Pharmacokinetics of Clofazimine in Healthy Volunteers[1]

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Clofazimine, 3-(p-chloroanilino)-10-(p-chlorophenyl)-2,10-di-hydro-2-(isopropyl-imino)phenazine (Fig. 1), is active against *Mycobacterium leprae* in experimental animals and in man ([4, 11, 12]). In the form of Lamprene®, it is in use for the treatment of leprosy ([2–5, 10, 13]). Although clofazimine was introduced into leprosy treatment in the 1960s, only a few studies on its disposition, either in humans or in animals, have been reported ([1, 8, 9, 14]). Information on the pharmacokinetics of clofazimine in man is still lacking.

The present paper describes the results of investigations on the pharmacokinetics of clofazimine after single and multiple oral administration to healthy volunteers.

SUBJECTS AND METHODS

Subjects. Twelve healthy male volunteers between 30 and 60 years of age (mean = 42 years) and weighing 64–92 kg (mean = 74 kg) participated in this study, and gave their informed consent after the properties of the drug and the aims of the study had been explained to them. They remained under medical supervision throughout the study. The volunteers were asked to take no medication for at least 2 weeks before the study, and no other drugs except clofazimine during the study.

Dosing and collection of samples. The study was carried out in three experiments. In the first experiment, three subjects received single oral doses of 200 mg of clofazimine (four capsules of Lamprene®, each containing 50 mg of clofazimine) on two occasions in random sequence separated by 4 weeks. On one of these occasions, clofazimine was administered on an empty stomach after an overnight fast. The subjects continued to fast for another 2 hr. Then a standardized breakfast, consisting of two rolls with jam and decaffeinated black coffee, was served to them. On the other occasion, clofazimine was administered 10 min after a breakfast containing fat and proteins (two rolls with butter and jam, coffee with milk).

In the second experiment, a single oral dose of 200 mg of clofazimine was given to six subjects 10 min after a breakfast containing fat and proteins.

In the third, multiple-dose experiment, three subjects received 50-mg oral doses of clofazimine in the morning 10 min after breakfast for 8 consecutive days.

Blood samples were withdrawn into heparinized venojects before and 1, 2, 4, 8, 12, 24, 48, 96, 168, (192), 216, (240), and 264

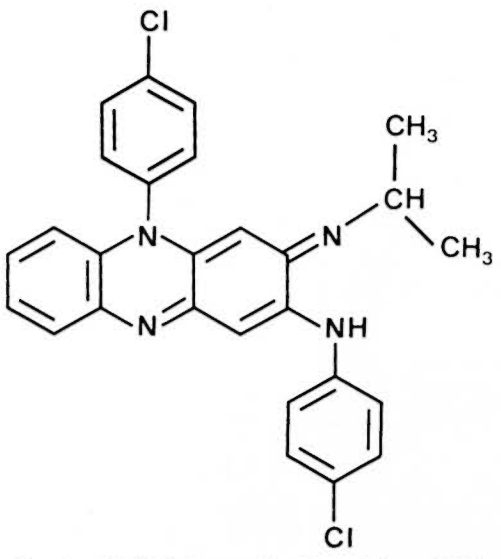

FIG. 1. Clofazimine, molecular weight = 473.4.

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hr after administration of the single dose. During repeated administration, blood samples were withdrawn immediately before administration of the daily dose on days 1, 3, 5, and 8, as well as 1, 2, 4, 8, 12, 24, 48, 96, 168, 216, and 264 hr after the last dose (day 8). The blood samples were centrifuged as soon as possible, and the plasma samples were stored at −20°C until analyzed.

Analysis. The concentrations of clofazimine in plasma were measured by the thin-layer chromatographic method published previously ([7]), using a sample volume of 1 ml for analysis. The method was validated on a daily basis by analyzing plasma samples spiked with clofazimine.

Pharmacokinetic analysis. The area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal rule. The elimination half-life of clofazimine was determined from the log-linear plot of the terminal phase of the concentration-time curve.

To predict the plasma concentrations following multiple dosing, the mean experimental plasma concentration-time curve of clofazimine C(t) was fitted by a sum of three exponential terms,

$$C(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t}$$

in which λ_1, λ_2, and λ_3 are the slopes and A_1, A_2, and A_3 are the zero-time intercepts of the three segments, into which the log-linear plot of the concentration-time curve was resolved.

RESULTS

Single-dose experiments. The plasma concentration-time curves of clofazimine obtained in six volunteers after administration of a single oral dose of 200 mg of clofazimine 10 min after breakfast are shown in Figure 2. The corresponding areas under the concentration-time curve in plasma (AUC, 0–264 hr), the maximum concentrations (Cmax), the times to peak (Tmax), and the elimination half-lives (t_{50}) are listed in Table 1.

Maximum concentrations of clofazimine in plasma of the six subjects were observed between 4 and 8 hr after dosing. The re-

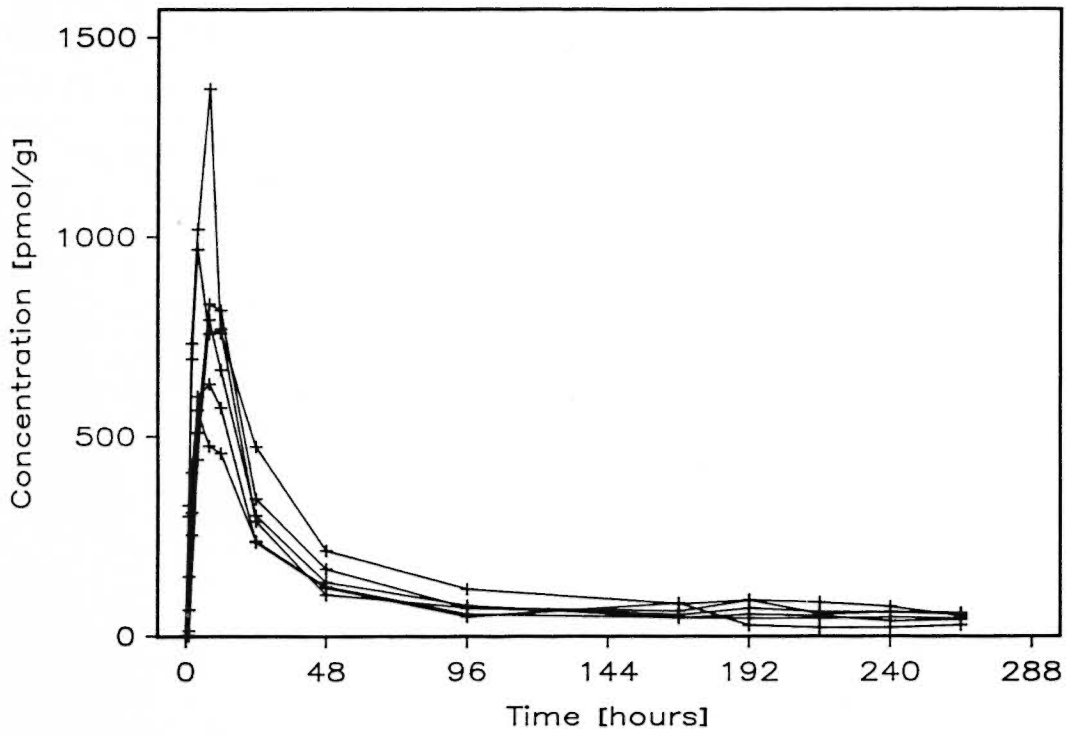

FIG. 2. Plasma concentrations of clofazimine in six healthy volunteers following single oral doses of 200 mg (4 × 50 mg) of clofazimine with breakfast.

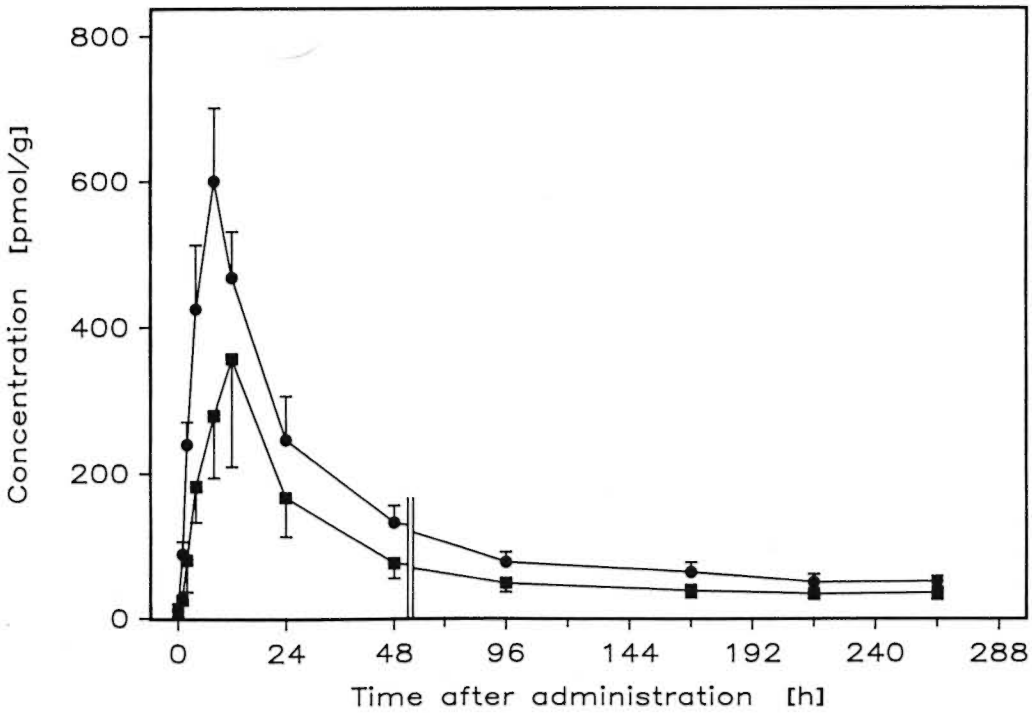

FIG. 3. Mean plasma concentrations of clofazimine after a single 200-mg dose (4 × 50 mg) in healthy volunteers. (■——■) = fasted volunteers (N = 3); (●——●) = 10 min after breakfast (N = 3).

spective concentrations ranged from 567 to 1372 pmol/g, with a mean ± S.D. of 861 ± 289 pmol/g. The mean AUC value ± S.D. was 33.9 ± 8.4 nmol·h/g.

Table 2 summarizes the AUC values (0–264 hr), the Cmax values, and the peak times determined in the three subjects dosed with 200 mg of clofazimine in the fasting state or immediately after a breakfast. The mean ± S.D. plasma concentration-time curves with and without breakfast are shown in Figure 3.

Figure 4 illustrates an individual plasma concentration profile of one of the subjects dosed after breakfast in a linear (A) and semi-logarithmic (B) plot. After both modes of administration, Cmax of clofazimine was reached within 8–12 hr. Its mean values (±S.D., N = 3) were 604 ± 175 and 469 ± 102 pmol/g with and without food, respectively. Correspondingly, the mean AUC values were different, i.e., 29.1 ± 8.7 nmol·hr/g with breakfast and 18.0 ± 4.5 nmol·hr/g without breakfast.

TABLE 1. *Descriptive pharmacokinetic parameters obtained after administration of a single oral dose of 200 mg (4 × 50 mg) of clofazimine with breakfast in six healthy volunteers.*

Subject no.	AUC (0–264 hr) (nmol·hr/g)	Cmax (pmol/g)	Tmax (hr)	t_{50} (days)
1	34.1	968	4	11.8
2	30.7	792	8	9.5
3	37.6	832	8	13.8
4	26.0	567	4	16.0
5	48.6	1372	8	6.2
6	26.6	633	8	6.4
Mean ± S.D.	33.9 ± 8.4	861 ± 289	8[a]	10.6 ± 4.0

[a] Median.

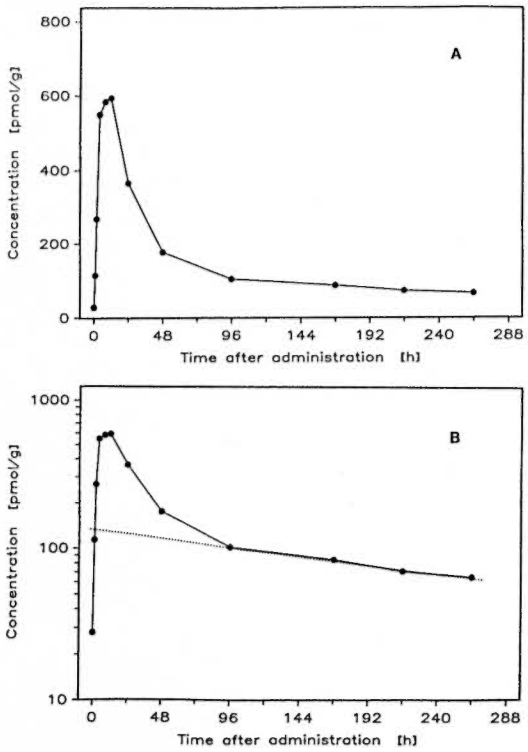

FIG. 4. Plasma concentrations of clofazimine in a healthy volunteer following a single oral dose of 200 mg (4 × 50 mg) after breakfast plotted versus time in linear plot (**A**) and semi-logarithmic plot (**B**).

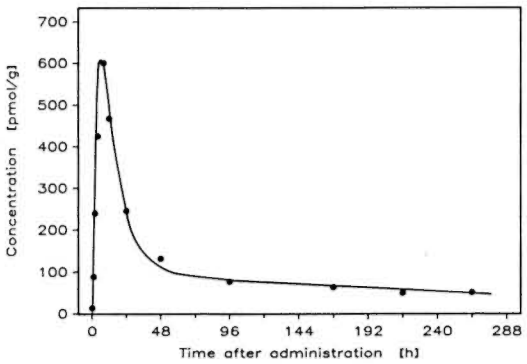

FIG. 5. Mean plasma concentrations of clofazimine following a single oral dose of 200 mg in healthy volunteers simulated by a triexponential function. (●) = mean experimental values (N = 3); (——) = triexponential equation: $C(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t}$; $A_1 = -1700$ pmol/g, $\lambda_1 = 0.3$ hr^{-1}; $A_2 = 1325$ pmol/g, $\lambda_2 = 0.09$ hr^{-1}; $A_3 = 106$ pmol/g, $\lambda_3 = 0.00275$ hr^{-1}.

The mean concentration–time curve obtained after the single dose with breakfast (Fig. 3) was fitted by a sum of three exponential functions, and the correspondence of the fitted curve with the experimental values is shown in Figure 5. This function was used to predict the trough concentrations as well as the plasma concentration profile after the last daily dose of multiple dosing.

Multiple-dose experiment. The concentrations of clofazimine in plasma were measured during repeated oral administration of 50 mg of clofazimine per day for 8 days. In Figure 6 are shown the mean concentrations from three subjects measured just before ingestion of the daily dose on days 1, 3, 5, and 8 as well as the entire profile after the last dose (day 8). The predicted curve using the fitted sum of three exponentials obtained from the single-dose experiment is also depicted in Figure 6. There is very good agreement of the simulated curve with the trough concentrations on days 3, 5, and 8 on one side and with the elimination phase on days 9 through 19 on the other side.

TABLE 2. *Descriptive pharmacokinetic parameters obtained after administration of a single oral dose of 200 mg (4 × 50 mg) of clofazimine with and without breakfast in three healthy volunteers.*

Subject no.	Clofazimine in plasma					
	With breakfast			Fasted		
	AUC (0–264 hr) (nmol·hr/g)	Cmax (pmol/g)	Tmax (hr)	AUC (0–264 hr) (nmol·hr/g)	Cmax (pmol/g)	Tmax (hr)
1	38.5	594	12	17.4	421	8
2	21.4	434	8	22.7	400	12
3	27.3	783	8	13.8	586	12
Mean ± S.D.	29.1 ± 8.7	604 ± 175	8[a]	18.0 ± 4.5	469 ± 102	12[a]

[a] Median.

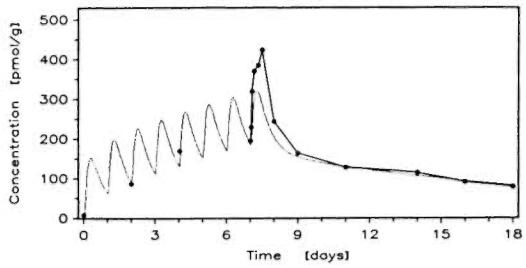

FIG. 6. Comparison between the observed mean plasma clofazimine concentrations after 50 mg once a day for 8 days in healthy volunteers and the predicted concentrations based on single-dose pharmacokinetic values. (●) = mean experimental values (N = 3).

DISCUSSION

The kinetics of clofazimine in plasma following a single oral dose of 200 mg of clofazimine was similar to that reported previously (Fig. 2) ([7]). After reaching the peak at 8–12 hr, the plasma concentrations declined biexponentially. This suggests a distribution of clofazimine from the central compartment to a peripheral compartment, followed by a slow re-equilibration to the central compartment from where the drug is eliminated (Fig. 4). The corresponding mean elimination half-life was 10.6 ± 4.0 days (±S.D., N = 6). The dotted line in Figure 4B extrapolated to time zero intersects the concentration–time curve, thus showing that absorption is faster than distribution of clofazimine.

Administration of clofazimine to healthy volunteers together with food containing fat and proteins resulted in a 62% higher bioavailability compared to administration to the fasted volunteers (Fig. 3). Also, the peak plasma concentrations were higher, and the time to reach the peak was shorter when the dose was given concomitantly with food.

The plasma concentrations of clofazimine measured immediately before administering the 50-mg dose on days 3, 5, and 8 of repeated dosing indicate that on day 8 the steady-state level had not yet been reached (Fig. 6). This finding is consistent with the long elimination half-life of about 10 days estimated from the single-dose experiments. Thus, plasma concentrations following multiple dosing are predictable in healthy volunteers from single-dose kinetics, provided that the pharmacokinetics of clofazimine is linear. An indication of the linearity of the kinetics of clofazimine can be obtained from the multiple-dose experiment and from the apparent dose–AUC relationship observed in a previous study ([6]). In fact, there is good agreement of the predicted multiple-dose curve, which has been calculated on the basis of parameters from the single-dose experiment (Fig. 5), with the trough concentrations on days 3, 5, and 8, as well as with the elimination phase on days 9 through 19 (Fig. 6). It is only the peak concentration on day 8 which has not been adequately predicted. This may be due

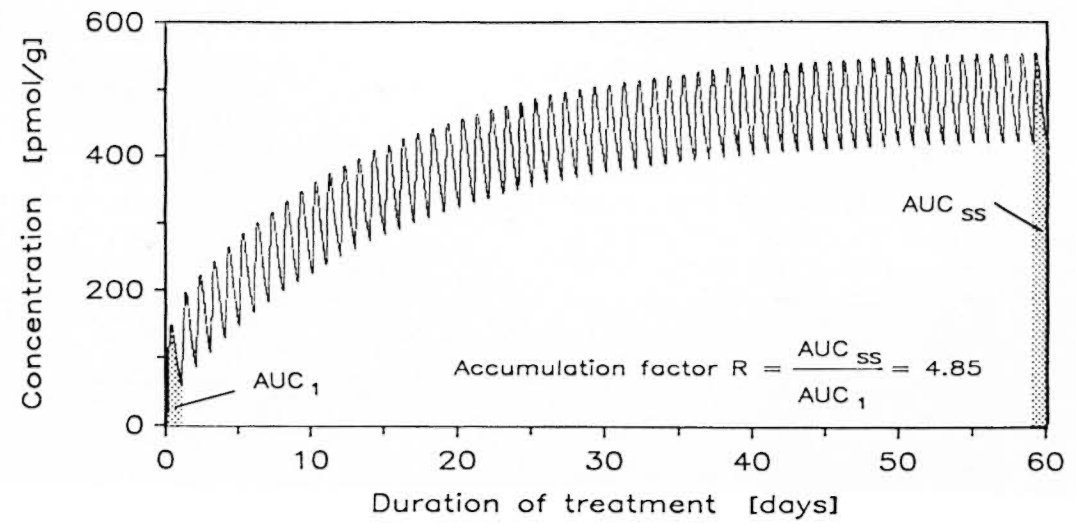

FIG. 7. Predicted clofazimine plasma concentrations following single daily oral doses of 50 mg.

to the inter-individual variation in the rate of absorption of clofazimine.

The terminal elimination half-life of clofazimine, calculated after the last 50-mg dose of repeated administration, was 8.8 ± 1.0 days (mean ± S.D., N = 3), i.e., similar to that determined after the single 200-mg dose. The half-life obtained from the fitted mean multiple-dose profile was 10.5 days.

The slow elimination of clofazimine has its implications for the treatment regimen in patients. When an oral dose of 50 mg of clofazimine is given daily, it is only after 30 days that the concentrations of clofazimine in plasma will come close to steady-state values (Fig. 7). The ratio AUC_{ss}:AUC_1 = 4.85 may be used to express accumulation ([6] and Fig. 7). This slow accumulation toward the steady state could only be avoided by giving higher loading doses at the beginning of treatment followed by daily administration of the maintenance dose.

SUMMARY

The pharmacokinetics of clofazimine was evaluated in 12 healthy male volunteers following single and multiple oral doses of clofazimine. Six volunteers received a single dose of 200 mg together with food. A 200-mg dose was administered to three volunteers either with or without food. In a multiple-dose experiment, three volunteers were repeatedly dosed with 50 mg per day together with food for 8 days.

Following a single oral dose of 200 mg, the mean peak plasma concentration of clofazimine was 861 ± 289 pmol/g (±S.D., N = 6) after 8 hr (median). The mean terminal half-life was 10.6 ± 4.0 days. Comparison of the bioavailability of clofazimine administered with or without food revealed a 60% higher mean area under the curve (AUC) value and a 30% higher mean maximum concentration (Cmax) value with food (N = 3). The median of times to peak (Tmax) was 8 hr with food and 12 hr without food.

In the multiple-dose study, good agreement was found between the mean experimental plasma concentration values and the plasma concentration profile predicted from the single-dose pharmacokinetics. The elimination half-life calculated from the terminal phase of the individual profiles after the last dose was 8.8 ± 1.0 days (±S.D., N = 3).The half-life obtained from the fitted mean multiple-dose profile was 10.5 days.

The slow elimination of clofazimine has its implications for the treatment regimen in patients. To avoid the long-lasting accumulation toward the steady state, higher daily loading doses are recommended at the beginning of therapy followed by a daily maintenance dose.

RESUMEN

Se valoró la farmacocinética de la clofazimina en 12 voluntarios sanos que recibieron una o múltiples dosis orales de la droga. Seis voluntarios recibieron una sola dosis de 200 mg junto con comida. Tres voluntarios recibieron una dosis de 200 mg con o sin comida. En un experimento con dosis múltiples, 3 voluntarios recibieron 50 mg por día junto con comida durante 8 días.

Después de una sola dosis oral de 200 mg, la concentración máxima promedio de clofazimina en plasma fue de 861 ± 289 pmol/g (±D.E., N = 6) a las 8 horas. La vida media terminal de la droga fué de 10.6 ± 4.0 días. La comparación de la bioaccesibilidad de la clofazimina administrada con o sin alimento reveló un área media bajo la curva 60% menor y una concentración media 30% mayor, cuando la droga se administró con alimento (N = 3). La mediana del tiempo de máxima concentración (Tmax) fue de 8 horas con comida y de 12 horas sin ella.

En el estudio con dosis múltiples, se encontró buena concordancia entre los valores medios de la concentración plasmática experimental y los valores de concentración calculados de la farmacocinética con dosis únicas. El tiempo de eliminación media calculado de la fase terminal después de la última dosis fue de 8.8 ± 1.0 días (±D.S., N = 3); el tiempo obtenido a partir del perfil de eliminación promedio administrando dosis múltiples fue de 10.5 días.

Debido a la lenta eliminación de la clofazimina, para evitar la acumulación prolongada de la droga durante la etapa de mantenimiento se recomienda administrar dosis altas al principio de la terapia y después las dosis diarias de mantenimiento.

RÉSUMÉ

Chez 12 volontaires masculins en bonne santé, on a évalué la pharmacocinétique de la clofazimine à la suite de doses simples ou multiples de clofazimine, administrées par voie orale. Six volontaires ont reçu une dose unique de 200 mg dans les aliments. Une dose de 200 mg a été administrée à trois volontaires, avec ou sans aliments. Dans un essai de posologie répétée, trois volontaires ont reçu 50 mg par jour, dans les aliments, pendant 8 jours.

A la suite d'une dose orale unique de 200 mg, la valeur maximale moyenne des concentrations plas-

matiques de clofazimine a été de 861 ± 289 pmol/g (±S.D., N = 6) après 8 heures (médiane). La demi-période terminale moyenne était de 10,6 ± 4,0 jours. Une comparaison de la biodisponibilité de la clofazimine administrée avec ou sans aliments a montré une surface moyenne de 60% plus étendue sous la courbe des valeurs (AUC), et une concentration maximale moyenne plus élevée de 30% (Cmax) avec aliments (N = 3). La médiane des périodes nécessaires pour atteindre la concentration maximale (Tmax) était de 8 heures avec aliments et de 12 heures sans aliments.

Dans l'étude menée avec des doses répétées, on a observé une concordance satisfaisante entre les valeurs moyennes de concentration plasmatique expérimentale, et les profils de concentration plasmatique prédits à la suite d'expériences de pharmacocinétique menées avec une dose unique. La demi-période d'élimination, calculée à partir de la phase terminale des profils individuels après la dernière dose, était de 8,8 ± 1,0 jours (±S.D., N = 3). La demi-période obtenue à partir des profils moyens ajustés lors de doses multiples lissés était de 10,5 jours.

L'élimination lente de la clofazimine a des implications pour la posologie thérapeutique à utiliser chez les malades. En vue d'éviter une accumulation prolongée qui aboutirait à un plateau, on recommande d'administrer des doses quotidiennes plus élevées au début de la thérapeutique, ces doses devant être ensuite suivies par une dose de maintien quotidienne.

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