ABSORPTION AND EXCRETION OF DDS IN LEPROSY

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INTRODUCTION

The sulfone treatment of leprosy is long since beyond the experimental state. The so-called parent substance of the sulfone drugs, 4,4'-diamino-diphenyl sulfone (DDS), has established itself as an important drug in leprosy therapy. Smith ([8]) showed that sulfone compounds were effective in treatment due to their breaking down into DDS in the body. Experiments with small doses of that drug showed good results. It was also found that DDS given orally in a dose of 100-200 mgm. daily was capable of maintaining an adequate blood level, comparable in terms of chemical equivalents with that obtained by using its derivatives.

Without attempting to review the early literature fully, it may be note that Floch and Destombes ([3]) used DDS by both oral and intramuscular routes, and found that in either case 200 mgm. a day is well tolerated. Lowe ([5]) reported that 100 mgm. daily was enough to produce good results. Dharmendra *et al.* ([2]) confirmed that DDS administered orally was quite effective. The object of the present investigation has been to study the nature of absorption and excretion of DDS in blood and urine.

MATERIALS AND METHODS

This study was carried out in early and advanced cases of both the lepromatous and tuberculoid types of leprosy. Twenty-one patients (10 lepromatous and 11 tuberculoid) were included, all being inpatients of the Acworth Leprosy Home, Wadala, Bombay. All patients, of different ages, regularly took 100 mgm. of DDS a day by the oral route, on 6 days a week (excluding Sundays) for from 2 to 4 years; they had no side sickness. The experiment comprised 4 batches of patients, each batch studied differently at different times. Each experiment lasted for 8 days.

Blood extractions were performed at about 9 a.m. daily, followed by the administration of the drug. Similarly, 24-hour urine specimens were collected daily. The blood and urine samples were analyzed for their DDS contents by the method of Simpson ([7]), which is based on the development of a purplish color by coupling the diazotized DDS with N-(1-naphthyl)-ethylene diamine hydrochloride.

RESULTS

Table 1 and Fig. 1 represent the daily concentration of DDS in the blood under the conditions of the experiment. It will be seen that the blood levels ranged from 0.62 to 0.68, and from 0.64 and 0.71, mgm./% in the lepromatous and tuberculoid cases respectively. Table 2 and Fig.

TABLE 1.—*Concentration of DDS (in mgm./%) in the blood at intervals after the oral administration of 100 mgm.*

Time interval	Lepromatous (10 cases)	Tuberculoid (11 cases)
0 hours	0.6218	0.6423
24 hours	0.6418	0.6604
48 hours	0.6486	0.6702
72 hours	0.6669	0.6874
96 hours	0.6739	0.7055
120 hours	0.6888	0.7110
168 hours	0.6200	0.6400

TABLE 2.—*Total absorption and excretion of DDS (in mgm.) in blood and urine 24 hours after the oral administration of 100 mgm.*

	Urine		Blood	
	Lepromatous (10 cases)	Tuberculoid (11 cases)	Lepromatous (10 cases)	Tuberculoid (11 cases)
Monday/ Tuesday	74.3557	76.0969	0.8452	0.6721
Tuesday/ Wednesday	82.0560	84.0944	0.2873	0.3638
Wednesday/ Thursday	76.6330	77.7095	0.7735	0.6387
Thursday/ Friday	83.6139	75.1947	0.2758	0.6780
Friday/ Saturday	78.2286	86.0486	0.6297	0.2042

2 represent the amounts of DDS excreted daily with the urine, and the relation between the absorption and excretion of the drug. From this it is observed that the daily excretion of DDS in urine varied between 74 and 86 mgm./%. In the table the values of DDS in blood represent the amount of the drug that was absorbed in the whole amount of blood in 24 hours, out of the 100 mgm. of DDS administered.

DISCUSSION

From Table 1 it will be observed that there is no influence of the type of the disease on the blood levels of DDS. Smith ([8]) reported that on oral doses of 100-400 mgm. DDS a day, the mean minimal blood concentration varies from 0.4-1.5 mgm./%, and on a dose of 100 mgm. he found it to be 0.4 mgm./% Dharmendra ([2]) reported it to be 0.6 mgm./% on the same dose.

It will be observed that the concentration of DDS in the blood rises from Monday through Saturday as the DDS is administered daily. This rise is very sharp, but also very negligible. During Sunday, when the

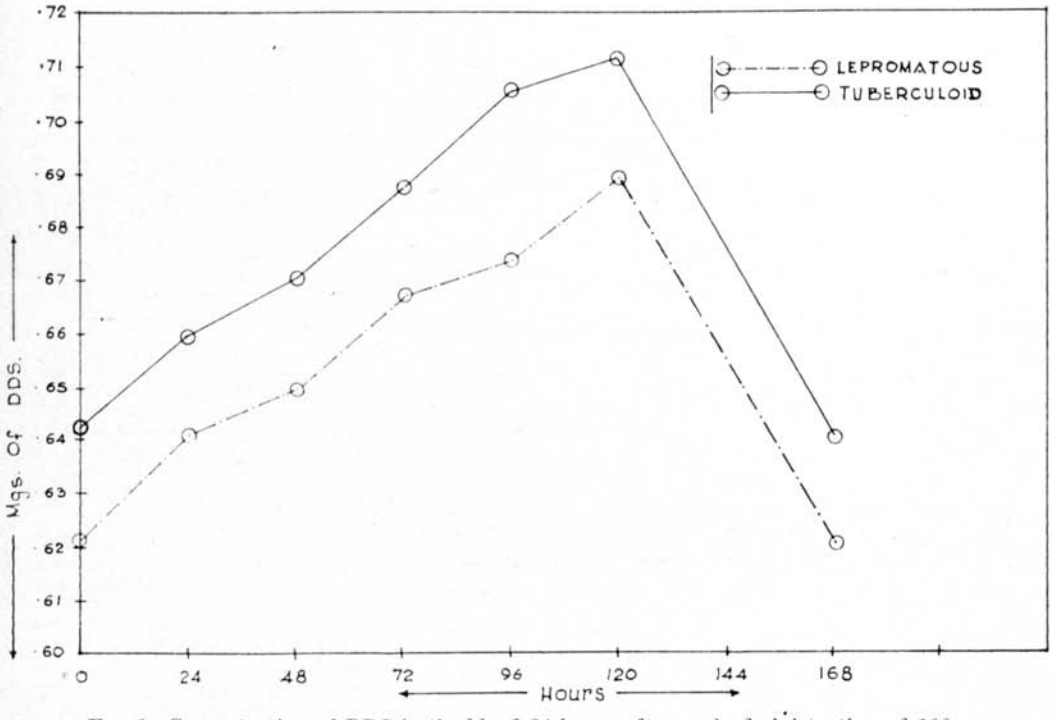

FIG. 1. Concentration of DDS in the blood 24 hours after oral administration of 100 mgm.

dose was not administered, titer falls suddenly and comes to normal on Monday morning, almost to the same level it was on the previous Monday. So, the reason for not administering the drug on Sunday may be primarily to keep the blood level constant, and hence to avoid toxic reactions due to excess accumulation of the drug in the body. Another thing to be seen is that the daily slight increase in the DDS absorption is not the same, and it may vary with individuals depending upon excretion in urine.

Kidneys play an important role in the excretion of DDS, as 70-80 per cent of the total dose administered is excreted in the urine. The amount so excreted is subject to considerable variations ([1]). Smith ([8]) reported the excretion of DDS in urine to be 80 mgm./%. Lowe ([6]) reported that the absorption of orally administered DDS is almost complete, about 85 per cent appearing in the urine. Dharmendra ([2]) found it to be 75 mgm./% on a daily dose of 100 mgm. by mouth. Imaeda ([4]) found that the proportions range from 70-90 per cent.

In the present investigation we found that, on the same dosage, the daily excretion of DDS in urine was 74-85 mgm./% The variations in the daily excretion of DDS in the urine are directly related to the daily absorption of DDS in the blood. From Table 2 and Fig. 2 it will be seen that there is an inverse relation between absorption and excretion. When there is a fall in the excretion the absorption is higher, and vice versa.

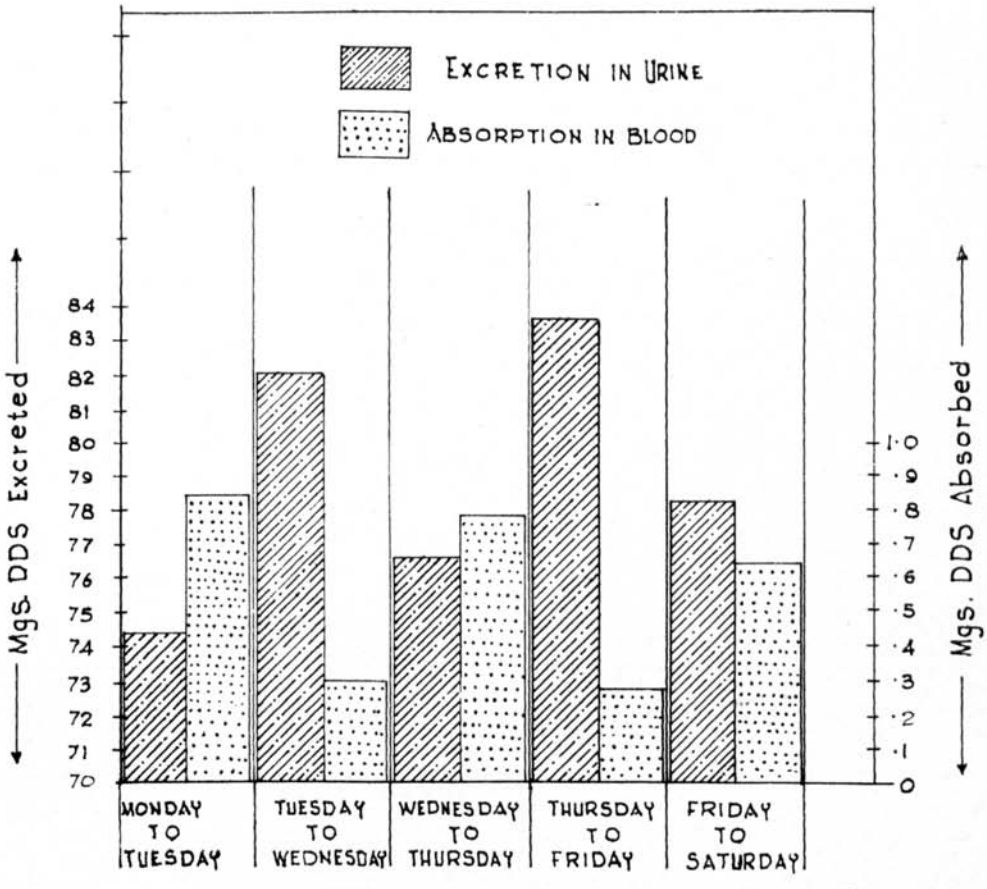

FIG. 2. Relation between the total absorption and excretion of DDS in 24 hours.

So, as stated earlier, the slight rise in the percentage concentration in the blood depends on its excretion in the urine. Due to some technical difficulties, it was not possible in the present investigation to estimate the concentration of DDS in the feces and the skin.

An attempt was made, by means of one *in vitro* experiment, to ascertain the possible reason for the lepra reaction which appears as a toxic effect of DDS.

Six blood samples of a leprosy patient receiving regularly 100 mgm. DDS daily were taken, and their initial DDS concentrations were determined. Then a known amount of pure DDS was added to each specimen, and all the samples were incubated at 37°C for 5 days. One sample at a time was analyzed for its DDS contents daily.

It was found that no change in the concentration occurred, and it was concluded that the lepra reaction is not due to the DDS concentration in blood. However, the possible reason for the lepra reaction may be the concentration of the drug in the tissues and skin. In tissues a part of

DDS may be converted into some unknown substance, which may be the active substance in healing the disease. As the concentration of DDS in tissues goes on increasing, its conversion into this active unknown substance must also be increasing, and when the concentration of this active substance exceeds a particular limit the lepra reaction takes place, which is ultimately a toxic effect of DDS.

SUMMARY

The absorption and excretion of DDS in blood and urine were determined in batches of patients with the lepromatous and tuberculoid types of leprosy who were given 100 mgm. of DDS a day orally. Simpson's method for the sulfone estimations was followed.

The average concentration in the blood was 0.64 mgm./%, and the average excretion in the urine was 74-82 mgm./%. Neither absorption nor excretion is constant, and there is an inverse relation between each other.

An attempt has been made to find the probable reason for the occurrence of lepra reaction.

RESUMEN

En lotes de enfermos con las formas lepromatosa y tuberculoidea de la lepra que exibían 100 mgm. de DDS al día por vía bucal, se determinaron la absorción y la excreción de la droga en la sangre y la orina. Se siguió el método de Simpson para los cálculos de la sulfona.

La concentración media en la sangre fué de 0.64 mgm. % y la excreción media en la orina media 74-82 mgm. % en la orina. Ni la absorción ni la excreción fueron constantes, pero existe una relación inversa entre ambas.

No se ha tratado de descubrir la probable razón para la aparición de la reacción leprosa observada.

RESUMÉ

L'absorption de la DDS dans le sang et son élimination dans l'urine ont été déterminées dans des groupes de malades atteints de lèpre lépromateuse et de lèpre tuberculoïde auxquels étaient quotidiennement administrés 100 g de DDS par voie buccale. Le dosage des sulfones a été pratiqué d'après la méthode de Simpson.

La concentration moyenne dans le sang a été de 0.64 mg/%. L'absorption et l'élimination ne sont ni l'un ni l'autre constantes, et chacune est en rapport inverse de l'autre.

On a essayé de trouver la raison vraisemblable de l'apparition de la réaction lépreuse.

Acknowledgments.—Thanks are due to Dr. N. Figueredo, ex-Superintendent and at present Special Leprosy Officer, and to Dr. N. D. Katdare, Superintendent of Acworth Leprosy Home, Wadala, Bombay, for their help and cooperation in carrying out this work.

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