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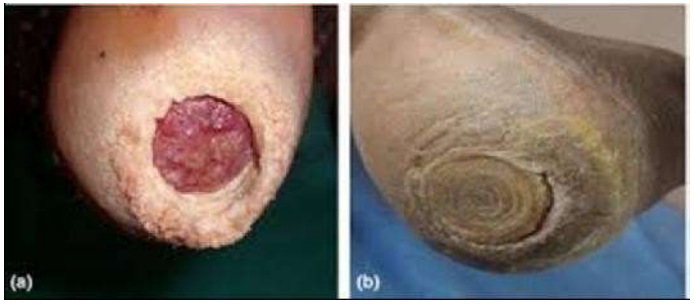
Subject: Pharmacolgy-III (BP 602T)
Unit: III
Topic: Anti Leprotic Drugs

Introduction



Leprosy is caused by a slow-growing type of bacteria called Mycobacterium leprae (M. leprae)
Also known as Hansen's disease, after the scientist ho discovered M. leprae in 1873
It primarily affects the skin and the peripheral nerves
Long Incubation period (3 – 5 years)

Antileprotic Drugs

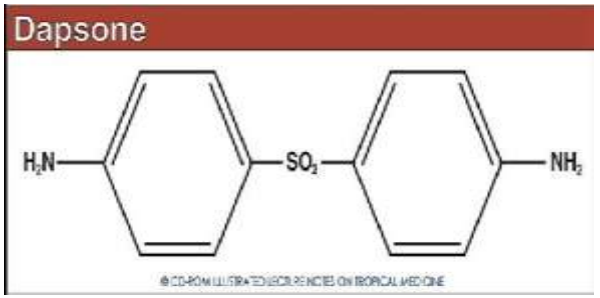
Sulfones – DAPSONE (DDS)-DIAMINO DIPHENYL SULFONE

Phenazine Derivative - CLOFAZIMINE

Antitubercular Drugs - RIFAMPICIN, ETHIONAMIDE

Antibiotics: OFLOXACIN, MOXIFLOXACIN, MINOCYCLINE AND CLARITHROMYCIN

Dapsone (DDS)



The simplest, oldest, cheapest

MOA: Leprostatic even at low concentration

Chemically related to Sulfonamides – same mechanism – inhibition of incorporation of PABA into folic acid (folic acid synthase)

Specificity to *M leprae* – affinity for folate synthase

Activity: Used alone – resistance – MDT needed

Resistance – Primary and Secondary (mutation of folate synthase – lower affinity)

However, 100 mg/day – high MIC -500 times and continued to be effective to low and moderately resistant Bacilli (low % of resistant patient) Persisters. Also has antiprotozoal action (Falciparum and T. gondii)

Dapsone (DDS)

Pharmacokinetics: Complete oral absorption and high distribution (less CNS penetration) Half life 24-36 Hrs, but cumulative

- 70% bound to plasma protein – concentrated in Skin, liver, muscle and kidney
- Acetylated and glucoronidated and sulfate conjugated – enterohepatic circulation

ADRs: Generally Well tolerated drug

- Haemolytic anaemia (oxidizing property) - G-6-PD are more susceptible
- Gastric - intolerance, nausea, gastritis
- Methaemoglobinaemia, paresthesia, allergic rashes, FDE, phototoxicity, exfoliative dermatitis and hepatotoxicity etc.

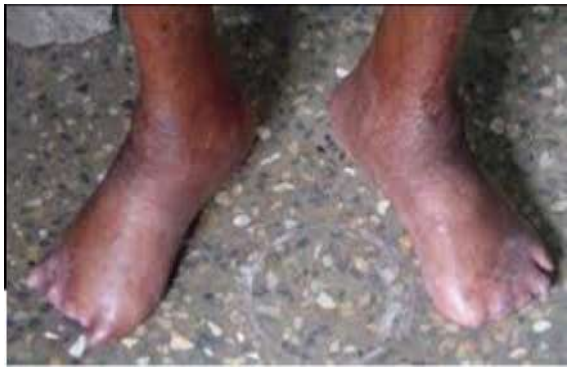
Dapsone (DDS)

Active against protozoa
Combined with pyrimethamine alternative to sulfadoxine-pyrimethamine for P.falciparum and toxoplasma gondii infection
Active against Pneumocystis jirovecii
Also has anti-inflammatory property

Sulfone Syndrome

Symptoms: Fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anemia
Starts after 4- 6 weeks of therapy, more common with MDT
Management: stopping of Dapsone, corticosteroid therapy
Dapsone contraindications: Severe anaemia and G-6-PD deficiency

Clofazimine



Phenazine dye – antileprotic, anti-inflammatory and Bacteriostatic

MOA: Interference with template function of DNA

Alteration of membrane structure and transport

Disruption of mitochondrial electron transport

Monotherapy causes resistance in 1 – 3 years

Dapsone resistants respond to Clofazimine

Kinetics: absorbed orally (70%) and gets deposited in subcutaneous tissues – as crystals

Half life – 70 days

Clofazimine

ADRs: well tolerated

Skin: Reddish-black discolouration of skin, discolouration of hair and body secretions

Dryness of skin and troublesome itching, phototoxicity, conjunctival pigmentation

GIT: Nausea, anorexia, abdominal pain and loose stool (early and late) – dreaded enteritis

Contraindication: Early pregnancy, liver and kidney diseases

Rifampicin

Rifampicin: Cidal. 99.99% killed in 3-7 days, skin symptoms regress within 2 months

- Included in MDT to shorten the duration of treatment and also to prevent resistance
- No toxic dose as single dose only
- Should not be used in ENL and Reversal phenomenon

Ofloxacin: all fluoroquinolones except ciprofloxacin are active. Used as alternative to Rifampicin

Minocycline: Lipophillic - enters M leprae. Less marked effect than Rifampicin

ETHIONAMIDE

Anti leprotic and anti tubercular
It is a fast acting drug than dapsone
But it is more expensive and more toxic
It is orally effective and it is administered daily
Poorly tolerated –hepatotoxicity
250mg/day

Clarithomycin

Only macrolide with activity against M. leprae
Less bactericidal than rifampin
Monotherapy- 500mg daily/ 8wks- 99.9% killing
Synergistic action with minocycline
Used in alternative MDT regimen

MINOCYCLINE

High lipophilicity –penetrates into M.leprae
100mg/day
Antileprotic activity rif>mino >Clari
8 wks treatment

LEPRA REACTION

The acute exacerbation which occurs during the course of leprosy is called as lepra reaction
It occursin LL type- after starting with chemotherapy and intercurrent infections
Jerish Hexheimer (Arthus) type reaction due to release of antigens from killed bacilli
May be mild severe or life threatening ENL- erythema Nodosum Leprosum
Treatment-clofazimine -200mg
Dapsone temporary withdrawal
Severe reaction- prednisone-40-60 mg.. Tapered in 2-3 months
Thalidomide –alternative to prednisolone in ENL

Reversal reaction

TT and BL cases

Manisfestation of delayed hypersensitivity to M.leprae antigens

Cutaneous ulceration, multiple nerve involvement with tender nerves

Treatment-Clofazimine/ corticosteroids

Classification-Ridley and Jopling - 1966

Lepromatous-LL
Borderline –BL
Borderline tubercular-BT
Tuberculoid TT

Conventional monotherapy
MT-Dapsone 100-200m-/ 5/7 days in week
TT-4-5 yrs
LT- 8-12 yrs or life long

Tuberculoid and Lepromatous

Tuberculoid	Lepromatous
Anaesthetic patch	Diffuse skin and mucous membrane, nodules
CMI-cell mediated immunity is normal	CMI is absent
Lepromin test is positive	Lepromin test is negetive
Bacilli rarely found in biopsy	Skin and mucous membr biopsy +ve for bacilli
Prolonged remission with periodic exacerbations	Prognosis to anaesthesia of distal parts, atropy

Treatment of Leprosy - NLEP

Monotherapy - 1982 and since then MDT
Elimination achieved in India in 2005 (prevalence rate ?)
Leprosy classified as LL, BL, BB, BT and TT
For operational purposes:
Paucibacillary: few bacilli and non-infectious – TT and BT
Multibacillary: large bacilli load and infectious – LL, BL and BB types

Single lesion Paucibacillary: single lesion

MULTIBACILLARY	**PAUCIBACILLARY**
RIFAMPIN-600mg OD/once per month	RIFAMPIN-600mg OD/once per month
Dapsone -100mg daily	Dapsone -100mg daily
Clofazimine-300mg once/month 50mg-OD	
Duration -12 months	6 months

Alternative regimens			
Intermittent ROM	Rifampin 600mg +	Oflox 400mg +	Minocycline 100
	Once/month	PBL	3-6months
		MBL	12-24 months
Clofazimine 50mg + (any 2) 6months	Ofoxacin 400mg	Minocycline 100mg	Clarithromycin 500mg
RMMx regimen Moxiflox 400mg +	minocycline 200mg	Rifampin 600mg	PBL- 6doses MBL-12 doses
Clofazimine 50mg (any 1) **4 drug regimen** Rifampin 600mg For 12wks is similar to standard MDT for	Ofloxacin 400mg Minocycline 100mg Sparfloxacin 200mg	18 months Clarithromycin 500mg	 Minocycline 100mg