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Clinical Pharmacokinetic Considerations in the Treatment of Patients with Leprosy

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Summary

On the basis of the efficacy of the available agents, the World Health Organization has recommended only 4 drugs for combined chemotherapy of leprosy: rifampicin, dapsone, clofazimine and ethionamide/prothionamide. Thiacetazone and isoniazid are also used to a lesser extent by some physicians. Pyrazinamide may find a place in treating 'persister' bacilli.

Dapsone is absorbed slowly after oral administration. Peak plasma drug concentration is reached at about 4 hours; absorption half-life is 1.1 hours; elimination half-life is about 30 hours. Oral availability is around 90%. Dapsone is approximately 70% protein-bound, while its monoacetylated metabolite is amost entirely bound. Dapsone crosses the placenta and is excreted into breast milk. It is metabolised via acetylation and N-hydroxylation, but acetylation polymorphism has no effect on dapsone handling by leprosy patients. Dapsone penetrates into sciatic nerves of experimental animals but its presence has not been demonstrated in Schwann cells.

Oral doses of rifampicin are rapidly and completely absorbed. The bioavailability is greater when the drug is given before meals; peak concentrations occur at 1 to 2 hours. 80 to 90% of rifampicin is bound to plasma proteins, and the drug is found in saliva, cerebrospinal fluid and breast milk. Its main metabolite, desacetyl rifampicin, also exhibits antimycobacterial activity in tuberculosis. Rifampicin induces its own metabolism, as well

as that of dapsone and steroids. Absorption of dapsone and rifampicin is reported to be reduced in leprosy patients.

Clofazimine has been in use in leprosy treatment since 1960. In higher doses it exerts an anti-inflammatory action which is useful in treating leprosy patients in reaction. Oral absorption of the drug is slow and dose-dependent; faecal excretion also increases with dose. Single- and multiple-dose studies have shown a plasma half-life of around 10 days. Bioavailability of the drug is higher when given with food than when fasting; the peak plasma concentration occurs at 4 to 8 hours when the drug is administered with breakfast. After absorption, the drug is thought to circulate in protein-bound form, accounting for the fact that it is deposited in various tissues. Uneven distribution and prolonged retention in the tissues are special features of clofazimine metabolism. One unconjugated and 2 conjugated metabolites have been detected in urine, and the urinary excretion of both the parent compound and its metabolites is around 1% of the dose. Clofazimine crosses the placental barrier and is excreted into breast milk, but does not cross the blood-brain barrier. Small amounts of the drug are found in sebum and sweat.

The pharmacokinetic properties of ethionamide and prothionamide are similar in man. Both are absorbed rapidly and completely following oral administration. Peak plasma concentration of prothionamide occurs at around 18 minutes; plasma half-life is about 2 hours. The sulphoxide metabolite of the drug is active against Mycobacterium leprae.

The pharmacokinetics of thiacetazone, isoniazid and pyrazinamide are reviewed briefly. All 3 drugs are well absorbed after oral administration.

Haematological, dermatological and neurological effects and gastrointestinal symptoms are some of the side effects of the drugs reviewed. These may not pose serious problems at therapeutic dosages in leprosy, but the increased incidence of hepatotoxicity on combining rifampicin and ethionamide/prothionamide causes serious concern.

Rifampicin increases the excretion of dapsone, although this is not of therapeutic significance. Dapsone plus clofazimine reduces the absorption of rifampicin, while rifampicin plus dapsone does not affect absorption of clofazimine. Isoniazid treatment lowers the tissue concentration of clofazimine and increases its urinary excretion.

The modern era of leprosy chemotherapy began in the 1940s with the introduction of the sulphones (Faget et al. 1943), of which dapsone (4,4′-diaminodiphenyl sulphone) remains the mainstay of treatment even today, as one of the main components of various multidrug regimens advocated by physicians everywhere. However, the widespread emergence of dapsone-resistant strains of *Mycobacterium leprae* in lepromatous leprosy patients on dapsone monotherapy (WHO 1977) has forced leprologists to develop a rationally sound combination chemotherapy involving companion antileprosy drugs. The bacteriological and pharmacological activities of these drugs have been evaluated and compared by Colston et al. (1978a). Dapsone, clofazimine (a phenazine derivative), rifampicin and ethionamide/prothionamide are the only bactericidal drugs being considered as candidates for limited duration multidrug regimens (WHO 1982). Thiacetazone (thiosemicarbazone) and acedapsone (diacetyl dapsone), which exerts its antibacterial activity on conversion to dapsone, are reported to be useful in treating leprosy patients (Colston et al. 1978a; Zuidema et al. 1986). The usefulness of isoniazid is debatable (Freerksen 1975; Molesworth 1975; Pattyn et al. 1981; Shepard 1967), but pyrazinamide may prove helpful for the treatment of 'persister' bacilli in multi-bacillary leprosy cases (Katoch et al. 1988). The structures and the important bacteriological and pharmacological properties of the major drugs are given in figure 1 and table I. This review deals with the fundamental pharmacokinetic properties of the above-mentioned antileprosy drugs, and with their parti-

cular considerations in the treatment of leprosy patients.

1. Fundamental Pharmacokinetic Properties of Antileprosy Drugs

1.1 Dapsone

1.1.1 Absorption and Bioavailability

The rate of absorption of dapsone is rather slow, with a mean absorption half-life ($t_{½\alpha}$) of 1.1 hours [absorption rate constant (k_a) = $0.6h^{-1}$] after a single oral dose of 100mg (Ahmad & Rogers 1980a). An incomplete absorption of about 70 to 80% has been suggested on the basis of the findings of isotope studies in leprosy patients (Alexander et al. 1970). The absolute oral availability of dapsone has been reported to be 86 to 104% in healthy volunteers after a single oral dose of 100mg (Pieters & Zuidema 1987).

Concentration-time profiles in healthy volun-

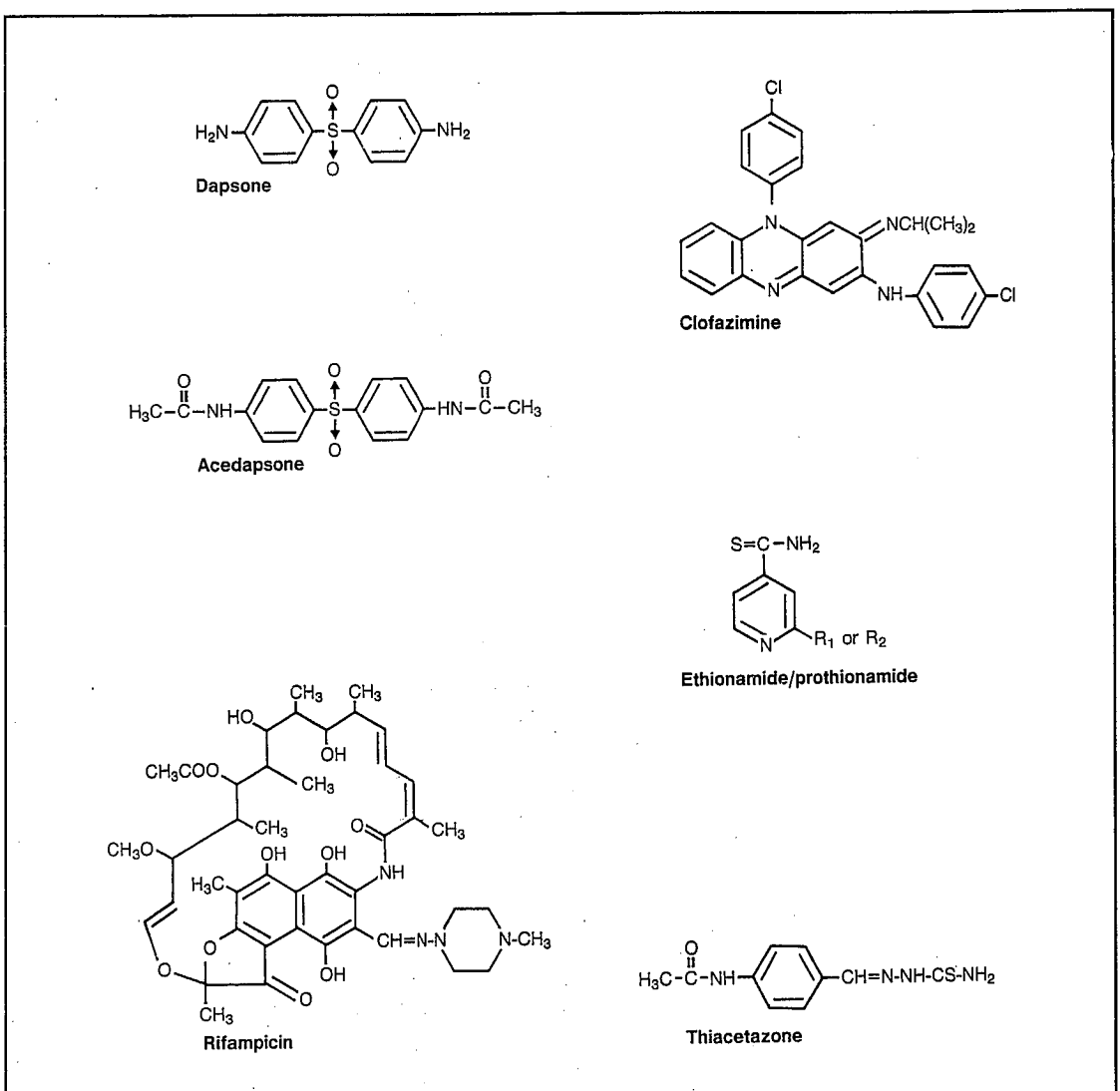

Fig. 1. Structure of common antileprosy drugs.

Table I. Bacteriological and pharmacological properties of common antileprosy drugs

Drug	MIC	Dose (mg)	Ratio of C_{max} to MIC[a]	No. of days during which C_{max} exceeds MIC[b]	Bactericidal activity
Dapsone	0.003	100	500	1	Low
Acedapsone	0.003	225	15	200	None
Rifampicin	0.3	600	30	1	High
Clofazimine[d]		50-100			Low
Ethionamide	0.05	375-500	60	1	Intermediate
Prothionamide	0.05	375-500	40	1	Intermediate
Thiacetazone	0.2	150	8	2	None

a Ratio of C_{max} in humans, after a single dose, to MIC determined in the mouse.
b Serum concentrations in humans after a single dose.
c Figures for MIC and C_{max} refer to the values of dapsone, as acedapsone is active against *M. leprae* after conversion to dapsone.
d Estimation of MIC is not possible because of uneven distribution of the drug in tissues.
Abbreviations: MIC = minimum inhibitory concentration; C_{max} = peak serum drug concentration.

teers and leprosy patients have been calculated by several groups after administration of dapsone by various routes, and this aspect has recently been reviewed by Zuidema et al. (1986). Peak serum or plasma concentrations are reached at approximately 2 to 6 hours after oral administration (Ahmad & Rogers 1980a,b; Alexander et al. 1970; Pieters & Zuidema 1987). Dapsone and its monoacetylated metabolite appear to have the same elimination half-life ($t_{½\beta}$), the values ranging from 14 to 83 hours (Glazko et al. 1968b; Peters et al. 1972, 1975, 1979; Swain et al. 1983). About 90% of a single dose of dapsone 100mg will be eliminated within 9 days, but following long term administration the drug has been detected in the body for up to 35 days after discontinuation of treatment (Lang 1979).

Dapsone concentration-time profiles in healthy volunteers after an intravenous infusion of the drug have recently been reported by Pieters and Zuidema (1987). The various pharmacokinetic parameters reported in studies of single-dose oral administration and intravenous infusion are shown in table II.

Zuidema et al. (1986), reviewing the pharmacokinetics of dapsone, mentioned a number of studies on plasma/serum concentrations of dapsone in leprosy patients and healthy volunteers following different single doses and also at steady-state. The findings of these studies suggest a proportionality between dose and peak blood drug concentration within the dose range of 50 to 300mg. Steady-state concentrations after daily oral doses of dapsone 100mg are roughly twice as high as concentrations from a single dose (Ahmad & Rogers 1980a; Halmekoski et al. 1978; Modderman et al. 1983). At steady-state a trough concentration of 0.5 mg/L for both dapsone and monoacetyl dapsone was found at any time during the 24 hours after the last oral dose of dapsone 100mg (Garg et al. 1988). It can be seen that at steady-states achieved by daily oral doses of dapsone 100mg, the serum or plasma concentration at any time will be about 150 times greater than the minimum inhibitory concentration (MIC) for *M. leprae* in blood (as determined in mice), and this fact is therapeutically significant.

Steady-state serum drug concentrations in leprosy patients following repeated intramuscular injections of dapsone 375mg in oily vehicle (UNICEF injection) have been reported by Modderman et al. (1983). During the week following the final injection, dapsone concentrations of 1 mg/L (300

times greater than MIC) were maintained. A monthly intra-adipose injection (in the gluteal subcutaneous fat layer) of rounded double-pyramidal crystals of defined size in an aqueous vehicle has been reported to result in an absorption rate which is sufficiently sustained for therapeutic purposes in terms of serum concentration well above MIC for *M. leprae* (Zuidema et al. 1986); this parenteral approach may be clinically useful, as it permits supervised monthly administration.

Monoacetyl dapsone and acedapsone are known prodrugs of dapsone. Intramuscular injection of acedapsone 225mg in benzyl benzoate/castor oil (4 : 6) results in blood concentrations of 0.02 to 0.08 mg/L during a 75-day period (George & Balakrishnan 1986; Glazko et al. 1968a), 6 to 25 times higher than the MIC for dapsone. In the context of the frequent emergence of dapsone resistance under such low therapeutic concentrations of the drug, its usefulness in leprosy chemotherapy is questioned by Zuidema et al. (1986). Repeated monthly injections of monoacetyl dapsone 700mg (equivalent to dapsone 600mg) produce blood concentrations between those of dapsone and monoacetyl dapsone (in the range of 0.5 to 1 mg/L) and are 180 to 300 times higher than the MIC (Zuidema et al. 1984).

1.1.2 Distribution and Protein Binding

While about 70 to 80% of dapsone is bound to plasma proteins, its main metabolite monoacetyl dapsone is almost entirely protein bound (Ahmad & Rogers 1980b; Biggs et al. 1979; Modderman et al. 1983; Peters et al. 1981). It has also been reported that monoacetyl dapsone is 20-25-fold more highly bound than dapsone (Glazko et al. 1969).

Dapsone seems to be widely distributed throughout the tissues, concentrations of the drug being nearly the same as those in blood (Chatterjee & Poddar 1957; Peters et al. 1977). Dapsone readily penetrates into the sciatic nerves of dogs and sheep, concentrations in nerve tissues equalling total plasma concentration (Allen et al. 1975). However, penetration of the drug into Schwann cells of nerves was not demonstrable in mice with advanced neuropathy (Boddingius & Stolz 1981).

The salivary glands are highly permeable for dapsone and particularly monoacetyl dapsone. Saliva concentrations of dapsone are about 18 to 27% of the blood concentration (Zuidema & Van Ginneken 1983a,b). Dapsone crosses the placenta (Hocking 1968), but no serious harmful effects on the child *in utero* have been reported (Jopling 1978). It is excreted in breast milk (Sanders et al. 1982); however, despite its presence in the urine of breast-

Table II. Pharmacokinetic parameters of dapsone (single dose) in healthy volunteers

No. of subjects	Dose (mg)[a]	Route	C_{max} (mg/L)[b]	$t_{½β}$ (h)[a]	k_e (h^{-1})[a]	k_a (h^{-1})	AUC (0-48h) (mg/L · h)[b]	Vd (L/kg)[a]	F (%)[a]	Reference
5	48.3 ± 2.0	IV	0.65-1.17	22.4 ± 5.6	0.033 ± 0.008		13.3-37.5	0.98 ± 0.12		Pieters & Zuidema (1987)
5	100	PO	1.12-2.28	21.7 ± 5.7	0.034 ± 0.009		24.0-75.4		93 ± 8	Pieters & Zuidema (1987)
1	100	PO	1.9	30	0.02	0.6		1.5		Ahmad & Rogers (1980a)

a Mean ± SD.

b Range.

Abbreviations: C_{max} = peak serum drug concentration; $t_{½β}$ = terminal half-life; k_e = elimination rate constant; k_a = absorption rate constant; AUC (0-48h) = area under the concentration-time curve from zero time to 48 hours post-dose; Vd = apparent volume of distribution; F = bioavailability; IV = intravenous; PO = oral.

fed infants, only 2 cases of neonatal haemolysis have been reported (Hocking 1968; Sanders et al. 1982). It has been suggested by Jopling (1978) that the presence of antileprosy drugs in the milk may protect the child from leprosy infection.

1.1.3 Metabolism and Excretion

Acetylation and *N*-hydroxylation are the 2 main pathways of dapsone metabolism (Glazko et al. 1969; Karim et al 1981; Zuidema et al. 1986). While the parent compound is easily acetylated to monoacetyl dapsone, further acetylation of the metabolite does not occur to any significant extent (Jones & Ovenell 1979; Lammintausta et al. 1979; Murray et al. 1971). A constant equilibrium between acetylation and deacetylation is reached within a few hours after the oral administration of either dapsone or monoacetyl dapsone (Gelber et al. 1971). However, deacetylation is a rather slow process compared with acetylation (Zuidema et al. 1986), probably owing to the extensive protein binding of monoacetyl dapsone. Acedapsone is also deacetylated *in vivo* to form monoacetyl dapsone and dapsone (Glazko et al. 1968b). Both the prodrugs exert their antibacterial effect only after conversion to dapsone. Individual variability in acetylation because of the genetically determined *N*-acetyl transferase activity has been shown to be of 3 acetylator phenotypes, viz. 'slow', 'fast' and 'intermediate' (Gelber et al. 1971; Peters et al. 1972, 1975, 1979). However, this acetylation polymorphism does not seem to affect the pharmacokinetic parameters of the drug (Zuidema et al. 1986).

Hydroxylation is the other main pathway of metabolism of dapsone. Probably about 2 to 7% of *N*-hydroxyl dapsone is excreted in the free form and 30 to 50% in the conjugated form. A high renal clearance of these metabolites has been suggested (Zuidema et al. 1986).

Five to 15% of the dapsone dose is excreted as unchanged drug (Ellard 1966; Gelber et al. 1971). The amount of monoacetyl dapsone excreted in urine is very small, and acedapsone does not appear to be excreted as such (Zuidema et al. 1986).

Monoacetyl dapsone and other *N*-substituted sulphones are much less effective than dapsone in terms of antibacterial action (Bawden & Tute 1981), and probably do not contribute to the therapeutic effect in leprosy as indicated by an absence of a relationship between acetylation status and the development of resistance in leprosy patients (Balakrishnan & Ramu 1977; Gelber & Rees 1975; Peters et al. 1976). The concentrations of NOH metabolites in blood are extremely low and their contribution to the effect in leprosy can be ignored (Zuidema et al. 1986).

1.2 Rifampicin

The semi-synthetic antibiotic rifampicin is the 3-(4-methyl-1-piperazinyl-iminomethyl) derivative of rifamycin SV. Of the available antileprosy drugs, rifampicin possesses the highest bactericidal activity against *M. leprae*, having an MIC of 0.3 mg/L in mice (table I).

1.2.1 Absorption and Bioavailability

The absorption of orally administered rifampicin is both rapid and nearly complete. The rate of absorption is not dose-related, since the time required for the drug to reach its peak serum concentration has been found to be the same at different dosage levels (Acocella 1978; Lecaillon et al. 1981). The mean values of the absorption half-life of rifampicin in leprosy patients after a single oral dose of 600mg are reported to be 0.56 to 0.67 hour (Mehta et al. 1985). The peak plasma concentration is attained after 1 to 4 hours and reaches values of approximately 6 and 9 mg/L after single oral doses of 450 and 600mg, respectively. The peak serum concentration and area under the concentration-time curve (AUC) are greater if rifampicin is taken before breakfast than after; but the serum concentrations remain above MIC (for *M. tuberculosis*) for the same length of time in both cases (Riess 1969; Siegler et al. 1974).

Using high performance liquid chromatography (HPLC), Acocella et al. (1985) have calculated the pharmacokinetics of rifampicin in 4 male patients attending a chest clinic. For an oral dose of 8.1 ± 0.7 mg/kg bodyweight, the reported parameters were: peak plasma drug concentration (C_{max}) = 6.3

± 0.5 mg/L, time to reach C_{max} (t_{max}) = 3.2 ± 0.2 hours, area under the concentration-time curve (AUC) [0-12h] = 36.0 ± 5.5 mg/L · h and elimination half-life ($t_{½\beta}$) = 4.7 ± 1.9 hours, while corresponding figures for its major metabolite desacetyl rifampicin were C_{max} = 0.8 ± 0.1 mg/L, t_{max} = 5.0 ± 1.0 hours and AUC = 4.9 ± 1.3 mg/L · h (± standard error). The pharmacokinetic parameters reported in a study in leprosy patients by Mehta et al. (1985) do not appear to vary much from those reported in patients with chest ailments by Acocella et al. (1985).

During continuous administration of rifampicin the serum concentration and half-life are usually higher after the first dose than subsequent doses (Furesz 1970; Maggi et al. 1969). Steady-state concentrations are not reached until after a relatively long time; the high liposolubility of the drug may account for this observation (Seydel 1970). The maximal induction of rifampicin metabolism, and presumably that of the hepatic microsomal enzyme system in general, is probably attained after about 7 daily doses (300, 450 and 600mg) of the drug (Acocella et al. 1971; Immanuel et al. 1985).

1.2.2 Distribution and Protein Binding

Rifampicin diffuses rapidly from plasma into the other body fluids, tissues and organs. In the liver, bile, gallbladder and urine, rifampicin reaches concentrations which are higher than those found in the blood, and salivary concentrations are approximately 20% of the serum concentration (Pawlowska & Pniewski 1979). Rifampicin has been shown to cross the blood-brain barrier (Pilheu & Sippel 1975) and the placental barrier (Rocker 1977). A study in Japanese women has shown that values for t_{max} for rifampicin are about the same in cord blood and maternal blood and that the fetal serum concentrations at birth range between 12 and 33% of those in the maternal serum (Kenny & Strates 1981). The ability of rifampicin to cross the placental barrier does not result in adverse effects to the fetus.

A mean plasma protein binding rate of 88.9 ± 0.9% has been reported in healthy subjects (Boman & Ringberger 1974). The percentage of protein binding has been found to be unrelated to the plasma concentration of the drug (Kenny & Strates 1981).

1.2.3 Metabolism and Excretion

In a review of the pharmacokinetics of rifampicin by Acocella (1978), the drug is metabolised into compounds such as 25-desacetyl rifampicin, rifampicin quinone, desacetyl rifampicin quinone, 3-formyl rifampicin SV, 3-formyl desacetyl rifampicin and a few others. The modern technique of HPLC has made it possible to study rifampicin and its metabolites separately yet simultaneously (Gidoh & Tsutsumi 1981; Lecaillon et al. 1978). These metabolites are eliminated from the system through the bile and also the urine. The major metabolite, 25-desacetyl rifampicin, has been shown to be active against *M. tuberculosis* as rifampicin itself (Acocella 1978). The quantity of rifampicin and 3 of its metabolites – 25-desacetyl rifampicin, 3-formyl rifampicin SV and 3-formyl desacetyl rifampicin – recovered in the urine has been found to rise from 3% of the dose after oral administration of 150mg to approximately 12% after a 600mg dose (Lecaillon et al. 1981).

1.3 Clofazimine

Clofazimine [3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-di-hydro-2-(isopropylimino) phenazine] is active against *M. leprae* in mice and in humans (Browne et al. 1981; Pettit & Rees 1966; Shepard 1976; Shepard & Chang 1964). In addition, this drug possesses anti-inflammatory properties when used in higher doses, which has been found useful in treating lepromatous leprosy in the reactive phase (Browne 1965).

1.3.1 Absorption and Bioavailability

The exact mechanism of clofazimine absorption from the gastrointestinal tract is not clear. Studies carried out on various laboratory animals have revealed a species variation: absorption is good in mice, rats and monkeys, decidedly poorer in rabbits and guinea-pigs and practically negligible in dogs (Barry et al. 1960; Vischer 1969).

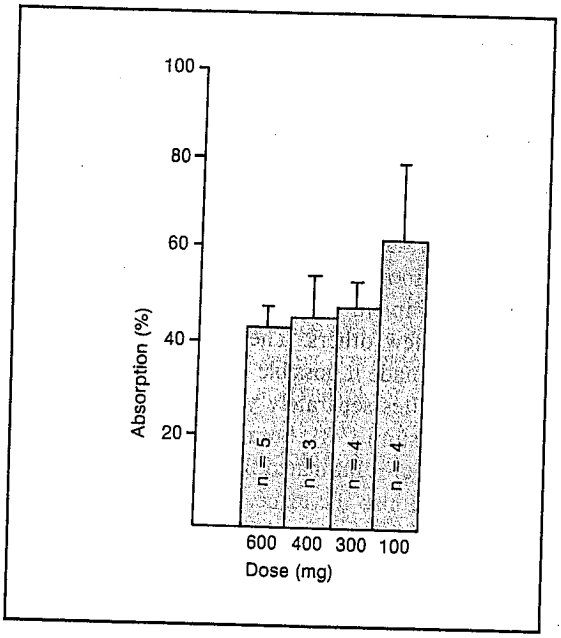

Fig. 2. Percentage absorption of clofazimine from the alimentary tract in relation to single oral doses of clofazimine; n = number of leprosy patients in age group; error bar denotes upper range of SD. Student's t-test: 100mg *vs* 600mg $p < 0.01$, 100mg *vs* 400mg $p > 0.01 < 0.05$, 100mg *vs* 300mg $p = 0.1$ (after Mathur et al. 1985).

In humans, only about 20% of the crystalline substance is absorbed after oral administration, but this figure rises to 50% when the micronised form of the drug is used, and may reach 85% with oral administration in the form of a suspension in oil. Very slow absorption from the site of intramuscular injection has limited drug administration to the oral route (Vischer 1969).

Faecal excretion of clofazimine by humans is variable; on average 11 to 59% of a single dose is excreted in 3 days (Levy 1974). Dose-dependent absorption in leprosy patients has also been reported by Mathur et al. (1985) in a study on faecal excretion in relation to various single doses of the drug. While 70% of a single dose of clofazimine 100mg ('Lamprene' capsule) was absorbed from the gut, only about 45% was absorbed after administration of a single dose of 600mg (fig. 2).

In 6 subjects in whom it was assessed, maximum plasma drug concentrations occurred between 4 and 8 hours after a single oral dose of clofazimine 200mg, taken 10 minutes after breakfast (Lanyi et al. 1987). The mean plasma concentration was 407.6 ± 136.81 ng/g as determined by a thin layer chromatographic method described by Lanyi and Dubois (1982). The mean AUC (0-264h) for plasma was 16.05 ± 0.398 μg/g · h, but AUC was lower when the drug was administered in the fasting state. Oral administration of clofazimine to healthy volunteers with food containing proteins and fat resulted in an increase in bioavailability by about 62% compared with administration in fasting conditions (fig. 3).

A few studies have been published on plasma concentrations of clofazimine in leprosy patients employing spectrophotometric methods based on that described by Barry et al. (1960). An average plasma concentration of 1.15 mg/L has been reported in leprosy patients receiving a daily dose of 300mg (Balakrishnan et al. 1976; Venkatesan et al. 1980). Leprosy patients receiving clofazimine 100mg thrice weekly or 100, 300 or 400mg daily

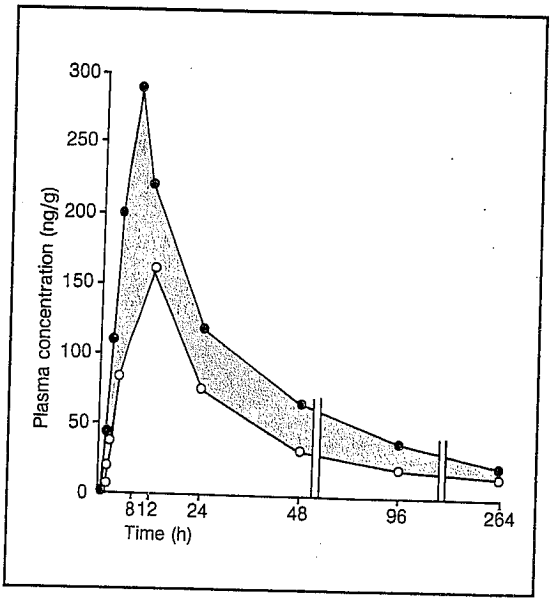

Fig. 3. Mean plasma concentration-time curves of clofazimine in healthy subjects (n = 3) after a single oral dose of 200mg with (●) and without (○) breakfast after overnight fast; □ = area showing an increase in bioavailability in terms of AUC (0-264h) [after Lanyi et al. 1987].

for varying periods have plasma drug concentrations of 0.5, 0.7, 1.0 and 1.4 mg/L, respectively (Mansfield 1974). A single oral dose of clofazimine 300mg given to leprosy patients has been shown to result in a plasma drug concentration of 0.2 mg/L (Banerjee et al. 1974); this low concentration has been suggested to be due either to incomplete absorption from the gut or to rapid hepatic removal of the absorbed drug via the portal vein (first-pass effect). The above findings indicate that, as after a single dose, the plasma concentration of the drug is also dose-related during continued administration, although there does not appear to be a linear relationship between dosage and plasma concentrations.

1.3.2 Distribution and Protein Binding

The distribution of clofazimine is relatively slower than the absorption (Vischer 1969). Clofazimine and related phenazines have been reported to show very selective tissue distribution in humans and experimental animals (Barry et al. 1959; Byrne et al. 1969). A significant proportion of these drugs is found in adipose tissue and in cells of the reticuloendothelial system, where they can be seen concentrated in phagosome-type inclusions and ultimately as crystals of pure drug (Conalty & Jackson 1962). Presumably, clofazimine after absorption circulates bound to plasma proteins and is engulfed in this form by the cells of the reticuloendothelial system, where it remains after digestion of the protein (Vischer 1969).

At autopsies performed on 3 leprosy patients, clofazimine was found predominantly in the mesenteric lymph node, adrenals, subcutaneous fat, liver, bile, gallbladder, spleen, small intestine, muscle, bone and skin, and to a small extent in nerve tissue. In these patients, who had received clofazimine in varying doses of up to 300mg daily for 35 to 243 days, the brain concentration was near zero (Mansfield 1974). In another autopsy study 'ghosts' of clofazimine crystals have been found in histological sections of intestinal mucosa (Desikan & Balakrishnan 1976). Yet another detailed autopsy study by Balakrishnan et al. (1976) showed high clofazimine content in spleen, small intestine and mesenteric lymph node, relatively low concentration in liver, omentum and lungs, and an absence of drug in brain tissue. There was a fairly sharp fall in the skin concentration of clofazimine in the first 2 months following cessation of treatment, but traces of clofazimine (about 4 μg/g) were found in the skin even after 1 to 2 years. Dose and duration of treatment did not appear to influence the amount of drug in the skin (Balakrishnan et al. 1976).

Little is known about the penetration of the drug into nerves. McDougall & Jones (1981) noticed foamy perineural macrophages containing amorphous material, histologically identified as lipofuscin, in a nerve biopsy of a leprosy patient in the reactive phase, and interpreted this as evidence of previous clofazimine treatment.

Based on an observation that infants born to mothers who had received the drug during pregnancy were deeply pigmented at birth, Waters (1969) reported that clofazimine crosses the placenta. There is no report of any teratogenic effect associated with the drug (Schulz 1971). Clofazimine is excreted in breast milk to such an extent as to colour the milk (personal observation). Experimental studies in female mice, rats, guinea-pigs and rabbits have shown similar observations (Vischer 1969).

1.3.3 Metabolism and Excretion

The exact manner in which clofazimine is metabolised in humans is still not fully known. At least 3 metabolites have been detected in urine of leprosy patients receiving clofazimine 300mg daily. Two of the metabolites are conjugated; they are 3-(B-D-glucopyranosiduronic acid)-10-(*p*-chlorophenyl)-2,10-dihydro-2-isopropyl iminophenazine and 3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-4,10-dihydro-4-(B-D-glucopyranosiduronic acid)-2-isopropyl iminophenazine. The third metabolite, an unconjugated one, is 3-(*p*-hydroxy anilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-isopropyl iminophenazine (fig. 4).

These metabolites are excreted in very small amounts constituting only 0.6% of the daily dose (assuming 70% drug absorption), while about 1%

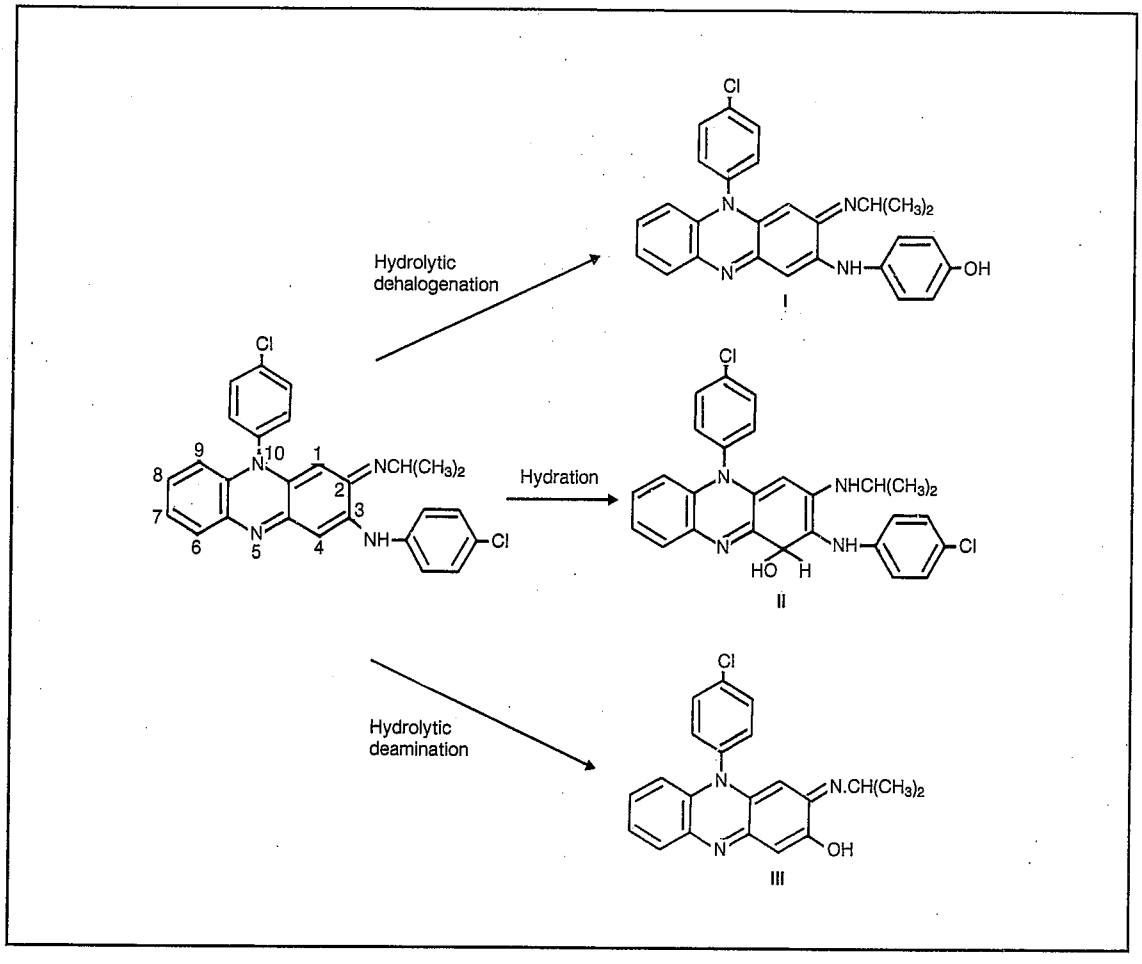

Fig. 4. *In vivo* metabolic pathways of clofazimine in humans. Metabolite I: 3-(*p*-hydroxyanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine; metabolite II: 3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-4,10-dihydro-4-hydroxy-2-isopropyliminophenazine; metabolite III: 3-(hydroxy)-10-(*p*-chlorophenyl)-2,10-dihydro-2-isopropyl-iminophenazine. Metabolites II and III are excreted in urine after conjugation to D-glucopyranosiduronic acid, while metabolite I is excreted in free form (after Feng et al. 1981, 1982).

is excreted unchanged (Feng et al. 1981; 1982; Levy 1974). The low excretion rate of clofazimine and its metabolites is probably due to the long residence time of the drug in the body. Presumably an equilibrium between intake and output of the drug would eventually be reached, but when this occurs for a given dose of the drug is not certain. The clofazimine metabolites found in urine could also be the products of intestinal bacterial metabolism of the parent drug which is deposited on intestinal walls (Feng et al. 1982). In addition to urinary excretion, a small amount of the drug is also eliminated in the sebum and sweat (Vischer 1969).

The mean terminal half-life has been reported to be 10.6 ± 4.0 days on administration of a single dose of clofazimine 50mg and 8.8 ± 1.0 days after dosing with 50mg daily for 8 days together with food (Lanyi et al. 1987).

Spectral studies have shown binding of clofazimine to deoxyribonucleic acid, non-involvement of an intercalation and involvement of binding to guanine residues as possible events in the mode of

action of the drug (Morrison & Morley 1976, 1977). Unidimensional cross-resistance between clofazimine and rifampicin has been reported, suggesting an involvement of clofazimine in transcription (Morrison 1972). Clofazimine resistance appears to be extremely rare and there is only 1 reliable report of such a case (Warndorff-van Diepen 1982).

1.4 Ethionamide and Prothionamide

The thioamides ethionamide and prothionamide are very potent bactericidal antileprosy drugs, surpassed in this respect only by rifampicin. The pharmacokinetics of both the thioamides and their circulatory *S*-oxide metabolites have been studied in detail in rats and armadillos (Peters et al. 1983) as well as human volunteers (Jenner & Ellard 1981; Jenner et al. 1984; Jenner & Smith 1987) using HPLC.

The absorption of prothionamide following oral administration appears to be rapid. Peak concentration is reported to occur whithin 30 minutes of ingestion, making an accurate estimation of its absorption half-life difficult; however, it has been calculated to be 18.5 ± 2.7 minutes. Peak plasma ethionamide concentration is reported to be reached in about 90 minutes. Lack of evidence of significant faecal elimination of the unmetabolised drugs and the systemic availabilities calculated for both these drugs (1.1 and 0.9 for ethionamide and prothionamide, respectively) suggest complete absorption from the gut and an absence of first-pass metabolism (Jenner & Smith 1987). It has been reported in single oral dose studies that the elimination half-life of both drugs is about 2 hours, but the plasma concentrations of prothionamide from 1 hour onwards are only about half those of ethionamide (Jenner et al. 1981). The observed differences in the pharmacokinetics of the 2 drugs have been shown not to be due to greater conversion of prothionamide to its metabolite (Peters et al. 1983).

Following intravenous administration, plasma concentrations of thioamides have been reported to decline biexponentially, with half-lives of 7.2 and 5.8 minutes for the distribution phases of ethionamide and prothionamide, respectively (Jenner &

Table III. Mean (± SD) pharmacokinetic parameters of ethionamide and prothionamide in humans, rats and armadillos

Parameters (units)	Humans (n = 1)[a]				Rats (n = 4)[b]		Armadillos (n = 2)[b]
	ETH[c]	PTH[c]	ETH[d]	PTH[d]	PTH[e]	PTH[f]	PTH[g]
AUC(0→∞) [mg/L · min]	55	48	1215	870	11.6 (32.0)[h]	11.9 (17.4)	5.1
t_{max} (min)			90	30			
$t_{½\alpha}$ (min)	7.2	5.8					
$t_{½\beta}$ (h)	1.77 ± 0.07	2.06 ± 0.12	1.6 ± 0.31	1.49 ± 0.13	0.74 (0.69)	0.43 (0.86)	0.52
$t_{½a}$ (min)			18.5 ± 2.7				
Vd (L)	79	93					
f			1.1	0.9			

a Jenner & Smith (1981).
b Peters et al. (1983).
c 25mg intravenous dose.
d 500mg oral dose.
e 32 mg/kg intravenous dose.
f 32 mg/kg oral dose.
g 16 mg/kg intravenous dose.
h Values in parentheses are those for prothionamide-*S*-oxide.

Abbreviations: ETH = ethionamide; PTH = prothionamide; AUC(0→∞) = area under the concentration-time curve from zero time to infinity; t_{max} = time to reach peak serum drug concentration; $t_{½\alpha}$ = half-life of the distribution phase; $t_{½\beta}$ = elimination half-life; $t_{½a}$ = absorption half-life; Vd = apparent volume of distribution; f = bioavailability.

Smith 1987). The reported pharmacokinetic parameters of both drugs in experimental animals and in humans are given in table III.

The thioamides are converted into *S*-oxides in the body, and this metabolite has been reported to have inhibitory and bactericidal activity against *M. leprae* (Matsuo et al. 1981). Prothionamide has not been shown to induce its own metabolism in studies in rats and armadillos, as indicated by lack of significant differences in serum concentrations of either the parent compound or prothionamide-*S*-oxide after single and multiple doses (Peters et al. 1983).

The cumulative urinary excretion of ethionamide and prothionamide has been reported to be around 0.15% and 0.05%, respectively, of the administered dose (Jenner & Ellard 1981).

1.5 Thiacetazone

Thiacetazone (*p*-acetyl amino benzaldehyde thiosemicarbazone) is still used by some physicians as an antileprosy drug, although it does not feature in the widely used 'standard' multidrug regimens because of its relatively lower antileprosy activity and the evolution of drug-resistant bacilli. The use of this drug in the treatment of leprosy was first described by Lowe (1954). While comparing the activity of thiacetazone and thiambutosine in the chemotherapy of experimental leprosy in mice, Colston & Hilston (1976) found that the MIC of thiacetazone was 0.26 mg/L.

Thiacetazone is well absorbed after a single oral dose. Peak serum concentrations have been reported to occur about 4 to 5 hours after administration of a 150mg dose of the drug. However, peak concentrations are reached much later after higher doses (up to 600mg), possibly because absorption of the larger doses is prolonged owing to its low aqueous solubility. Peak drug concentrations are reported to be proportional to the dosage. The half-life of thiacetazone in humans averages a little under 12 hours (Ellard et al. 1974). Reported serum drug concentrations following oral doses of thiacetazone 150mg in tuberculosis patients are shown in table IV.

Thiacetazone is not extensively deacetylated or cleaved to form its metabolites *p*-acetyl amino benzaldehyde and thiosemicarbazone. On average, about 20% of the administered dose is excreted in urine over a period of 3 days, 15% or more representing unchanged drug (Ellard et al. 1974).

1.6 Isoniazid

Isoniazid is bacteriostatic for *M. leprae* (Shepard 1967) and indications for the use of this drug in leprosy are limited from the bacteriological point of view (Pattyn et al. 1981; Shepard 1967). Nevertheless, multidrug regimens comprising rifampicin, dapsone and isoniazid plus prothionamide ('Isoprodian') have been employed by several workers (Depasquale 1975; Freerksen 1975). There is a report that a combination of dapsone with thiacetazone and isoniazid performed well in leprosy treatment (Molesworth 1975). The pharmacokinetics of isoniazid have been extensively reviewed by Weber and Hein (1979) and need not be covered here since the drug has only limited use in the

Table IV. Mean (± SD) concentrations of thiacetazone in serum (mg/L) [after Ellard et al. 1974]

Dosage	Time after dose (h)					
	0	2	4	6	24	48
150mg once (n = 18)		0.9 ± 0.5[a]	1.2 ± 0.6	0.9 ± 0.7	0.3 ± 0.2	0.0 ± 0.2
150mg daily (n = 21)	0.4 ± 0.4[b]		1.2 ± 0.7			
150mg daily (n = 24)	0.5 ± 0.4[c]	1.4 ± 0.7	1.6 ± 0.9	1.2 ± 0.9	0.6 ± 0.4	

a UV photometry.
b UV photometry, colorimetry and fluorimetry.
c UV photometry and fluorimetry.

Table V. Mean (± SD) pharmacokinetic parameters of isoniazid and pyrazinamide (after Acocella et al. 1985)

Parameter (units)	Isoniazid[a] (n = 4)	Pyrazinamide[b] (n = 4)
Dose[c] (mg/kg)	5.6 ± 0.4	24.6 ± 2.4
C_{max} (mg/L)	9.2 ± 1.2	30.8 ± 3.6
	(1.8 ± 0.4)	(5.5 ± 1.4)
AUC (0-12h)	49.7 ± 7.8	224.7 ± 21.5
(mg/L · h)	(16.3 ± 4.0)	(38.6 ± 3.6)
t_{max} (h)	2.2 ± 0.5	1.5 ± 0.3
	(5.7 ± 1.3)	(3.5 ± 0.3)
$t_{1/2\beta}$ (h)	3.6 ± 0.4	7.4 ± 1.0
		(11.6 ± 5.5)

a Values in parentheses are for acetyl isoniazid.
b Values in parentheses are for pyrazinoic acid.
c Doses given orally.
Abbreviations: C_{max} = peak serum drug concentration; AUC (0-12h) = area under the concentration-time curve from zero time to 12 hours post-dose; t_{max} = time to reach C_{max}; $t_{1/2\beta}$ = terminal half-life.

treatment of leprosy. Recently Acocella et al. (1985) have reported on the pharmacokinetics of isoniazid after a single oral dose in patients with chest disease. The pharmacokinetic parameters described in their work are shown in table V.

1.7 Pyrazinamide

'Persister' bacilli are known to exist in leprosy even after several years of chemotherapy (Ellard 1984). On the basis of experience using pyrazinamide together with other antitubercular bactericidal drugs for effectively eliminating the 'persister' organisms in tuberculosis, it is thought that pyrazinamide could serve as a companion antileprosy drug (Katoch et al. 1988). As drug combinations involving pyrazinamide may be used in the future, the pharmacokinetics of this drug are briefly reviewed here.

Absorption of pyrazinamide from the alimentary tract appears to be extremely rapid. Peak serum drug concentrations are achieved within 2 hours, and are dose-related over the range of pyrazinamide 0.5 to 3g for both the drug and its metabolite, pyrazinoic acid. Non-detection of pyrazinamide in faeces collected after administration of 3g of the drug suggests that there is complete absorption of the drug in the alimentary tract (Ellard 1969).

Recently, Acocella et al. (1985) using HPLC have calculated the pharmacokinetic parameters of pyrazinamide and its pyrazinoic acid metabolite (table V). Serum half-life of pyrazinamide is not related to length of treatment (Ellard 1969).

After absorption from the gut, pyrazinamide is rapidly distributed throughout the whole body water (Ellard 1969). The ready penetration of unchanged pyrazinamide into tissue membranes and sciatic nerves of both dogs and rabbits has been reported (Allen et al. 1975; Yu et al. 1957).

Konno et al. (1967) have suggested that pyrazinamide may exert its antituberculosis activity through *in vivo* pyrazinoic acid. Tuberculosis patients have been shown to excrete about 4% of the dose unchanged and 30% as the metabolite, irrespective of the size of the dose up to 3g. Pyrazinamide filtered by the kidney is reabsorbed while pyrazinoic acid is not (Ellard 1969); the elimination half-life of pyrazinamide is 7.4 ± 1.0 hours (table V).

2. *Side Effects of Antileprosy Drugs*

2.1 Dapsone

The most frequent side effects of dapsone are haematological in nature, and are dose-dependent. Methaemoglobinaemia caused by NOH metabolites of dapsone has been reported to be severe in glucose-6-phosphate dehydrogenase-deficient patients and to cause cyanosis, tiredness, dyspnoea, tachycardia, headache, dizziness, nausea and mild jaundice (Zuidema et al. 1986). Haemolysis is the second most important haematological side effect of dapsone, but is not easy to detect following daily doses of 100mg or less in healthy subjects and 50mg or less in healthy glucose-6-phosphate dehydrogenase-deficient individuals (DeGowin 1967).

2.2 Rifampicin

An uncommon side effect of intermittent administration of rifampicin is hepatitis, while even more rare are thrombocytopenia, psychosis and osteomalacia. Most of the side effects such as 'flu'-syndrome shock, dyspnoea, haemolytic anaemia and renal failure, which are associated with intermittent therapy in tuberculosis, are unlikely in leprosy patients receiving monthly doses of rifampicin on the basis of the WHO recommendation (WHO 1982).

Rifampicin reduces the effectiveness of steroids and oral contraceptives. In leprosy patients with adrenal cortical dysfunction it can be dangerous to administer the drug during erythema nodosum leprosum reactions as, in addition to counteracting the effect of exogenous prednisolone, rifampicin also counteracts endogenous cortisol (Jopling 1983).

2.3 Clofazimine

Jopling (1983) has reviewed the side effects of clofazimine, which may be mild or serious. The mild effects are dose-related and reversible, the commonest effect being a red-brown discoloration of the skin and a much darker brownish-black pigmentation of the leprosy lesions. These changes are naturally less obvious in individuals with dark skins. The less common side effects include gastrointestinal symptoms and general dryness of the skin, which may progress to ichthyosis in limbs. Serious side effects are confined to the small bowel and are dose-related. A 'late syndrome' which is of greater significance occurs after long term administration of high dosages of clofazimine. In this condition, persistent diarrhoea, abdominal pain and weight loss are seen.

2.4 Ethionamide and Prothionamide

Both ethionamide and prothionamide give rise to gastrointestinal side effects, but the latter drug appears to be well tolerated when administered in a daily dosage of 500 to 1000mg as used in tuberculosis patients (Fox et al. 1969). Ethionamide has also been reported to cause peripheral neuropathy in high doses (Leggat 1962). A pellagra-like encephalopathy has been described as an uncommon but serious side effect of ethionamide, and simultaneous administration of isoniazid with ethionamide is likely to enhance the occurrence of this condition. Hypothyroidism, hypoglycaemia, alopecia and gynaecomastia are other side effects which have been reported as rare but serious (Jopling 1983). One case of hepatitis among 102 multibacillary leprosy patients receiving monotherapy with ethionamide 500mg daily has been reported by Rollier & Rollier (1972). An unacceptable incidence of hepatotoxicity (4.5 to 15%) on combining thioamides with rifampicin for leprosy treatment has been reported by many workers (Cartel et al. 1983; Ji et al. 1984; Pattyn et al. 1984).

2.5 Thiacetazone

Mild side effects of thiacetazone include gastrointestinal symptoms, transient rash, dizziness, headache and drowsiness. Serious side effects involve skin, blood, liver and hearing. Because of the risk of hepatotoxicity induced by thiacetazone, it is not advisable to give the drug to patients with liver dysfunction (Jopling 1983; Lowe 1954; Pines 1964; Webb 1973).

The frequency of side effects and acceptability of the drug are influenced by racial and geographical factors and therefore a general statement on these aspects may not be meaningful.

3. Pharmacokinetics in Various Pathophysiological States

Dose recommendations in the literature have only an empirical character. For leprosy patients the use of 50 to 100 mg/day of dapsone has been recommended (Zuidema et al. 1986). A decreased bioavailability of the drug after oral administration has been reported in severely leprotic patients (Kubo et al. 1983). A decrease in skin concentrations of dapsone and an increase in urinary excretion of the parent compound and its metabolites have been observed in lepromatous leprosy patients

with severe albuminuria (Venkatesan et al., unpublished data). Although renal function impairment occurs frequently in leprosy (Zuidema et al. 1986), its influence on the renal excretion of dapsone and its metabolites has not been studied.

The dosage of rifampicin used in infants and children varies from 300 to 450mg either as a monthly loading dose or as daily administration during initial intensive therapy (Government of India 1982). The dosage in adult leprosy patients is 450mg for those with bodyweight of less than 35kg and 600mg for those weighing more. Whereas a slight decrease in serum drug concentrations in leprosy patients relative to that in healthy subjects has been suggested by Mehta et al. (1985), these workers did not demonstrate a significant difference in the pharmacokinetics of rifampicin between multi- and paucibacillary leprosy patients.

4. *Implications for the Treatment of Leprosy*

The minimum inhibitory concentration of an antileprosy drug is defined as the serum concentration present in mice fed with the minimum effective dose of the drug for effective inhibition of the growth of *M. leprae* in mouse foot pad. Assuming that MIC for *M. leprae* in humans is similar to that in the mouse, the recommended doses of antileprosy drugs must result in serum concentrations much higher than the estimated MIC in experimental mice (table I). The markedly superior ratios of peak serum concentrations to MIC, therefore, denote therapeutic efficacy of the antileprosy drug. MICs have been defined for dapsone (Levy & Peters 1976), rifampicin (Holmes 1974; Holmes & Hilson 1972), prothionamide and ethionamide (Colston et al. 1978a,b) and thiacetazone (Colston & Hilson 1976). It has not been possible to estimate the MIC for clofazimine owing to its uneven distribution and prolonged retention in the tissues.

It appears likely that the therapeutic effect of dapsone is contributed by the unchanged drug and not by its metabolites such as monoacetyl dapsone or other *N*-substituted sulphones (Bawden & Tute 1981). Daily administration of dapsone 100mg to leprosy patients has been reported to produce a trough plasma drug concentration of 0.5 mg/L at any time during the 24-hour dosing interval once steady-state is reached (Halmekoski et al. 1978; Garg et al. 1988). This is roughly 160 times higher than the MIC for this drug.

A single intramuscular injection of acedapsone is reported to produce a serum concentration of 0.015 to 0.085 mg/L (George & Balakrishnan 1986) which is 5 to 25 times more than the MIC for dapsone, although a steady-state concentration of about 0.5 mg/L seems to be desirable for therapeutic efficiency (Zuidema et al. 1986). Recently, Jagannathan & Mahadevan (1986) have suggested an MIC of 0.028 mg/L using their *in vitro* macrophage assay system.

Simultaneous administration of rifampicin has been reported to decrease the half-life of dapsone by a factor of about 2 and lower its plasma, skin and nerve concentrations considerably (Balakrishnan & Seshadri 1981; Gelber & Rees 1975; Gelber et al. 1975; Peters et al. 1977). These studies also show that the serum concentration of dapsone is still about 300 times higher than the MIC for the drug. A monthly pulse of oral rifampicin 600mg (WHO 1982) with an initial intensive therapy of rifampicin 600mg daily for 14 days (Government of India 1982) is the recommended dosage in multidrug regimens (table VI). The effect of rifampicin on blood concentrations and urinary excretion of dapsone during this period of rifampicin administration has not been found to be significant in terms of MIC (George et al. 1988). The dapsone-lowering effect of rifampicin has also not been found to vary among the various phenotypes of acetylators for dapsone (George et al. 1988; Venkatesan et al. 1980).

As may be seen from table VII, simultaneous administration of either prothionamide or clofazimine has not been shown to exert any effect on plasma concentrations, half-life and urinary excretion of dapsone (George et al. 1988; Mathur et al. 1986; Venkatesan et al. 1986). Serum concentrations of dapsone and urinary excretion of the drug and its conjugated metabolites have not been found to differ between patients on dapsone monother-

Table VI. Multidrug regimens recommended by WHO (1982) and Government of India (1982)

Recommendation	Multibacillary leprosy			Paucibacillary leprosy		
	regimen	dosage	duration	regimen	dosage	duration
WHO (1982)	Rifampicin	600 mg monthly pulse[a]	Minimum 2 years or till smear negativity whichever is longer	Rifampicin	600mg monthly pulse	6 months
	Clofazimine[b]	300mg monthly pulse and 50mg daily				
	Dapsone	100mg daily		Dapsone	100mg daily	
Government of India	Rifampicin	600mg daily for initial 14 days[a] and 600mg monthly	Minimum of two years or till smear negativity	Rifampicin	600mg monthly pulse	Minimum 6 months or till clinical inactivity
	Clofazimine, Dapsone	As in WHO (1982)		Dapsone	100mg daily	

a Monthly doses of clofazimine and rifampicin and daily doses of rifampicin are administered to the patients under supervision.
b Where clofazimine is totally unacceptable owing to the coloration of skin lesions that it causes, replacement by 250 to 375mg self-administered daily doses of ethionamide/prothionamide should be considered.

apy for 1 to 3 years and those on multidrug therapy comprising daily dapsone and clofazimine on alternate days together with monthly pulses of rifampicin for the same time period (Venkatesan et al. 1987). However, there is one report that mobilisation of tissue dapsone occurs, based on the observation of increased urinary excretion in 9 of the 17 patients treated with both clofazimine and dapsone (Grabosz & Wheate 1975).

Probenecid has been shown to cause a significant reduction in the urinary excretion of free and conjugated dapsone together with an increase in dapsone concentrations in blood (Goodwin & Sparell 1969). Pyrimethamine is reported to lower peak serum concentrations of dapsone without altering the half-life of dapsone and monoacetyl dapsone (Ahmad & Rogers 1980b).

A single dose of rifampicin 600mg is estimated to maintain the plasma concentration above its MIC for about 24 hours (WHO 1982). The therapeutic efficacy of rifampicin has been reported to be such that 99.9% of *M. leprae* are killed within 4 days of administration of a single oral dose of 600mg (Levy et al. 1976).

Simultaneous administration of *para*-aminosalicylic acid, isoniazid, pyrazinamide or streptomycin in various combinations has not been shown to exert any significant effect on the absorption, metabolism and excretion of rifampicin in tuberculosis patients (Acocella et al. 1985; Boman 1974). Studies of Venkatesan et al. (1986) and Mathur et al. (1986) have not shown any pharmacokinetic interactions between rifampicin and clofazimine or prothionamide (table VII). On the other hand, Mehta et al. (1985) have reported that clofazimine significantly reduced the absorption of rifampicin, resulting in delayed time to reach peak serum concentrations and increased half-life of the drug. Nevertheless, the bioavailability in terms of AUC and peak serum concentrations was not found to be significantly affected. The pharmacokinetic properties of rifampicin have not been found to vary among multibacillary and paucibacillary leprosy patients as reported by Mehta et al. (1985).

The reduced effectiveness of steroids when given concurrently with rifampicin is a point to be noted. This has been suggested to be due to the latter's ability to induce hepatic microsomal enzymes which increase the metabolic degradation of steroids (Jopling 1983). Since rifampicin is administered as a monthly pulse in the WHO regimen, this effect may not be of consequence while treating reactional erythema nodosum leprosum cases of leprosy with steroids.

Probenecid has been reported to increase the plasma concentrations of rifampicin by competing for hepatic uptake (Kenwright & Levi 1973).

In patients receiving clofazimine 100 to 200mg daily, it is not until treatment has continued for about 50 days that the rate of bacterial killing matches that at the start of therapy with dapsone 50mg in lepromatous leprosy patients (Levy et al. 1972). However, clofazimine also displays an anti-inflammatory effect in high doses, and hence is clinically valuable in controlling erythema nodosum leprosum (Browne 1965).

Neither rifampicin nor dapsone diminished the gastrointestinal absorption of simultaneously administered clofazimine (unpublished data). A lowering of the clofazimine content of the skin of leprosy patients receiving both clofazimine and isoniazid has been reported by Venkatesan et al. (1980). Ramu and Iyer (1976) had earlier observed that the intensity of skin colour in 10 cases treated with isoniazid and clofazimine was much less compared with those on clofazimine alone.

When an oral dose of clofazimine 50mg is given daily, it is only after 30 days that the concentration in plasma will come close to steady-state values and that bioavailability (in terms of AUC_{ss}/AUC_1) will be 4.85 times higher. Lanyi et al. (1987) suggested that slow accumulation towards the steady-state could be avoided by giving higher loading doses at the beginning of the treatment, followed

Table VII. Multiple dose pharmacokinetic parameters (mean ± SD/SE) after the last oral dose of dapsone and rifampicin, before and after addition of clofazimine or prothionamide to dapsone or dapsone plus rifampicin regimen, in leprosy patients

Reference	No. of pts	Drug regimen	Dapsone			Rifampicin		
			$t_{1/2\beta}$ (h)	C (24h) (mg/L)	Ae (mg)	$t_{1/2\beta}$ (h)	AUC (0-12h) (mg/L · h)	Ae (mg)
Mathur et al. (1986)	15[a]	Rifampicin + dapsone	18.0 ± 2.1	0.86 ± 0.10	67.9 ± 13.6	3.20 ± 0.31	58.6 ± 6.3	92.6 ± 21.5
		Rifampicin + dapsone + prothionamide	19.0 ± 2.1	0.89 ± 0.15	70.4 ± 11.5	3.70 ± 0.31	60.3 ± 5.2	106.4 ± 24.4
Venkatesan et al. (1986)	15[b]	Rifampicin + dapsone	18.2 ± 1.8	0.89 ± 0.10	72.1 ± 12.7	3.13 ± 0.46	62.9 ± 7.2	97.1 ± 21.3
		Rifampicin + dapsone + clofazimine	18.4 ± 1.5	0.94 ± 0.10	64.8 ± 9.4	3.31 ± 0.48	64.1 ± 9.5	101.4 ± 24.6
George et al. (1988)	30[c]	Dapsone + clofazimine		1.41 ± 0.14[d] (1.39 ± 0.12)				

a Daily administration of rifampicin 600mg and dapsone 100mg for 7 days, followed by the same drug regimen plus prothionamide 500mg daily for a further 7 days.

b Drug regimen as in (a) but clofazimine 100mg replaced prothionamide.

c Dapsone 100mg and clofazimine 100mg (both daily) for 15 days.

d Mean ± SE on the 8th day after oral dose; plasma concentrations on 15th day are given in parentheses.

Abbreviations: $t_{1/2\beta}$ = terminal half-life; C (24h) = plasma drug concentration 24 hours post-dose; Ae = 24-hour urinary excretion; AUC (0-12h) = area under the concentration-time curve from zero time to 12 hours post-dose.

by daily administration of the maintenance dose. However, the findings of Mathur et al. (1985) and Levy (1974) that increased dosage of clofazimine results in increased faecal excretion should be borne in mind. At present the World Health Organization (WHO 1982) recommends a monthly loading dose of 300mg.

Many clofazimine analogues have been tested for their activity against *M. leprae* in the mouse foot pad system, but none has been shown to be as active as the parent drug itself (Levy 1981). Recently, a few clofazimine analogues have been developed by O'Sullivan et al. (1988) and these are active against a clofazimine-resistant *M. smegmatis* strain. These analogues have also been shown to have growth-inhibitory activity against human-derived *M. leprae* in murine macrophage culture.

The pharmacokinetic properties of ethionamide and prothionamide have been reported to differ only slightly and without clinical significance (Jenner & Smith 1987). Experimental studies have also failed to demonstrate any differences in the inhibitory and bactericidal activities of these 2 agents against *M. leprae* (Colston et al. 1978a), or between their sulphoxide metabolites which also possess substantial antimycobacterial activities (Libermann et al. 1963; Matsuo et al. 1981). Although larger doses of ethionamide, as used in tuberculosis treatment, are less well tolerated than prothionamide (Fox et al. 1969), the regularity of intake of both the thioamides self-administered by leprosy patients has been reported to be similar at daily doses of 250mg of either drug (Stanley et al. 1986). Inclusion of thioamides in treating a leprosy patient will be dictated by therapeutic necessity, cost, availability and tolerance of the drug by the patient, and the past history of treatment with either thiacetazone or thioamides, in view of the reported cross-resistance between ethionamide and either prothionamide or thiacetazone in *M. leprae* (Pattyn & Colston 1978) and a probable cross-resistance between thiacetazone and ethionamide or prothionamide (Ji 1985). It would be advisable not to use multidrug regimens containing prothionamide or ethionamide in therapy for patients who previously had been treated with thiacetazone for more than 2 years.

The effect of companion antileprosy drugs on the pharmacokinetics of these thioamides is not known. Prothionamide has not been shown to induece its own metabolism (Peters et al. 1983). A single dose of prothionamide 500mg results in a serum drug concentration which will be above its MIC for 1 day only, thus necessitating the daily administration of the drug for effective chemotherapeutic activity (WHO 1982).

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