CONTINUING MEDICAL EDUCATION

CHEMOTHERAPY OF LEPROSY--PAST AND PRESENT

V N Sehgal and G Srivastava

The efforts for the effective treatment and control of leprosy in the Indian subcontinent are gaining momentum under the *National Leprosy Eradication Programme* of the country. However, the presence of a sizeable population of leprosy patients poses a challenge to its effective control. This becomes all the more crucial in the wake of the emergence of the drug-resistant strains of *Mycobacterium leprae* to various therapeutic agents. For a successful impact in achieving our target, a well regimented schedule of multi-drug therapy has to be evolved and strictly obeyed. A brief knowledge of our past experiences with the antileprosy drugs will prove invaluable in chiselling out a better regimen for the successful chemotherapy of leprosy.

Presently, the chief antileprosy drugs used in various permutations and combinations, are diamino-diphenyl sulfone (DDS), rifampicin (RFM), clofazimine (C), ethionamide and prothionamide. Earlier, thiacetazone, isoniazid (INH), streptomycin and thiambutosine have also been tried.

Dapsone

The use of sulfones, for the treatment of leprosy, was initiated in 1943 and dapsone (4, 4 diamino-diphenyl sulfone) in particular, in 1948. Dapsone, which has a bacteriostatic as well as a slow bactericidal action, acts as a synthetase inhibitor in the folate synthesizing enzyme system of *M. leprae*. The usual weekly dosage is 6 to 10 mg per kilogram of body weight divided in equal daily dosages. It has proved to be a sheet-anchor in leprosy therapy. The peak blood level after a single oral dose of 100 mg is 500 times the minimum inhibitory concentration (MIC) of fully sensitive strains of *M. Leprae*.[1]

Secondary dapsone resistance : The phenomenon of secondary dapsone resistance was first established by Pettit and Rees[2] after the successful use of dapsone for over 16 years. Subsequently, many reports[3-14] appeared from various countries describing clinical as well as experimental evidence of bacterial resistance to diamino-diphenyl sulfone. The problem of secondary dapsone resistance has considerably been accentuated by its increasing prevalence rates which were initially estimated to be 1 per 1000 in Malaysia by Pettit et al.[3] Till date, various reports documenting diverse prevalence rates of secondary dapsone resistant cases are available from different countries.[5,6,10,12-17] The factors predisposing to such a situation include low-dosage dapsone therapy as well as irregular and inadequate treatment,[3-7] but it is also seen in patients treated adequately and regularly.[15-17]

Primary dapsone resistance : An acquired dapsone resistant leprosy patient poses a serious risk of infecting his contacts with resistant bacilli, out of which a proportion will develop an overt disease refractory to dapsone treatment from the very beginning. Pearson et al[18] were the first ever investigators to report a proved primary dapsone resistant leprosy patient in

From the Department of Dermatology and Venereolgy, Maulana Azad Medical College and Associated LNJPN and GB Pant Hospitals, New Delhi-110 002, India.

Address correspondence to : Dr. V. N. Sehgal, A/6, Panchwati, Delhi -110 033.

the year 1977. Shortly thereafter, Girdhar et al[19] reported a similar situation in India. Thereafter, many authors[20-22] documented the occurrence of this entity from various countries. Although, the primary dapsone resistant bacilli can be demonstrated in multibacillary patients by mouse-foot-pad inoculation, this is not possible in paucibacillary cases. Nevertheless, such a possibility should constantly be considered while treating fresh leprosy patients.

Clofazimine

The efficacy of this fat soluble, red, riminophenazine dye in leprosy patients was first established in 1962 by Brown and Hogerzeil.[23] Presently, it forms one of the major antileprosy drugs. It is also used both for the prevention[24-26] and the treatment[26,27] of erythema nodosum leprosum (ENL) reaction. In addition, its use in the treatment of dapsone-resistant leprosy is unequivocal.[10, 25, 26, 28] It is primarily a bacteriostatic drug, with a slow bactericidal activity. Its average daily adult dose is 100 mg. However, during the episodes of reactions the daily dosage required is in the range of 300 or 400 mg. As the drug is unevenly distributed in the tissues, it is difficult to accurately estimate the minimum inhibitory concentration (MIC) of this drug.[1]

So far, only one case of proved clofazimine resistant leprosy has been reported by Warndorff-van-Diapen in the year 1982.[28]

Rifampicin

This drug was introduced in 1970 as an antileprosy drug[30,31] although its precursor, rifamycin SV was tried as early as 1963 by Opromolla.[32] It exerts a bactericidal action by inhibiting the RNA synthesis of *M. leprae*. The usual daily adult dosage is 450 mg or 600 mg before breakfast depending on the body weight of the patient. However, the opinions differ among leprologists regarding its dosage, dosage interval and duration of treatment.[33-36] A single oral dose of 600 mg attains a peak serum concentration which is 300 times the MIC.[1] Continuous as well as intermittent dosages of rifampicin have been studied in several works[34,37-39] and their efficacy and incidence of side effects determined. Gyselen[40] observed that side effects, generally, are not recorded when the dosage below 15 mg/kg body weight are administered intermittently.

The development of rifampicin-resistant *M. leprae*, with experimental confirmation was first reported by Jacobson and Hasting[41] in a patient on rifampicin monotherapy.

Ethionamide and Prothionamide

Ethionamide was initially used by Flouch et al[42] in 1968. Both the drugs are thioamides with different side chains but have identical activity. The dosage is 375-500 mg daily when they exert a bactericidal action. At a single dose of 375 mg, the peak blood level for ethionamide is about 60 times, and for prothionamide, 40 times the MIC.[1] Resistant strains of *M. leprae* to these chemotherapeutic agents have also been documented in the recent past.[43,44]

Thiacetazone and Thiambutosine

Thiacetazone, a thiosemicarbazone derivative, is a bacteriostatic drug[45] but its monotherapy leads to the rapid development of bacterial resistance. It is preferred to be given along with other drugs, especially when the patient concomittently suffers from tuberculosis as well. The daily adult dosage is 100-150 mg while the dosage for children is 2 mg/kg body weight. After a single dose of 150 mg, its peak serum level is 8 times the minimum inhibitory concentration (MIC).[46]

Thiambutosine, on the other hand, is a diphenyl thiourea derivative and is used in the daily adult dosage of 2 gm by mouth, the therapy being initiated with a low dose. It is also bacteriostatic[47] and the peak serum concentration after a single oral dose of 2 gm reaches just upto the MIC.[46] Rees[48] found

that DDS-resistant strains of *M. leprae* were sensitive to thiambutosine.

Resistant strains of *M. leprae* for both the above chemotherapeutic agents have also been demonstrated.[44]

The concept of persister

The term 'Persister' is applied to the viable, fully drug susceptible forms of *M. leprae* which are able to survive for many years in the patients despite the presence of bactericidal concentration of an antileprosy drug.[46] They are regarded as physiologically dormant forms favouring certain sites like peripheral nerves, smooth and striated muscles and internal viscera. Such viable and fully drug-sensitive strains have successfully been isolated from the patients who were treated for 10 to 12 years with dapsone[49] and for 5 years with rifampicin.[50,51] They can survive a period of over 20 years and are responsible for the relapse in a proportion of cases.

Compliance

The long duration of treatment of leprosy, e. g. dapsone monotherapy being administered for 5 years in tuberculoid and for 20 years or more in lepromatous patients, suppresses the incentive of these patients for taking a regular treatment.[1] In a computorised study of 29,000 patients, Collier[52] found that 50 per cent of the patients were lost to follow-up within 3.5 years of commencing the treatment, the rate of loss of lepromatous patients was striking and as rapid as that of tuberculoid patients, which calls for immediate attention for devising a short course chemotherapy of leprosy for better compliance and thus for the successful control of the disease.

Therapeutic regimens

Following the discovery by Cochrane[53] that dapsone, chemically the simplest sulfone, was found to be very efficacious, relatively non-toxic when used in dosage of 1-2 mg/kg body weight daily and cheap, dapsone monotherapy formed the treatment of choice for all types of leprosy. It reigned from 1947 until 1977. Multidrug therapy came in picture only later, first for the treatment of multibacillary and subsequently also for paucibacillary leprosy.[46]

Twenty years of dapsone monotherapy brought to light two serious shortcomings. They were,(1) the necessity for long term treatment, and (2) the appearance of dapsone-resistant strains of *M. leprae*. These warranted the need for a multiple drug therapy required for a shorter period, like that used in the treatment of tuberculosis. Various multidrug regimens were, thus, worked out and tried by various workers[54-63] using various permutations and combinations of different drugs namely diamino-diphenyl sulfone, rifampicin, clofazimine, isoniazid (INH), ethionamide, streptomycin, paraaminosalicylic acid (PAS), thiacetazone and thiambutosine.

An ideal chemotherapeutic regimen should fulfill certain prerequisites such as, preventing further bacterial multiplication, rapidly rendering the patient non-infectious, preventing the emergence of drug-resistant strains, acceptable to the patient and last but not the least the cost and uniform availability throughout the country.

In the wake of an alarming rise in the emergence of dapsone resistant strains of *M. leprae* and the compounding danger of development of resistance against other chemotherapeutic agents in future, the expert Committee of WHO[46] recommended multi-drug therapy for the first time in 1982 for all types of leprosy patients. It assigned different therapeutic regimens to paucibacillary and multibacillary patients. Paucibacillary patients include TT and BT where the bacteriological index (BI) is less than 2, while multibacillary patients include BB, BL and LL with BI equal to or more than 2.

Multibacillary leprosy : The rationale should be that the treatment be started with the maximum daily dosages using 2 bactericidal and one bacteriostatic drugs for the first 3 months, followed by a continuation phase with

2 bactericidal drugs during the next 3 months.[64] However, WHO[46] recommends rifampicin 600 mg (450 mg, if patient is less than 35 kg) once a month under supervision, clofazimine 300 mg once a month supervised and 50 mg daily self administered, and diamino-diphenyl sulfone 100 mg daily by self administration. This regimen can, in addition, be supplemented by a monthly supervised dose of ethionamide or prothionamide.[46] Clofazimine can be replaced by ethionamide or prothionamide if it is unacceptable to the patient. This triple drug regimen should be given for a minimum period of 2 years, and whenever possible, until each multibacillary patient has achieved smear negativity.[46] Two doses of rifampicin on consecutive days each month is sometimes preferred to a single monthly dose.[1] However, Opromolla et al[65] found a single monthly supervised dose of 1200 mg rifampicin for 6 consecutive months to be very effective and tolerable to the patient while Girdhar et al[66] document weekly dose of 900 mg to be more efficaceous than daily or monthly dosage.

The treatment should never be stopped during episodes of reactions which should receive their own specific therapy.

Doubts exist whether such a regimen can eradicate the 'persisters'. However, in one study[36] statistically significant fewer persisters were detected at 6-month intervals in a small group of LL patients treated with daily dosage of dapsone and rifampicin when compared with a control group treated with dapsone monotherapy.

In order to successfully abridge the multifold pitfalls of various regimens, we prefer to use the daily dosage of 3 drugs at the commencement of therapy (diamino-diphenyl sulfone 100 mg, rifampicin 600 mg or 450 mg, and clofazimine 100 mg) for first 3 months. Rifampicin is stopped after 90 days and clofazimine after completion of one year. Dapsone, on the other hand, is continued till the patient becomes smear negative.

Paucibacillary leprosy : The recommended dosage schedule by WHO[46] comprises rifampicin 600 mg (or 450 mg) once a month under supervision and dapsone 100 mg daily by self administration. The total duration of treatment is 6 months. It is found to be very effective in a few other studies too.[67,68] In paucibacillary patients, the possibility of emergence of drug-resistant bacilli is insignificant because of a low bacterial load. Moreover, any persisters remaining at the end of a full course of chemotherapy can be effectively eradicated by the cell-mediated immune responses of the host. Our institution at present follows a continuous rifampicin therapy for first 90 days along with daily dosage of 100 mg diamino-diphenyl sulfone which is continued till the completion of 18 months. At the end of 18 months bacteriological and histopathological assessment of each patient is undertaken before releasing him from control (rfc).

References

1. Waters MFR : The treatment of leprosy, Tubercle, 1983; 64 : 221-232.
2. Pettit JHS and Rees RJW : Sulfone resistance in leprosy, an experimental and clinical study, Lancet, 1964; 2 : 673-674.
3. Pettit JHS, Rees RJW and Ridley DS : Studies on sulfone resistance in leprosy, Intern J Leprosy, 1966; 34 : 375-390.
4. Jacobson KR : Sulfone resistant leprosy, etiology, incidence and treatment in United States, Intern J Leprosy, 1973; 41 : 684.
5. Meade TW, Pearson JMH, Rees RJW et al : The epidemiology of sulfone resistant leprosy, (Abstract), Intern J Leprosy, 1973 ; 41 : 684.
6. Pearson JMH, Rees RJW and Water MFR : Sulfone resistance in leprosy, A review of 100 proven clinical cases, Lancet, 1975; 2 : 69-72.
7. Roy Choudhury SB and Desikan KV : Sulfone resistance in leprosy. A report of 3 cases, Leprosy India, 1975 : 47 : 283-286.
8. Roy Choudhury SB : Clinical recognition and therapeutic confirmation of sulfone-resistant leprosy patients, Leprosy India, 1976; 48 : 784-788.

9. Taylor PM and Alexander R : Clofazimine in the treatment of dapsone resistant leprosy, Leprosy India, 1976; 48 : 709-712.

10. Taylor PM, Chacko CJG and Job CK : Studies of sulfone resistance in leprosy patients in India, Leprosy Rev, 1976; 47 : 5-11.

11. Fajardo TT and Abalos RM : A study of proven dapsone-resistant leprosy in Cebu, Philippines, Intern J Leprosy, 1979; 47 : 415.

12. Jacobson RR and Trautman JR : The treatment of leprosy with sulfones, Intern J Leprosy, 1971; 39 : 726-737.

13. Pearson JMH, Ross WF and Rees RJW : DDS resistance in Ethiopia, a progress report, Intern J Leprosy, 1976; 44 : 140-142.

14. Peters JH, Shepard CC, Gordon GR et al : The incidence of DDS resistance in lepromatous patients in Costa Rica : their metabolic disposition of DDS, Intern J Leprosy, 1976; 44 : 143-151.

15. Levy L, Rubin GS and Sheskin J : The prevalence of dapsone resistance leprosy in Israel, Leprosy Rev, 1977; 48 : 107-112.

16. Balraj V, Jesudasan K, Chacko CJG et al : Prevalence of secondary dapsone resistance in Gudiyattam Taluk, the leprosy control area of the Schieffelin leprosy research and training centre. Preliminary report, Intern J Leprosy, 1980; 48 : 397-401.

17. Pearson JMH : Problem of dapsone-resistant leprosy, Intern J Leprosy, 1981; 49 : 417-420.

18. Pearson JMH, Haile GS and Rees RJW : Primary dapsone resistant leprosy, Leprosy Rev, 1977; 48 : 129-132.

19. Girdhar BK, Srcevatsa and Desikan KV : Primary sulfone resistance, a preliminary report, Leprosy India, 1978; 50 : 352-355.

20. Jacobson RR and Hasting RC : Primary sulfone resistant leprosy, Intern J Leprosy, 1978; 46 : 116.

21. Pearson JMH, Haile GS, Barnetson RSC et al : Dapsone resistant leprosy in Ethiopia, Leprosy Rev, 1979; 50 : 183-199.

22. Guinto RS, Cellona RV, Fazardo TT et al : Primary dapsone resistant leprosy in Cebu, Philippines, Intern J Leprosy, 1981; 49 : 427-430.

23. Browne SG and Hogerzeil LM : B-663 in the treatment of leprosy, Leprosy Rev, 1962; 33 : 6-14.

24. Browne SG : B-663, further observations on its suspected anti-inflammatory action, Leprosy Rev, 1966; 37 : 141-145.

25. Azulay RD, DaSilva NC and Jesus M : Experience with clofazimine in the treatment of leprosy, Leprosy Rev, 1975; 46 : 99-102.

26. Browne SG, Harman DJ, Waudby H et al : Clofazimine in the treatment of lepromatous leprosy in United Kingdom, Intern J Leprosy, 1981; 49 : 167-171.

27. Schulz EJ : Forty-four month's experience with clofazimine, Leprosy Rev, 1972; 42 : 178-182.

28. Levy L, Shepard CC and Fasal P : Clofazimine therapy of lepromatous leprosy caused by dapsone-resistance *M. leprae*, Amer J Trop Med Hyg, 1972; 21 : 315-319.

29. Warndorff-van Diepen T : Clofazimine resistant leprosy, Intern J Leprosy, 1982; 50 : 139-142.

30. Leiker DL and Kamp H : First results of treatment of leprosy with Rifadin, Leprosy Rev, 1970; 41 : 25-30.

31. Rees RJW, Pearson JMH and Waters MFR : Experimental and clinical studies on rifampicin in treatment of leprosy, Brit Med J, 1970; 1 : 89-92.

32. Opromolla DVA : First results of the use of rifampicin SV in the treatment of lepromatous leprosy, Intern J Leprosy, 1963; 31 : 552-560.

33. Levy L, Shepard CC and Fasal P : Death of *M. leprae* following treatment of leprosy patients with 1500 mg rifampicin in a single dose, Intern J Leprosy, 1973; 41 : 490.

34. Pattyn SR, Rollier MT, Rollier R et al : A controlled clinical trial on initial 3 months continuous and intermittent rifampicin therapy in lepromatous leprosy, Leprosy Rev, 1975; 46 : 129-139.

35. Namba M and Hazama S : Effect of rifampicin on leprosy : Comparative study with several doses and intervals of administration, Intern J Leprosy, 1976; 44 : 198.

36. Waters MFR, Rees RJW, Pearson JMH et al : Rifampicin for lepromatous leprosy : A 9 years experience, Brit Med J, 1978; 1 : 133-136.

37. Gomi J : Intermittent rifampicin in treatment of pulmonary tuberculosis, Acta Tub Pneumol Belg, 1971; 62 : 313-314.

38. Shepard CC, Levy L and Fasal P : Further experience with the rapid bactericidal effect of rifampicin on *M. leprae*, Amer J Trop Med Hyg, 1974; 23 : 1120-1124.

39. Languillon J, Yawalkar SJ and McDougall AC : Therapeutic effects of adding Rimactane (Rifampicin)

450 mg daily or 1200 mg once monthly in a single dose of dapsone 50 mg daily in patients with lepromatous leprosy, Intern J Leprosy, 1979; 47 : 37-43.

40. Gyselen A : International symposium on intermittent treatment with rifampicin, Acta Tub Pneumol Belg, 1971; 62 : 336-338.
41. Jacobson RR and Hasting RC : Rifampicin resistant leprosy, Lancet, 1976; 2 : 1304-1305.
42. Flouch HA, Rist N and Jacobi JC : Interest in ethionamide in antileprosy therapy, Bull Soc Path Exot, 1966; 59 : 715. (Abstract) Intern J Leprosy 1968; 36 : 108.
43. Pattyn SR, Rollier MT, Rollier R et al : Sensibilite Envers la Dapsone, la sulphamethoxapyridazine et l 'Ethionamide, de *M. leprae*, Intern J Leprosy, 1975; 43 : 356-363.
44. Pattyn SR : Further data on the effect of prothionamide and ethionamide in experimental leprosy, Leprosy Rev, 1978; 49 : 199-202.
45. Colston MJ, Ellard GA and Gammon PT : Drugs for combined therapy, experimental studies on the antileprosy activity of ethionamide and prothionamide and general review, Leprosy Rev, 1978; 49 : 115-126.
46. World Health Organization Expert Committee on Leprosy : Chemotherapy of leprosy for control programmes, WHO Technical Report Series, No. 675, 1982.
47. Colston MJ and Hilson GRF : The activity of thiacetazone, thiambutosine and thiocarlide in the chemotherapy of experimental leprosy, Intern J Leprosy, 1976; 44 : 123-126.
48. Rees RJW : Studies on drug resistance in leprosy using the mouse foot pad infection, Intern J Leprosy, 1968; 36 : 650.
49. Waters MFR, Rees RJW, McDougall AC et al : Ten years of dapsone in lepromatous leprosy, Clinical, bacteriological and histological assessment and the findings of viable leprosy, bacilli, Leprosy Rev, 1974; 45 : 288-298.
50. Rees RJW, Waters MFR, Person JMH et al : Long term treatment of dapsone resistant leprosy with rifampicin. Clinical and bacteriological studies, Intern J Leprosy, 1976; 44 : 159-169.
51. Gelber RH, Waters MFR, Pearson JMH et al : Dapsone alone compared with dapsone plus rifampicin in short term therapy of lepromatous leprosy, Leprosy Rev, 1977; 48 : 223-229.
52. Collier PJ : A study of case holding in leprosy patients in Asia, based on duration of treatment, 1976-80, Leprosy Rev, 1983; 54 : 89-94.
53. Cochrane RG, Ramanujam K, Paul H et al : Two and a half years experimental work on the sulfone group of drugs, Leprosy Rev, 1949; 20 : 4-16.
54. Shepard CC : A kinetic method for the study of activity of drugs against *M. leprae* in mice, Intern J Leprosy, 1967; 35 : 429-435.
55. Rosenfeld M, Freerksen JP, Retzlasff E et al : New results in chemotherapy of mycobacteriosis, Intern J Leprosy, 1971; 39 : 358-360.
56. Shepard CC : Combination of drugs against *M. leprae* studied in mice, Intern J Leprosy, 1972; 40 : 33-39.
57. Freerksen E : Preliminary experience with combined therapy using rifampicin and isoprodian, Leprosy Rev, 1975; 46 : 161-165.
58. Gatti JC : Combined therapy in leprosy, Leprosy Rev, 1975; 46 : 155-159.
59. Aschhoff M : Treatment of leprosy with rifampicin and isoprodian in 38 patients at St. Thomas Hospital, Chetput, South India, Leprosy Rev, 1975; 46 : 173.
60. Innami S, Leguizamon OR and Alvarenga AE : Clinical and bacteriological effects of rifampicin in combination with L73A in leprosy. Observation for 6 months, Leprosy Rev, 1975; 46 : 169-172.
61. Vomstein E : Preliminary report of a drug trial conducted at leprosy relief rural centre Chettipatty, South India, Leprosy Rev, 1975; 46 : 207-211.
62. Ghosh S, Hazra SK, Kundu S et al : Clinical trial with rifampicin in the treatment of leprosy, Leprosy India, 1976; 48 : 775-780.
63. Shepard CC : Combinations involving dapsone, rifampicin, clofazimine and ethionamide in the treatment of *M. leprae* infections in mice, Intern J Leprosy, 1976; 44 : 135.
64. Pattyn SR : The strategy of leprosy treatment : a personal view, Ann Soc Belg Med Trop, 1980; 60 : 253-262.
65. Opromolla DVA, Tonello CJS, McDougall AC et al : A controlled trial to compare the therapeutic effects of dapsone in combination with daily or once monthly rifampicin in patients with lepromatous leprosy, Intern J Leprosy, 1981; 49 : 393-397.
66. Girdhar BK, Sreevatsa and Desikan KV : Intermittent rifampicin therapy in lepromatous leprosy, Leprosy India, 1980; 52 : 89-96.
67. WHO document (unpublished) : TDR/THELEP-SWG(3)/80 : 3 Report of the 3rd meeting of the Scientific Working Group on the Chemotherapy of Leprosy, Geneva, 1980; 20-22. (Quoted by Waters 1983).
68. Warndorff J, Bourland J and Pattyn SR : Follow-up on short course two month rifampicin treatment of paucibacillary leprosy, Leprosy Rev, 1982; 53 : 9-16.