INTERNATIONAL JOURNAL OF LEPROSY Volume 56, Number 1
Printed in the U.S.A.

A Field Trial Among Leprosy Patients in Nigeria with Depot Injections of Dapsone and Monoacetyldapsone[1]

Frans A. J. M. Pieters, Frits Woonink, and Jan Zuidema[2]

Dapsone (diaminodiphenylsulfone, DDS) has proven its efficacy in leprosy, dermatitis herpetiformis, and several other dermatological disorders ([12]). One of the major problems in leprosy control, however, is poor patient compliance. Apart from the fact that this will lead to an incomplete cure, the threat of spreading the disease exists, because the patient remains infectious. Almost certainly patient noncompliance is one of the most important causes of DDS resistance ([10, 21]). The necessity to develop a sustained-release DDS formulation to combat this low patient compliance was stated by the WHO in 1982 ([29]).

After early attempts by several research groups, some more successful than others ([3, 5, 6, 9, 13, 16, 17, 19, 27]), Modderman, *et al.* ([14]) started to reinvestigate the possibility of using an aqueous suspension of DDS for an injectable slow-release formulation, judging it incorrect to rely on figures and conclusions published 20 to 30 years earlier. They finally came up with an injection consisting of bipyramidally shaped DDS crystals with a particle size of 38–63 μm suspended in an aqueous vehicle. Recrystallization, milling, and sieving techniques were used to obtain adequate crystal properties.

A trial, conducted at the All-African Leprosy and Rehabilitation Training Centre (ALERT) in Addis Ababa, Ethiopia, demonstrated that intramuscular administration of this injection yielded sufficient sustained-release characteristics in female patients only ([15]). The explanation seemed to be the difference between the sexes in the thickness of the fatty layer at the injection site. Therefore, in females, unlike in males, the injection was presumably placed in fat instead of in muscle ([4]).

After a single intentional administration of the injection into fatty tissue (this route of administration is henceforth called intra-adipose, as suggested by Morrison [18]), acceptable DDS concentration/time profiles were observed in both male and female healthy volunteers without important local side effects ([26]).

Meanwhile a comparable monoacetyldapsone injection had been developed. Monoacetyldapsone (MADDS) is the major metabolite of DDS in blood, and since deacetylation of MADDS occurs it can be used as a prodrug of DDS ([8, 30]). MADDS has a lower aqueous solubility than DDS, and therefore the sustained-release results might be improved by using MADDS instead of DDS. Besides, different crystal properties might lead to a better syringeability of the injection.

An intramuscular study with this MADDS injection in a limited number of healthy volunteers demonstrated similar discrepancies as observed with the DDS injection ([30]). In the subsequent intra-adipose study in healthy volunteers, an almost perfect zero order sustained drug release was observed. In most of the subjects, substantial DDS concentrations were measured until at least 56 days after injection. Compared to the DDS injection, lower DDS concentrations were measured for a longer period after administration ([24]).

Between May and October 1986 new insights in the applicability of both injections were obtained by conducting two field trials in Plateau State, Nigeria. In one clinic, 52 leprosy outpatients were treated with the DDS injection for 16 weeks. In another clinic, 22 patients started a trial with the MADDS injection. The results of both studies are presented in this paper.

MATERIALS AND METHODS

Preparation of the injection. The DDS injection, a suspension of bipyramidally

[1] Received for publication on 22 June 1987; accepted for publication in revised form on 1 September 1987.

[2] F. A. J. M. Pieters, Pharm.D., and J. Zuidema, Ph.D., Department of Biopharmaceutics, University of Amsterdam, Plantage Muidergracht 14, 1080 TV Amsterdam, The Netherlands. F. Woonink, M.D., Mangu Leprosy and Rehabilitation Centre (COCIN), Private Mail Bag 2127, Jos, Plateau State, Nigeria.

TABLE 1. *Patient characteristics and pre-study clinical data.*

	DDS study		MADDS study	
	Males	Females	Males	Females
No. patients	30	22	11	11
Age (yr)	40 ± 12[a]	40 ± 8	47 ± 9	45 ± 6
Body weight (kg)	56 ± 7	49 ± 8	57 ± 11	54 ± 8
Skin fold (mm)	18 ± 5	21 ± 7	14 ± 10	20 ± 9
Leprosy type and no.				
T[b]	3	5	—	2
BT	5	3	2	3
BL	9	4	4	2
L	13	10	5	4
Duration disease (yr)	19 ± 11	18 ± 11	21 ± 14	22 ± 15
Duration treatment (yr)	14 ± 11	14 ± 11	18 ± 13	21 ± 15
Clinic attendance (%)	87 ± 17	96 ± 6	78 ± 18	83 ± 20

[a] Age, body weight, skin fold, duration disease, duration treatment, and clinic attendance are given as mean ± S.D.

[b] T = tuberculoid; BT = borderline tuberculoid; BL = borderline lepromatous; L = lepromatous.

shaped DDS crystals with a particle size between 38 μm and 63 μm in an aqueous vehicle, was prepared according to the method described by Modderman, *et al.* ([15]). The injection contained 250 mg DDS per ml suspension.

The preparation and quality control of the MADDS injection were described by Pieters and Zuidema ([24]). The suspension contained 250 mg MADDS per ml suspension.

Subjects. The participants in the DDS trial were 30 male and 22 female leprosy outpatients, while 11 males and 11 females entered the MADDS study. Their characteristics are summarized in Table 1. The data of this table were collected as follows: age, duration of the disease and of the treatment were obtained by asking the patient. Skin folds were measured using a skin-fold meter donated by Servier Nederland B.V. The classification of patients into tuberculoid (T), borderline (BT, BL) and lepromatous (L) cases was done by one of us (FW). The clinic attendance was derived from the register held by the leprosy supervisor responsible for the clinics. Only the 1986 attendance before the start of the study (June 1986) was taken into account. The patients were scheduled to come to the clinic once a week.

Most of the patients had been on oral DDS monotherapy for more than 5 years at the start of the study. Apart from leprosy, no diseases were reported to be present in any of the patients. One woman in the DDS trial delivered a healthy baby 3 weeks after receiving the first injection.

Study design. Essentially, the study designs of the DDS and the MADDS studies were identical. Before the start of both studies an ethical clearance was obtained. The State Commissioner of the Plateau State Ministry of Health and the Sole Administrator of the Jos Local Government Council gave their informed consent and full cooperation for the studies, as did the patients. The oral DDS treatment was withdrawn 1 week before the start of the project.

The body weight of each patient was measured to determine the dose to be administered. The patients received a body-weight dependent dose as mentioned in Table 2. The amounts of MADDS given were the molar equivalents of the DDS doses (1175 mg MADDS equals 1000 mg DDS).

The injections were administered at a depth of ⅓ of the thickness of the skin fold measured at the injection site (the upper

TABLE 2. *Relation between body weight of the patient and the administered dose.*

Body weight (kg)	DDS study		MADDS study	
	Injection volume (ml)	DDS dose (mg)	Injection volume (ml)	MADDS dose (mg)
<50	3.0	750	3.5	875
50–59	3.6	900	4.2	1050
60–69	4.2	1050	4.9	1225
>69	4.8	1200	5.6	1400

outer quadrant of the buttock), corresponding with ⅔ of the skin-to-muscle distance. An 18 gauge 1½ inch needle (Terumo Europe NV, 3030 Leuven, Belgium) was used to administer the injection.

Each patient received four injections with intervals of 4 weeks between injections. Blood samples (5 ml each) were taken before the first injection, 1, 3, 5, 7, 14, 21, and 28 days after the first and fourth injections, 7 and 28 days after the second injection, and 7, 14, and 28 days after the third injection to establish the concentration of DDS and MADDS in serum. Minor changes in the sampling scheme occurred in individual patients, however, and some patients failed to attend the clinic each time. No sample was collected 28 days after the last MADDS injection.

Simultaneously with the start of both studies multidrug therapy (MDT) was introduced consisting of rifampin 600 mg every 4 weeks plus the injection to which a daily dose of 100 mg clofazimine was added for the L and BL patients. This was a slightly modified version of the MDT regimen for leprosy control programs as proposed by WHO in 1982 ([29]). No other drugs were reported to be taken. During the study the patients had to visit the clinic at least once a week. Patients' comments were kept on records. At the end of the study the patients were asked for their judgment on the injections and their preference for either the injections or the oral therapy by a questionnaire.

Determination methods. Serum samples were frozen at −20°C pending transport to Amsterdam, where analysis was performed. DDS and MADDS concentrations were measured using the HPLC method with fluorometric detection as described previously ([25]).

Pharmacokinetic and statistical analysis. The area under the DDS concentration/time curve until 28 days after administration of the first [AUC (1)] and fourth [AUC (4)] injection was calculated using the trapezoidal rule. The AUC (4) : AUC (1) ratio was calculated to determine whether accumulation occurred. The ratio between the DDS concentration 28 and 7 days after every administration was taken as a measure of the sustained-release effect of the injection.

Differences between male and female patients or changes occurring during the study were investigated using Student *t* tests. The differences were considered to be statistically significant if $p < 0.05$.

RESULTS

DDS injection. The study was completed by 19 female (86%) and 30 (100%) male patients. One patient refused to take her last injection; the blood sampling seemed to be the problem. One patient was not able to complete the study because she did not feel well enough to come to the clinic every time. One patient started a new job, which did not allow her to attend regularly. The overall attendance of the patients during the study was very satisfying. Fifteen patients (12 males, 3 females) had a 100% attendance, while on the average 91 ± 2% of the planned blood samples was actually taken.

An overview of the results is presented in Figure 1 A and B. In most of the patients a good sustained-release effect was observed. DDS concentrations higher than 3.0 mg/l did not occur in any of the patients; on the other hand, concentrations below 0.1 mg/l were measured in only 4.2% of the blood samples (34 of the 816 taken). Over 70% of the samples contained more than 0.5 mg/l DDS.

The results are summarized in Table 3. The DDS serum concentrations reached after the first DDS injection are lower in females than in males. From the second injection onward this difference disappears but the ratio between the AUCs after the fourth and the first injection (an indication of the accumulation) is statistically significantly higher in females than in males. Generally, none of the sex differences is clinically relevant.

During the study one male patient suffered from a local infiltration which developed into an abscess. After incision some pus escaped and the symptoms rapidly disappeared. Despite this inconvenience the patient preferred to continue the injection treatment. None of the other patients reported serious local side effects from the injections. The depot was readily palpable most of the time, even 4 weeks after injection, but no sign of inflammation could be found.

A questionnaire was obtained from 44 patients (17 females, 27 males). None of them found the administration of the injection painful. No patient reported serious local side effects at the injection site except for the above-mentioned male patient. Forty-one of 44 patients preferred the injection to tablets, 1 patient was indifferent to the choice between the two regimens, while 2 (1 male, 1 female) preferred tablets.

MADDS injection. Unfortunately, the MADDS study was disturbed by the appearance of a number of abscesses at the injection site. Mainly as a result of these side effects, only 13 patients (8 males, 5 females) completed the study. Two patients discontinued the study because they objected to blood sampling; one patient stayed away from the clinic at an early stage for unknown reasons and one patient died in a car accident. Among the patients who completed the study the attendance rate averaged 81%.

The abscesses were characterized by local pain, swelling, and heat, but general fever was not reported and skin rashes were not observed. After puncturing, pus was released in which the MADDS suspension was clearly visible. The microbiological department of the Jos University Teaching Hospital discovered a gram-negative coliform bacillus, sensitive to kanamycin, ampicillin, and lincomycin, in the exudate obtained from two patients.

Only 5 patients (4 males, 1 female) completed the study without having experienced any abscesses. The individual DDS concentration/time curves of these patients are presented in Figure 2; Table 4 gives the average results. The sustained release of MADDS from the depot is obvious. In contrast with the results of the DDS injection, no clear peak is detectable in the DDS concentration/time curve. The DDS concentration measured 28 days after the third injection is significantly higher than 28 days after the first injection. The differences in DDS concentrations 1, 3, 5, 7, 14, and 21 days after the first compared to the fourth injection are also statistically significant. The ratio between the DDS concentration 28 and 7 days after administration is another indication of the excellent sustained release of MADDS from the depot.

Obviously the local side effects had their impact on the attitude of the patients toward the injection. Eighteen questionnaires were obtained. The administration of the injection did not yield any problems, but pain was a regular complaint, associated with the abscesses. The patients who remained free of abscesses did not report any side effects. Eleven patients, who all completed the study, preferred the injection; 7 would rather have had tablets.

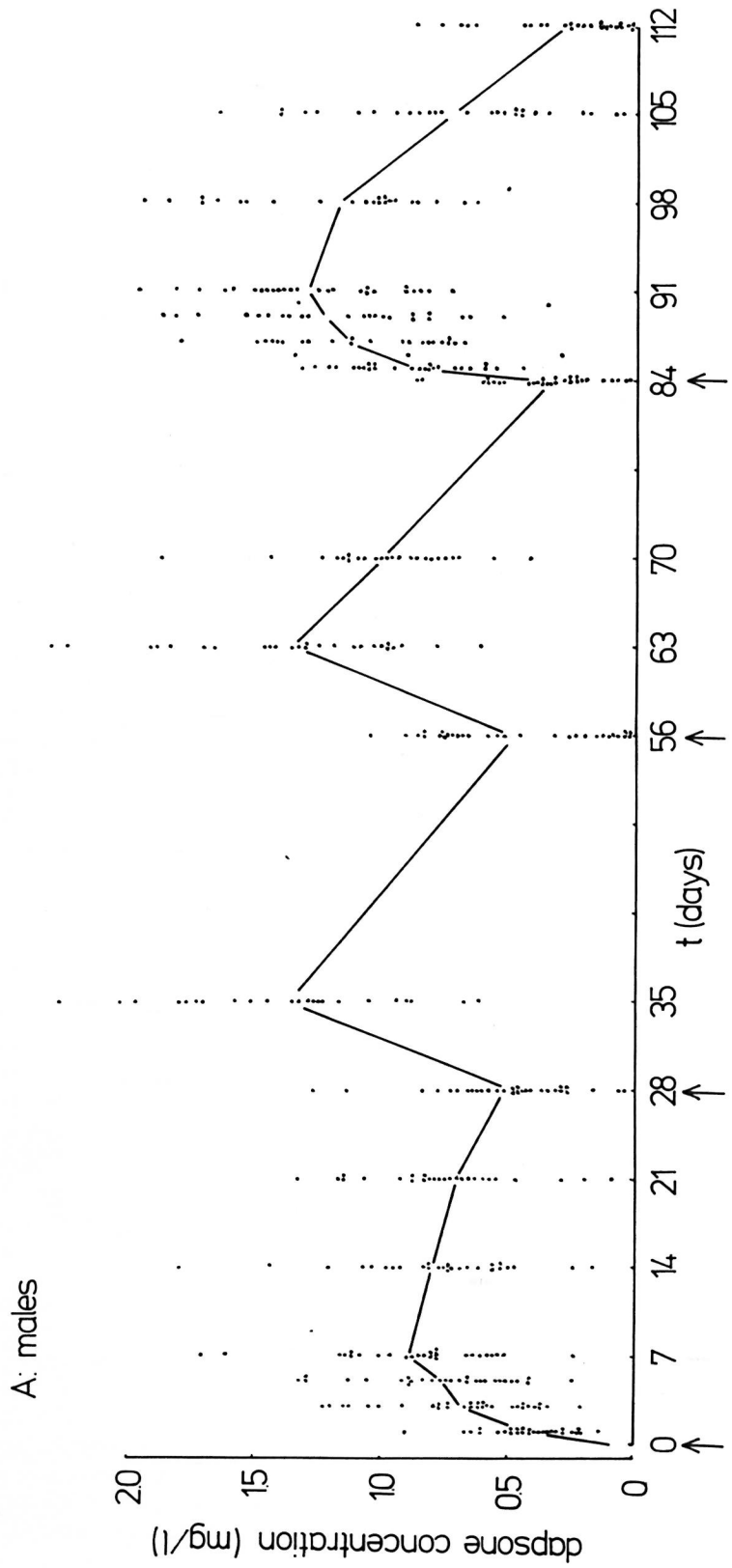
DISCUSSION

The assumption is confirmed that the sex differences observed in Ethiopia ([15]) were attributable to the differences between men and women in the thickness of the fat layer at the injection site as observed by Cockshott, *et al.* ([4]). Such discrepancies were found with other drugs as well, e.g., procaine penicillin ([11]) and cephradine ([28]). Apparently the lower perfusion rate of fat compared to muscle resulted in a slower release of the poorly water-soluble DDS.

This may explain the much higher DDS concentration 28 days after the first DDS injection in the male patients in this study compared to the Ethiopian males (0.50 ± 0.27 vs 0.11 ± 0.09 mg/l). The ratio between the DDS concentration 28 and 7 days after administration was much higher than in the Ethiopian study as well (0.56 ± 0.28 vs 0.05), indicative of a much better sustained-release effect after intra-adipose than after intramuscular injection.

Modderman, *et al.* ([15]) could not detect accumulation after repeated administration of the DDS injection every 4 weeks, neither in men nor in women, possibly due to the relatively small number of observations. In this study, a statistically significant difference was found between the AUC measured until 28 days after the first and after the fourth DDS injection (in males the AUC_4/AUC_1 averaged 1.43 ± 0.54, in females 1.86 ± 0.77), indicating accumulation.

It is uncertain why after the first DDS injection differences occurred between males and females (Table 3). It might have been due to a slight difference in vascularization at the injection site, but the possibility cannot be ruled out that in one or two very lean males at least a part of the dose was inadvertently placed intramuscularly, which


A: males
dapsone concentration (mg/l)
2.0
1.5
1.0
0.5
0
0
7
14
21
28
35
56
63
70
84
91
98
105
112
t (days)

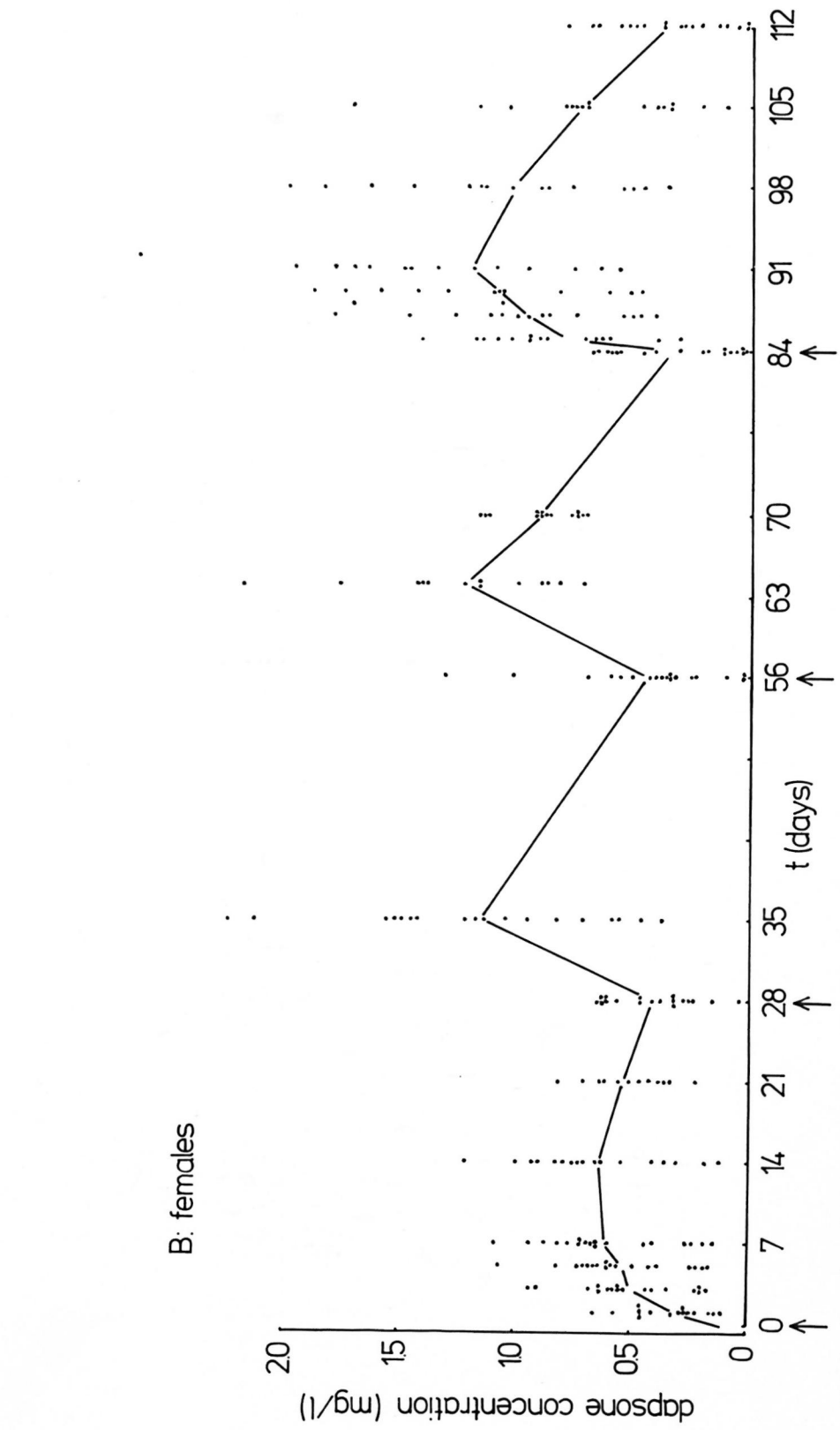


FIG. 1. Overview of DDS concentrations found in every blood sample taken in Jos during the DDS study; A = male and B = female patients. Solid line indicates average results; arrows = days of administration. Individual DDS concentration/time curves are available on request from the first author.

TABLE 3. *Mean results (±S.D.) after administration of DDS to men and women.*

		Males	Females	$p_{males-females}$
DDS serum concentration	day 0 (mg/l)	0.07 ± 0.11 (29)[a]	0.10 ± 0.14 (17)	NS[d]
	1	0.42 ± 0.16 (28)	0.32 ± 0.14 (17)	0.0448
	3	0.67 ± 0.27 (30)	0.49 ± 0.23 (18)	0.0227
	5	0.75 ± 0.28 (29)	0.54 ± 0.24 (18)	0.0097
	7	0.88 ± 0.34 (27)	0.66 ± 0.31 (22)	0.0231
	14	0.78 ± 0.32 (30)	0.63 ± 0.30 (18)	NS
	21	0.73 ± 0.28 (30)	0.54 ± 0.15 (18)	0.0126
	28	0.50 ± 0.27 (30)	0.44 ± 0.20 (22)	NS
	35	1.37 ± 0.44 (23)	1.22 ± 0.58 (21)	NS
	56	0.47 ± 0.34 (30)	0.47 ± 0.37 (20)	NS
	63	1.36 ± 0.44 (26)	1.46 ± 0.67 (16)	NS
	70	0.98 ± 0.29 (24)	0.89 ± 0.16 (14)	NS
	84	0.35 ± 0.22 (30)	0.34 ± 0.24 (19)	NS
	85	0.87 ± 0.25 (30)	0.80 ± 0.32 (18)	NS
	87	1.11 ± 0.33 (28)	0.96 ± 0.37 (18)	NS
	89	1.22 ± 0.40 (28)	1.08 ± 0.42 (18)	NS
	91	1.28 ± 0.43 (29)	1.22 ± 0.57 (17)	NS
	98	1.16 ± 0.49 (29)	1.01 ± 0.49 (18)	NS
	105	0.72 ± 0.42 (28)	0.72 ± 0.47 (18)	NS
	112	0.26 ± 0.23 (28)	0.36 ± 0.26 (18)	NS
$conc_{max}$ (1)[b] (mg/l)		0.98 ± 0.34 (30)	0.83 ± 0.57 (21)	NS
$conc_{max}$ (4) (mg/l)		1.49 ± 0.53 (29)	1.33 ± 0.54 (17)	NS
t_{max} (1) (d)		11 ± 7 (30)	12 ± 6 (21)	NS
t_{max} (4) (d)		9 ± 6 (29)	10 ± 6 (17)	NS
$conc_{28}$ (mean) (mg/l)		0.40 ± 0.19 (30)	0.37 ± 0.17 (18)	NS
c_{28}/c_7[c] (1)		0.69 ± 0.44 (27)	0.80 ± 0.42 (22)	NS
c_{28}/c_7 (2)		0.40 ± 0.30 (23)	0.49 ± 0.34 (20)	NS
c_{28}/c_7 (3)		0.27 ± 0.19 (26)	0.29 ± 0.24 (14)	NS
c_{28}/c_7 (4)		0.22 ± 0.22 (27)	0.36 ± 0.26 (17)	NS
c_{28}/c_7 (mean)		0.39 ± 0.19 (29)	0.46 ± 0.20 (18)	NS
AUC (1) (mg d/l)		19.25 ± 5.58 (29)	15.13 ± 5.17 (20)	0.014
AUC (4) (mg d/l)		26.38 ± 7.51 (26)	24.61 ± 9.02 (17)	NS
AUC (4)/AUC (1)		1.43 ± 0.54 (25)	1.86 ± 0.77 (17)	0.042

[a] Number of observations in parentheses.
[b] (1), (2), (3), and (4) refer to the first, second, third, and fourth injections.
[c] c_7 and c_{28} refer to DDS serum concentrations 7 and 28 days after injection.
[d] NS = not statistically significant.

might have led to a more rapid release of DDS and so to a bias of the average results of the males.

It is also difficult to explain why in males the DDS trough concentration (days 28, 56, 84, and 112) appears to be progressively lower after repeated injections of DDS (Table 3). Self-inducing effects of DDS on its own metabolism and elimination do not seem to have been the reason, since the patients had already received DDS before the study. Neither does enzyme induction by rifampin seem to be a reasonable explanation. Rifampin strongly increases the elimination rate of dapsone through the induction of hydroxylating enzymes ([7]). Even one single ingestion of rifampin exerts a considerable influence (Pieters, *et al.* submitted for publication). Normally, however, the enzyme induction does not last for more than 2 weeks after the last rifampin intake ([2]).

After the second, third, and fourth DDS injection the terminal slope of the DDS concentration/time curve is steeper than after

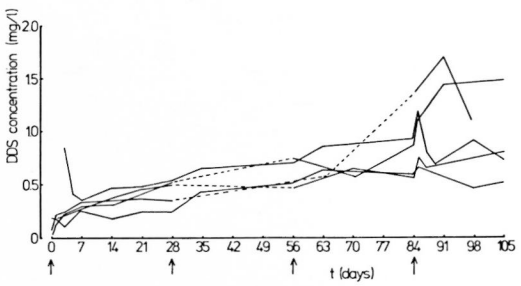


FIG. 2. Individual DDS concentration/time curves of five patients in the MADDS study in Bukuru, in whom no abscesses occurred.

the first (Fig. 1 A and B). This might be explained assuming that the peak concentration reached after repeated injections are partly determined by the DDS release from the previous injection, while 28 days after injection the previous depot is empty and does not contribute to the DDS concentration any more.

After corrections for dose and body weight, the AUC seems to be higher in this DDS study (males 19.3 ± 5.6 mg d/l; females 15.1 ± 5.2 mg d/l) than in a previous study in healthy volunteers (males 10.5 ± 4.4; females 13.8 ± 5.2 mg d/l [26]), despite the coadministration of rifampin. The previously observed, shorter DDS elimination half-life in healthy subjects compared to leprosy patients ([23]) seems to be confirmed. No explanation for this observation is at hand, since no evidence exists of impaired renal or hepatic function in leprosy patients, except for a small group of lepromatous patients in whom late renal complications might occur ([1, 22]).

Due to the abscesses, it is not possible to come to definite conclusions with respect to the MADDS injection. Only five patients remained free of abscesses throughout the whole study period. In these patients a very distinct sustained drug release is observed as demonstrated by the ratio between the concentrations 28 and 7 days after administration (total mean: 1.36 ± 0.57) and by the marked difference between the DDS concentrations reached after the first and fourth injection. Apparently, the lower aqueous solubility of MADDS ([30]) leads to a slower drug release than after DDS injection. The AUC between 0 and 28 days after the first injection of MADDS is smaller than the AUC found after administration of the first injection of an equivalent amount of DDS. This is an indication of the better sustained-release effect of the MADDS injection compared to the DDS formulation, since a previous study proved that after intra-adipose MADDS injection the bioavailability was essentially complete ([24]), which is a prerequisite to make such a comparison.

One can only speculate on the cause of the abscesses. The origin has probably been bacterial, since a tissue reaction (a sterile abscess) would surely have been observed in earlier studies. Unfortunately, the local circumstances did not provide the opportunity to do more than the two microbiological tests mentioned.

TABLE 4. *Mean results (±S.D.) after administration of MADDS in patients not complicated by abscesses (N = 5).*

DDS serum concentration	0 (mg/l)	0.06 ± 0.08
	1	0.17 ± 0.07
	3	0.32 ± 0.30
	5	0.31 ± 0.12
	7	0.30 ± 0.05
	14	0.34 ± 0.11
	21	0.40 ± 0.09
	28	0.43 ± 0.13
	35	0.55 ± 0.16
	56	0.61 ± 0.13
	63	0.65 ± 0.12
	70	0.71 ± 0.14
	84	0.87 ± 0.32
	85	0.95 ± 0.24
	87	0.90 ± 0.31
	89	0.95 ± 0.42
	91	1.02 ± 0.51
	98	0.94 ± 0.38
	105	0.88 ± 0.42
c_{28}/c_7[a] (1)[b]		1.39 ± 0.59
c_{28}/c_7 (2)		1.13 ± 0.09
c_{28}/c_7 (3)		1.48 ± 0.82
c_{28}/c_7 (mean)		1.36 ± 0.57
AUC (1)		10.7 ± 2.8

[a] (1), (2), and (3) refer to the first, second, and third injections.

[b] c_7 and c_{28} refer to DDS concentrations 7 and 28 days after injection.

The suspension is not stable enough to be manufactured as such, and therefore the vehicle must be added to the dried DDS or MADDS crystals at the time of giving the injections. Several precautions, such as thorough disinfecting of all parts of the injection equipment and of the patients' skin, and the use of disposables, are taken. In a previously executed microbiological study, DDS appeared to inhibit the growth of certain strains of *Staphylococcus aureus,* a very common skin bacterium and, thus, a potential infectious hazard (unpublished results). MADDS did not show such activity. The observed difference between the two injections with respect to the occurrence of abscesses might be due to a self-preservative effect of the DDS injection.

The combination of DDS and MADDS in one injection might be considered. The potential preservative effect of DDS would be combined with the more favorable sustained-release action of the MADDS injection. Abscesses might also be prevented by

adding a preservative to the vehicle of the injections.

After almost 4 months of treating these patients with the DDS injection, it is possible to make a comparison with the oral treatment. Three aspects have to be taken into consideration: a) the possibility to reach and to sustain sufficiently high DDS concentrations without the risk of toxicity throughout the time interval chosen (preferably 4 weeks); b) the acceptability of the treatment to the patient; and, finally, c) the manageability of the injection in the hands of those who will have to work with it in the future.

As long as DDS serum concentrations remain below 5 mg/l no side effects will occur usually. It is more difficult to reliably indicate the lower boundary of the therapeutic index. Ozawa, *et al.* ([20]) estimated the minimal inhibitory concentration of DDS for *M. leprae* at 2.5 to 10 ng/ml. Presumably a lower limit of the DDS serum concentration of 0.1 mg/l is safe with respect to the prevention of resistance. This study shows that in most cases a sufficient sustained-release effect is obtained with the DDS injection to fulfill the criteria as stated above. Such requirements can also be met using tablets. However, noncompliance among leprosy patients is widespread ([10, 21, 29]). In fact, this was the initial reason for this study.

The DDS injection was well received by the patients. This is quite important, since the clinic attendance will largely depend on the acceptability to the patient of the injection. During the studies, the injections were prepared and administrated by one of us (FP). The syringeability of the DDS injection appeared to be good. After 16 weeks, the responsibility for administering the DDS injection was handed over to a Nigerian leprosy supervisor. The blood sampling was stopped. Paucibacillary patients were discharged after 6 months of treatment, while multibacillary cases will continue treatment for 2 years. No difficulties were encountered with the administration of the injection.

As far as the MADDS injection is concerned, the abscesses are a serious drawback. However, the results of the five patients who remained free of local side effects are indicative of good future prospects, provided something can be done about the abscesses. In that case, most of what is stated about the DDS injection also applies to the MADDS formulation, which has even better sustained-release qualities. The patient acceptability of the MADDS injection will have to be re-established after the necessary measures have been taken to prevent further abscess formation.

It can be concluded that the DDS injection can provide a valuable tool in the treatment of leprosy. Implementation in the multidrug program as suggested by the WHO ([29]) could be considered to combat poor therapeutic compliance among leprosy patients. The MADDS injection still needs further development.

SUMMARY

In two field trials in Nigeria, 74 male and female leprosy outpatients received intra-adipose depot injections of either dapsone (DDS) or monoacetyldapsone (MADDS) at 4-week intervals. Blood samples were taken regularly and sent to Amsterdam to determine the DDS and MADDS concentrations in serum using high-pressure liquid chromatography (HPLC).

The DDS injection yielded a good sustained drug release. After repeated administration accumulation occurred, demonstrated by a statistically significant increase in the area under the curve (AUC) in time: until 28 days after the first injection, the mean AUC (±S.D.) amounted to 19.3 ± 5.6 mg d/l in males and 15.1 ± 5.2 in females; after the fourth injection, 26.4 ± 7.5 and 24.6 ± 9.0 mg d/l, respectively ($p < 0.001$). One male patient developed an abscess at the injection site; otherwise no side effects were observed.

Even better sustained-release results were observed with the MADDS injection. Unfortunately, the injection caused a number of abscesses. Consequently, the DDS injection was very well received by the patients of the DDS study, while half of the patients in the MADDS study would prefer tablets to the MADDS injection.

Further investigations are required to find the cause of the abscesses before one of the injections, or possibly a combination of both, could be implemented in the multidrug treatment regimen proposed by WHO to provide a valuable tool to combat noncompliance among leprosy patients.

RESUMEN

En 2 estudios de campo realizados en Nigeria, 74 pacientes externos con lepra (hombres y mujeres), recibieron inyecciones intra-adiposas de dapsona (DDS) o de monoacetil dapsona (MADDS) a intervalos de 4 semanas. Posteriormente se tomaron muestras periódicas de sangre y se mandaron a Amsterdam para determinar las concentraciones séricas de DDS y MADDS por cromatografía de líquidos de alta presión.

La inyección intra-adiposa de DDS permitió una buena liberación sostenida de la droga. Después de la administración repetida de la droga ocurrió su acumulación en suero. Esto se demostró por un incremento estadísticamente significativo en el área bajo la curva en función del tiempo: hasta 28 días después de la primera inyección, el área promedio bajo la curvo correspondió a 19.3 ± 5.6 mg d/l en los hombres y 15.1 ± 5.2 en las mujeres; después de la cuarta inyección, los valores fueron 26.4 ± 7.5 y 24.6 ± 9.0 mg d/l, respectivamente ($p < 0.001$). Un paciente masculino desarrolló un absceso en el sitio de inyección. Excepto por esto, no se observaron efectos colaterales.

Una mejor liberación sostenida de la droga se observó inyectando MADDS. Desafortunadamente, la inyección de esta droga causó un número mayor de abscesos. Consecuentemente, la inyección de DDS fue muy bien recibida por los pacientes del estudio con DDS en tanto que la mitad de los pacientes inyectados con MADDS prefirieron la administración de tabletas y no la inyección de la droga.

Se requiere más investigación para encontrar la causa de los abscesos y para implementar el tratamiento dentro del esquema de terapia múltiple propuesto por la OMS para combatir la deserción de los pacientos al tratamiento anti-leproso.

RÉSUMÉ

Au cours de deux essais sur le terrain menés au Nigéria, 74 malades ambulatoires de lèpre, des deux sexes, ont reçu des injections d'un dépôt intra-adipeux de dapsone (DDS) ou de monoacetyl-dapsone (MADDS). A des intervalles de 4 semaines, on a prélevé régulièrement des échantillons de sang, qui ont été envoyés à Amsterdam en vue de déterminer les concentrations sériques de DDS et de MADDS, au moyen d'une technique de chromotographie liquide à haute pression (HPLC).

L'injection de DDS a entraîné une libération excellente et soutenue du médicament. Après administration répétée, on a observé une accumulation, confirmée par une augmentation statistiquement significative de la zone située sous la courbe (AUC) par rapport au temps: jusqu'à 28 jours après la première injection, l'AUC moyenne (±D.S.) se situait à 19,3 ± 5,6 mg d/l chez les hommes et à 15,1 ± 5,2 chez les femmes. Après la quatrième injection, les valeurs étaient respectivement de 26,4 ± 7,5 et de 24,6 ± 9,0 mg d/l ($p < 0,001$). L'un des malades de sexe masculin a fait un abcès à l'endroit de l'injection. A part ce cas, aucun effet secondaire n'a été observé.

Une libération encore plus soutenue a été observée après l'injection de MADDS. Malheureusement, cette injection a entraîné un certain nombre d'abcès. Dès lors, l'injection de DDS a été beaucoup mieux acceptée par les malades du groupe recevant de la DDS, alors que la moitié des malades dans le groupe recevant du MADDS auraient préféré recevoir des comprimés plutôt que l'injection de MADDS.

De plus amples investigations sont requises pour trouver la cause des abcès; ceci devrait être réalisé avant qu'un de ces régimes thérapeutiques ou, éventuellement une combinaison des deux, puissent être introduits dans le traitement polymédicamenteux proposé par l'O.M.S., et fournir ainsi une contribution utile pour améliorer la régularité des malades au traitement.

Acknowledgments. Dr. S. Z. Jebwi, Chief Medical Officer of the Plateau State Ministry of Health, and Dr. J. Y. Gbefwi, Chief Pharmacist of the Jos University Teaching Hospital, are acknowledged for their kind cooperation in this project.

This investigation received financial support from the Chemotherapy of Leprosy (THELEP) component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

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