ABSORPTION AND EXCRETION OF DAPSONE IN LEPROSY PATIENTS

S. S. NAIK,* A. B. SANE† AND R. GANAPATI‡

Summary

It is possible to divide patients arbitrarily into three groups of "slow, moderate and rapid excretors" of Dapsone on the basis of the estimation of the diazotizable material excreted by them in the urine during 24 hours, following an oral dose of 100 mg of the drug.

Thirty two lepromatous patients rendered bacteriologically negative after a prolonged treatment with DDS were studied with respect to the concentration in the blood and excretion in the urine of free as well as total DDS, during the administration of standard dose of 100 mg of the drug daily. The findings are discussed.

When the same patients were subjected to a test dose of 100 mg a study of their 24 hours urinary excretory pattern revealed that none of them belonged to the group of 'rapid excretors'. However, in an attempt to correlate clinical improvement with the excretory pattern of DDS, it is stressed that the estimation of the drug in the tissues should be taken into consideration.

Introduction

Inspite of the unique position held by Dapsone in the therapy for leprosy for over a quarter century, some metabolic aspects of the drug in man and animals have not been fully established. According to Bushby (1967) the treatment is still 'empirical'. The effectiveness of Dapsone when administered in doses as low as 1 mg daily as reported by Sheppard et al (1966) and Waters et al (1968) would point to the fact that high blood levels of the drug are not the important criteria for deciding the response to treatment. However, taking into consideration the factors like emergence of drug resistant Mycobacterium leprae etc. W.H.O. Expert Committee on Leprosy (1970) has cautiously recommended 6 to 10 mg. of DDS per Kg body weight per week for general leprosy control work. So at present, the fixation of the standard dose in the treatment of leprosy is passing through a confusing phase. The proper understanding of the metabolism of Dapsone in man would warrant further studies on the subject.

The aim of the present study is to find out correlation, if any, between the absorption and excretion of DDS and improvement with the standard doses of the drug (600 mg per week). Part I of the presentation shows the pattern of absorption and excretion of DDS following test doses of DDS while Part II shows the patterns obtained in lepromatous patients on prolonged treatment for over ten years with 600 mg of DDS per week.

* Research Assistant (Biochemistry)
† Formerly Research Assistant (Statistics)
‡ Research Officer, Acworth Leprosy Hospital, Wadala, Bombay-31
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Part I

Patterns of Absorption and Excretion of DDS Following Oral Test Doses of Dapsone

Urinary excretory pattern of Dapsone in Leprosy patients on a test dose of 100 mg was reported by Ganapati and Naik[5]. They stressed the existence of wide variations in the excretory pattern and pointed out the probable immutability of the same in individuals. In this presentation some more cases have been added to those already investigated in an attempt to see whether the patients can be differentiated into definite significant groups on the basis of the excretion of diazotizable material during 24 hours following an oral test dose of 100 mg of DDS.

Material and Method

Two hundred and eighty five patients suffering from leprosy (259 males, 26 females) of ages ranging from 12 to 66 years, attending the Acworth Leprosy Hospital Clinic, Wadala, Bombay, were the subjects for the investigation. The patients were residents of Greater Bombay belonging to a heterogenous socio-economic group.

Before the investigation, the routine administration of DDS was stopped in all these patients for varying periods till the urine did not show even a trace of DDS. After an oral administration of a test dose of 100 mg of DDS, urine passed during 24 hours was collected using toluene as a preservative. Patients without obvious kidney disease alone were selected for the study, those showing albuminuria or 'oedema' being excluded. To check the completeness of urine collection, total creatinine estimation was carried out by the Bonsenes and Tausky[6] method. The total diazotizable material was estimated by the calorimetric method of Bratton and Marshall modified by Simpson[7] on a Klett-Summerson photoelectric calorimeter. For the estimation of "Free Dapsone" or unchanged drug the method recommended by Francis and Spinks[8] was followed.

On the basis of our previous experience, the peak concentration of DDS in the blood occurs 6 to 8 hours after oral administration of 100 mg Dapsone. The blood samples were collected at 6 hours and 24 hours after the oral administration of the drug.

Results

The distribution of patients according to the 24 hour excretory pattern of diazotizable material following an oral test dose of 100 mg is shown in Graph1.

64 (22.5%) patients excreted below 35 mg of DDS, 169 (59.3%) between 35 & 52 (18.2%) above 55 mg. It can be seen that 81.08% excreted below 55 mg of DDS.

The mean excretion for 285 patients is 44.36 mg (with standard deviation of 12.41)

As judged from the excretory pattern using 100 mg of DDS as a test dose, it appears that there are two statistically significant groups viz., "Slow excretors" (58 mg & below) who form 87%, and rapid excretors (above 58 mg) who form 13%, with mean excretion for the two groups being 41.68 mg and 62.66 mg respectively.

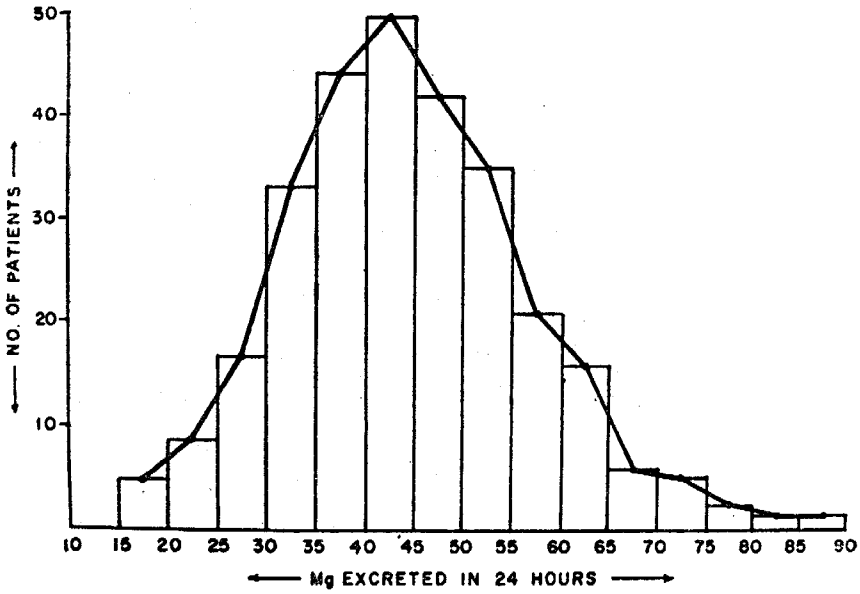
However, for practical purposes, it is suggested that individuals can be divided arbitrarily into three groups, e.g. "slow excretors" (below 35 mg), "moderate excretors" (between 35-55 mg), and "rapid or fast excretors" (above 55 mg)

It is also suggested that this division may be used to find out a correlation, if any, between the clinical improvement

under treatment and the excretory pattern of DDS.

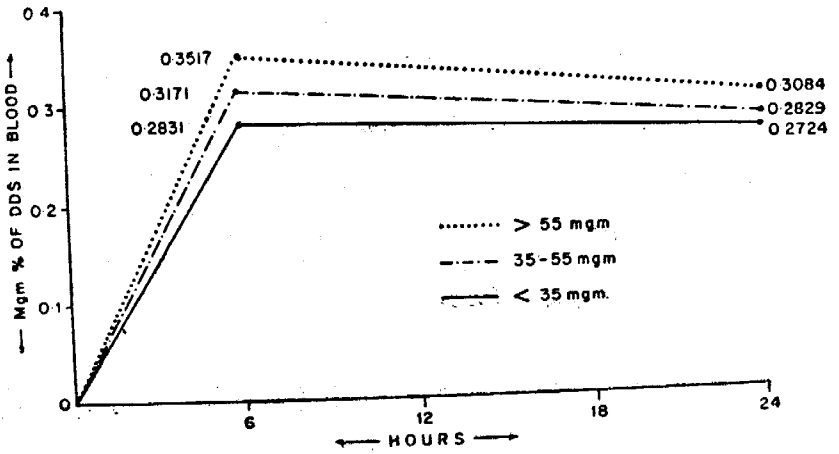
Graph 2 shows the blood concentration in the three different groups (as stated above)

The concentration of DDS in the blood of 'slow excretors' at sixth hour is lower than that of 'rapid excretors'. In the earlier study (Ganapati and Naik[5])



Graph 1

Distribution of patients according to the Excretory pattern on DDS



Graph 2

Blood Concentration of DDS in three Excretion Groups

Out of these 285 cases, the concentration of DDS in the blood after 6 and 24 hours, was estimated in 224 cases, following oral test dose of DDS.

the peak concentration in the blood was found to be reached 6 hours after the administration of DDS in the case of those who excreted the drug rapidly

(70 mg in 24 hours), where as the same was reached after 8 hours in the case of those who excreted the drug slowly (30 mg in 24 hours).

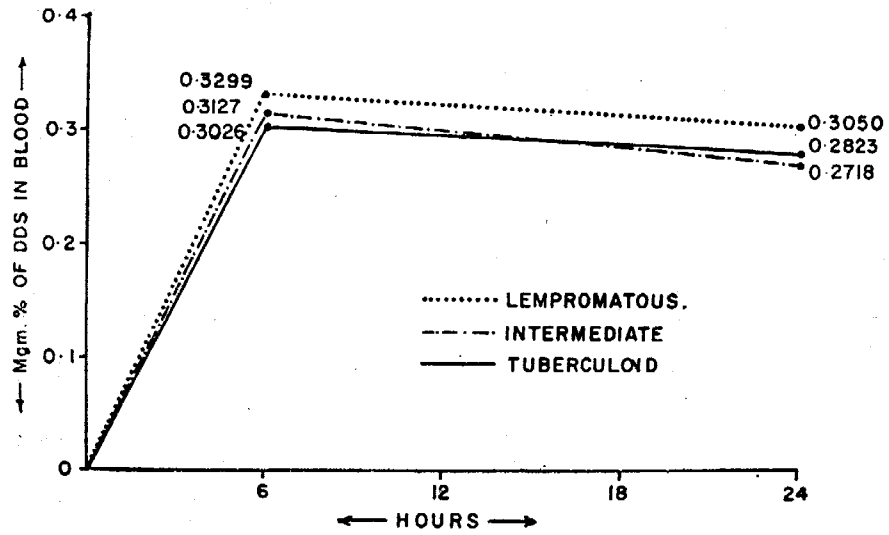
Table 1 : shows the excretory pattern of 285 patients according to their clinical types :

was administered instead of 100 mg, it was found that there was no significant difference in the percentage excretion of the drug during 24 hours (the average range of difference being 6.49 mg which was within the limits of the experimental error and hence negligible)

TABLE 1

The excretory pattern in various clinical types of leprosy

Group	Tuberculoid	Intermediate	Lepromatous	Total
Slow excretors	12	15	37	64
Moderate Excretors	57	39	73	169
Rapid Excretors	18	17	17	52
Total	87	71	127	285



Graph 3

Blood Concentration of DDS in different types of Leprosy

No significant difference was noted in the level of DDS in blood in three different groups of excretors i.e., slow, moderate and rapid. Similarly, there was no significant correlation between the absorption and the excretion of the drug and the clinical types of leprosy.

The experiment was repeated in 18 patients taking their weight into consideration. When a test dose of 2 mg/kg

Twenty seven leprosy patients were investigated after administration of a test dose of 300 mg, with a view to study the "free DDS" fraction as compared to the total diazotizable material excreted in 24 hours, in the acidic urine. The test was repeated after oral alkali, at a pH range of 7.3 to 8.0. The total diazotizable material and free DDS levels in blood were determined at 6 and 24 hours. The results are shown in Tables 2 and 3.

TABLE 2

The urinary excretion of DDS after oral administration of 300 mg.

	Acidic urine				Alkaline urine			
	Free DDS in mg.	Total DDS in mg.	Percentage Excretion of Free DDS in total DDS	Percentage Excretion of DDS in 24 hr.	Free DDS in mg.	Total DDS in mg.	Percentage of Free DDS in total DDS	Percentage Excretion of DDS in 24 hr.
1st Day	24.32	139.12	8.10	46.37	15.99	127.93	5.33	42.64
2nd Day	9.68	80.55	3.23	50.00	7.49	75.78	2.50	45.06

TABLE 3

The blood concentration of DDS of 6 and 24 hrs. after oral administration of 300 mg DDS

	Free DDS mg. %	Total DDS mg. %	Ratio of Free DDS to Total DDS
6 hr.	0.3623 ± 0.1118 (0.1778 — 0.5580)	0.7623 ± 0.1467 S.D. (0.5603 — 0.9137)	0.47
24 hr.	0.2387 ± 0.0954 S.D. (0.1037 — 0.4000)	0.5571 ± 0.1220 S.D. (0.3103 — 0.8545)	0.43

The pH of urine has an important role in the excretion of the drug in the form of free DDS. The level of free DDS is considerably low in the alkaline urine. This is in line with the observations made by Ellard and Gammon.[9]

It can be seen that the percentage of the drug excreted on the first and the second day did not differ appreciably.

In the 27 cases studied, it was observed that the percentage of the orally administered drug excreted during the 24 hours was same whether the test dose employed was 300 mg or 100 mg.

The ratio of free DDS to total DDS in blood was found to be 0.47 and 0.43 after 6 hours and 24 hours respectively.

Comments

The measurement of the rate of excretion of a drug or a dye has been used as one of the methods to establish the criteria of zyogosity. It is also known that the genetic polymorphism of dapsone acetylation exists in human beings. Peters et al[10] have shown that human subjects after ingestion of DDS, establish a MADDS/DDS ratio which is constant for the individual and consistent with the rapid or slow acetylation phenotype as determined by isoniazid or sulfamethazine. Thus the study of the excretion rate of DDS after administration of a test dose and its peak concentration in the blood, in the families of patients and in healthy individuals will be interesting and will throw some light on the genetic aspects of the metabolism of DDS.

Part II

Patterns of Absorption and Excretion of DDS in Lepromatous Patients on Prolonged Treatment

So far as the minimum effective dose of DDS and its concentration in the blood responsible for clinical improvement are concerned, probably Lowe[11] was the first to report that blood levels as low as 0.15 to 0.20 mg% of DDS which can be obtained by daily

administration of 30 mg of the drug are adequate. As no reports are available in the literature on the absorption and excretion of DDS in lepromatous cases rendered bacteriologically negative with the standard dose of DDS, present investigations were undertaken.

Material and Method

Thirty two lepromatous cases who were on treatment with DDS on standard doses for a minimum of 10 years and remained bacteriologically negative for at least 5 years and had no complications such as reaction etc., were selected. All the patients were inmates of the Acworth Leprosy Hospital, Wadala, Bombay. All of them were males of the ages ranging from 27 to 65 years, and on regular treatment with 100 mg of oral DDS daily, for 6 days per week.

Before the commencement of the study, the patients were standardised on this dosage of 100 mg DDS for 6 days a week for 2 months under supervision. (Monday to Saturday, excluding Sunday).

The blood of the patients was collected at about 9 A.M. daily, followed by the administration of 100 mg of oral DDS. 24 hour urine specimens were collected daily with toluene as the preservative. To check the completeness of 24 hours urine collection, the estimation of its creatinine content was carried out.

The total diazotizable compound as well as free DDS in the blood and urine were measured.

The pH of the urine was acidic (in the range of 5.6 to 6.0). To ensure the kidney function was normal in these patients, during this experiment, the creatinine clearance test was performed as described by Camara et al[12]. For the control group, creatinine clearance test was performed in 10 normal healthy members of the staff of the Acworth Leprosy Hospital.

The urinary excretory pattern of DDS, by giving the test dose of 100mg, was also studied in 30 out of 32 patients after suspending DDS treatment, till the urine did not show any trace of the drug.

Results

Table 4 shows the concentration of total and free DDS in the blood at various intervals in the patients on standard doses of DDS (daily oral administration of 100mg DDS at about 9 A.M.)

Graph 4 shows the proportion of free DDS to total DDS in the blood at varying intervals.

It will be seen that the average blood levels of free DDS and total DDS are 0.21 mg% (in the range of 0.18 to 0.22 mg %) and 0.37 mg % (in the range of 0.28 to 0.42 mg %) respectively. The average percentage of free DDS in the total DDS in blood is 57.

The excretion of free DDS and total DDS in 24 hours collection of urine of 32 lepromatous cases is shown in Table 5.

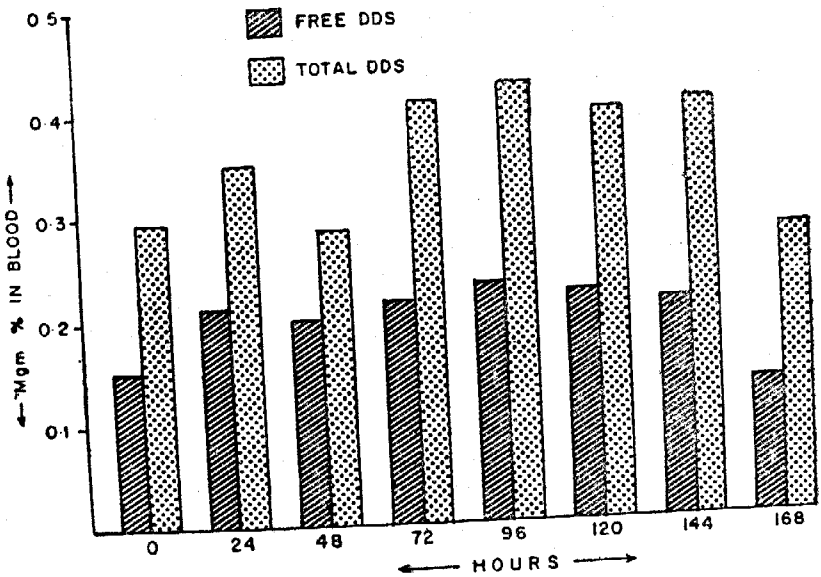
Graph 5 shows the proportion of free DDS to the total DDS excreted in the urine during 24 hours.

It is observed that the daily excretion of free DDS varied from 9.46 to 16.97 mg, with the mean average of 13.71 mg and the total DDS varied from 61·93 to 89.93 mg with the mean average of 79.32. The free DDS in urine amounted to an average of 17.14 % of the total DDS.

TABLE 4

Concentration of DDS in blood on Standard doses

Time in hours	Mg. % of free DDS	Mg. % of total DDS	Ratio of Free DDS to total DDS
0 hr.	0.1482 ± 0.0846 (0.0593 — 0.2074)	0.2926 ± 0.0718 (0.1552 — 0.3798)	0.51
24 hr.	0.2073 ± 0.0950 (0.1480 — 0.3556)	0.3446 ± 0.093 (0.2672 — 0.4655)	0.60
48 hr.	0.1799 ± 0.0751 (0.1185 — 0.2963)	0.2829 ± 0.1128 (0.2327 — 0.4761)	0.64
72 hr,	0.2150 ± 0.0853 (0.1333 — 0.3259)	0.4041 ± 0.1015 (0.2835 — 0.4579)	0.53
96 hr.	0.2239 ± 0.0813 (0.1778 — 0.3405)	0.4152 ± 0.0956 (0.2758 — 0.5172)	0.55
120 hr.	0.2199 ± 0.0783 (0.1529 — 0.2963)	0.3871 ± 0.0990 (0.2672 — 0.5000)	0.59
144 hr.	0.2106 ± 0.0722 (0.1481 — 0.3111)	0.4005 ± 0.0905 (0.2758 — 0.5258)	0.53
168 hr.	0.1360 ± 0.0480 (0.0741 — 0.1778)	0.2815 ± 0.0653 (0.2069 — 0.3706)	0.48



Graph 4

Proportion of free DDS to total DDS in Blood

Creatinine clearance test :

The creatinine clearance test was conducted in 32 lepromatous patients and 10 healthy members of the staff in the process of the experiment. Results are shown in Table 6.

Due to some technical difficulty, the correction of the surface area could not be done for the creatinine clearance test. It is seen from the above that there is a slight impairment of kidney function in leprosy patients as compared to the healthy subjects as shown by the creatinine clearance values.

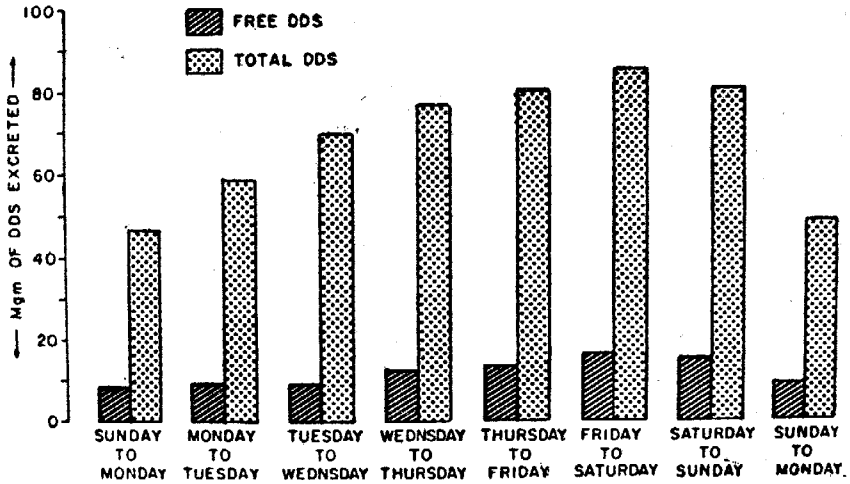
Excretory Pattern following a test dose

The urinary excretory pattern of DDS was studied in 30 of the above patients

TABLE 5

Urinary excretory pattern of DDS in treated lepromatous cases

	Free DDS in mg.	Total DDS in mg.	Percentage of free DDS in the total DDS
Sunday / Monday	9.20 ± 3.25 (5.50 — 14.75)	49.35 ± 11 09 (36.0 — 64.20)	18.65
Monday / Tuesday	9.46 ± 3.62 (5.04 — 14.72)	61.94 ± 10.48 (43.20 — 78.96)	15.27
Tuesday / Wednesday	11.64 ± 4.41 (5.89 — 16.12)	72.98 ± 14.71 (61.43 — 88.00)	16.01
Wednesday / Thursday	13.32 ± 3.37 (7.88 — 17.62	81.00 ± 15.26 (65.43 — 91.90)	16.41
Thursday / Friday	14.52 ± 4.65 (8.95 — 21.36)	84.65 ± 14.24 (65.04 — 96.20)	17.15
Friday / Saturday	16.97 ± 5.75 (10.20 — 27.23)	89.93 ± 16.78 (64.00 — 103.70)	18.87
Saturday / Sunday	16.36 ± 4.84 (10.63 — 21.95)	85.36 ± 13.94 (71.02 — 104.30)	19.14
Sunday / Monday	9.99 ± 2.51 (6.90 — 14.62)	53.67 ± 10.76 (35.56 — 66 70)	18.61



Graph 5

Proportion of free DDS to total DDS in Urine

TABLE 6

Creatinine clearance test in leprosy patients and healthy subjects

	32 Lepromatous Patients	10 Healthy Subjects
Creatinine clearance	Mean 86.71 ± 15.79 c.c. / minutes range (60.15 — 166.50)	Mean 108 ± 19.94 c.c. / minutes range (76.38 — 139.70)

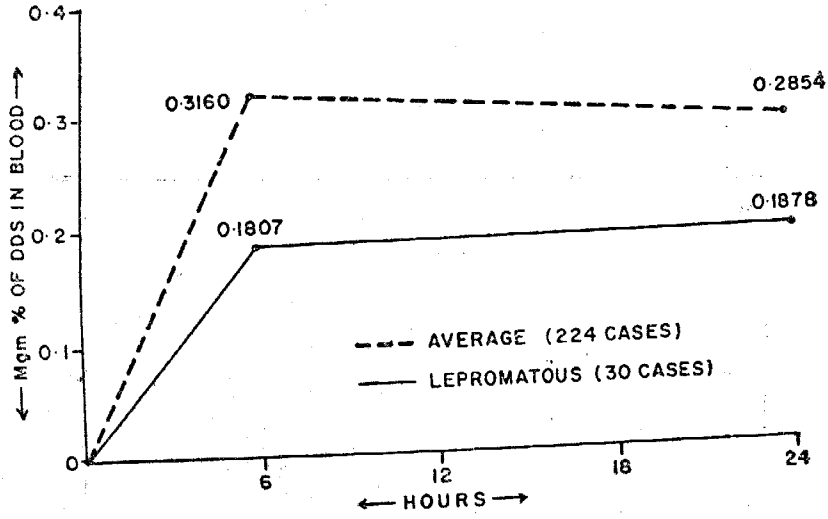
after oral administration of a test dose of 100 mg of DDS. These patients have been divided into three groups of slow, moderate and rapid excretors as suggested in Part I. The results are shown in Table 7.

TABLE 7

Distribution of patients according to the excretory pattern of DDS

Slow Excretors (Below 35 mg)	20 Patients
Moderate Excretors (a) 35 mg to 45 mg)	8 Patients
(b) 45 mg to 55 mg)	2 Patients
Rapid Excretors (above 55 mg)	None
Total	30

Graph 6 and Table 8 show the blood concentration curve following an oral test dose of 100 mg of DDS in 30 patients.



Graph 6

Blood Concentration Curve after a test dose of DDS in Lepromatous patients, improved under treatment

TABLE 8

The blood concentration of DDS of 6 and 24 hrs. after oral administration of 100 mg DDS in 30 patients
Total DDS mg % in blood.

	Range	Mean	S.D.
6 hr.	0.111 — 0.2586	0.1807	0.057
24 hr.	0.1034 — 0.2672	0.1878	0 082

The graph indicates a slow absorption of DDS and maintenance of the same level at 24 hours.

Our findings as regards the concentration of the drug in the blood in this experiment are 0.37 mg % total DDS and 0.21 mg % free DDS.

Discussion

The concentration of DDS in the blood on daily oral doses of 100 mg of DDS as reported by other workers under similar conditions is as follows : Smith[13] 0.4 mg %, Dharmendra et al[14] 0.6 mg %; Dhople and Mager [15] 0.64%.

The total excretion of DDS in the urine reported by Smith was 50%,

Dharmendra 75%, Lowe 85% and Dhople 79%. In the present investigations average excretion on standard doses of 600 mg per week in lepromatous cases is 79.32 % out of which free DDS is 13.71 mg.

It is observed that the concentration of DDS in the form of free DDS and total DDS in blood rises from Monday to Saturday with daily administration of DDS. This rise however, is negligible. On Sunday when DDS is not administered, the blood concentration of both free and total DDS falls down considerably and reaches almost the same level on next Monday morning as on the previous Monday. These observations confirm the findings of Dhople and Mager[15]. This break of one day in the week helps to maintain the blood level constant and avoid the toxic effects due to the excess accumulation of the drug.

An average of 57 % of the drug is available in the form of free DDS in the blood circulation and the remaining as metabolites of DDS. It is difficult to say whether the antileprotic action of DDS is due to the free form or its metabolites. However, the study of the concentration of DDS and its metabolites in the tissues might be helpful.

DDS absorption and excretion study on a test dose of 100 mg DDS in 30 cases rendered bacteriologically negative on routine treatment shows that the majority of these cases (20) are " Slow excretors ", 10 are " moderate excretors " (8 are on the lower side and 2 are on the higher side of the "moderate excretors ") and none of them was a " rapid excretor ".

The absorption curve of the DDS in the blood suggests very slow absorption and maintenance of the same level at 24 hours. This probably shows fair chances of accumulation of the drug in the body and the maintenance of optimum concentration of the drug in the tissues, which might have helped these patients in their being rendered bacteriologically negative. Even temporary drop out of treatment for a few months would not have affected these patients much, because being slow absorbers and also slow excretors, the release of drug in the blood stream from probable depot in the tissues might have maintained sufficiently the optimum drug concentration for improvement.

As far as the excretion of DDS on a standard dose is concerned, these patients excreted 79% of the drug through the urine as it had been reported by other workers. The study of the excretory pattern alone does not appear to be sufficient to explain the improvement or the lack of improvement of the cases. The concentraton of DDS in the blood and particularly in the tissues seems to be more responsible for the improvement. In an attempt to correlate clinical improvement with excretory pattern of DDS, the estimation of the drug in the tissues would be more helpful.

Acknowledgement

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True

An entity first described in 1965, it presents as multiple soft elevations in the mucous membrane of the mouth with soft, keratotic or verrucous surface. The condition has occurred in families and have been mainly reported from the Americas, presenting a problem of differential diagnosis for dentists and dermatologists. The histopathology shows acanthotic stratified squamous epithelium with marked reticulation and anastamosing of the rete pegs and some increase in mitosis.

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