Antimycobacterial agents

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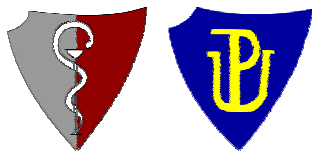
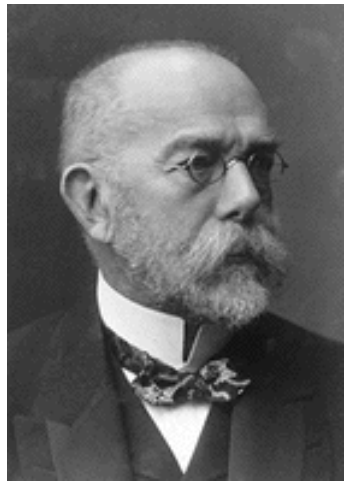
Ústav farmakologie LF UP



November 14, 2005

Intro

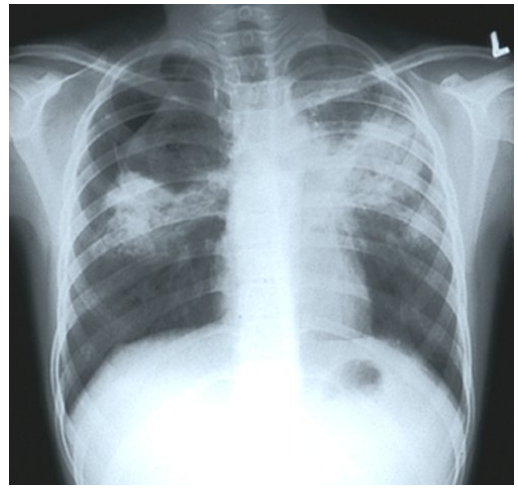
- Tuberculosis
  - mycobacterium tuberculosis
- Leprosy
  - mycobacterium leprae



both can survive after phagocytosis inside macrophages
need T helper 1 lymphocytes to activate these

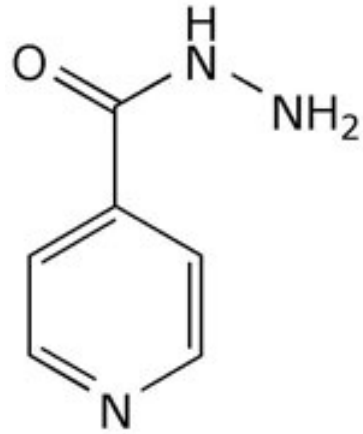
Tuberculosis

- Tuberculosis
  - *mycobacterium tuberculosis*
  - incurable -> curable -> ??
  - resistant strains
  - 2 milion deaths each year
  - synergy between mycobacteria and HIV
  - leading cause of death from a single agent
- Treatment
  - initial phase 2 months - 3 drugs
  - continuation phase - 2 drugs



Isoniazid

- Isoniazid
  - only acts on mycobacteria
  - passes into cells
  - interferes with metabolism, details not clear
  - resistance by decreased penetration
  - no crossed resistance



Kinetics and side effects

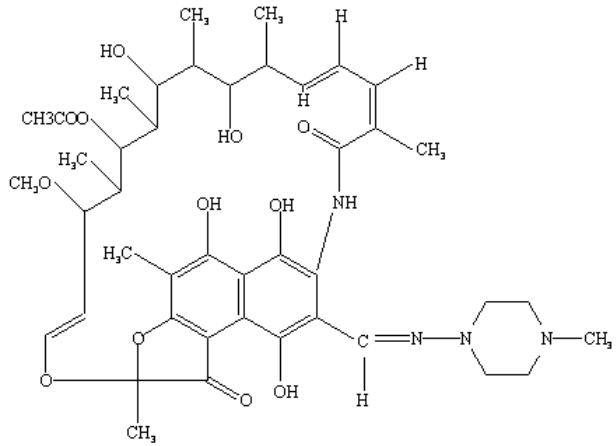
- oral administration
- slow and rapid acetylators (half-life 1-3 hours)
- allergies, inhibits metabolism of some antiepileptics

Rifampicin

- Rifampicin (Rifampin)
  - binds to and inhibits DNA dependent RNA polymerase
  - only active in procaryontic cells
  - most active antituberculotic
  - rapid resistance development (single step)

Kinetics and side effects

- oral administration
- rapid distribution
- colours body fluids orange
- powerful CYP inductor

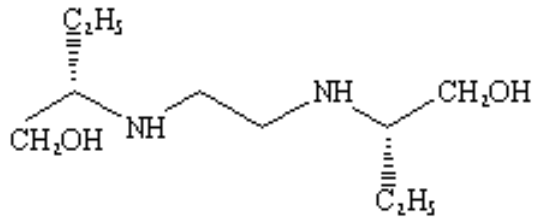


Ethambutol

- Ethambutol
  - only acts on mycobacteria
  - unknown action
  - taken up into the cell and after 24 hours inhibits growth
  - rapid resistance if used alone

Kinetics and side effects

- oral administration
- taken up by erythrocytes and then released
- optic neuritis
- colour vision impairment

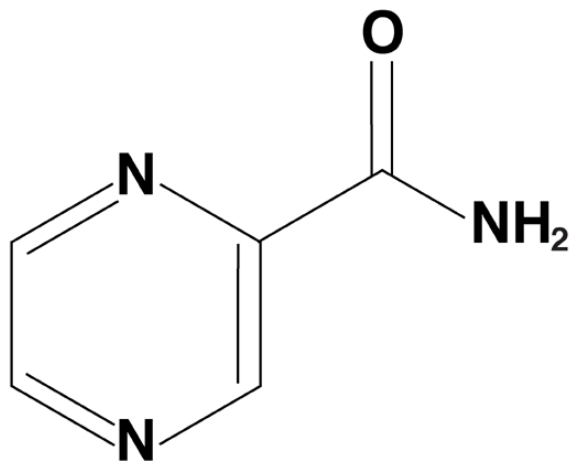


Pyrazinamide

- Pyrazinamide
  - inactive at neutral pH, tuberculostatic at acid pH
  - phagolysosomes have low pH

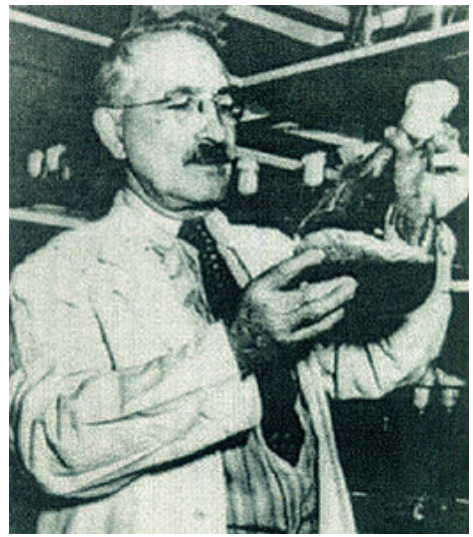
Kinetics and side effects

- oral administration
- rapid absorption
- gout
- liver damage (esp. in high doses)



Second line

- Capreomycin
  - peptide antibiotic
  - kidney damage, ototoxicity
  - not to be combined with aminoglycosides
- Cycloserine
  - broad spectrum antibiotic
  - prevents D-Ala D-Ala dipeptide formation
  - CNS side effects
- Streptomycin
  - rarely used today



Waksman, 1944

Reserve line

- p-aminosalicylic acid
  - first used, high doses are needed
- Protionamide
  - izonicotinic acid derivate
  - mycobacteriostatic
  - rapid resistance
- Terizidon
  - two serine residues, toxic

Therapy regimes

	initial phase	continuation phase
standard short-term treatment (6-7 months)	izoniazide + rifampicin + pyrazinamide + ethambutol or streptomycine for 2 or 3 months	izoniazide + rifampicin for 4 months
9-12 month treatment	izoniazide + rifampicin + ethambutol or streptomycine or pro protionamid for 2 or 3 months	izoniazide + rifampicin for 7-10 months

thank you for your attention