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Intra-adipose Administration of Monoacetyldapsone to Healthy Volunteers[1]

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The effectiveness of dapsone (diaminodiphenylsulfone, DDS) in the treatment of leprosy is threatened by the increasing prevalence of dapsone-resistant strains of *Mycobacterium leprae* ([8, 13]). The irregularity with which many leprosy patients self-administer dapsone is believed to be one of the most important causes of this increasing dapsone resistance ([1, 3, 5, 6, 8, 13]). In order to combat the problem of poor dapsone compliance, the development of a sustained-release dapsone formulation was recommended as a priority in leprosy research ([13]).

To this end, we have developed an injectable, sustained-release dapsone formulation ([7]). After intramuscular injection of this formulation, differences in dapsone concentration/time course in serum between men and women were encountered. A poorer sustained-release effect was achieved in male than in female subjects, with higher dapsone peak concentrations in serum and a more rapid decline. The differences were explained by assuming that in the majority of women the injection was unintentionally administered into adipose tissue instead of muscular tissue, due to the fact that the adipose layer overlying the gluteus maximus is thicker in women than in men ([2]). The absorption rate of dapsone from the adipose tissue injection site is slower than that from the muscular injection site, and is believed to be caused by the poorer vascularization of adipose tissue than of muscle tissue.

This assumption was confirmed in a trial in which healthy volunteers received the injection in adipose tissue overlying the gluteus maximus ("intra-adiposely") ([12]). This time no sex differences occurred, and a good sustained-release effect was achieved in both male and female subjects.

Monoacetyldapsone, the major metabolite of dapsone in humans, appears to be deacetylated to dapsone after oral ([4]) and after intramuscular ([15]) administration, and can therefore be used as a prodrug of dapsone.

The solubility of dapsone at 37°C in a phosphate buffer is 0.3 mg/ml; of monoacetyldapsone, 0.05 mg/ml; and of diacetyldapsone, 0.004 mg/ml. The *in vitro* dissolution rate of monoacetyldapsone is intermediate between dapsone and diacetyldapsone, another prodrug of dapsone ([15]). Leprosy has been treated in the past by the intramuscular injection every 11 weeks of 225 mg diacetyldapsone, the drug being administered as a suspension in benzoylbenzoate/castor oil (4:6). However, blood levels of dapsone obtained by this method are very low (30–60 ng/ml). In view of the present information available on the development of resistance, these levels are considered to be too low for good chemotherapy of leprosy.

These considerations lead to the concept of a depot injection consisting of an aqueous suspension of monoacetyldapsone. In a pilot study, this injection was administered to six healthy volunteers who received doses of 700 to 1000 mg intramuscularly ([15]). In 4 of the subjects (2 males, 2 females) dapsone concentrations of 0.1 to 0.3 mg/l were sustained over a period of at least 2 months. After repeated once-monthly administration of the injection, accumulation occurred in three of them, leading to steady-state concentrations between 0.3 and 0.5 mg/l.

The other two (male) subjects showed quite a different concentration/time pattern with relatively high concentrations shortly after administration followed by a rapid decline of the dapsone concentration. It appeared likely, in a similar way as has been found for the intramuscular dapsone injection, that in these latter two subjects the

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injection was actually administered intramuscularly, while the other four received the injection intra-adiposely.

This paper presents the results of a more extensive study in which the depot properties of the monoacetyldapsone injection after intra-adipose administration were investigated in a group of 22 healthy volunteers.

MATERIALS AND METHODS

Preparation of the injection. Monoacetyldapsone with a particle size <20 μm was synthesized in a simple and cheap route by partial acetylation of dapsone using acetic anhydride, followed by a separation of MADDS from dapsone and diacetyldapsone using differences in solubility in diluted sulfuric acid between these three substances. Purity of the monoacetyldapsone was investigated by performing the tests on acidity, chloride, and sulfates as described in the Dutch *Pharmacopoeia,* 8th ed. The results met the requirements for sulfadimidine and sulfamerazine.

The particle size of the monoacetyldapsone was determined by an eye image splitting technique, and appeared to be <20 μm. Attempts to obtain larger crystals by recrystallization have not been successful to date.

The injection consisted of two components: an ampoule containing 1500 mg of monoacetyldapsone, sterilized by dry heating at 150°C for 1 hr, and an ampoule containing 5 ml of vehicle (a solution of 0.5% methylcellulose [400 mPa·s*], 0.5% Tween 80, and 0.9% sodium chloride in water for injection), sterilized by autoclaving. Immediately before injection, 4.95 ml of vehicle was added to 1500 mg of monoacetyldapsone. The mixture was shaken by hand to homogeneity to produce a suspension of 1175 mg of monoacetyldapsone per 4.7 ml.

Subjects. The injection was administered to 11 male and 11 female volunteers. All had participated in earlier studies ([11, 12]) in which the oral and intra-adipose pharmacokinetics of dapsone were investigated. Their ages ranged from 21 to 37 years (mean ± S.D. = 25 ± 5 years) and from 20 to 29 years (24 ± 3 years) for men and women, respectively. The men weighed 62 to 85 kg (72 ± 7 kg), while the women weighed 53 to 67 kg (59 ± 5 kg). Skinfolds, measured prior to the administration of the injection, ranged from 10 to 45 mm in men (22 ± 11 mm) and from 27 to 45 mm in women (34 ± 6 mm). Six female and five male subjects were slow acetylators according to the criteria employed by Philip, *et al.* ([10]).

Study design. After giving their informed written consent and after medical examination by the university medical service, the subjects received an oral dose of 100 mg dapsone to avoid possible allergic reactions or other side effects after the administration of the injection. Methemoglobin values were measured before and 24 hr after ingestion. As already stated, all of the volunteers had previously participated in oral and intra-adipose dapsone studies without encountering significant side effects. After a 2-week wash-out period, the injection was administered in the upper outer quadrant of the buttock. To establish the injection depth, the skinfold thickness was measured at the injection site. A dose of 1175 mg of monoacetyldapsone, which is equivalent to 1000 mg of dapsone, was injected at a depth equal to one third the thickness of the skinfold, being two thirds the skin-to-muscle distance. An 18 G 1½ inch needle (Terumo Europe NV, 3030 Leuven, Belgium) was used to administer the injection. Blood samples of 5 ml were collected before and 1, 3, 5, 7, 14, 21, 28, 35, 42, 49, and 56 days after injection to determine dapsone and monoacetyldapsone concentrations in serum. Three volunteers, two females and one male, did not complete the sampling scheme of 56 days (two until day 35 and one until day 42) for personal reasons not related to the experiment.

Analytical methods. Serum samples were frozen at −20°C pending analysis. Dapsone and monoacetyldapsone concentrations were determined using the high-pressure liquid chromatography (HPLC) method with fluorometric detection according to Peters, *et al.* ([9]). The detection limit was 6 ng/ml both for dapsone and monoacetyldapsone.

Pharmacokinetic and statistical analysis. Dapsone and monoacetyldapsone concen-

* The index 400 mPa·s indicates the 2% viscosity at 20°C of methylcellulose in an aqueous medium (1 millipascal·second = 1 centipoise).

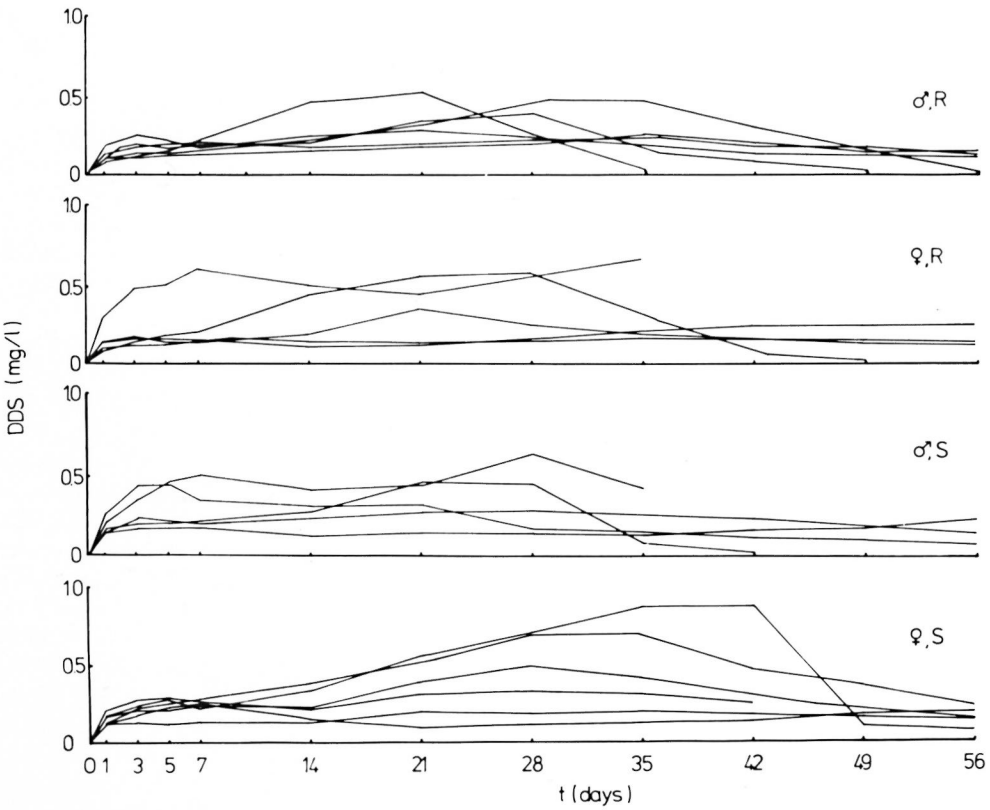

FIG. 1. Individual dapsone concentration/time courses after intra-adipose administration of 1175 mg monoacetyldapsone. From top to bottom: male rapid, female rapid, male slow, and female slow acetylators.

tration/time curves in serum were constructed for each subject. Areas under the curve (AUC) were calculated using the trapezoidal rule.

Assuming complete bioavailability (F_{or}) after oral administration of 100 mg dapsone half life ($t_{½DDS}$), the elimination rate constant (k_e) and distribution volume (V_D) had been calculated in the related study ([11]). The fraction of the dose released from the intra-adipose injection site during the study period (F_{ia}) was estimated using these values for k_e and V_D for each individual subject, using the equation $F_{ia} = AUC_{ia} \cdot k_e \cdot V_D \cdot 24/D$. In this equation the dose (D) is 1000 mg (dapsone, the equivalent of 1175 mg monoacetyldapsone).

Volunteer characteristics and results of pharmacokinetic analysis are presented as ranges and/or as mean ± standard deviation.

A rank sign test according to Kendall was performed to investigate if correlation existed between the monoacetyldapsone-to-dapsone concentration ratio in serum after intra-adipose administration of dapsone ([12]) and monoacetyldapsone. The correlation between AUC after oral and intra-adipose administration was investigated using linear regression analysis. Wilcoxon rank sign tests were used to decide whether results of men and women or of rapid and slow acetylators differed from each other with statistical significance. Results were considered to be statistically significant when p was lower than the level of significance $\alpha = 0.05$.

RESULTS

The pilot dapsone dose given prior to the intra-adipose experiment did not result in side effects attributable to dapsone in any of the volunteers. Methemoglobin values measured 24 hr after the oral dose remained below 5%.

Individual dapsone concentration/time

THE TABLE. *Individual characteristics of the subjects after oral ingestion of 100 mg dapsone ([11]) and summarized results after intra-adipose administration of 1175 mg monoacetyldapsone.*

Subj. no.	BW[a] (kg)	Acet.[b] R/S[c]	$t_{½DDS}$[b] (hr)	AUC_{or}[b] (mg·h/l)	AUC_{DDS} (mg·day/l)	AUC_{MAD} (mg·day/l)	M/D-rat[a]	c_{max} (mg/l)	$c_{t=56}$ (mg/l)	AUC/28 (mg/l)	F_{ia} (%)
						Women					
1	60	S	16.9	40.3	8.9	3.9	0.44	0.19	0.13	0.32	53
2	60	R	13.6	32.2	6.7	6.2	0.93	0.14	0.11	0.24	50
3	67	R	13.4	34.2	8.7	8.2	0.94	0.22	0.22	0.30	61
4	62	R	15.8	30.6	9.6	6.6	0.69	0.33	0.09	0.34	75
5	66	S	18.7	40.9	7.8	3.0	0.38	0.23	0.18	0.28	46
6	53	S	24.9	69.9	11.5	4.2	0.37	0.32	—	0.41	40
7	57	R	29.2	75.4	17.3	13.1	0.76	0.65	—	0.61	55
8	58	S	27.3	66.9	24.8	8.0	0.32	0.69	0.21	0.88	89
9	56	R	13.8	29.0	14.3	13.3	0.93	0.56	0	0.52	118
10	54	S	16.6	48.0	18.4	6.8	0.37	0.48	0.14	0.66	92
11	53	S	20.1	57.6	25.3	9.8	0.38	0.85	0.05	0.90	107
Mean	59		19.1	47.7	13.9			0.42	0.13	0.50	71
S.D.	5		5.6	17.0	6.7			0.24	0.07	0.24	27
						Men					
12	70	R	16.7	28.4	9.0	10.0	1.11	0.21	0.10	0.32	76
13	65	S	15.1	26.5	7.4	3.6	0.49	0.21	0.21	0.26	67
14	72	S	17.9	32.4	11.5	6.5	0.57	0.26	0.12	0.42	85
15	80	R	11.9	22.2	9.6	6.6	0.69	0.22	0.10	0.34	104
16	75	R	21.5	34.0	9.5	9.5	1.00	0.27	0.09	0.34	67
17	66	S	22.1	47.2	15.0	6.2	0.41	0.62	—	0.54	76
18	71	S	16.8	30.1	10.9	4.5	0.41	0.43	0.05	0.38	87
19	70	R	17.3	30.5	13.6	15.5	1.14	0.45	0	0.48	107
20	62	S	15.8	33.2	10.3	4.7	0.46	0.45	0	0.36	75
21	77	R	15.1	23.9	8.7	11.2	1.29	0.36	0	0.32	87
22	85	S	11.5	20.3	9.3	10.1	1.09	0.50	0	0.34	110
Mean	72		16.5	29.9	10.4			0.36	0.07	0.37	86
S.D.	7		3.3	7.3	2.2			0.14	0.07	0.08	15
TM[e]			17.8	38.8	12.2			0.39	0.09	0.44	79
S.D.			4.7	15.7	5.2			0.19	0.08	0.19	22

[a] BW = body weight.
[b] Results after oral administration ([11]).
[c] R = rapid; S = slow acetylator.
[d] M/D-rat = monoacetyldapsone-to-dapsone concentration ratio.
[e] TM = total mean of men and women.
For explanation of the other symbols, see text.

curves in serum after intra-adipose administration of monoacetyldapsone are illustrated in Figure 1. The results of male and female rapid and slow acetylators are shown separately. It can be seen that the intra-adipose administration of the monoacetyldapsone depot injection yielded flat concentration/time profiles, indicating good sustained almost zero-order release characteristics. No differences were detectable between rapid and slow acetylators or between men and women.

The Table summarizes the individual results of the subjects. Highest dapsone concentrations in serum varied from 0.14 to 0.85 mg/l in all of the volunteers, while 28, 42, and 56 days after injection dapsone concentrations averaged 0.33, 0.19, and 0.10 mg/l, respectively. After 56 days, dapsone concentrations in serum still were measurable in 14 out of the 19 volunteers remaining in the trial at that time. The AUC amounted to between 6.7 and 25.3 mg·day·l^{-1}. The apparent bioavailability over the study period ranged from 40% to 118% of the dose (79 ± 22%). In the five subjects in whom the dapsone concentrations in serum had declined to below the detection limit within 56 days, the apparent bioavailability was essentially complete. Values of between 75% and 118% (99 ± 18%) were found.

In the subjects previously classified as slow acetylators, the monoacetyldapsone-to-dapsone concentration ratio varied from

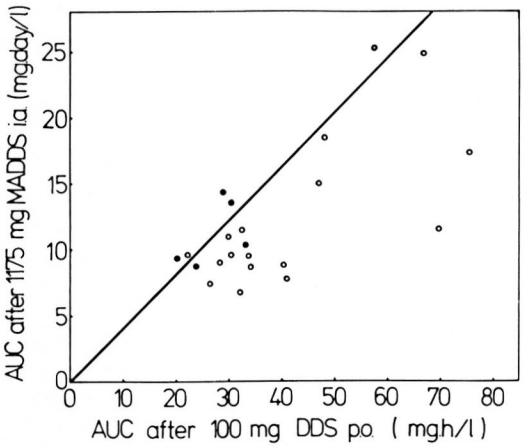

FIG. 2. Comparison of the AUC after oral administration of 100 mg dapsone and after intra-adipose administration of 1175 mg monoacetyldapsone to the same subjects. ○ = subjects who still had measurable dapsone serum concentrations 56 days after monoacetyldapsone administration; ● = those who did not. Line = equal bioavailability after oral and intra-adipose administration.

0.32 to 0.57. In those previously classified as rapid acetylators, a monoacetyldapsone-to-dapsone concentration ratio between 0.69 and 1.29 was found.

The injection was well tolerated by the volunteers. The administration itself was not painful, and complaints were restricted to a slight sensitivity at the injection site that never lasted longer than 1 week.

DISCUSSION

In a previous study, the advantage of intra-adipose instead of intramuscular administration of a slow-release dapsone formulation was demonstrated ([12]). After intra-adipose administration, a more sustained release was achieved than after intramuscular injection and no differences existed in the dapsone concentration profiles as found in the sera of males and females.

In this study, no differences existed in slow-release characteristics of the monoacetyl formulation between men and women. This reinforces the conclusion that the discrepancies observed in the monoacetyldapsone pilot study of Zuidema, *et al.* ([15]) were also caused by the unintentional intra-adipose administration of the injection in females and in some of the males.

After intra-adipose administration of monoacetyldapsone, a more prolonged sustained-release effect was achieved than after the intra-adipose administration of dapsone, but the measured dapsone concentrations in serum were lower ([12]). However, it was not possible to calculate mean residence times, mean absorption times, or other parameters which can be used to measure this difference objectively, since the final measured dapsone concentrations were too high in most of the subjects to permit extrapolation until infinity. Nevertheless, the difference is clear directly from the curves.

At least two factors can be expected to have contributed to differences in the sustained-release behavior between the dapsone and the monoacetyldapsone injection after intra-adipose administration. First, the solubility of monoacetyldapsone is lower than that of dapsone; 0.05 versus 0.3 mg/l in a phosphate buffer (pH 7.4) of 37°C ([15]). Second, the monoacetyldapsone particles were smaller than the dapsone particles in the previous studies, resulting in a larger specific surface area of monoacetyldapsone and thus possibly in a faster dissolution. On the other hand, the smaller particle size combined with the large hydrophobic surface of the monoacetyldapsone might lead to aggregation of particles at the injection site. Aggregation could lower the dissolution rate of a drug. Attempts to prepare larger monoacetyldapsone crystals have so far not been successful.

Repeated once-monthly administration will probably lead to accumulation of monoacetyldapsone as was previously shown by Zuidema, *et al.* ([15]). The AUC divided by 28 is a low estimation of the mean steady-state dapsone concentration reached when the injection should be administered every 28 days. Since extrapolation until infinity is not possible in most of the curves, real steady-state concentrations will be higher than the calculated AUC/28 values. AUC/28 ranged from 0.24 to 0.90 mg/l in this study. All of the individual results of these calculations are shown in The Table.

A good correlation appears to exist between the monoacetyldapsone-to-dapsone concentration ratio after the intra-adipose administration of dapsone, as found in the earlier study ([12]) and after monoacetyldap-

sone, as found in this study ($p < 0.005$). However, the monoacetyldapsone-to-dapsone concentration ratio reached after monoacetyldapsone was about 40% higher than after dapsone, indicating that deacetylation occurs after absorption and that it is a rather slow process compared to acetylation. The same observations were made by Gelber, *et al.* ([4]) and by Zuidema, *et al.* ([15]). The acetylation status has no influence on absorption or elimination rates ([14]) and has, therefore, no influence on the duration of action of this injection.

In Figure 2, the AUC after oral administration of 100 mg dapsone is compared to the AUC after intra-adipose monoacetyldapsone injection. The closed circles demonstrate the complete bioavailability in the five subjects in whom dapsone concentrations in serum had declined below the detection limit before the end of the study, in contrast with the other subjects, represented by the open circles. The correlation coefficient amounts to 0.676 ($N = 22$, $p < 0.005$), while the regression coefficient is 0.233 and the intercept 3.54. An impression of the not released fraction of the injection at the end of the study can be derived by $1 - F_{ia}$ (The Table).

It can be concluded that good sustained-release effects can be achieved with the monoacetyldapsone depot injection used in this study. Results may even improve after repeated intra-adipose injection. In the future it might contribute to combat noncompliance among leprosy patients, which is believed to be one of the main causes of dapsone resistance.

SUMMARY

The pharmacokinetics of intra-adiposely administered monoacetyldapsone (particle size < 20 μm) were investigated in 11 male and 11 female healthy volunteers. Dapsone and monoacetyldapsone concentrations in serum were determined by high-pressure liquid chromatography (HPLC).

Injection of 1175 mg monoacetyldapsone, which is equivalent to 1000 mg dapsone, resulted in dapsone concentration/time profiles in all the volunteers characterized by peak concentrations ranging from 0.14 to 0.85 mg/l, and by averaged dapsone concentrations after 28, 42, and 56 days of 0.33, 0.19, and 0.10 mg/l, respectively. Areas under the curves ranged from 6.7 to 25.3 mg·day/l. Detectable concentrations (>6 ng/ml) of dapsone were achieved for 56 days in most of the subjects. An estimation of the mean concentration after repeated injection every 4 weeks ranged from 0.24 to 0.90 mg/l. No differences in dapsone concentration/time course were detectable between men and women or between rapid and slow acetylators.

The injection was generally well tolerated by the subjects. This, combined with the excellent sustained release properties, makes it a promising injection. In the future, it might contribute to combat noncompliance among leprosy patients, which is believed to be one of the main causes of dapsone resistance.

RESUMEN

Se investigó la farmacocinética de la monoacetil dapsona administrada intra-adiposamente (partículas menores de 20 μm) en 11 mujeres y 11 hombres, todos ellos voluntarios sanos. Las concentraciones de dapsona y de monoacetil dapsona en suero se determinaron por cromatografía de líquidos de alta presión (HPLC).

La inyección de 1175 mg de monoacetil dapsona, equivalente a 1000 mg de dapsona, dió origen a perfiles de concentración de dapsona caracterizados por máximos que variaron de 0.14 a 0.85 mg/l, y por concentraciones promedio de dapsona de 0.33, 0.19 y 0.10 mg/l, después de 28, 42 y 56 días, respectivamente. Las áreas bajo las curvas variaron de 6.7 a 25.3 mg/día/l. En la mayoría de los sujetos se alcanzaron concentraciones medibles de dapsona hacia el día 56. La concentración promedio de dapsona después de la inyección repetida cada 4 semanas, varió de 0.24 a 0.90 mg/l. No se encontraron diferencias en la concentración de dapsona respecto al tiempo ni entre hombres y mujeres ni entre acetiladores rápidos y lentos.

La inyección fue generalmente bien tolerada por los sujetos. Esto, combinado con las excelentes propiedades de liberación de la droga, hace que esta via de inyección sea muy promisoria. En el futuro ésto podría contribuir a combatir la medicación irregular entre los pacientes con lepra la cual es la causa principal de la resistencia a la dapsona.

RÉSUMÉ

Chez 11 sujets masculins et chez 11 sujets féminins en bonne santé, on a étudié la pharmacocinétique de la monoacétyldapsone administrée dans le tissu adipeux (la dimension des particules du produit étant inférieure à 20 μm). Les concentrations de dapsone et monoacétyldapsone dans le sérum ont été déterminées

par une méthode de chromatographie liquide élevé pression (HPLC).

L'injection de 1175 mg de monoacétyldapsone, soit l'équivalent de 1000 mg de dapsone, a entraîné des profils de concentration de dapsone en fonction du temps qui, chez tous les volontaires, étaient caractérisés par des concentrations maximales allant de 0,14 à 0,85 mg/l, et par des concentrations moyennes de 0,33, 0,19, et 0,10 mg/l après respectivement 28, 42, et 56 jours. Les surfaces recouvertes par les courbes s'étendaient de 6,7 à 25,3 mg par jour et par litre. Chez la plupart des sujets, des concentrations de dapsone décelables (c.à.d. supérieures à 6 ng/ml) ont été observées pendant 56 jours. L'estimation de la concentration moyenne après injections répétées toutes les quatre semaines a révélé des concentrations de 0,24 à 0,90 mg/l. Aucune différence dans les concentrations de dapsone au cours du temps n'a été observée entre les hommes et les femmes, ou entre les acétylateurs rapides et lents.

L'injection était généralement bien tolérée par les sujets. On peut dès lors considérer que cette méthode d'administration est prometteuse, d'autant plus que la libération prolongée du dépôt se révèle excellente. A l'avenir, cette méthode pourra contribuer à combattre le manque d'assiduité des malades de la lèpre au traitement, dont on peut croire qu'il est l'une des causes principales de la résistance à la dapsone.

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