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Leprosy treatment in Nepal with multidrug regimens

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Summary New multidrug treatment regimens have recently been recommended for use in Leprosy Control Programmes by the World Health Organization. This study was performed at Green Pastures Leprosy Hospital, Pokhara, Nepal where multidrug regimens have been in use for seven months. It was aimed at detecting problems resulting from the introduction of the new treatment.

No major difficulties with the use of multidrug regimens for leprosy treatment have been encountered, although several initial practical problems have arisen which may easily be remedied.

This study has failed to detect any significant side-effects associated with the use of multidrug regimens. Furthermore, few leprosy 'reactions' during multidrug treatment regimens have been reported.

Introduction

In the last 5 years it has become apparent that there are several problems with chemotherapy for leprosy control. An increasing number of cases of primary and secondary dapsone resistance have been reported in addition to problems with bacterial persistence after long periods of treatment.[1]

In order to resolve these problems, the World Health Organization (WHO) convened a Study Group in Geneva in October 1981. As a result of the meeting, a report on the 'Chemotherapy of Leprosy for Control Programmes' was produced in early 1982.[2] The report recommends multidrug regimens (MDR) for the treatment of all types of leprosy.

In November 1981 the 'Second National Workshop on Leprosy Control' was initiated by Dr Adigia (Chief of Leprosy Services in Nepal). Multidrug regimens were devised for The National Leprosy Control Project based on the WHO recommendations.[3] Introduction of the new regimens was begun in 1982 with the intention of extending MDR treatment to all areas within 2 years. The aims are: to eradicate leprosy as soon as possible; to limit the time of treatment and infectivity; and to avoid the dangers of drug resistance.

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This is a vast undertaking. Nepal has an estimated 100,000 leprosy patients with relatively high prevalence rates of primary and secondary dapsone resistance.[4]

The first phase of the introduction in the Western region of Nepal began at Green Pastures Leprosy Hospital, Pokhara in April 1982. This hospital acts as a major regional referral centre for Western Nepal and undertakes outpatient treatment of leprosy patients who choose Green Pastures Leprosy Hospital as their treatment centre. It is run by the International Nepal Fellowship, which has been involved in the National Leprosy Control Project in Western Nepal since 1975.[5]

Three months after the MDR was introduced at Green Pastures Leprosy Hospital a standing order containing a well-defined protocol was produced for use under field conditions. This is available in both English and Nepali.[6] Details of multidrug regimens used in Nepal are given in Table 1.

Table 1. Details of multidrug regimens used in Nepal

Multibacillary			
First choice	Adults	Daily	100 mg dapsone
			50 mg clofazimine
		Monthly	600 mg rifampicin
			300 mg clofazimine
	Children and adults		< 35 kg
		Daily	50 mg dapsone
			50 mg clofazimine
		Monthly	300 mg rifampicin
Second choice	Adults	Daily	2 tablets isoprodian
		Monthly	600 mg rifampicin
Paucibacillary			
First choice	Adults	Daily	100 mg dapsone
		Monthly	600 mg rifampicin
	Children and adults	< 35 kg	
		Daily	50 mg dapsone
		Monthly	300 mg rifampicin

The WHO report encourages continuous measurement of progress and periodic assessment by independent teams. As an elective Medical Student based at Green Pastures Leprosy Hospital from October to December 1982, I was able to perform this study as an outside observer during my daily work in the hospital. At this time the MDR had been in operation for 7 months at the hospital and had also been recently introduced in 4 other districts, 2 in the Western region and 2 in the Mid-western region of Nepal.

Materials and methods

The study was carried out at Green Pastures Leprosy Hospital, Pokhara, Nepal on all patients from the Kaski District (the area immediately surrounding the hospital) who attend the Outpatients Department for their leprosy treatment. Information was gathered from the following 3 sources:

A DATA-FORMS

All the notes of leprosy patients in Kaski registered at Green Pastures Leprosy Hospital were reviewed. A data-form was filled in for each patient to extract relevant information about their past leprosy history and current MDR treatment.

B COMPLIANCE STUDY

A study was carried out on those patients taking multibacillary MDR treatment who attended Green Pastures Leprosy Hospital outpatients department during a 6-week period. This regimen includes the drug clofazimine (lamprene) which causes skin coloration. A form was completed for each patient indicating whether clofazimine skin coloration was present or not. This was assessed by Nepali paramedical workers who are experienced in observing skin colour.

C OBSERVATIONS

During my 8 weeks at Green Pastures Leprosy Hospital I was able to observe the management of inpatients and outpatients who were receiving MDR treatment.

Results

The data-forms, results of the compliance study and observations were evaluated, enabling the following results to be extracted.

A GENERAL STATISTICS (Table 2)

In Kaski, 73% of patients attending Green Pastures Leprosy Hospital are now receiving MDR treatment. Of those who are not, the majority were given more than 6-month supplies of dapsone treatment (according to the old regimen[7]) in the 6 months preceding the introduction of MDR. (In Nepal it is sometimes necessary to give large supplies of drugs to patients who live many days walking distance from the hospital.) These patients will eventually be started on MDR treatment. There are a number of patients who have not been started on the MDR

because they have defaulted. Four patients (2 paucibacillary and 2 multibacillary cases) have refused to start the MDR. Three of these patients were very old, infirm and unable to walk well, so would have had difficulty in attending for their supplies of drugs. The fourth patient had a history of poor compliance and at the same time refused admission for an infected ulcer because of a 'bad home situation'. These 4 patients were all continued on the old treatment regimens and given 6- or 12-month supplies of dapsone to take away.

Only 4 patients were unable to start the MDR because they had one of the conditions listed in the standing order exempting them from starting. They were all suffering from tuberculosis.

Table 2. General analysis of patients in the study

	Male	Female	Total
No. of patients registered in Kaski	239	111	350
No. of patients on MDR	172	83	255
No. of patients on multibacillary MDR	95	34	129
No. of patients on paucibacillary MDR	77	49	126

B PAST LEPROSY HISTORY (Table 3)

The majority of patients started on the MDR are old cases previously treated on the old regimens. Forty-four per cent of multibacillary cases and 36% of paucibacillary cases have been registered for more than ten years. It seems likely that among the paucibacillary cases on treatment for over 10 years there may be some patients who should have been released from control and never started on

Table 3. Past leprosy history of patients on the multidrug regimen

No. of years registered	Multibacillary	Paucibacillary
New cases	5	16
1–5	37	43
6–10	28	19
11–15	33	21
16–20	15	23
21+	9	1
?	2	3

the MDR. Unfortunately, at the time of the study no data was collected on the length of inactivity before starting MDR treatment.

C CHOICE OF MULTIDRUG REGIMEN (Table 4)

All the patients on the MDR are on the first choice regimens. In the standing order it is emphasized that the second choice multibacillary MDR regimen should only be used for those who refuse to take clofazimine. When MDR treatment was commenced in Western Nepal a second choice regimen without clofazimine was included because no data was available on the acceptability of clofazimine skin coloration to Nepali leprosy patients. However, the first choice regimen is

Table 4. Numbers of patients for each choice of multidrug regimen

	Multibacillary		Paucibacillary
	First choice regimen	Second choice regimen	First choice regimen
Adults	126	0	125
Children	3	0	1
Adults < 35 kg	0	0	0

preferable. In fact, 5 patients in this study refused to continue taking clofazimine. They had been taking clofazimine for 2–4 months as part of the MDR. One patient had been on the MDR for 3 months, but was noted not to show clofazimine skin coloration. In the case of 3 of these patients MDR treatment was stopped and dapsone treatment according to the old regimen was started. The other 2 patients were transferred to the paucibacillary regimen as their disease had been inactive for over 10 years. It was decided not to offer these patients the second choice regimen. If it became public knowledge that alternative treatment without clofazimine was available, an unacceptably large number of patients might demand to be put on the second choice regimen.

D DURATION OF MULTIDRUG REGIMEN TREATMENT (Table 5)

A total of 35 patients have been released from the paucibacillary MDR after completing the full course of treatment (twenty-eight per cent of the total number

Table 5. Details of duration of multidrug regimen treatment

Number of months on MDR	Multibacillary	Paucibacillary
1	3	11
2	2	14
3	9	12
4	19	13
5	22	25
6	23	16
7	46	
8	4	35
9	—	(released from treatment)
10	1	

number on the paucibacillary regimen.) Of these, 26 were released at least a month before this study took place. Eight patients had been released from treatment on the date of their last supervised dose of rifampicin when they were given a further month's supply of daily dapsone. It states clearly in the standing order that patients should be released only on completion of the full course of daily drugs. No smears or examinations were performed on release from treatment, as demanded by the standing order. These will take place at the time of the patient's next annual examination.

E COMPLIANCE (Table 6)

The data on compliance extracted from the data-forms suggests that attendance may be slightly better for MDR treatment compared to the old regimens. Unfortunately the numbers are too small to draw any definite conclusions; however the figures obtained indicate that of those who were poor attenders for the old regimen, 54% continue to be so for the MDR.

The most common reason for missed once-monthly doses of MDR treatment is illness, in particular foot ulcers, which may make travel difficult. Some patients were unable to attend because of social problems or a 'bad home situation'. Others could not attend as they had to travel out of the area.

In addition it was noted that 10 patients were late for treatment because they said they were still taking their daily dapsone and did not need further supplies. Some admitted obtaining dapsone from other sources (often a friend or relative) but it seems likely that many of these patients had not taken their dapsone daily. Conversely, patients returned early to collect their MDR treatment because they

Table 6. Comparison between regularity of monthly attendance for treatment in patients changed from old regimen to MDR

	Old regimen	MDR
No. of patients with > 75% regularity	178	192
No. of patients with < 75% regularity	37	23

$$\text{Regularity} = \frac{\text{No. of months attended for treatment}}{\text{Total No. of months treatment possible}} \times 100\%$$

Total number of patients (215) excludes new cases, those with incomplete notes and those who withdrew from MDR because of clofazimine skin coloration.

had 'lost' their medicine. One patient returned early for this reason in 3 consecutive months. He was probably an unreliable character but the possibility does exist that he was selling his supplies.

The compliance study for patients on the multibacillary MDR attending outpatients showed that 98% of patients had clofazimine skin coloration and were therefore assumed to be taking their medicine regularly. This is a subjective method of measuring compliance, but these results do indicate that no major problems with poor compliance may be expected.

F UNSUPERVISED DOSES (Table 7)

In the standing order it states that at least half of the once-monthly drugs should be given under supervision. (This is not in accordance with the WHO report which recommends full supervision. However, the inaccessibility of many regions in Nepal renders it necessary to allow unsupervised doses to be given under field conditions where patients may have to walk for many days to collect treatment.) At any one clinic attendance no more than 2 doses of monthly drugs should be given, one as a supervised dose then, and another unsupervised dose for the following month. No more than one unsupervised dose should be given consecutively—if a patient cannot attend once every 2 months, then he should be continued on daily drugs only and the treatment period prolonged until he is able to attend for the required number of once-monthly supervised doses.

Many patients were given one dose of unsupervised once-monthly drugs and this was occasionally collected by a proxy (usually a close relative). However 9

Table 7. Supervision of once-monthly drugs

Number of unsupervised doses during 7 months of MDR treatment	Multibacillary	Paucibacillary
1	54	49
2	21	18
3	4	9
4	6	1
5	3	2
6	—	—

patients on the multibacillary MDR and 3 patients on the paucibacillary MDR were given more than 3 of their requisite 6 monthly doses unsupervised.

G LEPROSY 'REACTIONS' DURING MDR TREATMENT (Table 8)

No leprosy 'reactions' occurred in patients on the paucibacillary MDR. Six patients on the multibacillary MDR (5% of those receiving multibacillary treatment) suffered reactions; 4 were reversal reactions and 2 were ENL reactions. Four of these patients had had previous reactions on the old regimen, one had had none on the old regimen and another patient was a new case.

From these initial observations it appears that very few patients have suffered 'reactions' during MDR treatment.

Table 8. Occurrence of leprosy 'reactions' during MDR treatment

	Type of leprosy	Type of reaction	Month of MDR treatment reaction occurred	Previous reactions on old regimen
1	BL	Reversal reaction	1	Reversal reaction and ENLs. (Possibly dapsone resistant.)
2	BL	Reversal reaction	4–6	Reversal reaction
3	L	Mild ENL	1–2	Recurrent ENLs
4	L	Reversal reaction	3–4	Recurrent ENLs
5	BL	Reversal reaction	1–2	New case
6	L	Severe ENL	1–3	None previously

ENL = erythema nodosum leprosum

H SIDE-EFFECTS OF MDR TREATMENT (Table 9)

During the 7 months since the introduction of the MDR no major side-effects have been reported and no patients have had their MDR treatment halted because of side-effects. There have been 7 cases of 'flu syndrome possibly attributed to rifampicin treatment. However several of these cases coincided with a 'flu epidemic in the area and it is impossible to directly attribute such symptoms to MDR treatment. Eight patients complained of non-specific abdominal symptoms for which no obvious cause was detected on examination or investigation. It must again be stated that this is a common complaint in Nepal and impossible to attribute directly to MDR treatment. One patient complained that dapsone made him 'feel bad'. In all of these patients their problems were relieved with symptomatic treatment.

Table 9. Side-effects of MDR treatment

	Multibacillary	Paucibacillary
? 'Flu syndrome		
First month of treatment	3	3
Second month of treatment	—	1
Unexplained abdominal symptoms		
First month of treatment	3	1
Second month of treatment	3	1
Third month of treatment	1	—
Others		
Dapsone made him 'feel bad'	—	1

Discussion

It must be emphasized that this study had many limitations. Most of the data was collected from patients' notes which may not be complete, although the standard of note keeping appeared to be very high. The study was conducted over a limited time period by someone inexperienced in leprosy and unable to speak Nepali. It was performed in addition to daily responsibilities in the hospital, which was without a resident doctor during this time.

The overall findings of the study are that the introduction of the WHO MDR at Green Pastures Leprosy Hospital for patients in the Kaski District has been a well planned and executed undertaking. There have been very few problems so far with the operation of the new regimens. I was very impressed with how efficiently MDR treatment is carried out, especially since the MDR is complex compared to

the old regimens, with a far more demanding workload on medical and paramedical staff.

The problems that have arisen are mostly related to the uncertainties associated with the introduction of the regimens before the standing order was produced. The standing order was designed for use under field conditions and not specifically for use at Green Pastures Leprosy Hospital. In addition there have been several changeovers of Nepali paramedical staff and expatriate medical staff during the introductory period. They are all relatively minor problems and may be overcome with ease as the paramedical and medical workers involved become more familiar and experienced with using the MDR.

This study was not aimed at evaluating the effectiveness of MDR treatment in the control of leprosy. This is a task which will have to be performed later when the MDR has been running for a longer period of time. However, it is significant that in the seven months the MDR has been in operation, no major side-effects have occurred. In addition, very few leprosy 'reactions' have been seen in patients on the MDR. It is hoped that the introduction of the MDR to all treatment areas over the next 2 years will continue, subject to availability of the necessary drugs and trained personnel.

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