

A Report on a Controlled Clinical Trial with Conventional and One Third Conventional Dose of Dapsone Administered Orally Once a Week in Lepromatous Patients*

K. RAMANUJAM, C. G. S. IYER AND G. RAMU

*Central Leprosy Institute,
P.O. Tirumani, Chingleput 603001, S. India*

Therapeutic investigation with dapsone administered orally in the conventional (10 mg/kg of body weight/week—Group A), and one third of the conventional dose (3.33 mg/kg of body weight/week—Group B), as a single dose once a week to lepromatous cases, using double-blind procedures over a period of 130 to 265 weeks was concluded in September, 1973. The findings of the study showed (1) DDS administered as a single dose once a week was therapeutically effective. (2) One third the conventional dose was as effective (perhaps better) as the conventional dose. (3) Lepra reaction occurred in both the groups but tended to be more severe in Group A and (4) Insomnia was a frequent and sometimes a disturbing side-effect in this regimen of therapy.

Objectives

(i) To compare the results of DDS therapy in lepromatous leprosy using the conventional dose (10 mg of DDS/kg body weight/week) and one third of this amount (3.3 mg/kg body weight/week) administered orally as a single dose once a week. (ii) To determine the relationship between blood levels of the drug and the clinical and bacteriological results.

To the above 2 main objectives the following were added: (i) The study of the incidence of complications/side-effects in the 2 groups. (ii) The trend in the blood sulphone level in respect of the dose of the drug and the duration of treatment and (iii) The study of the effect of this regimen of treatment on the renal, hepatic and haemopoietic systems.

* This investigation received financial support from the WHO.

Method

This trial was conducted using double-blind procedures.

The subjects

Active male lepromatous cases in reasonably good general health and without complicating diseases, preferably untreated or who had received specific anti-leprosy treatment for 6 months or less, constituted the subjects for the study.

Dosage schedule

One group—Group A, was given the conventional dose of DDS *viz.* 10 mg/kg body weight/week, this being reached by stages over a period of 22 weeks according to a previously worked out schedule. The other group, Group B, was given a maximum dose which was one third of the conventional dose *viz.* 3.33 mg/kg body weight/week, this being built up gradually over a period of 6 weeks. These doses were prescribed each month in strict relation to body weight.

Allocation to the 2 groups

Patients were allocated to Group A or Group B according to the table of random allocation provided by the WHO.

Administration of the drug

The appropriate dose of DDS was administered to each case every Monday, packed in gelatin capsules. On the rest of the 6 days in the week, the patients received capsules identical in appearance and number containing an innocuous substance like calcium lactate or sodi. bicarb.

Investigations, initial and follow-up

These comprised (i) Diagrammatic representation of the clinical status of the patient, repeated once a quarter without reference to the previous recording. (ii) Bacteriological examination, involving taking of 6 skin smears and evaluated with reference to bacterial density—Bacteriological Index, and morphology of organisms—Morphological Index, repeated every 3 months. (iii) Laboratory investigations comprising of haemogram, urinalysis, stools examination and liver function tests performed at the time of entry of the subjects into the study and repeated thereafter every 3 months in order to keep a watch on the haemopoietic, urinary and hepatic systems. (iv) Estimation of blood level of sulphone, as far as possible, every month. (v) Skin biopsy from a representative skin lesion before entry into the study and thereafter once a year preferably from the same lesion. (vi) Lepromin test with the antigen supplied by the WHO (160 million/mm³) at the time of entry into the study and repeated at the termination of the study.

Assessment of results

The progress of cases under treatment was gauged by periodical assessment of these cases, clinical and bacteriological, once in 3 months. In addition, the

incidence of complications and side-effects were also recorded and taken into account during assessment of progress of cases.

The study proper

The study was commenced on 2 September, 1968. Between September, 1968 and March, 1969, 40 cases were admitted into the study. The investigation was originally planned for 2 years and should have terminated by September, 1970. However, in view of the small number of cases participating in the study towards the end of the 2 year period, and the importance of the investigation, the investigation was continued for 3 more years after adding 15 new subjects to the study. Over the 5 year period of the investigation 34 cases were lost to the study, only 21 cases continuing treatment up to September 1973. Ten of these were receiving DDS in the conventional dose (Group A) and 11, a third of the conventional dose (Group B) once a week.

Findings of the Study

Clinical progress

All the cases registered progressive clinical improvement including those who had become subjects of recurrent reactive episodes. One case in Group B, after initial improvement, showed clinical and bacteriological deterioration with a rise in the Morphological Index. He was suspected to be developing sulphone-resistance and hence changed to Group A. His further deterioration was stemmed. Other unusual developments observed during the follow-up were: One case in Group A improved progressively under treatment but developed 2 fresh nodules after 170 weeks' treatment and got progressively worse. One case in Group B, developed a fresh nodule 222 weeks after commencement of treatment, after registering progressive improvement. No further nodules appeared. A third case in Group A, developed 1 fresh nodule after registering appreciable improvement during 235 weeks' regular treatment. Further nodules did not appear.

Bacteriological progress

All the 21 cases registered a progressive fall in the Morphological Index to a level of less than 1%. One case however in Group B, showed a tendency for an increase in the MI after an initial fall to less than 1%. This coincided with the clinical deterioration observed in the case.

The fall in the BI was progressive except in 2 cases—1 case on one third of the conventional dose who became a subject of recurrent pustular lepra reaction and another receiving the conventional dose. The latter registered initial progressive improvement but later showed progressive bacteriological deterioration for no apparent reason.

A case in Group A, a subject of recurrent pustular lepra reaction and steroid dependent, and another case in Group B with recurrent lepra reaction showed considerable clinical and bacteriological improvement in spite of recurrent reactive episodes. No case became bacteriologically "negative".

Occurrence of complications

Lepra reaction of varying grades of severity and frequency occurred in both the groups. It was difficult to predict or anticipate the onset of reactive states. The factor or factors provoking the reactive state were not identifiable either, except in one instance—a case in Group B, who developed the first attack of lepra reaction and glycosuria following severe local reaction to Vole bacillus antigen. The glycosuria reappeared with each bout of lepra reaction. Although the incidence of the reactive state was more in Group B, it tended to be more severe in Group A.

Side-effects

Insomnia was observed to be one of the undesirable and disturbing side-effects which arose in many of the cases in the early part of the investigation. This occurred in both the groups but was more frequent and perhaps more intense in the cases in Group A. In 1 patient in Group B, the persistent insomnia led to an explosive mental episode when the patient became aggressive and assaulted other patients in the Sanatorium.

Findings of the laboratory investigation

Laboratory investigations such as haemogram, urinalysis and liver function tests carried out on these cases every three months did not reveal any abnormal findings attributable to this regimen of therapy. In all but 2 instances, levels of sulphone in blood tended to be commensurate with the dose of DDS administered orally.

Acceptance of the therapy by patients

It may be stated that this method of treatment was acceptable to the patients except in instances where insomnia became persistent.

Results

Assessment done on these groups of cases at the end of 3–5 years showed: (i) None of the cases became “Negative”. Cases receiving the smaller dose had done better than those receiving the conventional dose, 9 out of 11 of them having “Much Improved”, (ii) The average uptake of DDS was definitely more in Group B than Group A, (iii) The incidence of reactive episodes was more in the group getting the smaller dose, 8 out of 11 cases having manifested moderate to severe reactions as against 5 out of 10 cases in Group A. However, recurrent reactive episodes were more in Group A than Group B.

Conclusion

(i) DDS is therapeutically effective when administered orally as a single dose once a week. (ii) One third of the conventional dose is as effective as the conventional dose, perhaps better. However, there is the possibility of this small dose proving ineffective in an occasional case. (iii) Complications like lepra reaction occurred in both the groups although the severity appeared to be more in Group A. (iv) Insomnia of varying grades of severity and duration was the

predominant undesirable side-effect of this regimen of therapy. (v) Adverse effects attributable to this regimen of treatment were not observed on the haemopoietic, renal or hepatic systems. (vi) Once a week regimen is generally acceptable to the patient except in instances where insomnia proved irksome.