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Feasibility of Multidrug Therapy (MDT) in Hansen's Disease in an Urban Population—Curupaiti State Hospital, Rio de Janeiro, Brazil[1]

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Curupaiti State Hospital is located in the urban zone of Rio de Janeiro, Brazil, in the borough of Jacarepaguá, and is one of the two hospitals specialized in Hansen's disease of the State Health Secretariat. In 1982, the old Curupaiti Colony was divided into the Jacarepaguá Community Institute (700 residents) and the Curupaiti State Hospital (150 beds) designated for the treatment of clinical and surgical problems and severe reactions of Hansen's disease patients from the health centers and posts from both the municipality and state of Rio de Janeiro.

A multidrug therapy (MDT) (WHO regimen) feasibility study was begun in 1983 at the hospital to assess the practicability of the WHO recommended regimens ([18]) and to examine the acceptability of the proposed scheme to the patients.

MATERIALS AND METHODS

Patients. From September 1983 to December 1985, 171 multibacillary patients were put on the WHO regimen—46 of them were previously untreated patients and 125 had previously been treated with rifampin 600 mg daily for the first 3 months and dapsone 100 mg daily throughout the regimen. There were 22 multibacillary cases who had previously received dapsone monotherapy, and these patients were put on an alternative therapeutic scheme using four drugs. The 27 paucibacillary patients included in the study received the WHO regimen; 14 of them were previously untreated and 13 had previously been under dapsone monotherapy.

Of the 220 patients included in this study, 60 are residents of the Jacarepaguá Community Institute and 160 reside in either the municipality or the state of Rio de Janeiro. The patients' homes range from 18 to 130 kilometers from the outpatient clinic at the hospital where patients come spontaneously to receive MDT for Hansen's disease.

Methodology. In the preparatory phase of the study a 1-week training course was organized for the health workers responsible for the development of the project. To ensure patient control, it was necessary to introduce a data registration system. A technical and administrative reorganization of the outpatient clinic was carried out during the course of the study.

The basic aspects of Hansen's disease—the names of the drugs; a therapy chart; special care of hands, feet, and eyes; the likelihood of reactional episodes; and the importance of members of the family coming for contact screening—were passed on to all of the patients.

The differentiation between multibacillary and paucibacillary patients was made in accordance with the following criteria: a) Patients previously untreated and clinically classified as L or B, according to the Madrid classification, showing acid-fast bacilli (AFB) in at least one smear were considered multibacillary. Indeterminate cases with a negative lepromin reaction were also considered multibacillary ([17]). b) Paucibacillary cases included tuberculoid and indeterminate patients who were lepromin positive with the absence of AFB in all smears. Lepromin negativity was defined as ≤ 5 mm diameter induration at the skin test sites 4 weeks after the intradermal injection of in-

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tegral lepromin A, 0.1 ml containing 4.0×10^6 heat-killed *M. leprae*. Lepromin positivity was induration >5 mm in diameter.

The 158 multibacillary patients were put on a course of 24 doses in 24 months or until becoming bacteriologically negative, using a monthly supervised dose of rifampin 600 mg, clofazimine 300 mg, and dapsone 100 mg plus a daily dose of dapsone 100 mg and every other day clofazimine 100 mg, self-administered. The paucibacillary cases were given a 6-month treatment with monthly supervised doses of rifampin 600 mg plus dapsone 100 mg daily, self-administered.

A single 100 mg tablet of dapsone was also included in the supervised administration of the adopted regimens in an attempt to win back its credibility, in accordance with the technique used by Rose (Rose, P., unpublished observations, 1981).

Prothionamide or ethionamide was added to the regimens of the 22 multibacillary patients who had been on dapsone monotherapy for more than 5 years and who were still bacteriologically positive. The regimen utilized was: rifampin 600 mg/month plus clofazimine 300 mg/month, both taken under supervision, plus clofazimine 100 mg on alternate days, ethionamide or prothionamide 250 mg/day and dapsone 100 mg/day, self-administered. In 13 multibacillary cases, ethionamide or prothionamide was used to substitute for either clofazimine or dapsone. In four paucibacillary patients it was necessary to substitute clofazimine for dapsone (Table 1).

The patients came to the outpatient clinic once a month for a prearranged consultation, to take the supervised doses, to collect their month's supply of drugs for self-administration, and to undergo a clinical checkup. Patients in reaction and under treatment with prednisolone underwent a clinical evaluation every week for the first month of therapy and subsequently once a month. In addition, the patients were advised to come to the clinic should there be any change in their clinical state. After completing the period of supervised therapy, the patients underwent systematic examination every 6 months.

All patients were subjected to slit-skin smear examination before treatment and subsequently at 6-month intervals using the Leiker-McDougall method ([12]). Laboratory tests were carried out at the beginning of treatment and subsequently at 6-month intervals or whenever clinically indicated in accordance with signs or symptoms. These examinations included: transaminases (SGOT/SGPT), bilirubin, alkaline phosphatase, prothrombin time, urea, creatinine, glucose, cholesterol, hemogram, erythrocyte sedimentation rate (ESR), fecal parasitology, urinalysis, and in fertile females, an immunological test for pregnancy.

When during treatment a transaminase serum level of more than twice the limit of normal (SGOT 72 IU and SGPT 64 IU) was found the tests were repeated every month. Australian antigen testing was not done. Liver function tests were performed with kits from various laboratories.

Patient regularity was measured by appearance at the pre-arranged appointments for supervised medication. Reasons given for the failure to appear at these consultations on the arranged date were evaluated, as well as the causes for abandonment of treatment.

RESULTS

Table 2 shows the main characteristics of the study group. Among the 220 patients, 13 (5.9%) were under 15 years of age. There were 77 women and 143 men whose average age was 32.7 years. The proportion of male patients was 2:1.

Two paucibacillary (PB) and 151 multibacillary (MB) patients are still under treatment, 43 patients (23 PB and 20 MB) completed the prescribed treatment, and 23 patients (10.5%) abandoned therapy. Seven of these 23 patients refused treatment for the most part due to the high number of tablets and capsules to be taken. Other reasons given were: transfer to a health center nearer home = 4; pregnancy = 1; lack of faith in the treatment = 2; refusal without citing a reason = 3; family not knowing the whereabouts of the patient = 1; under treatment at a spiritualist center = 1; alcoholism = 2; tuberculosis during the course of MDT = 1; impossibility of transport to and from clinic = 1.

There was one death in the group, an elderly patient on prednisolone. The cause of death given by the autopsy was necrohem-

TABLE 1. *Multidrug regimens used.*

	Regimens	Patients		Total
		Multi-bacillary	Pauci-bacillary	
1[a]	RMP[b] 600 mg, CLO[c] 300 mg, DDS[d] 100 mg } monthly, supervised + CLO 100 mg every other day, DDS 100 mg daily } self-administered	158	—	158
2[a]	RMP 600 mg monthly, supervised DDS 100 mg daily, self-administered	—	23	23
3	RMP 600 mg monthly, supervised CLO 100 mg monthly, supervised ETH[e] 250 mg daily, self-administered DDS 100 mg daily, self-administered CLO 100 mg every other day, self-administered	22	—	22
4	RMP 600 mg monthly, supervised ETH 250 mg daily, self-administered + A third drug (dapsone or clofazimine)	13	—	13
5	RMP 600 mg monthly, supervised CLO 100 mg every other day, self-administered	—	4	4

[a] WHO standard regimens.
[b] RMP = rifampin.
[c] CLO = clofazimine.
[d] DDS = dapsone.
[e] ETH = ethionamide.

orrhagic pancreatitis, apparently without relation to Hansen's disease.

Of the 169 patients who started treatment with the WHO multibacillary regimen, 8 (4.7%) rejected clofazimine due to the cutaneous hyperpigmentation; 6 of these patients were of mixed race. Of the group, 100 (45.4%) were Caucasian and 40 (22.3%) were Negro.

There was cutaneous allergic reaction to dapsone in 6 patients; in 3 multibacillary patients ethionamide was used in place of dapsone, and in 3 paucibacillary patients we substituted clofazimine. One paucibacillary patient was found to have methemoglobinemia, and continued the treatment with clofazimine.

Of the 196 (89%) patients under control, 3 paucibacillary patients experienced type 1 reaction; 2 during the therapeutic course and 1 began treatment in reaction. Of the multibacillary patients, 56 (32.7%) commenced treatment with a reactional episode, while 55 (32.1%) experienced reactional episodes during treatment (Table 3).

Of the total of 57 patients who began MDT in a reactional state and the 57 who experienced reactions during MDT, the percentages of old cases were 79% and 80.7%, respectively.

The side effects of therapy among the total number of patients in the group included five complaints of epigastralgia and 12 ep-

TABLE 2. *Main characteristics of cases included in MDT study group.*

Category	Patients		Total
	Multi-bacillary	Pauci-bacillary	
No. patients at start	193	27	220
Males			
No.	131	12	143
Age mean (median)	33.9 (39)	27.4 (27)	
Females			
No.	62	15	77
Age mean (median)	32.4 (32.5)	28.1 (27)	
Completed treatment	20	23	43
Excluded from study	22[a]	2	24

[a] Includes one death.

TABLE 3. *Patients with reactions.*

Classification	Began MDT with reaction		Had reaction during MDT		Had no reaction		Total	
	No.	%	No.	%	No.	%	No.	%
Paucibacillary	1	4.0	2	8.0	22	88.0	25	12.8
Multibacillary	56	32.7	55	32.1	60	35.0	171	87.2
Totals	57	29.0	57	29.0	82	41.8	196	100.0

isodes of nausea and/or heartburn. There was no indication for the withdrawal or the substitution of any one drug, and all of these problems were solved by symptomatic treatment.

Of the 196 patients, 54 (27.6%) showed alterations in their liver function tests. Other than 8 (4.1%) who presented with jaundice, the values were never found to be more than twice the standard norms, and the therapeutic regimen was maintained in a majority of cases ([2]), results of subsequent tests being within normal parameters.

Patient regularity on the WHO regimens (Table 4) was greater than 80% for both multibacillary and paucibacillary patients.

It is worthwhile pointing out the importance of contact examinations through which 21 (35%) of the total of new cases were diagnosed. Two cases came to the clinic as a result of the health education program.

DISCUSSION

The experience of the Curupaiti State Hospital demonstrates that in practice the introduction of multidrug therapy in Hansen's disease does not only involve the introduction in itself of a therapeutic regimen. Other strategic elements must comprise basic control activities ([14]), such as: complete upgrading of medical personnel and health workers; standardization of bacilloscopic examination; establishment of a service of prevention of deformities by simple techniques; provisions, availability, and systems of distribution and storage of drugs utilized; an organized data reporting system; implementation of health education activities; and rigorous post-therapeutic follow-up of patients—all of which are essential for the successful outcome of the proposed program.

We believe that the supervised dose not only guarantees the monthly return of the patients but also acts as a direct incentive for their commitment to the treatment.

In the official therapeutic regimen in this country, rifampin is self-administered. As well as guaranteeing its efficiency ([13]), the use of rifampin in a supervised dose has the advantage of avoiding the emergence of rifampin-resistant pockets ([4–6]) and avoids its improper use for other pathologies, a common occurrence in our services.

The acceptability of MDT, as measured by patient regularity in attendance for previously arranged supervised doses, was excellent for a metropolis such as Rio de Janeiro. These results are similar to those obtained by Rose (unpublished observations, 1981), Keeler ([10]), Birch ([1]), and Kaur, *et al.* ([9]).

The acceptance of the treatment is due mainly to the support of activities such as

TABLE 4. *Regularity to WHO MDT scheme.*

Classification	Regular[a]		Irregular[b]		Excluded[c]		Total	
	No.	%	No.	%	No.	%	No.	%
Paucibacillary	24	88.8	1	3.7	2	7.4	27	100
Multibacillary	162	84.0	9	4.6	22[d]	11.3	193	100
Totals	186	84.5	10	4.5	24	11.0	220	100

[a] Regular = patients who took >90% of prescribed supervised doses.
[b] Irregular = patients who took 50%–89% of prescribed supervised doses.
[c] Excluded = patients who took <50% of prescribed doses.
[d] Includes one death.

prevention and treatment of disabilities. This is because the Hansen's disease patients consider "treatment" as the resolution of these problems and the mere ingestion of drugs does not put to rest these concerns.

The large number of patients who accepted clofazimine does not agree with the findings of several specialists in this country. We believe that the relationship established between the patients and the health professionals and the emphasis on the importance of effectiveness on both their parts is one of the crucial factors in avoiding the rejection of the hyperpigmentation brought about by the clofazimine.

As far as the presentation of reactional episodes during MDT is concerned, our observations would seem to indicate that the therapeutic regimen did not contribute to their occurrence: We did not observe any aggravation of episodes, which is similar to the findings in Trinidad and Tobago by Keeler ([10]).

When WHO presented the proposals for MDT in 1982, we asked: Will the Hansen's disease patient accept being medicated under monthly supervision? The results obtained to date respond to this question in the affirmative.

SUMMARY

The acceptance of the WHO regimen in a group of 220 patients was approximately 84.5%. Only 11% abandoned the treatment, and the substitution of ethionamide or prothionamide for clofazimine due to excessive hyperpigmentation was necessary in only eight cases.

The WHO regimens adopted provided a more frequent (monthly) relationship between the patients and their health service. It was necessary to: a) reorganize the technical-administrative infrastructure, with the intention of providing an improved service to the patients for treatment and control; and b) pay more attention to the problem of deformities and health education activities.

As for the side effects of the drugs, 54 patients showed alterations in their liver function tests, which were usually mild and which resolved despite continuation of the treatment.

Of the reactional episodes observed during MDT, it would not appear that the therapeutic regimens contributed to their occurrence or aggravation.

RESUMEN

La aceptación del esquema de tratamiento propuesto por la OMS en un grupo de 220 pacientes fue de aproximadamente el 84.5%. Solo 11% de los pacientes abandonaron el tratamiento y la substitución de la clofazimina por etionamida o protionamida solo fue necesaria en 8 casos debido a una hiperpigmentación excesiva.

El esquema de la OMS adoptado, permitió una relación más frecuente (mensual) entre los pacientes y sus Servicios de Salud. Para el estudio, fue necesario: (a) reorganizar la infraestructura técnica-administrativa con objeto de mejorar el tratamiento y control de los pacientes, y (b) poner más atención al problema de las deformidades y a las actividades de educación sanitaria.

En cuanto a los efectos colaterales de las drogas, 54 pacientes mostraron alteraciones en sus pruebas de función hepática, pero éstas fueron moderadas y se resolvieron no obstante la continuación del tratamiento.

De los episodios reaccionales observados durante el estudio, no hubieron evidencias de que los regímenes terapeúticos contribuyeran a su ocurrencia o agravamiento.

RÉSUMÉ

Le schéma de traitement prescrit par l'OMS s'est révélé acceptable chez 80,5%, parmi 220 malades. Onze pour cent seulement ont abandonné ce traitement. Chez huit cas seulement on a du remplacer la clofazimine par l'éthionamide ou la prothionamide, par suite d'une hyperpygmentation excessive.

Les schémas de l'OMS qui avaient été adoptés ont permis un contact plus fréquent, mensuel, entre les malades et les services de santé. Il a cependant été nécessaire d'abord de réorganiser l'infrastructure technique et administrative, afin de proposer un service amélioré aux malades en ce qui concerne la traitement et la lutte contre la lèpre. De plus, il a fallu accorder plus d'attention au problème des difformités, ainsi qu'aux activités d'éducation pour la santé.

En ce qui regarde les effets secondaires des médicaments, 54 malades ont montré des altérations dans les épreuves fonctionnelles hépatiques. Ces altérations étaient habituellement légères; elles se sont estompées, et ceci même alors que la traitement était poursuivi.

Quant aux épisodes réactionnels observés au cours de la polychimiothérapie, il ne semble pas que les schémas thérapeutiques aient contribué à leur apparition et à leur aggravation.

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