

BLOOD DAPSONE LEVELS IN LEPROSY PATIENTS TREATED WITH ACEDAPSONEJOSEPH GEORGE¹ AND S. BALAKRISHNAN²

ABSTRACT : *The metabolism of the repository drug acedapsone (DADDS, 4,4'-diacetyldiaminodiphenyl sulfone) was studied in 15 individuals receiving 225 mg of DADDS, intramuscularly for a period of 75 days. Plasma levels of DDS were determined on the 2nd, 7th, 15th, 30th, 60th and 75th day after administration of the drug by spectrophoto-fluorometric technique. The mean peak levels of DDS (85.36 ng/ml) were noticed on 7th day followed by a gradual decrease in DDS concentration. The mean half-life level (44.53 ng/ml) of DDS were observed around the 15th day. The mean DDS level for the entire period of observation after one dose was 41.95 ng/ml. On the 75th day, the DDS level reached the minimum value of 14.76 ng/ml which was still about 5 times more than the minimal inhibitory concentration (MIC) level of DDS against M. leprae (3 ng/ml). The results are discussed.*

INTRODUCTION

Acedapsone (Hansolar, DADDS) is a diacetyl derivative of diaminodiphenyl sulfone (DDS) which exerts antibacterial activity against *Mycobacterium leprae*. Its anti-leprosy activity was first demonstrated by Shepard (1967) employing mouse foot-pad technique. Later so many investigators have found it an effective anti-leprosy drug (Sloan, *et al.*, 1971, 1972a; Russell, *et al.*, 1971, 1975a; Shepard, *et al.*, 1972) and especially useful for the prophylaxis of the disease (Russell, *et al.*, 1973, 1974, 1975b; Neelan, *et al.*, 1983).

It was first reported by Shepard *et al* (1968) that a standard adult dose of 225 mg of this repository drug in 1.5 ml of the suspension releases DDS at a rate of approximately 2.4 mg per day. Similar observation has also been made by Ellard *et al* (1971). The corresponding serum concentration was found to be 60 ng/ml (Shepard *et al* 1968) about 20 times higher than the minimum inhibitory concentration (MIC) of DDS which is about 3 ng/ml (Colston *et al.*, 1978). Average blood levels for DDS in leprosy patients after an acedapsone injection at intervals of 77 days have been reported to be around 50 ng/ml by Ozawa *et al* (1971). Sloan *et al* (1972b) and Gordon *et al* (1974). More recently Anand and Rathore (1979) have found that the serum

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level of DDS in patients with lepromatous leprosy remained well above the MIC upto 60 days after a single intramuscular injection of DADDs. The aim of our present investigation was to determine the amount of DDS released in the blood of leprosy patients on 2nd, 7th, 15th, 30th, 60th and 75th days after a 225 mg acedapsona injection over a period of 75 days.

MATERIALS AND METHODS

Fifteen adult multibacillary leprosy cases were selected for the study. The patients were admitted in the ward and kept under supervision during the period of investigation. Hansolar (Acedapsona) was obtained from Parke Davis Ltd., Rio de Janeiro, Brazil, through World Health Organisation, Geneva. This was given once in 75 days by an intramuscular injection into the buttocks at a standard adult dose of 225 mg in 1.5 ml suspension in castor oil and benzylbenzoate. The blood was collected on 2nd, 7th, 15th, 30th, 60th and 75th day after administration of the drug. The DDS levels in plasma were determined by the spectrophotofluorometric technique of Ellard and Gammon (1969). Spectroscopic grade ethyl acetate (BDH) was used for the extraction of DDS from plasma. An Aminco-Bowman Spectrophotofluorometer (American Instrument Company, Silver Spring, Maryland 20910, U.S.A.) was used throughout the experiment. The standard DDS powder was obtained from Wellcome Research Laboratories, Beckenham, England BR3 3BS.

RESULTS

The results obtained in the study are presented in the following table and figure. The mean DDS level for the entire period of observation after one dose of injection was 41.95 ± 10.56 ng/ml with a coefficient of variation 61.67%. The peak DDS level (85.36 ± 7.12 ng/ml) was noticed on 7th day followed by a substantial decrease in DDS level. The lowest drug level encountered on 75th day was 8.4 ng/ml which is around 3 times higher than the MIC of DDS against *M. leprae*. The drug level never went below the MIC of DDS against *M. leprae* in any of the patients during the study.

TABLE 1 : Concentration of DDS in Plasma, ng/ml n=15

| DATE AFTER ADMINISTRATION | ARITHMETICAL MEAN \pm STANDARD ERROR | COEFFICIENT OF VARIATION (%) |
|---------------------------|--|------------------------------|
| 2nd day | 55.29 ± 3.03 | 21.26 |
| 7th day | 85.36 ± 7.12 | 32.33 |
| 15th day | 44.53 ± 2.51 | 21.82 |
| 30th day | 29.22 ± 1.63 | 21.59 |
| 60th day | 22.54 ± 1.41 | 24.22 |
| 75th day | 14.76 ± 0.96 | 25.27 |

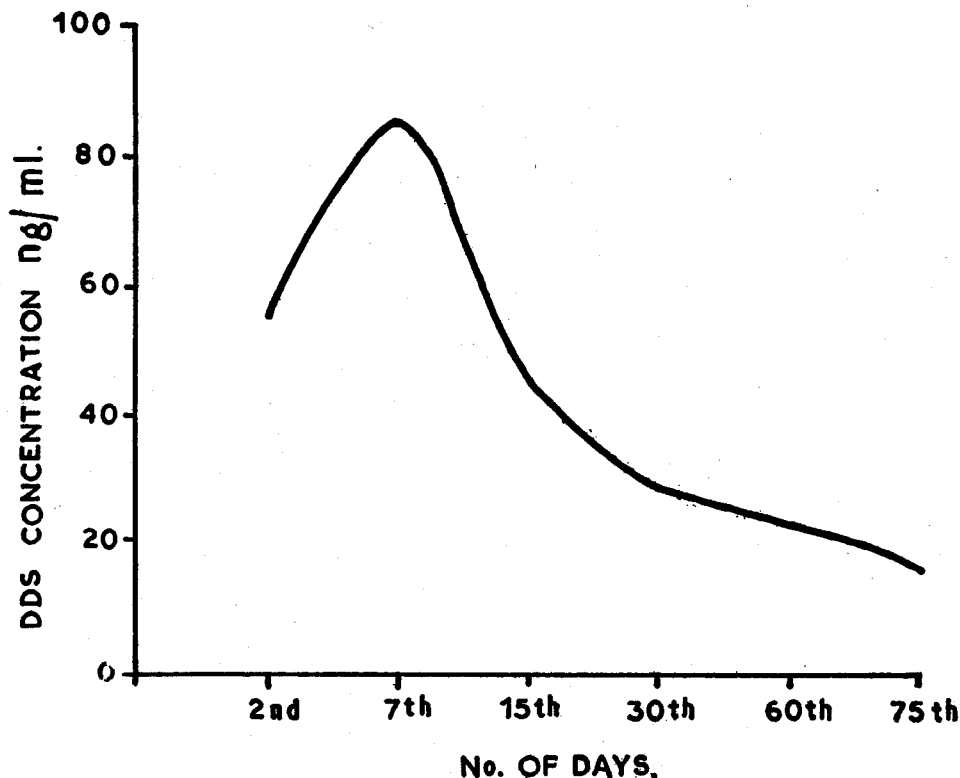


Fig. Mean DDS levels in plasma after DADDS injection.

DISCUSSION

A mean DDS level 41.95 nanogram(ng) per millilitre of plasma with a coefficient of variation 61.67% was obtained in the present study. A comparison of our results with the earlier ones shows a good correlation. Sloan *et al* (1972b) reported a very low, steady release of DDS over a period of 77 days, with DDS blood levels averaging about 50 ng/ml during that time. Gordon *et al* (1974) observed a mean DDS level of 47.4 ng/ml from 85 patients. Murray *et al* (1974a) reported the mean DDS level as 31.3 ng/ml in plasma samples taken 75 days after administration of DADDS. According to Ozawa *et al* (1971) the average DDS level in plasma was 50 ng/ml after acedapsone injection.

The mean peak DDS level of 85.36 ng/ml was noticed on 7th day in the present study. Murray *et al* (1974b) reported a peak mean DDS level, 45 ng/ml at 3 weeks. Peters *et al* (1974) also reported a same peak DDS level of ng/ml at 3-5 weeks. Thus the mean peak DDS level obtained in the present investigation is much higher compared with the earlier findings. This

may be due to the racial difference in the subjects of the different studies.

In the present investigation, the average DDS level on 75th day (at 11th week) was 14.76 ng/ml. This is quite comparable with the reports of other investigations. McRae *et al* (1972) reported a serum DDS of 22 ng/ml in a girl on 75th day after administration of a standard dose of acedapsone. Murray *et al* (1974b) observed a DDS level of 25 ng/ml at 11 weeks. Gordon *et al* (1974) reported that, no significant differences were noted in the mean levels of DDS, MADDS or DADDS in plasma obtained at 75 to 77 days from the different groups of patients. They reported a mean DDS level of 30.5 ng/ml during this period from 286 patients. Peters *et al* (1974) observed a mean DDS level of 25 ng/ml at 11 weeks. According to Ganapati *et al* (1976) the dapsons levels in the blood were more than 10 ng/ml before each fresh administration of acedapsone.

Attention may be drawn to the mean DDS levels on different days obtained in the present study (Table and figure) as compared to the earlier reports. While the time taken for reaching the peak levels is more or less the same in all the studies, there is some difference between our studies and those reported by Glazko *et al* (1968a, 1968b) in regard to maintenance of blood levels. They noticed that the peak blood levels reached in about 6-8 days, fell to 28-35 ng in two weeks and remained at this level for two months followed by a rapid fall with a half-life of about 43 days. In the present study as well as that of Anand and Rathore (1979) the half-life of DDS after DADDS injection is around the 15th day. The maintenance of the plateau blood level was not observed. On the other hand, there was a progressive fall in the DDS level reaching the minimum around the 75th day.

The lowest drug level encountered in the present investigation is 8.4 ng/ml which is also agreeable with the results of other workers. Murray *et al* (1974b) reported the lowest DDS level observed in their study as 14 ng/ml plasma. Gordon *et al* (1974) reported the lowest level of DDS encountered as 8.9 ng/ml. According to Ganapati *et al* (1976) the dapsons level in the blood was never decreased below 10 ng/ml during the course of study. It is quite significant to note that all the investigators who have followed the blood DDS levels after DADDS injection have reported DDS level well above, the minimal inhibitory concentration of the drug against *M. leprae*.

ACKNOWLEDGEMENTS

The authors are greatly thankful to Dr. P.S. Seshadri and Dr. H.K. Kar for providing patients for the study. We also acknowledge the technical

assistance of Mr. J.A. Rozario and Mr. D. Anandan. The authors are thankful to Dr. P.N. Neelan, Director and Dr. V.N. Bhatia, Deputy Director (Labs) for their encouragement in the study. The assistance of Mr. C. Samuel for preparation of graph and the secretarial assistance of Mr. R. Rajan, Stenographer is duly acknowledged.

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