Factors influencing the level of dapsone in blood

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The level of dapsone in the blood 4 and 6 h after the ingestion of the 7th daily dose of 100 mg of the drug was investigated in 36 adult males with leprosy who had normal renal function and were free of diarrhoea and emesis. The bimodal distribution of the dapsone levels at 6 h was shown by multiple regression analysis to be due to a negative correlation between this trait and the haematocrit value. Among the patients with high dapsone blood levels, 81.8 % presented haematocrit values under 36 %, whereas only 20 % of those with low levels showed low haematocrit values. Partial regression coefficients, calculated for the dapsone level on the age, weight of the patient, estimated number of years since the onset of leprosy, number of years under sulfone treatment, and blood levels of haemoglobin, albumin, and globulins, did not show statistical significance.

It is now accepted that the conversion of dapsone to its monoacetylated form (monoacetyl-dapsone) is readily accompanied *in vivo* by its deacetylation, but that the individual monoacetyl-dapsone : dapsone ratio in the plasma is a constant and reproducible characteristic (1). Since this trait parallels the individual acetylation capacity for both isoniazid and sulfadimidine (1, 2, 3), it follows that dapsone acetylation in man depends on the same genetic polymorphism as that for isoniazid and sulfadimidine acetylation. Thus the main gene that in homozygosis determines slow acetylation of isoniazid and sulfadimidine appears to be responsible also for the slow-acetylator phenotype for dapsone. Studies (4, 5) are in progress to determine whether this knowledge is applicable to leprosy therapy.

Further information on the metabolism of dapsone is provided by the present paper, which describes a pilot study to investigate the factors influencing the level of dapsone in blood.

MATERIALS AND METHODS

The study population consisted of 36 adult leprosy patients (31 lepromatous, 4 indeterminate, and 1 tuberculoid), all caucasoid males of Mediterranean origin, who were selected from one hospital (Sanatório Pirapitingui, São Paulo, Brazil) in order to include only individuals living under the same environmental and dietary conditions and not ingesting other drugs besides dapsone at the time of the investigation.

The clinical status of the patients was investigated by anamnesis, physical examination, and evaluation of laboratory data including routine urine analyses, complete haemograms, the level of urea in the blood, and proteinograms. None of the tested individuals manifested diarrhoea or emesis just before and during the experiment, and the results of the urine analyses and dosages of blood urea confirmed the clinical hypothesis that all the patients could be considered as having normal renal function.

A daily dose of 100 mg of dapsone (prepared by the Instituto Butantan, São Paulo, Brazil) was administered orally to each patient for 7 days in order to ensure the regular ingestion of the drug. Two venous blood samples were obtained from each patient 4 and 6 h after the ingestion of the 7th daily dose, for the photocolorimetric determination of the dapsone level in the blood. All these tests were performed by one of us (M.M.E.G.) according to the method described by Simpson in an appendix to a paper by Molesworth & Narayanaswami (6).

RESULTS

The data concerning the age and weight of the patients, the estimated number of years since the

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Table 1. Clinical data on 36 selected leprosy patients

No.	Age (years)	Weight (kg)	Duration of the disease (years)	Years of sulfone therapy	Haemato-crit value (%)	Haemo-globin (g/litre)	Globulins (g/litre)	Albumin (g/litre)	Dapsone (mg/litre)	
									4 h	6 h
1	34	61.8	10	8	47	123	36.6	27.4	3.8	3.2
2	30	76.2	6	1	40	110	29.9	40.1	3.3	4.1
3	33	66.0	13	2	42	114	31.9	43.1	2.8	2.6
4	30	65.5	14	10	44	110	39.0	31.0	4.9	5.5
5	45	58.4	12	2	34	92	40.0	30.0	7.2	5.1
6	43	59.4	16	4	40	105	35.3	36.7	0.9	1.0
7	44	65.6	35	7	32	92	35.3	28.7	6.9	7.5
8	33	57.8	21	12	45	100	39.2	40.8	2.5	3.3
9	31	53.1	20	10	41	92	38.1	31.9	3.6	3.7
10	39	59.1	16	7	35	92	28.6	46.4	3.6	4.4
11	33	48.8	16	6	38	110	30.8	41.2	2.2	3.8
12	46	62.6	20	16	39	110	31.0	29.0	0.6	0.8
13	33	57.6	4	1	38	105	36.8	38.2	4.4	3.8
14	44	60.4	20	17	42	105	33.9	36.1	5.1	3.9
15	39	69.4	12	10	41	110	35.7	33.3	4.5	4.2
16	43	66.7	30	15	42	100	33.8	36.2	3.4	3.3
17	54	69.1	40	26	39	92	37.5	31.5	3.8	3.9
18	49	74.0	23	22	34	92	36.0	34.0	5.5	6.3
19	49	73.1	10	2	32	70	30.8	31.2	5.2	1.9
20	44	62.6	36	23	35	100	31.5	36.5	5.7	5.7
21	40	74.0	27	17	35	88	31.9	39.1	5.0	4.4
22	35	60.9	19	11	37	100	32.4	35.6	1.0	0.7
23	49	61.5	42	29	43	110	30.3	34.7	4.1	4.1
24	38	63.5	9	6	42	105	38.6	39.4	3.2	2.8
25	51	62.5	15	3	35	92	30.3	34.7	7.4	6.3
26	52	67.1	41	13	40	100	37.6	37.4	2.5	2.1
27	53	58.9	34	29	37	97	37.8	32.2	5.8	5.5
28	54	77.2	33	12	35	119	30.3	39.7	1.7	2.4
29	53	69.1	33	23	32	74	33.0	36.0	6.2	6.8
30	52	72.7	32	17	44	97	29.4	40.6	3.9	2.9
31	53	39.9	48	29	37	88	40.7	31.3	5.7	7.1
32	55	80.5	28	22	32	92	33.2	38.8	6.3	5.8
33	40	62.6	28	28	35	97	26.6	33.4	6.2	6.7
34	40	66.4	12	3	33	74	33.6	41.4	4.3	3.8
35	31	60.8	5	1	40	105	34.9	25.1	3.3	3.4
36	32	67.9	6	5	38	92	41.6	24.4	3.8	3.0
Mean	42.33	64.24	21.83	12.47	38.19	98.7	34.3	35.2	41.8	40.5
S.D.	8.27	8.01	11.93	9.17	4.08	11.8	3.8	5.1	17.5	17.6

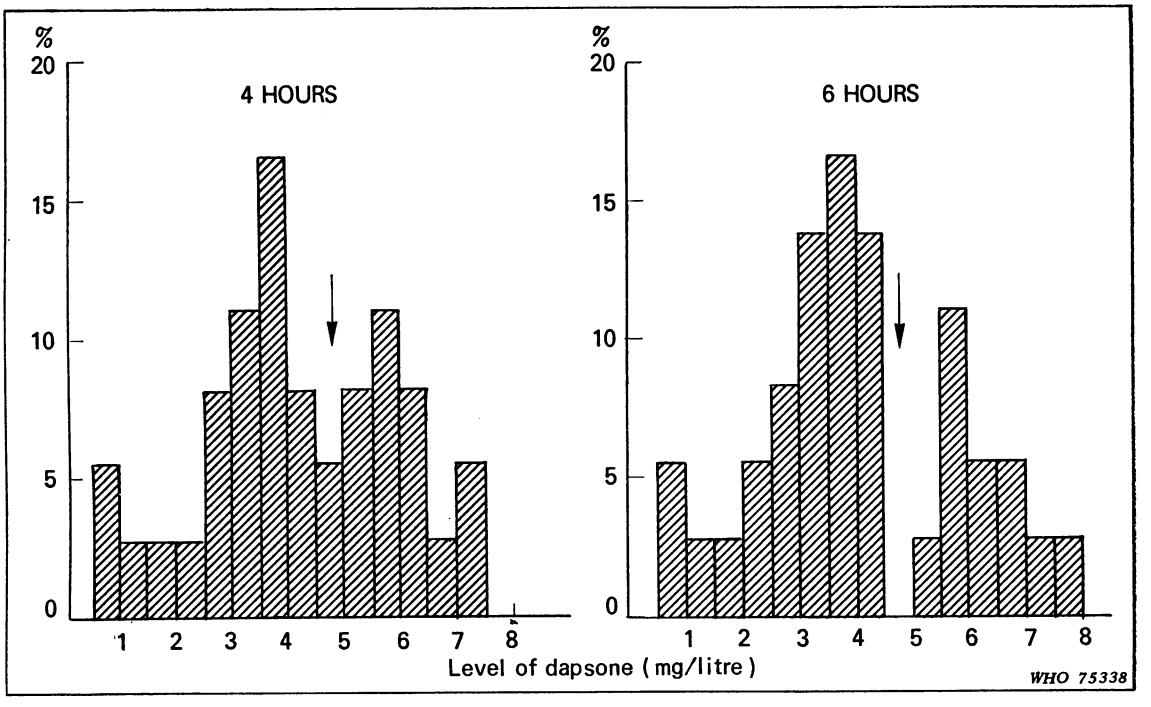

Fig. 1. Distribution of 36 leprosy patients according to the level of dapsone in the blood 4 h and 6 h after the ingestion of a 100-mg dose.

onset of leprosy, the number of years on sulfone treatment, haematocrit values, and blood levels of haemoglobin, albumin, globulins, and dapsone 4 and 6 h after ingestion of the 7th 100-mg dose of the drug are presented in Table 1. Fig. 1 shows the distribution of the study population according to blood levels of dapsone 4 and 6 h after the ingestion of the last dose.

DISCUSSION AND CONCLUSIONS

The distribution of patients according to the blood level of dapsone determined 6 h after ingestion of the 7th 100-mg dose suggested bimodality. This was obscured when the level was measured at 4 h, although the histogram of this distribution had already indicated a tendency to define the antimode observed later at the interval between 4.5 and 5.0 mg/litre.

Whereas the distribution at 6 h seemed to be the better for discriminating between two types of leprosy patient—i.e., those with high blood levels of dapsone (more than 4.5 mg/litre) and those with low blood levels (less than 4.5 mg/litre), it soon became obvious that such dimorphism was not related to that observed by Gelber et al. (1) and Peters et al. (2, 3) concerning the acetylating capacity for dapsone. As a matter of fact, if these traits were correlated one might expect to find a larger proportion of patients with high blood levels of dapsone than that observed (30.6%), since the frequency of slow acetylators of isoniazid, sulfadimidine, and dapsone varies around 60% among caucasoid populations (2, 3, 7).

A bimodal distribution may support a single-gene interpretation, since most of the inherited variation of many semidiscontinuous traits is determined by single main gene pairs. However, as the same distribution may be caused by heterogeneity of non-genetic origin, a multiple regression analysis was applied to the data presented in Table 1, before any tentative hypothesis was advanced to explain the bimodal distribution of the dapsone blood levels at 6 h. From the results of this analysis, shown in Table 2, it is easy to conclude that the level at 6 h does not depend on age, weight, the

Table 2. Results of the multiple regression analysis applied to the data of Table 1 when the blood level of dapsone 6 h after the ingestion of 100 mg of the drug is considered as the dependent variable

Variable	Regression coefficient	Standard error	t-Ratio 34 D.F.	P
Age	–0.0586	0.0542	–1.081	>0.20
Weight	–0.0145	0.0374	–0.388	>0.60
Duration of the disease	0.0115	0.0468	0.246	>0.80
Years under sulfone therapy	0.0894	0.0520	1.719	>0.05
Haematocrit value	–0.2317	0.0990	–2.340	<0.05
Haemoglobin	0.0005	0.3179	0.002	>0.90
Globulins	0.6950	0.8762	0.793	>0.40
Albumin	–0.0793	0.6009	–0.132	>0.80

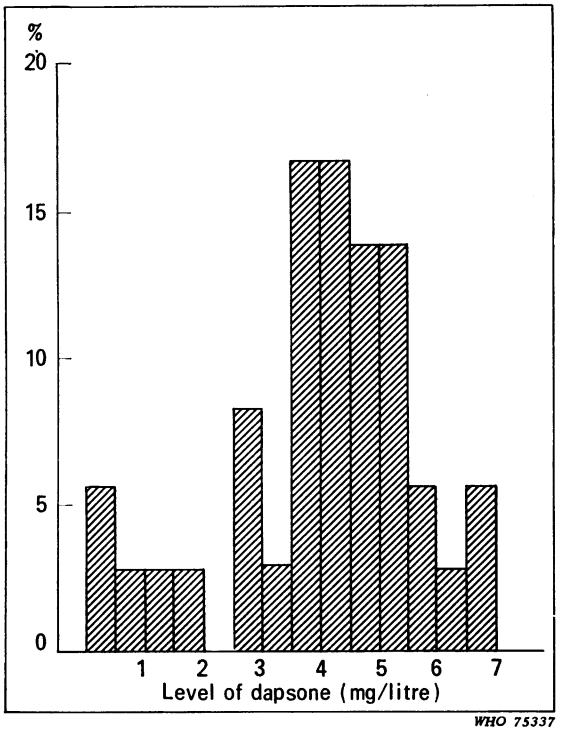

Fig. 2. Distribution of 36 leprosy patients according to the level of dapsone in the blood at 6 h, adjusted for the haematocrit value.

duration of leprosy, the length of sulfone treatment, or the blood levels of haemoglobin, globulins, and albumin, but that it is significantly and negatively correlated with the haematocrit value. Therefore, although the correlation analyses indicated a significant correlation between the dapsone blood level at 6 h and the number of years under sulfone therapy ($r=0.347$; $t=2.315$; 34 D.F.; $P<0.05$), the effect of the duration of treatment on the concentration of dapsone disappeared when all variables were simultaneously taken into account.

In view of this conclusion, the individual blood levels of dapsone were adjusted for haematocrit values according to the equation $Y_a = Y+(\bar{X}-X)b$, where Y_a is the adjusted value of the dapsone level observed at 6 h (Y), $\bar{X}$ is the mean of the haematocrit values (X), and b is the partial regression coefficient of the dapsone level on the haematocrit value.

Since the antimode of the bimodal distribution seen in Fig. 1 disappeared in the histogram constructed with the adjusted data (Fig. 2), it may also be concluded that the observed dimorphism of this trait was caused, in all probability, by the heterogeneity of the study population as regards individual haematocrit values. Indeed, the data in Table 1 show that 81.8% of the patients with high dapsone blood levels presented haematocrit values under 36% (the lower limit for normal values among adult males), whereas only 20% of those with a low level showed low haematocrit values (corrected $\chi^2=7.062$; 1 D.F.; $P<0.01$).

It seems premature to suggest an explanation for the negative correlation between the blood level of dapsone and the low haematocrit value before the role of the erythrocytes in the metabolism of this drug and the effect of dapsone on these cells have been investigated. Further research on the cause and effect of this phenomenon is needed.

ACKNOWLEDGEMENTS

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RÉSUMÉ

FACTEURS INFLUENÇANT LE TAUX DE DAPSONE DANS LE SANG

On a recherché la teneur du sang en dapsone 4 et 6 heures après l'ingestion de la dose quotidienne de 100 mg du médicament, au 7e jour du traitement, chez 36 hommes adultes atteints de lèpre, mais dont la fonction rénale était normale et qui ne présentaient ni diarrhée ni vomissements.

La distribution des taux de dapsone après 6 heures était bimodale et une analyse par régression multiple a montré que cette bimodalité était due à une corrélation négative entre la dapsonémie et la valeur de l'hématocrite. Parmi les patients à forte sulfonémie, 81,8% présentaient des valeurs de l'hématocrite inférieures à 36%, alors que 20% seulement des malades chez lesquels le taux de dapsone était peu élevé montraient de faibles valeurs de l'hématocrite.

Les coefficients de régression partiels calculés pour le taux de dapsone, l'âge, le poids, le nombre supposés d'années depuis l'apparition de la maladie, la durée du traitement par les sulfones, ainsi que les taux sanguins d'hémoglobine, d'albumine et de globulines se sont révélés sans signification statistique.

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