Pharmacotherapy of Leprosy

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- History
- Leprosy classification
- Drugs – classification and pharmacology
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History of Treatment

- Chaulmoogra oil was used as an antileprotic agent in Indian medicine for centuries.
- 1949 - Cochrane et al employed parental Dapsone at Chenglepet, Madras.
- 1949 - Lowe and Smith used Dapsone orally.
- 1981 - WHO introduced MDT of Leprosy.
Leprosy classification

Types

- Lepromatous leprosy (LL)
- Tuberculoid leprosy (TL)
- Borderline lepromatous leprosy (BL)
- Borderline tuberculoid leprosy (BT)
- Indeterminate
Classification

WHO classified for therapeutic purpose

**Paucibacillary leprosy** (non infectious) - TL, BT- with 2-5 skin lesions

**Multibacillary leprosy** (Infectious) – LL, BL.- more than 6 skin lesions
Drugs classification

- Sulfones: Dapsone (DDS)
- Phenazine derivatives: Clofazimine
- Antitubercular drugs: Rifampin, Ethionamide
- Other Antimicrobials: Ofloxacin, Moxifloxacin, Minocycline, Clarithromycin
Dapsone

- Acts through inhibition of bacterial folate synthesis.
- Exhibits bacteriostatic effect.
- Given orally, well absorbed and widely distributed.
- Produces ten times more concentration in diseased skin than in normal skin.
- Plasma half-life is 24-48 h.
- Dose is 100mg once daily.
ADVERSE DRUG REACTIONS

- Haemolysis of red cells
- Methaemoglobinemia,
- Anorexia, nausea and vomiting,
- Fever, allergic dermatitis and neuropathy.
- **Lepra reactions** (an exacerbation of lepromatous lesions) can occur
- Contraindicated:
  - severe anaemia (Hb < 7g/dl)
  - G6PD deficiency
Clofazimine

- Clofazimine is a phenazine dye
- It interferes with template function of DNA.
- has anti-inflammatory activity and
- useful in patients in whom dapsone causes drug reactions
- t ½ is 70 days
ADVERSE DRUG REACTIONS

- Relate to the fact that clofazimine is a dye.

- The most prominent untoward effect is red-brown to black skin discoloration.

- Dose-related nausea, giddiness, headache and gastrointestinal disturbances can also occur.
Rifampicin

- Anti tubercular drug also effective in leprosy
- A bactericidal drug
- Relieves nasal symptoms in 2-3 weeks and skin lesions start regression in 2-3 months
- Used in MDT at a dose of 600mg once a month
ADVERSE DRUG REACTIONS

- Urine & secretions may become red
- Respiratory syndrome:
  - Breathlessness, shock, collapse
- Cutaneous syndrome:
  - Flush, pruritis, rash, watering in eyes
- Flu syndrome:
- Abdominal syndrome
- CONTRAINDIATED: Hepatic & renal dysfunctions, ENL & Reversal reaction
Ethionamide

- It is Ethyl Isothionicotinamide
- Chemically related to Isoniazid
- Acts synergistically with dapsone
- Dose : 250mg / day
Fluoroquinolones

- Ofloxacin, moxifloxacin, sparfloxacin are effective.
- These are BACTERICIDAL.
- 400mg/day of Ofloxacin can kill 99.9% bacilli. (22 daily doses)
- Used as an alternate drug
- Moxifloxacin is the most potent drug.
Minocycline

- Lipid soluble tetracycline
- Penetrates M. leprae
- Inhibit bacterial protein synthesis
- A dose of 100mg/day produces plasma levels that exceed MIC of M. leprae 10 – 20 times.

**ADVERSE EFFECTS**: vertigo
Clarithromycin

- O-methyl derivative of Erythromycin.
- 500mg daily dose kills 99.9% bacilli of Lepromatous Leprosy patients in 8 weeks.

- **Metabolism** - in the liver converted to 14 α- hydroxy clarithromycin which also has antimicrobial activity
- **Excretion** - through Urine
- Dose adjustment needed in Kidney disease
## Mycobacterium leprae - resistant gene

<table>
<thead>
<tr>
<th>Drug</th>
<th>gene</th>
<th>Function of gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFP</td>
<td>rpoB</td>
<td>DNA dependent-RNA polymerase β subunit</td>
</tr>
<tr>
<td>DDS</td>
<td>folP</td>
<td>Dihydropteroate synthesis</td>
</tr>
<tr>
<td>OFLX</td>
<td>gyrA</td>
<td>DNA gyrase</td>
</tr>
</tbody>
</table>
MDT of Leprosy

- Irregular and inadequate duration of treatment with single drug have allowed emergence of resistance
- WHO introduced MDT in 1981
- Implemented under NLEP in India
MDT of Leprosy

Goals:

- To prevent the emergence of Dapsone resistance
- To render MBL cases noncontagious
- To reduce the duration of Therapy
- To eliminate dormant forms
### WHO recommended regimes

<table>
<thead>
<tr>
<th>WHO recommended regimes</th>
<th>Paucibacillary leprosy (D+R)</th>
<th>Multibacillary leprosy (DC+RC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paucibacillary</strong></td>
<td>Dapsone 100mg daily (self administered)</td>
<td>Dapsone 100mg + Clofazimine 50mg daily (self administered)</td>
</tr>
<tr>
<td><strong>leprosy</strong></td>
<td>Rifampicin 600mg once a month (supervision)</td>
<td>Rifampicin 600mg + Clofazimine 300mg once a month (supervision)</td>
</tr>
<tr>
<td><strong>(D+R)</strong></td>
<td></td>
<td>12 months</td>
</tr>
</tbody>
</table>

**6 months**
Alternative Regimens

- **Indicated in**
  - Dapsone resistance
  - MDT regimen is NOT advisable

- **Include**
  - Intermittent ROM
  - Four drug regimen
  - Intermittent RMMx.
## Alternative Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>PBL</th>
<th>MBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent ROM</td>
<td>R(600mg)+Ofl(400mg)+Min(100mg) once in month-upto 6 months</td>
<td>R(600mg)+Ofl(400mg)+Min(100mg) once in month-upto 24 months</td>
</tr>
<tr>
<td>Intermittent RMMx</td>
<td>Mox(400mg)+Min(200mg)+R(600mg) once in month-upto 6 months</td>
<td>Mox(400mg)+Min(200mg)+R(600mg) once in month-upto 12 months</td>
</tr>
<tr>
<td>Four drug Regimen</td>
<td>R(600mg)+Spar(200mg)+Clar(500mg)+Min(100mg)-3 months</td>
<td></td>
</tr>
</tbody>
</table>
Lepra reactions

- Due to release of Ag from killed bacilli

- Type I

- Type II
Type -1 Lepra Reaction

**TYPE 1 / REVERSAL REACTIONS**

Type IV Hypersensitivity
(Delayed hypersensitivity response)

Cutaneous ulcerations, multiple nerve involvement

Treatment: Corticosteroids, Clofazimine
Type -I Lepra Reaction

**Type II / Erythema Nodosum Leprae**

Type III Hypersensitivity
(Humoral antibody response)

Existing lesions enlarge, become red, inflamed and painful

Treatment: Clofazamine (200mg OD), corticosteroids (40-60 mg/day), Thalidomide (alternative to steroids)
Conclusion

- Drug therapy of Leprosy started with chalmoogra oil.
- Currently MDT therapy is advised.
- Alternative regimens are ROM, RMMx and Four drug regimen.
- Drug of choice in lepra reaction is corticosteroids.
THANK YOU