

Adverse effects :

- GIT disturbances .
- Alopecia .
- Cellulitis .
- Vinblastin is a more potent myelosuppressant .
- Vincristine: peripheral neuropathy + GIT disturbances (more .(
- The potential side effect of vincristine is that it can cause the syndrome of inappropriate secretion of antidiuretic hormone (SIADH.(
- Constipation is more frequently encountered with vincristine.

Cytotoxic antibiotics

1- Anthracyclines
2- Dactinomycin
3- Bleomycin

Bleomycin

(T&F)

- Liberates Oxygen free radical resulting in breaking of DNA strands and chromosomal aberration

- Pharmacokinetics:
  - SC,IM, IV
  - Bleomycin inactivating enzyme is high in liver spleen and low in lung and absent in skin
  - Most of the drug is excreted unchanged in urine
  - Not given orally

- Clinical uses:
  1- Hodgkin's and non Hodgkin's lymphoma
  2- Testicular tumors
  3- Carcinoma
- Toxicity:
  - Pneumonitis
  - Cough
  - Dyspnea
  - pulmonary fibrosis
  - hyper trophic skin changes and hyper pigmentation of hands
  - fever
  - alopecia

6 Antihelminthic Drugs

Antihelminthic drugs:-

- **May act by causing**:

a) Paralysis of the worm.

b) Damaging the worm leading to partial digestion or rejection by immune mechanism.

c) Interfere with metabolism of the worm.

✓ Worm or larva live in other tissues of host body like: muscles , viscera, meninges, lungs, subcutaneous tissue.

✓ Adult filariae live in the lymphatics, connective tissue or mesentery of host & produce live embryos or microfilariae, which goes to blood stream.

✓ Microfilariae are ingested by mosquitoes or similar insects, they develop to larvae in secondary host & pass to mouth parts of insect & reinjected to humans

Albendazole:

- ✓ Broad spectrum
- ✓ Drug of **choice** in treatment of **Hydatid cyst**, **cystecercosis** , **ascariasis** ,**tricurasis stroglyoidiasis**, **pinworm** , **hook worm** .

Mechanism of action :

- It inhibits **microtubules polymerization** by binding of **B tubulin**
- Inhibits **mitochondrial reductase** causing reduced **glucose** transport. Intestinal parasite are immobilized and die slowly
- It is **lavarcidal** in **hydatid** ,**cysticercosis** ,**ascariasis** and **hook worm** infections
- Also **ovicida**l in **ascariasis, ancylostomiasis**(hook worm)

Pharmacokinetics:

- It is benzimidazole carbamate
- Administrated **orally** ,absorbed **erratically** ,absorption increased with fatty meal
- Metabolized in liver and converted to **active** metabolites (Albendazole sulfoxide)
- T1/2 = 8-12
- Sulfoxide is mostly protein bound – distributed **well** to tissues and **enters bile** ,**CSF** and **hydatid cysts**
- Metabolites excreted in **urine**

Clinical uses:

- Used on **empty** stomach when used against **intra luminal** parasites but with **fatty meal** when against **tissue parasites**
- **In ascaris –tricuriasis- hook worm –pin worm infections**: children under 2 years→ 400 mg orally as single dose repeated for 2-3 days in heavy ascarisis ,2-3 weeks for pin worm
- **Hydatid cyst :** drug of choice ,400 mg twice with meals for one month or longer
- **Neuro-cysticercosis :** used with **corticosteroids** to reduce the inflammation caused by dying organism and it also decrease the duration of the course for 21 days
- **Other infections:** drug of **choice** in coetaneous and of visceral larva

Adverse Effects:

- Short term → no significant adverse effects
- Long term → when used in hydatid cyst and cysticercosis (abdominal pain, headache, fever fatigue, alopecia increased liver enzymes, pancytopenia) blood count and liver enzymes should be followed
- **Not** given during **pregnancy** and in **hyper sensitive people**

Mebendazole:

(MCQ)

- ✓ Synthetic benzimidazole
- ✓ Wider spectrum and is more safer than albendazole

Mechanism of action:

- It inhibits the micro tubules synthesis in nematodes that irreversibly impairs glucose uptake.
- intestinal parasites are immobilized and die slowly
- it kills hook worm –pinworm –ascariasis and trichuris eggs

Pharmacokinetics:

- Less than 10% of orally administrated drug is absorbed
- Absorption increased with fatty meal
- 90% protein bound
- Converted to inactive metabolites rapidly in liver
- It has t ½ = 2-6 hr
- It is primarily excreted in urine

Clinical uses:

- Taken orally before or after meal ,tab should be chewed before swallowing
- Pinworm
- Ascaris infections
- In adults and children over 2 years ,cure rates is 90- 100% except hookworm it is less
  (➲Has activity against hook worm*****.

💣Adverse Effects:

- No adverse effects in short term therapy, mild GIT disturbances
- With Increased dose→ hypersensitivity reactions, agranulocytosis ,alopecia, increased liver enzymes
- Used with caution under 2 years of age may cause convulsions
- Enzyme inducer and inhibitors affect plasma level of the drug

IVERmectin ”

- ✓ It is drug of **choice** for treatment of **strongyloidesis**
- ✓ It is macrocyclic lactone
- ✓ It is given **orally**
- ✓ Does **not cross BBB** (not completely)
- ✓ It has half life of 16 hours
- ✓ It is excreted **in urine**

Mechanism of action:

- Acts on the parasite`s **glutamate-gated Cl^- channel receptors**. Chloride influx ↑, hyperpolarization occurs resulting in paralysis of the worm.

Clinical uses:

- Drug of choice for: **(MCQ)**
  - **cutaneous larva migrans**
  - **strongyloids**
  - **Filariasis**
- It is also used for **scabies**

Adverse effect

- fatigue, dizziness, GI disturbance
- killing of microfilaria result in a **Mazotti-like reaction** (fever, headache, dizziness, somnolence, hypotension (
- **corneal opacities**.

Contraindication

- other drug that enhance GABA e.g. barbiturates, benzodiazepines, vaproaic acid.
- Pregnancy.
- Meningitis.
- Children under **5** years of age.

Chose :

❶Which one of the following drugs ,when used in filariasis ,is associated with sever reaction due to death of parasites?

a) Mebendazole.

b) Ivermectine.

c) Albendazole.

d) Piperazine.

❷Diethylcarbamazine :

a) Is the drug of choice in O.volvulus infestation .

b) Immobilized microfilariae through alteration in their surface area .

c) Is not effective orally .

d) Is rapidly excreted in alkaline urine .

T and F :

◎Niclosamide:

a) Is effective against T.solium and T.saginataa.

b) Has a larvicidal action .

c) Inhibits oxidative phosphorylation .

d) May cause neurocysticercosis.

◎Mixed infestation due to ascariasis, trichoriasis ,and enterobiasis can effectively be treated by:

a) Albendazole.

b) Niclosamide.

c) Diethylcarbamazine .

d) Ivermectin.

Match

- Match the following parasitic infestation with the drugs listed below:

a) Hookworm infestation .1

b) Visceral leishmaniasis.4

c) Fascioliasis.2

d) Schistosoiasis due to S.mansoni.3

1) Mebendazole.
2) Bithionol.
3) Oxamniquine .
4) Na^{+} stibogluconate .
5) Ivermectin.

" إن ما يدفعنا للإمام في الواقع ، هو ليس ما نطلبه من أنفسنا او الآخرين ، بل ذلك الذي نشجعه في أنفسنا "

ليليا كوني

☺

❼Drugs of leishmaniasis

Types of leishmaniasis:

- Cutaneons.
- Mucocutaneous .
- Vesiral

- ✓ Parasite in the blood stream
- ✓ It is transmitted from animals to humans & b/w humans by the bite of infected sand flay .
- ✓ It is diagnosed by biopsy
- ✓ Limitation of drugs→ due to toxicity .

Treatment:

- It is treated by antimonials as 1st line therapy .
- & with pentamidine & ampehotricine as 2nd line therapy .

Sodium stibogluconate

(T&F)

- ✓ Unknown mechanism .
- ✓ Evidence for production of oxygen free radicals.

Pharmacokinetics :

- It is not absorbed orally .
- The treatment is given once daily at sdose of 20 mg/d I.V or I.M for
  - ✓ 20 days → in coetaneous leishmaniasis
  - ✓ & 28 days → in visceral & muco-cotaneous disease .
- Distributed in extra-vascular compartment
- Metabolism is minimal(metabolized to some degree) ,
- and the drug is excreted in the urine .

💣adverse effects :

- pain at the injection site .
- gastrointestinal upset .
- cardiac arrhythmia .(different form of arrhythmia)
- myalgia ,fever, headache ,arthralagias.
- Renal & hepatic function should be monitored regularly.(in all anti-parasite drugs ,m7dsh yslm menhm be9ra7h abdn).

- Resistance to Na^+ stibogluconate is developing in endemic areas .
- **Rare** : renal failure,hepatic failure ,hemolytic anemia .

Pentamidin
"Isethionate "

(T&F)

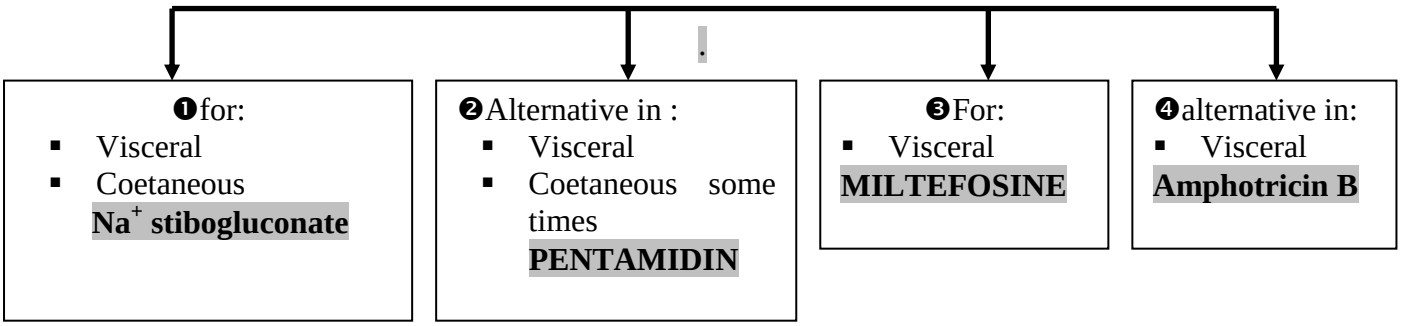
✓ Used as alternative to Na^+ stibogluconate for:
- ✘ the treatment of visceral lieshmania and
- ✘ some times used for cutaneous lesion but not routinely.

Pharmacokinetics :
- It is not absorbed orally
- It is accumulated ,eliminated very slowly in urine.
- T ½ = 12 days.

Mechanism of action :
- Unknown

Adverse effects :
- Pain at the site of injection with intramuscular administration .
- Hypotension
- Pancreatic toxicity → hypoglycemia in insulin dependent diabetic ptns.
- Reversible renal insufficiency.
- GIT disturbance .
- Cardiac arrhythmia .
- Abnormal liver function test .

Anti-Leishmeniasis drug



T&F:
Miltefosine is used in the treatment of :
a) Schistosomiasis.
b) Visceral leishmaniasis
c) Ascariasis
d) Filariasis

Have

A

Break,

have

A

KitKat

❽Anti-malarial drugs

Classification of ant-malarial drugs based on site of action :-

1. **Drugs effective against erythrocytic** form (blood schizontocides):
   - Chloroquine.
   - Quinine.
   - Mefloquine.
   - Proguanil & pyrimethamine.
   - Artemisinins.

2. **Drugs effective against exo-erythrocytic** form (tissue schizontocides) that kill <u>developing or dormant</u> liver stage:
   - Primaquine.

3. **Drugs effective against sexual stages in human blood** (gametocides):
   - Primaquine in→ P.Falciparum,
   - Chloroquine in→ P.vivax, malarae, ovale.

4. **Drugs effective against gametocytes in mosquito** (sporonticidal agent):
   - Proguanil & pyrimethamine.

5. **Antibiotics:**
   - Tetracyclins: Doxycyclin
   - Sulphonamides: sulphadiazine, sulphadoxine
   - Sulphones: Dapsone

6. **sulphonamides:-**
   - sulphadiazine
   - sulphadoxine
7. **sulphones:-**
   - dapsone

Chloroquine

❖ Chemistry:

- Synthetic 4-aminoquinoline (weak base)
- Chloroquine phosphate (oral),
- chloroquine hydrochloride (parentral)

❖ Mechanism of action:

- ✓ Blood schizonticide.
- ✓ Effective against gametocytes of P.vivax, ovale, malarae but not P.falciparum.
- ✓ Not active against liver stage parasites.
- ✓ Choroquine enter red blood cells & act by inhibiting polymerization of Hb breakdown products (heme) into hemozoine, thus build up of the heme that damage membrane & lead to lysis of both parasite & RBCs.
- ✓ Binding to heme & alkalinization of acidic food vacuole.

❖ Pharmacokinetics:

- Rapid & complete absorption after oral administration
- 50-65% protein bound
- Concentrates in erythrocytes, liver, spleen, kidney, lung & melanin containing tissues as well as leukocytes
- Has a large Vd (100-1000 L/kg)
- Drug penetrates into CNS & traverses the placenta
- Metabolized by hepatic microsomal enzymes. Some metabolite products retain anti-malarial activity
- Excreted predominantly in urine, excretion enhanced in acidic urine
- Because of its large Vd, a loading dose must be given in the treatment of acute attacks
- Excreted in urine with initial t1/2 = 3-5 days, terminal t1/2 = 1-2 months

❖Clinical uses:

1) **Drug of choice for treatment & prophylaxis of malaria especially P.falciparum but should be combined with Primaquine for P.vivax & ovale for radical cure**rrrrre
2) Acute malarial attacks
3) Chemoprophylaxis
4) Amebis liver abscess
5) Autoimmune disorders (RA)
6) Safe for pregnancy & children*

💀Adverse effects:

- ♣ GI disturbance
- ♣ CNS: headache, blurring of vision, field defects, impaired hearing
- ♣ Haemolysis in G6PD deficient persons
- ♣ Bleaching of hair
- ♣ Exfoliative dermatitis (until here these adverse effects are mild)
- ♣ Myopathy, peripheral neuropathy, irreversible retinopathy & ototoxicity → in large dose*
- ♣ CVS: T-wave changes & QRS widening, with rapid IV infusions or large I.M may lead to hypotension, respiratory & cardiac arrest (best avoided or slow use)
- ♣ Resistance to P.falciparum

☒Contraindications:aq

- ⅄ Used with caution in patients with liver & kidney dysfunction, neurologic or hematologic disorders
- ⅄ Exacerbate dermatitis produced by gold or phenylbutazone
- ⅄ Contraindicated in psoriasis or porphyria (may precipitate acute attacks)
- ⅄ Myopathy

❖Drug interactions:

⇒ Anti-diarrheal kaolin, antacids →interfere with chloroquie absorptio

Quinine & Quinidine

- ✓ Plant alkaloid
- ✓ Derived from the bark of cinchona tree
- ✓ Quinidine is d-isomer of quinine

❖ Pharmacokinetics:

- Given orally (sulphate) or parenetrally (hydrochloride or gluconate) for quinine
- Quinidine is given parenterally only
- Rapid absorption
- Peak blood level within 1-3 hours
- Widely distributed in body tissues
- 80% bound to plasma protein - highly bound to plasma protein -
- Quinine is metabolized mainly in the liver
- Excretion is mainly urinary & accelerated in acidic urine
- Pharmacokinetic varies among populations
- Patient with malaria develop→ higher protein binding,→↑ plasma levels & longer duration of action (18 h) than healthy controls (11 h)
- Quinidine has shorter t1/12

❖ Mechanism of action:

- Molecular mechanism is unknown

❖ Pharmacological actions:

➲ **Anti-malarial action:**

- ✓ Rapid action
- ✓ Highly effective blood schizonticide against the 4 malaria species
- ✓ Quinine is gametocidal for P.vivax & ovale but not P.falciparum
- ✓ Quinine has no effect on liver stages

Resistance: not common but start to develop

➲Other Pharmacological actions:

- ✓ Quinine has Quinidine-like effect on cardiac muscle
- ✓ Slight oxytocic action on gravid uterus especially in the 3rd trimester, but still can be used in pregnancy
- ✓ Quinine has a curare-like action on the motor endplate

❖ Therapeutic uses:

1. parenteral treatment of severe P.falciparum malaria (1st line therapy) quinine pi9'hydrochloride given slowly IM or IV (in devided doses or infusion)
2. Oral treatment of P.falciparum malaria resistant to chloroquine (sulphate is used with doxycyclin to limit duration of use to 3 days & toxicity)
3. Prophylaxis is not used routinely because of its potential toxicity, but used as prophylaxis in areas where P.falciparum is resistant to chloroquine & neither mefloquine or doxycyclin is available

☻ Adverse effects:

- GI: nausea, vomiting, epigastric pain
- Cinchonism (7-10 microgram/ml): headache, nausea, tinnitus, vertigo, dizziness, flushing
- Hematological effect: hemolysis (G6PD), leucopenia, agranulocytosis, thrombocytopenia
- Thrombophlebitis
- Severe hypotension & thrombophlebitis can follow too rapid IV administration
- Hypoglycemia (therapeutic doses) through stimulation of pancreatic B-cells
- Fetotoxic
- Hypersensitivity reaction: skin rash, bronchospasm, black water fever

⁝ **N.B**:-Black water fever :- a syndrome characterized by massive intra vascular hemolysis followed by haemoglobinuria, dark urine, renal failure & uremia

❖Drug interactions:

- Antacids delay absorption of quinine
- Quinine may raise serum levels of warfarin & digoxin
- Potentiate neuromuscular blockers

☒Contraindications:

- Quinine should be avoided if possible in patients with visual or auditory problems
- Cautions in cardiac patients & renal insufficiency
- Should not be given with mefloquine (because both are toxic on heart)or after it .

mefloquine hydrochloride

✓ a synthetic 4-quinline methanol, related to quinine.

❖ Pharmacokinetics:

- orally.
- local irritation with parentral use.
- well absorbed, peak plasma concentration reached 18 hr<< slow onset.
- extensively distributed in tissues,eliminated slowly.
- single does treatment regimen.
- elimination T1/2 is 20 days.
- metabolized in liver.
- excreted mainly via bile & it is undergoes enterohepatic recycling
- drug could be detected in blood after dosing ceases for a period of few months.

❖ Pharmacological action:

- mefloquine has strong blood schizonticidal activity.
- no effect on gametocytes.

❖ Clinical uses:

1. prophylaxis of chloroquine-resistant falciparum & other malaria species (the only recommended for prophylaxis in endemic areas)
2. treatment of acute attack of multi resistant falciparum.**
3. can be used in children older than 2 years & pregnancy Except 1st trimester.

⁒ **N.B**:

-sever falciparum→ quinine more potent & quicker action

👽 Adverse effect:

- ♣ no hemolysis*
- ♣ as qunine
- ♣ GIT disorder
- ♣ neuropsychiatric toxicity with treatment (depression, psychosis,confusion,seizures)
- ♣ thrombocytopenia.
- ♣ ECG changes, bradycardia, arrythmia espicially if taken with quinine & quinidine.

☒contrai;ndication:

- ⅄ psycaitric disorders.
- ⅄ Epilepsy.
- ⅄ cardiac conductiondisorder.
- ⅄ co-administration with quinine quinidine or halofantriene.

primaquine:

✓ primaquine phosphate is a synthetic 8-aminoquinoline derivative.

❖ Pharmacokinetics :-

- orally
- well absorbed
- peak plasma level in 1-2hr.
- never parentrally→ hypotention
- T1/2 = 3-8hr.
- widely distributed to tissues, but only a small amount is bound there.
- metabolized by oxidation to many compound.
- it`s metabolites have less antimalarial activity but more potential to induce hemolysis
- excreted in urine

❖ Pharmacological action :

- metabolites of primaquine acts as oxidants that are responsible for schizontocidal action.
- these intermediates may produce haemolysis & methaemoglobinemia associated with primaquine use.(im/p)

➲ **antimalarial action:** (T&F)

- ✓ active against hepatic stages of all human malaria parasites (tissue schizonicides)
- ✓ the only drug active against dormant hypnozoites of P.vivax & P.ovale and thus effects radical cure of these infections.**
- ✓ highly gametocidal action against the 4 malaria species.
- ✓ a single dose is occasionally used to render P.falciparum gametcytes non-infective.
- ✓ no effective against erythrocytic stage.
- ✓ resistance may develope.

❖ Clinical uses:

- the 1st drug for radical cure for dormant liver forms of acute vivax & ovale malaria **
- terminal prophylaxis of vivax & ovale.
- pneumocystis pnemonia →combined with chindamycin for mild & moderate pneumocystosis.
- not recommended for chemoprphylaxis of malaria.

Adverse effects:

- ♣ GIT disorders: pain,cramps
- ♣ Hematological disorders : Leukopenia & agranulaytosis, leukocytosis
- ♣ Arrythmias
- ♣ Haemolysis or methaemoglobinemia in person with (G6PD) deficiency
- ♣ patients should be tested for G6PD before primaquine use.

☒ contraindication:

- ⅄ should not be prescribed concurrently with myelosuppressive drug as quinidine.
- ⅄ granulocytopenia, methaemoglobenemia, G6PD deficiency.
- ⅄ pregnancy because the fetus is relativly G6PD deficient & at risk of hemolysis.
- ⅄ never parentrally (hypotension)

➲Dihydrofolate reductase inhibitors (T&F) "

Pyrimethamin and proguanil

- ✓ **Pyrimethamin :** Is 2 ,4 diminopyrimidine related to trimethoprim
- ✓ **Proguanil:** biguanide derivative

❖Pharmacokinetics:

Both are slowly but adequately absorbed

- Pyrimethmine the peak plasma after 2-6hr and bound to plasma protein and has an elimination half life of 3-5day,in prophylaxis it is given once per week
- Proguanil reaches peak plasma about 5hr and has elimination half life of about 16 hr so in prophylaxis it should be given daily
- Pyramethamine undergoes extensive metabolism before excretion
- Proguanil (prodrug) is converted to its active metabolite cyclo-guanil

❖Mechanism of action:

- Pyrimethamine and cyclo-guanil inhibit plasmodial DHF reductase thus inhibit folate synthesis required for biosynthesis of purines and pyrimidine
- They have high affinity for plasmodial DHF reductase more than human enzyme

➲Anti malarial activity:

- ✓ Slow action blood schizontal activity against all malarial species
- ✓ Have sporontocidalactivity in mosquitos gut
- ✓ Prevent the maturation of early p.falciprum hepatic schizont
- ✓ Neither drug is adequately gametocidal nor effective against persistant liver stages of p.vivax or p.ovale

❖Clinical Uses:

1- Chemoprophylaxis

- Resistance to both drugs is found worldwide for falciprum therefore prophylaxis either drug alone is no longer recommended
- Choloroquine (500mg)weekly and proguanil (200mg daily) used as alternative to mefloquine although less effective but less toxic
- Purimethameni combinations are not recommended coz of toxicity and resistance

2- Treatment of chloroquine resistant falciprum

- **Fansidar**
  - ✓ Pyrimethamine and sulfodoxine
  - ✓ As adjunct to quinine therapy to reduce the drug course and limit the toxicity
  - ✓ Not reliably effective against other species of malaria except falciprum
  - ✓ Not for sever malaria
- **Maloprim**
  - ✓ Pyrimethamine and dapsone(salfone)

3- Toxoplasmosis

- Treatment of choice is pyrimethamine in combination with sulfadiazine or clindamycin**
- Levcovorin Ca++ (folinic acid) is given to avoid heamatological disorders

👽 Adverse effects:

- ♣ **In malarial treatment:**
  - ✓ Well tolerated
  - ✓ GIT disturbances, skin rash
  - ✓ Mouth ulcers
  - ✓ Alopecia described with proguanil
- ♣ **High doses of pyrimethamnie for toxoplasmosis**
  - ✓ Folic acid deficiency
  - ✓ Megaloplastic anemia, agranulocytosis and thrompocytopenia
  - ✓ Gastric irritation
- ♣ **Neurological symptoms**
  - ✓ Headache
  - ✓ Insomnia
  - ✓ Depression
  - ✓ Ataxia
  - ✓ Tremors
  - ✓ Seizures
  - ✓ Respiratory depression

☒ Contraindications:

- ⅄ Renal and hepatic impairment, pyrimethamine should be used cautiously
- ⅄ Pyrimethamnie can be used in pregnancy but not in the first trimester of pregnancy
- ⅄ Proguanil can be used in pregnancy but folate supplement should be given

❾DRUGS FOR SCHISTOSOMIASIS

☺سؤال كامل تعداد للأدوية

❖Anti schistosomal drugs :-

1- Praziquantel. (all)

2- Metrifonate.(S. heamatobium).

3- Oxamniquine. (S .mansoni).

Infecting Organism	Drugs of Choice	Alternative Drugs
Trematodes (flukes)		
Schistosoma haematobium	Praziquantel	Metrifonate
Schistosoma mansoni	Praziquantel	Oxamniquine
Schistosoma japonicum	Praziquantel	None

Praziquantel

(MCQ)

- ✓ It is a synthetic isoquinoline-pyrazine derivative
- ✓ It is effective in the **treatment** of schistosome infections of **all** species and **most other trematodes and cestodes**.

Chemistry and pharmacokinetics:

- rapidly absorbed after **oral** intake.
- Maximum plasma concentration in 1-3 hr. .
- Cross **BBB**.
- bound to plasma protein
- It has a wide distribution and
- Undergoes 1st pass metabolism in liver to inactive metabolites (oxidative). → so short t½ .
- T½ = 0.8 -3 hr. (↑ in liver dizes).
- Execrated in **urine** (60-80%) &bile (20-40%).

Bioavailability :

- ↑ed by carbohydrate meal & cimetidine .
- ↓by corticosteroid & antiepileptics (pheytoin & carbamazepine).MCQ

Pharmacological action:

- ↑es cell membrane permeability to **Ca^{++}** resulting in muscular activity contraction & paralysis , dislodgement & death .MCQ
- **Broad spectrum anthelminthic** drug .
- **Effective** in the **treatment** of **schistisome.**
- Infections of **all species** & **most other tremaotodes** & **cestodes**(tape worms)**but not** (nematodes) **round worms** .
- **Effective** against **mature** & **immature** stages of worms.

Clinical uses :-

➲Schistosomiasis :

- ✓ Drug of choice for all forms (20mg/ kg) for two (s.mansoni & s.hematobium) or three(s.japonicem)doses at 4-6 h interval .
- ✓ Taken after meals with liquids without chewing (due to vomiting).
- ✓ The interval b/w the doses should not be less than 4hr& not more than 6hrs
- ✓ Effective in children & adult
- ✓ Not clear whether the drug can safely be used during acute stage of disease ,because release of antigens from drug of immature worm may exacerbate the symptoms .
- ✓ Effectiveness of the drug for chemoprophylaxis has been established .

➲Other cestode infection : (as a drug of choice except in neurocyrticercosis)

- Clonorchiasis (liver) and paragonimiasis (lung)
- Taeniasis and diphyllobothriasis
- Neurocyrticercosis ,but albendazole is preferred.
- Hymenolepis Nana .
- Hydatid cyst and others (Echinococcosis)

Adverse Reactions: (imp 3 :- CNS ,allergic reaction ,GI)

1. **Most frequent** are <u>headache, dizziness drowsiness and lassitude.</u>
2. **GIT disturbances**(N , V) .
3. Mild to minimal transient elevations of liver enzymes.
4. **Pruritus, urticaria, arthralgia, mylagia**
5. Low-grade fever, pruritus and skin rashes, augmented eosinophilia, may appear several days after starting the medication due to release of foreign protein from dying worms rather than direct toxicity. *(adverse effects maybe more, especially in S.mansoni infections).*
6. **neurocysticercosis** : neurologic abnormalities (headache , mental changes , seizures) increase by inflammation (so we give corticosteroids).

☒***Contraindications and cautions:***

- mainly in ocular cysticercosis, as parasite destruction in the eye may cause irreparable damage.
- Not safe for children under the age of 4 years, pregnancy ,&nursing mothers.
- Can used in liver impairment but dose should be reduced.
- Driving
- Activities require alertness & physical coordination should be prohibited .

Done ☺

By : 425 pharma Girls

بالتوفيق للجميع