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Sex Differences in the Absorption of Dapsone After Intramuscular Injection[1]

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Patient noncompliance ([1, 3, 4, 9, 12, 13, 17]) and the development of dapsone (DDS) resistance ([11, 15, 20, 21]) are important problems with dapsone therapy of leprosy. A long-acting DDS injection could be useful in combating noncompliance and may prevent DDS resistance.

In a pilot study with 20 leprosy patients in Nigeria ([19]), an intramuscular (i.m.) injection of 900 mg dapsone as a mixture of particle sizes 20% <90 μm and 80% 90–125 μm resulted in a serum level above 0.5 μg/ml for 18 ± 5 (mean ± S.D.) days with a mean peak concentration of 3.1 ± 0.9 μg/ml (n = 10). Injection of 1200 mg of the same mixture led to peak concentrations of 2.7 ± 1.0 μg/ml, and the level remained above 0.5 μg/ml for 25 ± 3 days (n = 5) after injection of 1200 mg (particle size <90 μm); serum levels stayed above 0.5 μg/ml for 21 ± 5 days, with a maximum concentration of 3.9 ± 1.2 μg/ml (n = 5).

These results were very encouraging and possibilities for further improvements were investigated. A lower peak level and a somewhat longer duration of action were the objectives. The large dapsone particles used in the Nigerian study had been prepared by wet-sieving of the bulk powder and consisted of aggregates of fine particles. Dapsone crystals proved to have a lower dissolution rate than sieved particles of the same size, and could be expected to result in lower peak levels after injection. Injections containing dapsone crystals were therefore prepared.

This study describes a trial with these injections in leprosy patients performed at ALERT, the All-Africa Leprosy and Rehabilitation Training Centre in Addis Ababa, Ethiopia. Serum and saliva levels of dapsone (DDS) and its metabolite, monoacetyldapsone (MADDS), were measured by high pressure liquid chromatography (HPLC). Methemoglobin levels were also measured, since methemoglobin formation is a side effect of dapsone therapy ([10, 26, 27]).

METHODS

Preparation of the injections. Dapsone bulk powder (Roussel) was recrystallized from 60% alcohol. The crystals obtained were washed with ice-cold diethyl ether and dried for 3 hr at 50°C. Particle size reduction was performed by milling for 1 hr in a porcelain ball mill. The fraction with particle size 38–63 μm was isolated by wet-sieving in an electromagnetic sieve. This fraction was dried overnight at a temperature of 50°C and sterilized for 1 hr at 150°C. The aqueous vehicle was prepared by autoclaving a solution of 0.5% methylcellulose 400 millipascal.second (mPa.s), 0.5% Tween 80 and 0.9% sodium chloride in distilled water. Immediately before injection, the vehicle was added to the dapsone crystals to produce a 30% suspension. A 19 G 1½ inch thin wall (TW) needle (Becton, Dickinson & Co., Rutherford, New Jersey, U.S.A.) was used for the i.m. injections.

Patients. Injections were administered to leprosy patients at ALERT in Addis Ababa, Ethiopia; 41 patients (13 women and 28 men) who had already been on oral or parenteral dapsone therapy for some years participated in the trial. All patients gave their informed consent. Their ages ranged from

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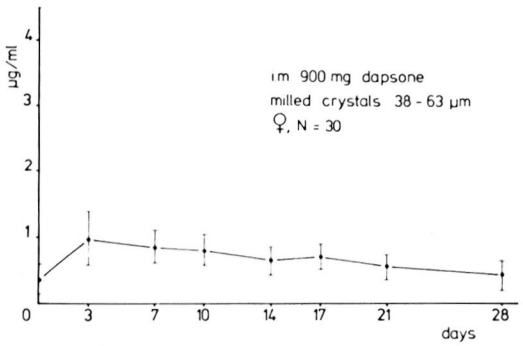

FIG. 1. Serum-level curves of DDS (mean ± S.D.) after administration of injections of 900 mg DDS to women. (N = number of injections: 2 women received one injection, 5 women received two injections, and 6 women received three injections.)

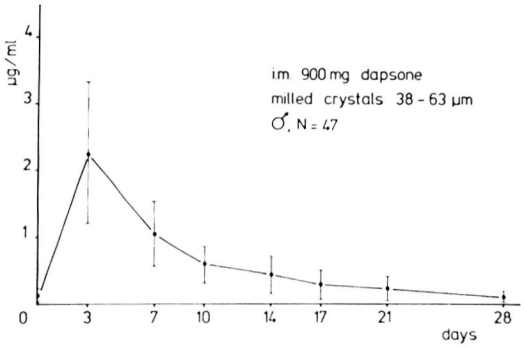

FIG. 2. Serum-level curves of DDS (mean ± S.D.) after administration of injections of 900 mg DDS to men. (N = number of injections: 6 men received one injection, 13 men received two injections, and 5 men received three injections.)

16–50 years. Body weight was 50.5 ± 7.8 kg for the women and 56.6 ± 7.7 kg for the men. Oral therapy with dapsone was stopped one week before the start of the trial; weekly oily dapsone injections ("UNICEF injections") were stopped two weeks before the trial. Depending upon the length of stay in the hospital, 1–3 i.m. injections were given to each patient at four-week intervals. In all, 77 injections of 900 mg and 20 injections of 1200 mg were administered. Samples were taken from hospitalized patients (n = 29) 0, 3, 7, 10, 14, 17, 21, and 28 days after administration of the injection. Samples were taken from out-patients (n = 12), most of whom received three injections, 0, 7, 14, 21, and 28 days after administration. Blood samples (5 ml) and unstimulated saliva samples (1–2 ml) were taken. One week after injection, 5 ml EDTA-blood was obtained from each patient, and this sample was filtered through a protein filter (Ultrafree®, Millipore Corporation, Bedford, Massachusetts, U.S.A.) to determine the protein-bound fraction of DDS and MADDS.

Analysis. Methemoglobin levels were determined in 0.5 ml EDTA-blood within 2 hr of sampling by a slight modification of the method of Evelyn and Malloy ([7]). Methemoglobin levels were expressed as percentage of total hemoglobin. The serum and saliva samples were frozen at −20°C awaiting transport to Amsterdam, The Netherlands, where DDS and MADDS concentrations were measured in serum and saliva by an HPLC method with fluorometric detection, according to the method of Peters, *et al.* ([25]). Results are expressed as mean ± S.D. Student's *t* test was used to evaluate the results.

RESULTS

An unexpected discrepancy was noticed between the curves of men and women receiving 900 mg dapsone. Therefore separate curves were made for men and women and are shown in Figure 1 and Figure 2. Women showed more sustained absorption than did men. In men a peak of 2.28 ± 1.06 µg/ml (mean ± S.D.) was observed in the first week. After two weeks the serum concentration had already fallen to 0.42 ± 0.29 µg/ml and after four weeks, to 0.11 ± 0.09 µg/ml. Following injection in women, the curves were smooth with a peak in the first week of only 1.04 ± 0.40 µg/ml, while the serum concentration after four weeks was still 0.42 ± 0.23 µg/ml. The difference between the mean curves for men and women was statistically significant ($p < 0.01$) except, of course, around the point of intersection of the curves. Ten patients received two injections of 1200 mg; all were men. Figure 3 shows the mean serum-level curve of DDS. In all these curves, mean MADDS serum levels have been omitted because the acetylation capacity for DDS shows genetic bimodality ([5, 8, 22, 23]).

There was no difference in the mean, weight-corrected areas under the curves (AUC) between men (17.02 µg/ml·day) and

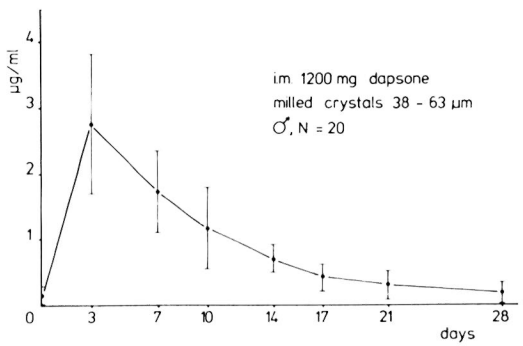

FIG. 3. Serum-level curve of DDS (mean ± S.D.) after administration of injections of 1200 mg DDS to men. (N = number of injections: 10 men received two injections.)

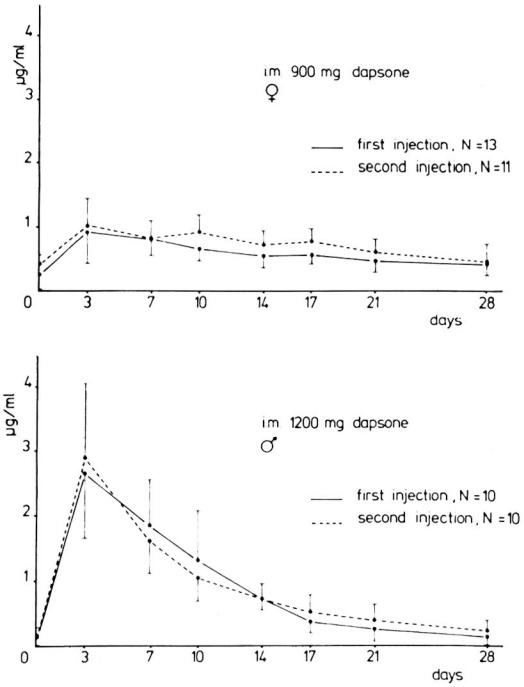

FIG. 4. Serum-level curve of DDS (mean ± S.D.) following first and second injections of 1200 mg DDS to men and 900 mg DDS to women. (N = number of injections.)

women (10.99 µg/ml·day) receiving 900 mg dapsone. The mean, weight-corrected AUC of the men receiving 1200 mg dapsone (24.00 µg/ml·day) was 35% higher than the mean AUC of men receiving 900 mg.

No indications were found of accumulation of DDS following a second or third injection; this is illustrated by the average curves of first and second injections of 1200 mg DDS in men and 900 mg DDS in women (Fig. 4). The mean DDS levels, measured after injection, are summarized in Table 1. In the saliva samples, 19.5 ± 7.0% of the DDS level in serum was found. The correlation coefficient for DDS levels in serum or saliva of the Ethiopian leprosy patients in this trial and in trials with oral dapsone therapy and weekly oily injections was r = 0.7542 ([18]). The nonprotein-bound fraction

TABLE 1. *Dapsone (DDS) serum levels (mean ± S.D.) measured in Ethiopian leprosy patients after long-acting DDS injections.*

Group	Day							
	0	3	7	10	14	17	21	28
900 mg, ♂ (N = 47)[a]	0.13 ±0.11	2.28 ±1.06	1.04 ±0.50	0.58 ±0.29	0.42 ±0.29	0.28 ±0.22	0.22 ±0.19	0.11 ±0.09
900 mg, ♀ (N = 30)[b]	0.36 ±0.23	0.98 ±0.42	0.85 ±0.26	0.81 ±0.25	0.64 ±0.23	0.71 ±0.21	0.54 ±0.20	0.42 ±0.23
Difference ♂ vs ♀	S.[c] $p < 0.001$	S. $p < 0.001$	N.S.[d]	S. $p < 0.05$	S. $p < 0.002$	S. $p < 0.001$	S. $p < 0.001$	S. $p < 0.001$
After correction for body weight	S. $p < 0.001$	S. $p < 0.001$	S. $p < 0.02$	S. $p < 0.01$	S. $p < 0.01$	S. $p < 0.001$	S. $p < 0.001$	S. $p < 0.001$
1200 mg, ♂ (N = 20)[e]	0.14 ±0.14	2.76 ±1.08	1.73 ±0.63	1.18 ±0.63	0.71 ±0.22	0.43 ±0.24	0.30 ±0.23	0.17 ±0.18

[a] N = total number of injections (2 women received 1 injection; 5 women received 2 injections; 6 women received 3 injections).

[b] N = total number of injections (6 men received 1 injection; 13 men received 2 injections; 5 men received 3 injections).

[c] Statistically significant, Student's *t* test.

[d] Not statistically significant, $p > 0.05$, Student's *t* test.

[e] N = total number of injections (10 men received 2 injections).

TABLE 2. *Methemoglobin levels in Ethiopian leprosy patients after long-acting dapone injections, shown as a percentage of total hemoglobin (mean ± S.D.).*

Group	Percentage methemoglobin[a]		N[b]
	Days 1–7	Days 8–28	
900 mg ♀	4.2 ± 0.8%	4.2 ± 1.0%	30
900 mg ♂	4.8 ± 1.8%	3.9 ± 1.2%	47
1200 mg ♂	5.8 ± 2.1%	4.4 ± 1.2%	20

[a] This is the mean of all samples taken in the indicated period.
[b] N = number of injections.

of dapsone in serum amounted to 17 ± 4% (mean ± S.D.). No MADDS could be detected in the filtered serum samples or in saliva.

In Table 2 the average methemoglobin levels are given as measured during a period of four weeks after injection. The average levels measured during the first week after injection are calculated separately. At the end of the trial, 6 of the 41 patients had moved to other places and the remaining 35 were interviewed. Of these patients, 33 reported that the injection was not particularly painful or even that it was painless. No side effects other than pain at the moment of injection and for some time afterwards were reported.

DISCUSSION

From the results obtained from 41 Ethiopian leprosy patients, it appears that women show a better sustained-release effect than do men. Cockshott, *et al.* ([2]), who recently measured the thickness of gluteal fat by computer tomography, concluded that most injections given in the buttock and intended to be intramuscular are, in fact, "intralipomatous." They found that the depth of gluteal fat is usually more than 3.5 cm, which is the usual length of the injection needle, and that the mean gluteal fat thickness is much greater in women than in men. Their experiences may explain the results of our investigations with long-acting dapsone injections. The Ethiopian volunteers had a low mean body weight (women = 50.5 kg; men = 56.6 kg). From the data of Cockshott and coworkers it can be concluded that, in their population, men weighing 57 kg had a mean gluteal fat thickness of approximately 2.5 cm, and this thickness was about 4 cm in women weighing 50 kg. If these values are also true for our Ethiopian patients, most of the women will have received their injections intralipomatously, while in the men most injections were given intramuscularly. Similar results were found by Vukovich, *et al.* ([28]) in 1975 after intramuscular administration of cephradine to healthy volunteers. They reported a sex difference in intramuscular absorption that was much more pronounced after injection into the gluteus maximus than after injection into the deltoid muscles or the vastus lateralis. Juhlin ([14]) found a slower intramuscular absorption in women after intragluteal injection of penicillin. He also found that the extent of the difference between men and women may depend on the formulation of the injection.

The sex difference in i.m. absorption of dapsone, apparent from this trial, could not be predicted from the results of our Nigerian trial in which 18 men participated but only two women were available for study. The use of milled crystals does not seem to have resulted in a more sustained release than the use of sieved particles. In fact, the difference between blood levels in Ethiopian men and women receiving exactly the same injection is much more pronounced than the difference between those of Ethiopian and Nigerian men receiving differently formulated injections in the same dose.

We previously had considered the effect of differences in body weight between men and women on the serum levels of DDS after oral therapy or weekly injections ([18]). When our results obtained using long-acting DDS injections are corrected for differences in body weight, a slight increase in the sex difference in the first week but a slight reduction in the difference over following weeks is shown. Nevertheless, the differences are still statistically significant ($p < 0.001$).

In the Ethiopian study, no cumulation of any significance was observed after two or three injections in either men or women. The 900 mg injection, given with a dosing interval of four weeks, seems to be suitable for women. Minimum levels of around 0.5 μg/ml are generally accepted as therapeutically active and safe because this is the minimum level after a daily oral dose of 50

mg. There is, however, discussion about levels considerably lower than 0.5 μg/ml because of the risk of developing resistance. Therefore, we do not draw conclusions from this study regarding dosage regimens for men.

In Ethiopian leprosy patients, we found that the nonprotein-bound fraction of DDS was 17 ± 4%, while the protein binding of MADDS was approximately 100%. These results are in agreement with those of Peters, *et al.* ([25]) but not with the study by Lammintausta, *et al.* ([16]) who found 50% protein binding of DDS and 59% of MADDS using a ultracentrifugation technique. The percentage DDS found in saliva (19.9 ± 7.0%) is in agreement with the nonprotein-bound fraction. Methemoglobin formation did not reach levels of clinical importance in this study. No abscess formation at the injection site or other significant side effects were observed. Acceptability of the injections by these Ethiopian leprosy patients was good. We interviewed 27 in-patient volunteers who had been taking oral therapy before the trial. The aqueous, long-acting injections were preferred by 22, 4 had no opinion, and 1 preferred tablets. The reasons given were that they had more confidence in the injections and that they easily either forgot to take or spoiled the tablets. We interviewed eight of the out-patient volunteers who had been having weekly oily DDS injections. They preferred the aqueous injections because they were less painful.

In Nigeria, we also found that the leprosy patients preferred the injections to tablets. Good acceptability is important for patient compliance.

Further investigations will now be focused on the use of aqueous suspensions of diacetyldapsone (DADDS) and monoacetyldapsone (MADDS) which both act as prodrugs of dapsone ([6, 8, 25]).

SUMMARY

A trial was performed with a long-acting dapsone (DDS) injection, consisting of an aqueous suspension of dapsone crystals, in doses of 900 mg and 1200 mg. Forty-one Ethiopian leprosy patients, 13 women and 28 men, participated in the study. There appeared to be a large discrepancy in the serum concentration curves of dapsone between men and women. Following injection of 900 mg dapsone in men, a peak of 2.28 ± 1.06 μg/ml (mean ± S.D.) was observed in the first week. After two weeks the serum concentrations had fallen to 0.42 ± 0.29 μg/ml, and after four weeks they fell to 0.11 ± 0.09 μg/ml. Following injection in women, the curves were smooth with a peak in the first week of only 1.04 ± 0.40 μg/ml, while the serum concentrations after four weeks were still 0.42 ± 0.23 μg/ml. The differences between the mean curves of men and women were statistically significant ($p < 0.001$). The 1200 mg dapsone injections were only given to men. The explanation of the sex difference in intramuscular absorption can probably be found in the differences in the thickness of gluteal fat in men and women. In these Ethiopian leprosy patients, the non-protein-bound fraction of dapsone comprised 17 ± 4%. In saliva, 19.5 ± 7.0% of the dapsone level in serum was found. Methemoglobin levels were raised but did not reach levels of clinical importance. No other significant side effects were observed.

RESUMEN

Se estudió la efectividad de la dapsona de acción prolongada inyectada en forma de suspensión acuosa en dosis de 900 mg ó 1200 mg, en 41 pacientes (13 mujeres y 28 hombres) de Etiopía afectados por la lepra.

Se encontró que las curvas de concentración sérica de dapsona fueron muy diferentes entre hombres y mujeres. Una semana después de la inyección de 900 mg de dapsona en los hombres, la concentración sérica de dapsona alcanzó un pico de 2.28 ± 1.06 μg/ml (Media ± D.E.). Después de 2 semanas, la concentración sérica decayó a 0.42 ± 0.29 μg/ml y después de 4 semanas hasta 0.11 ± 0.09 μg/ml. En las mujeres, las curvas de concentración fueron menos pronunciadas, con un pico en la primera semana de sólo 1.04 ± 0.40 μg/ml y valores relativamente altos (0.42 ± 0.23) aún después de 4 semanas. Las diferencias en las curvas medias entre hombres y mujeres fueron estadísticamente significativas ($p < 0.001$). Las inyecciones des 1200 mg sólo se aplicaron a los hombres. La diferente absorción intramuscular de la dapsona quizá pueda explicarse en base al diferente grosor de la grasa glútea entre hombres y mujeres. La fracción de dapsona sérica libre fue del 17% ± 4. En saliva se encontró el 19.5% ± 7 de la dapsona sérica. Los niveles de metahemoglobina estuvieron elevados pero no alcanzaron valores de importancia clínica. No se observaron otros efectos colaterales.

RÉSUMÉ

On a procédé à des essais d'injections de dapsone à effet-retard, consistant en une suspension aqueuse de

cristaux de dapsone, à des doses de 900 mg et 1200 mg. Quarante et un malades de la lèpre éthiopiens, dont 13 femmes et 28 hommes, ont participé à cette étude. On a constaté une grande discordance dans les courbes de concentration sérique de dapsone entre les hommes et les femmes. A la suite de l'injection de 900 mg de dapsone chez l'homme, on a constaté un pic de 2.28 ± 1.06 μg/ml (moyenne ± S.D.) au cours de la première semaine. Après deux semaines, les concentrations sériques tombaient à 0.42 ± 0.29 μg/ml, et après quatre semaines, ces concentrations atteignaient 0.11 ± 0.09 μg/ml. A la suite de l'injection chez les femmes, les courbes étaient aplaties, avec un pic au cours de la première semaine qui n'atteignait que 1.04 ± 0.40 μg/ml, alors que les concentrations sériques après 4 semaines étaient encore de 0.42 ± 0.23 μg/ml. Les différences entre les courbes observées chez les hommes et les femmes étaient significativement significatives ($p < 0.001$). Seuls les hommes ont reçu des injections de 1200 mg. L'explication des différences d'absorption intramusculaire entre les sexes peut être expliqué par l'épaisseur différente de la graisse fessière chez les hommes et les femmes. Chez ces malades de la lèpre éthiopiens, la fraction de dapsone non liée aux protéines s'élevait à 17 ± 4%. Les taux de dapsone mesurés dans la salive atteignaient 19.5 ± 7.0% de ceux relevés dans le serum. Les niveaux de méthémoglobine étaient élevés, mais n'atteignaient pas des taux importants au point de vue clinique. Aucun autre effet secondaire n'a été observé.

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