PHARMACOKINETICS OF CLOFAZIMINE WITH MULTIPLE DOSE ADMINISTRATION IN LEPROSY PATIENTS

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Clofazimine
( CAS 2030-63-9 )  M.wt. 476.3

3 (p-chloroanilino)-10-p-chlorophenyl
,10-dihydro-2-isopropyliminophenazine
and its analogues

are being tried with
varying degrees of success in the treatment
of leprosy, tuberculosis and
Mycobacterium avium complex (MAC) disease
Gastrointestinal Absorption of clofazimine and its bioavailability

* Exact mechanism of clofazimine absorption from GIT is not clear.

• Species variation reported in absorption.

• In humans as much as 85% of the orally administered micronized drug in the form of suspension in oil is absorbed.

* Very slow absorption from the site of intramuscular injection.

* Faecal excretion of clofazimine in humans is variable. On an average 11-59% of single dose is excreted in 3 days (Levy 1974). Dose dependent absorption has been reported by our group (Mathur et al, 1985).
Clofazimine is highly lipophilic and is distributed principally to fatty tissue and cells of the reticuloendothelial system; The drug is taken up by macrophages throughout the body. It accumulates in high concentrations in the mesenteric lymph nodes, adipose tissue, adrenals, liver, lungs, gallbladder, bile, and spleen and in lower concentrations in the skin, small intestine, lungs, heart, kidneys, pancreas, muscle, omentum, and bone. Clofazimine crystals have also been found in bone marrow, sputum, sebum, and sweat, and in the iris, conjunctiva, macula, sclera, and cornea. The drug does not appear to distribute into the brain or CSF (McEvoy, 1990). The drug is found in nerve tissue and foot pads of mice fed with the drug (Nirmala Deo et al 2007). It crosses the placental barrier.

A systematic study from JALMA, Agra has shown that in 8 lactating female leprosy patients on clofazimine 50 mg daily or 100 mg on alternate days for 1-18 months, mean plasma and milk clofazimine levels were 0.9 +/- 0.03 micrograms/ml and 1.33 +/- 0.09 micrograms/ml respectively and the amount of drug ingested by the breast-fed infants of the was 0.199 ± 0.013 mg/kg/day which represented 22.1 ± 1.9% of the maternal dose (Venkatesan et al 1997).
Drug interactions with Vitamin A and Isoniazid

In addition to the red and black pigmentation, ichthyosis which occurs in 66% of patients under Clofazimine is considered as adding to the stigma by patients. (Ramu and Iyer, 1976).

Reduced levels of vitamin-A have been observed in ichthyotic areas compared to non-ichthyotic area (Bharadwaj et al, 1982);

Reduced levels of vitamin- A have been also observed in the plasma of some cases under Clofazimine therapy for a long time with associated xerosis of the cornea and night blindness.

For symptoms of acute abdomen caused by accumulation of crystals in the submucous of the intestines and mesenteric glands, INH 200 mg a day has been found to relieve the symptoms (Ramu and Iyer, 1976) due to mobilization of Clofazimine from the tissue by INH (Venkatesan, 1989). However, in paralytic ileus, a serious side effect of Clofazimine therapy, INH does not help.
Pharmacokinetics of the drug: Plasma levels and bioavailability

Although clofazimine was introduced into leprosy treatment in the 1960s, only a few systematic studies on its disposition either in humans or animals have been reported. More information on pharmacokinetics of clofazimine in man is still needed.

The only systematic study on single and multiple dose clofazimine pharmacokinetics in healthy volunteers by Lanyi et al (1987). In healthy volunteers receiving a single dose of 200 mg clofazimine with food, the mean peak plasma concentrations of clofazimine was 861 ± 289 pmol/g (0.410 ± 138 μg/g) after 8 hr (median). The mean terminal half-life was 10.6 days. The mean AUC (0-264h) for plasma was 16.05±0.398 ug/g.h. Bioavailability in terms of plasma AUC was more with drug administered after breakfast or with breakfast compared to administration in empty stomach. In the multiple dose (50 mg daily for 8 days), agreement has been found between the mean experimental plasma concentration values and the plasma concentration profile predicted from the single dose pharmacokinetics.
Average Plasma levels in leprosy patients reported by various groups of researchers:

(Mansfield 1974)
0.5 µg/ml after 100 mg clofazimine thrice daily  
0.7 µg/ml after 100 mg clofazimine thrice daily  
1.0 µg/ml after 300 mg clofazimine daily;  1.41 µg/ml after 400 mg clofazimine daily

An average plasma concentration of 1.15 µg/ml in leprosy patients receiving 300 mg clofazimine daily (Balakrishnan et al, 1976; Venkatesan et al, 1980)

In female leprosy patients on clofazimine 50 mg daily or 100 mg on alternate days for 1-18 months, mean plasma clofazimine levels were 0.9 ± 0.03 µg/ml (Venkatesan et al 1997).

In view of the paucity of systematic data on multiple dose pharmacokinetics in leprosy patients,

A multiple dose pharmacokinetic study has been conducted in leprosy patients at National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra (India) by our group.
Material and Method

• Blood samples were collected from 20 leprosy patients (All male; Mean age 38Y) attending the Institute OPD and were on 30/60 daily doses of 50 mg clofazimine as part of MDT.

• Also 11 untreated patients (males; Mean age 40Y) admitted in the ward and on 50 mg clofazimine daily (with dapsone 100 mg) with breakfast for 7/14 days at 3,5,7,12 and 24 hrs after the last oral dose. Blood samples were collected and Clofazimine levels were determined in plasma by microadapted spectrophotometric method of Barry et al (1960), reported by Desikan and Balakrishnan (1976).

• AUC 0-12 h and AUC 0-24 h were calculated using trapezoidal rule.
Pharmacokinetics of Clofazimine in Leprosy Patients on multiple dose oral administration

<table>
<thead>
<tr>
<th>Clofazimine Dosage</th>
<th>Plasma drug levels μg/ml ± SD (at hours after last oral dose)</th>
<th>AUC 0-12h μg/ml.h</th>
<th>AUC 0-24h μg/ml.h</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mg daily X7 days (n=6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0h</td>
<td>3h</td>
<td>5h</td>
<td>7h</td>
</tr>
<tr>
<td>0.213 ± 0.02</td>
<td>0.297 ± 0.04</td>
<td>0.390 ± 0.03</td>
<td>0.468 ± 0.04</td>
</tr>
<tr>
<td>50 mg daily X 14 days (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.370 ± 0.02</td>
<td>0.470 ± 0.01</td>
<td>0.566 ± 0.04</td>
<td>0.684 ± 0.04</td>
</tr>
</tbody>
</table>
Pharmacokinetics of Clofazimine after multiple oral administration

- after 7 d x 50 mg daily
- after 14 d x 50 mg daily

Plasma Clofazimine level µg/ml

Hours after last dose

0 2 4 6 8 10 12 14 16 18 20 22 24

0.0 0.2 0.4 0.6 0.8
• With seven daily doses of 50 mg clofazimine the oral availability of the drug, as defined by Area under Concentration-Time Curve, Mean AUC 0-12 h was 4.49 mg/L.h while it was 6.72 mg/L.h after 14 daily doses. Mean AUC 0-24 h was 8.44 mg/L.h while it was 12.68 mg/L.h after 14 daily doses.

• The mean basal (trough) plasma levels were 0.28 and 0.42 mg/L respectively after 7 and 14 daily doses.

• The mean basal plasma drug levels in patients after 30 and 60 daily doses of 50mg of clofazimine were 0.7 and 0.8 mg/L respectively.
Conclusion

These findings show adequate bioavailability even with daily doses of 50 mg and suggest that a steady state might be reached with 30-60 daily doses of the drug as has been predicted by Lanyi et al (1987).

The observation that AUC values/basal plasma levels are not so much proportionate to the length of the drug administration is indicative of extensive deposition and retention of the drug in the tissues and slow release from there.

The drug has been found to circulate significantly bound to plasma proteins including lipoproteins (Personal findings).

These findings will have relevance in the light of administration of clofazimine for long periods.