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Pyrazinamide as a Part of Combination Therapy for BL and LL Patients—a Preliminary Report[1]

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Leprosy is a chronic disease, and persister bacilli are known to exist even after several years of chemotherapy ([10, 11, 13, 18]). In tuberculosis, these persister organisms can be effectively sterilized by combining pyrazinamide with other antitubercular bactericidal drugs, and it cuts short the duration of the treatment remarkably ([4, 8, 16]). Shepard and Chang ([14]) reported no inhibitory effect of pyrazinamide on *Mycobacterium leprae* multiplication in the mouse foot pad model when the drug was tried alone. But results in mice cannot always be directly extrapolated to humans. Clofazimine inhibited the growth of *M. tuberculosis* in the mouse model ([6, 17]) but, unfortunately, had no effect in human tuberculosis ([2]). However, there is no experimental data on pyrazinamide in which it has been used in combination with other bactericidal drugs especially to see its effect on prevention and eradication of persisters. Leprosy and tuberculosis have several aspects in common. In both, the bacillary populations are numerous and both have persister bacilli ([1]). Pyrazinamide has been reported to inhibit tubercle bacilli directly as well as through its metabolites, and it acts in the acidic environment of macrophages ([19]). Since *M. leprae* resides mainly in the macrophage, it would be of interest to see pyrazinamide's effect in human leprosy.

PATIENTS AND METHODS

Untreated borderline lepromatous (BL) and lepromatous leprosy (LL) patients who attended the outpatient department of Central JALMA Institute in Agra, India, and who were willing to be admitted for the first 2 months of therapy were included in the study. The patients were allotted to each of the first six regimens detailed below. Due to a misunderstanding, the patients were not randomized among the various regimens. Intake to one regimen was completed, followed by intake into another regimen, and so on. Patients were not selected for inclusion in any regimen but were allocated in the order of their arrival at the Institute's outpatient department. Intake of patients in regimens VII and VIII was done earlier than intake into regimens I through VI.

Regimen I. Dapsone (D) + rifampin (R) + pyrazinamide (P): Dapsone 100 mg daily until the skin smears became negative for acid-fast bacilli. Rifampin 450 mg daily for

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the first 2 months only. Pyrazinamide 1500 mg daily for the first 2 months only.

Regimen II. Dapsone (D) + clofazimine (C) + pyrazinamide (P): Dapsone 100 mg daily until the smears became negative. Clofazimine 100 mg daily for the first 2 months only. Pyrazinamide 1500 mg daily for the first 2 months only.

Regimen III. Dapsone (D) + isoniazid (I) + thiacetazone (T) + pyrazinamide (P): Dapsone 100 mg daily until the smears became negative. Isoniazid 300 mg daily until the smears became negative. Thiacetazone 150 mg daily until the smears became negative. Pyrazinamide 1500 mg daily for the first 2 months only.

Regimen IV. Dapsone (D) + pyrazinamide (P): Dapsone 100 mg daily until the smears became negative. Pyrazinamide 1500 mg daily for the first 2 months only.

For comparison, controls without pyrazinamide but on the same drug schedule as detailed above were also included.

Regimen V. Dapsone (D) + rifampin (R): Dapsone 100 mg daily until the smears became negative. Rifampin 450 mg daily for the first 2 months only.

Regimen VI. Dapsone (D) + clofazimine (C): Dapsone 100 mg daily until the smears became negative. Clofazimine 100 mg daily for the first 2 months only.

Regimen VII. Dapsone (D) + isoniazid (I) + thiacetazone (T): Dapsone 100 mg daily until the smears became negative. Isoniazid 300 mg daily until the smears became negative. Thiacetazone 150 mg daily until the smears became negative.

Regimen VIII. Dapsone (D): Dapsone 100 mg daily until the smears became negative.

The patients were 15–50 years old. There were 111 male and 3 female patients. All patients were admitted for 2 months for the initial intensive chemotherapy. A complete clinical examination was done on all patients, and the findings were carefully recorded on a body chart along with the clinical score ([9]). Skin smears were taken from four different sites, and the average bacterial index (BI) and morphological index (MI) were calculated and recorded ([12]). A skin biopsy was obtained from the back of each patient, and bacilli per gram of tissue were estimated and recorded. At the beginning of therapy, a hemogram, urinalysis, and liver and kidney function tests were carried out; these were repeated periodically. Drugs were stopped whenever there was evidence of derangement of liver and kidney functions. At the time of discharge after 2 months of intensive therapy, the patients were clinically re-evaluated, clinical score recorded, smears repeated, and a biopsy obtained for count of bacilli. Any side effect of the drugs was carefully noted. Subsequently, these investigations were repeated every year. Clinical examination, however, was carried out at intervals of 2–3 months. At the end of 2 years and between 4 and 5 years of therapy, tissue was obtained from the scrotal skin (areola tissue in females) and injected into the foot pads of normal mice for screening for persisters.

Scrotal biopsies were minced with scissors, homogenized, and suspended in Hanks' balanced salt solution, carrying out all procedures aseptically at low temperature over ice. The large particles were settled by allowing the suspension to stand for 3 min. The supernatant fluid was collected, and the bacterial enumeration was carried out as described by Hart, *et al.* ([5]). A batch of six randomly bred Rockerfeller mice was inoculated. Each hind foot pad was inoculated with 0.03 ml of a suspension containing up to 10^4 bacilli. The inoculated mice were kept at 25°C in an air-conditioned room. Harvests were made every month, beginning at 6 months after inoculation using one mouse at a time by the method described by Desikan and Venkataramaniah ([3]), and the bacilli were counted. A 10-fold increase in the harvest count compared to the inoculum is taken as true multiplication for this study.

RESULTS

The results are detailed in Tables 1–8. A few patients developed anemia, jaundice, and dermatitis; details of these conditions are shown in Table 2.

Multidrug therapy (MDT) was stopped in one patient on regimen I who developed severe anemia. Jaundice developed in two patients on regimen II and one patient on regimen III, and their treatment was stopped. One patient each on regimens III and IV developed a psychosis, and one patient on regimen III developed dermatitis. MDT was stopped in all of these patients until they recovered, and these patients were excluded from the study. In the rest of the

TABLE 1. *Clinical and bacteriological indices of patients for all regimens at start of therapy.*

Regimen[a]	Total no. patients	Avg. clinical score	Avg. BI[b] (range)	Avg. MI[c] (range)	Avg. no. bacilli/g tissue (range)	Type 2 reaction
I (D + R + P)	27	17	3.63 (3–5)	5.14 (0–7)	5.98×10^8 ($4.5–7.74 \times 10^8$)	1
II (D + C + P)	11	15	3.7 (3–5)	7.4 (0–8)	4.36×10^8 ($3.39–7.59 \times 10^8$)	0
III (D + I + T + P)	11	15	3.4 (3–5)	5.1 (0–7)	3.71×10^8 ($2.68–5.65 \times 10^8$)	0
IV (D + P)	14	14	4.6 (3–5.5)	3.25 (0–7)	3.53×10^8 ($2.18–6.21 \times 10^8$)	1
V (D + R)	14	16	3.63 (3–5)	3.13 (0–5)	5.15×10^8 ($2.82–6.67 \times 10^8$)	0
VI (D + C)	12	14	3.16 (3–5.5)	2.9 (0–5)	4.96×10^8 ($3.92–7.82 \times 10^8$)	0
VII (D + I + T)[d]	14	15	2.7[e] (2–3.5)	4 (0–5)	4.55×10^8 ($2.8–6.56 \times 10^8$)	0
VIII (D)[d]	11	14	3.2[e] (2–3.5)	2.75 (0–4)	ND[f]	0

[a] Abbreviations: D = dapsone, R = rifampin, P = pyrazinamide, C = clofazimine, I = isoniazid, T = thiacetazone.
[b] BI = bacterial index.
[c] MI = morphological index.
[d] Intake started earlier.
[e] BI calculated by Dharmendra scale.
[f] ND = not done.

patients, MDT was continued and additional antireaction treatment was also given when necessary.

The BI was calculated by the Ridley-Jopling scale in regimens I–VI and by the Dharmendra scale in regimens VII and VIII. At the time the patients were allotted to regimens VII and VIII, all smears in the outpatient department were read and reported by the Dharmendra scale. Subsequently, all patients were reported by the Ridley-Jopling scale. Table 1 details the bacteriological and clinical status of all of the patients on the different regimens at the start of therapy. The clinical and bacteriological status of the patients on the various regimens appears to be similar.

Two patients had a history of erythema nodosum leprosum (type 2) reaction even before they were put on MDT. Table 3 shows the results 2 months after the intensive therapy when the patients were hospitalized. As seen in Tables 2–5, lepra reaction (type 2) continued to occur, but in no case was treatment stopped because of reaction. Additional antireaction treatment consisting of clofazimine 300 mg or thalidomide 100–300 mg or prednisolone 20–60 mg daily was

TABLE 2. *Number of adverse reactions to MDT during first 2 months of intensive therapy.*

Regimen[a]	Anemia	Hepatitis	Dermatitis	Psychosis	Type 2 reaction
I (D + R + P)	1	0	0	0	3
II (D + C + P)	1	2	0	0	4
III (D + I + T + P)	0	1	1	1	0
IV (D + P)	1	0	0	1	0
V (D + R)	0	0	0	0	0
VI (D + C)	0	0	0	0	0
VII (D + I + T)	0	0	0	0	0
VIII (D)	0	0	0	0	1

[a] Abbreviations: see footnote a in Table 1.

TABLE 3. *Clinical and bacteriological indices of patients for all regimens 2 months after intensive therapy.*

Regimen[a]	Total no. patients	Avg. clinical score	Avg. BI (range)	Avg. MI (range)	Avg. no. bacilli/g tissue (range)	Type 2 reaction
I (D + R + P)	27	12	3.5 (3–5)	1.06 (0–2)	2.97×10^8 ($2.1–4.96 \times 10^8$)	3
II (D + C + P)	11	12	3.7 (3–5)	1.18 (0–2)	2.68×10^8 ($1.92–3.95 \times 10^8$)	4
III (D + I + T + P)	11	11	3.4 (3–5)	1 (0–2)	1.78×10^8 ($1.12–3.02 \times 10^8$)	0
IV (D + P)	14	11.5	3.8 (3–5)	0.75 (0–2)	1.33×10^8 ($0.92–3.58 \times 10^8$)	0
V (D + R)	14	13	3 (3–5)	1.03 (0–2)	1.93×10^8 ($0.96–2.59 \times 10^8$)	0
VI (D + C)	12	13	3.1 (3–5)	1.2 (0–3)	2.68×10^8 ($1.96–4.21 \times 10^8$)	0
VII (D + I + T)	14	12	2.6[b] (2–3.5)	0.65 (0–2)	2.55×10^8 ($2.1–4.37 \times 10^8$)	0
VIII (D)	11	12	2.8[b] (2–3.5)	2.5 (0–3)	ND[c]	1

[a] Abbreviations: see footnote a in Table 1.
[b] BI calculated by Dharmendra scale.
[c] ND = not done.

given in addition to the routine antileprosy treatment. The incidence of reaction was comparatively less in patients who received MDT in contrast to patients who were on dapsone monotherapy. The fall in the BI and counts per gram (ct/g) as seen in Tables 2–4 are nearly the same in all the groups studied. One patient in group II, 2 patients in group VI, and 5 patients in group VIII had solid-staining bacilli in their skin smears even 1 year after institution of therapy (Table 4). Among these patients only one had

TABLE 4. *Clinical and bacteriological indices of patients for all regimens 1 year after intake in the trial.*

Regimen[a]	Total no. patients	Avg. clinical score	Avg. BI (range)	Avg. MI	Avg. no. bacilli/g tissue (range)	Type 2 reaction
I (D + R + P)	27	10	3.14 (3–5)	0	2.04×10^8 ($0.96–2.5 \times 10^8$)	9
II (D + C + P)	11	10	2.4 (2–5)	0.125	0.50×10^8 ($0.22–2.01 \times 10^8$)	4
III (D + I +T + P)	11	10	3 (2.5–5)	0	0.61×10^8 ($0.46–1.96 \times 10^8$)	2
IV (D + P)	14	11	3.2 (2.5–5)	0	0.75×10^8 ($0.43–2.23 \times 10^8$)	3
V (D + R)	14	11	2.7 (2.5–5)	0	1.30×10^8 ($1.25–2.63 \times 10^8$)	3
VI (D + C)	12	11.5	2.7 (2.5–5)	0.6	1.34×10^8 ($0.75–2.55 \times 10^8$)	2
VII (D + I +T)	14	11	2[b] (1.5–4)	0	1.42×10^8 ($0.96–1.95 \times 10^8$)	4
VIII (D)	11	11	2.5[b] (2–4.5)	1.6	ND[c]	8

[a] Abbreviations: see footnote a in Table 1.
[b] BI calculated by Dharmendra scale.
[c] ND = not done.

TABLE 5. *Clinical and bacteriological assessment of patients for all regimens 2 years after intake in the trial.*

Regimen[a]	Total no. patients	Avg. clinical score	Lepra reactions	Avg. BI (range)	Avg. MI	Avg. no. bacilli/g tissue (range)	Scrotal biopsy results in normal mice
I (D + R + P)	27	8	9	2.1 (1.5–3)	0	0.69×10^8 ($0.59–0.98 \times 10^8$)	1/9[b]
II (D + C + P)	11	7	4	1.5 (1.25–3)	0	0.31×10^8 ($0.19–0.58 \times 10^8$)	0/4
III (D + I + T + P)	11	8	2	2 (1.5–3)	0	0.29×10^8 ($0.12–0.57 \times 10^8$)	0/3
IV (D + P)	14	7.5	3	2 (1.5–3)	0	0.27×10^8 ($0.21–0.65 \times 10^8$)	0/4
V (D + R)	14	8	3	2 (1.5–3)	0	0.78×10^8 ($0.64–0.92 \times 10^8$)	1/9
VI (D +C)	12	8	2	1.03 (1–3)	0.3	0.52×10^8 ($0.50–0.78 \times 10^8$)	2/10
VII (D + I + T)[c]	14	8.5	4	1.75[c] (1.5–3)	0	0.47×10^8 ($0.45–0.78 \times 10^8$)	2/11
VIII (D)[c]	11	9	8	1.8[c] (1.5–3)	0.15	ND[d]	4/8

[a] Abbreviations: see footnote a in Table 1.
[b] Positive takes/total number of biopsies inoculated.
[c] BI calculated by Dharmendra scale.
[d] ND = not done.

received pyrazinamide as a part of combination chemotherapy. Furthermore, when treatment was continued for a further period of 1 year, i.e., at the end of 2 years (Table 5), patients on regimens VI and VIII still had solid-staining bacilli in their skin smears. The falls in the clinical scores and counts per gram tissue were nearly the same in all the groups, as is seen in Tables 2–5.

At the end of 2 years, a smooth muscle biopsy (scrotal biopsy in males, areola biopsy in females) was done and inoculated into the foot pads of normal mice. It was difficult to convince the patients to undergo a scrotal biopsy since most patients misunderstood it to be a family planning operation. Therefore, the number of patients in whom scrotal biopsies were performed was less than the total number of patients on each regimen. However, the clinical scores, BIs, and MIs of those patients who underwent biopsy did not differ from the patients who refused biopsy. Table 5 details the number of patients on each regimen who had growth in the foot pads of mice. It may be noted that there was only one positive take on regimen I, and persisting bacilli could not be detected in other pyrazinamide-containing regimens (II–IV). On the other hand, growth was seen in 1 out of 9 on regimen V, 2 out of 10 on regimen VI, 2 out of 11 on regimen VII, and 4 out of 8 on regimen VIII among the cases on control regimens without pyrazinamide.

In view of the fact that some patients dropped out after prolonged therapy and

TABLE 6. *Clinical and bacteriological assessment at the end of 2 years in patients regrouped into two groups with and without pyrazinamide.*

Regimens	No. patients	Avg. clinical score	Avg. BI	Avg. MI	Avg. no. bacilli/g tissue	Results of animal inoculation
With pyrazinamide	63	7.6	1.9	0	0.39×10^8	1/20[a]
Without pyrazinamide	51	8.4	1.65	0.23	0.59×10^8	9/38

[a] Positive takes/total number of biopsies inoculated.

TABLE 7. *Clinical and bacteriological assessment 5 years after intake into the trial.*

	Given pyrazinamide	Not given pyrazinamide
Total no. patients studied	38	25
No. patients smear negative	1	1
Average BI (Ridley scale)	0.66	1.25
(range)	(0–1.25)	(0–2.5)
Average MI	0	0
Average no. bacilli/g tissue	0.030×10^8	0.061×10^8
(range)	($0–0.07 \times 10^8$)	($0–0.105 \times 10^8$)

that many of them refused scrotal biopsy, the number of patients at the end of the study was considerably reduced compared to the beginning. It was therefore felt that the different groups under the various regimens could be regrouped for comparison into those receiving pyrazinamide and those not receiving the drug. As is evident from Tables 2–5, the clinical scores, BIs, and numbers of bacilli per gram tissue are nearly the same for the patients on those regimens who received pyrazinamide as for those who did not receive pyrazinamide. Table 6 shows that growth in the mouse foot pad was observed in 1 out of 20 (5%) biopsies inoculated at the end of 2 years in patients who received pyrazinamide. In contrast, 9 out of 38 (23.68%) biopsies showed growth in the normal foot pad in the group of patients who did not receive pyrazinamide. These patients were further followed up to 5 years. The results are seen in Table 7. One patient in each group became smear negative by 5 years. The BIs and numbers of bacilli per gram of tissue were less in the group which received pyrazinamide as compared to the group which did not receive pyrazinamide. The results of the mouse foot pad inoculations are shown in Table 8.

TABLE 8. *Results of smooth muscle biopsy inoculation in normal mouse foot pad 4–5 years after initiation of therapy.*

	Given pyrazinamide	Not given pyrazinamide
No. patients studied	17	8
No growth in foot pad	14	5
Growth in foot pad	0	1
Not inoculated due to low count	2	1
Mice died	1	1

DISCUSSION

Bacterial persistence is a phenomenon commonly defined as the capability of microorganisms to survive in the host despite adequate antimicrobial treatment. This was first described for hemolytic streptococci by Hobby and her co-workers ([7]). They observed that about 1% of the drug-susceptible organisms were able to survive appropriate concentrations of the drug. Toman ([15]) described "persisters" as individual organisms that have the capacity to survive in the host despite adequate chemotherapy. This occurs as a result of an adaptive process. Under adverse conditions, some cells reduce their metabolic requirements to a minimum, assuming a state of dormancy that coincides with insusceptibility to drug action. This occurs in a crowded bacterial population, old necrotic lesions, sites with low oxygen tension, and intracellularly where the pH is acidic. The organisms are metabolically changed microbial cells and a population of them die, but some cells survive and behave like normal organisms. This microbial persistence is not inherited. One of the reasons for treatment failure in leprosy is attributed to persisters. Waters, *et al.* ([18]) reported growth in the mouse foot pad in 7 of 12 patients studied after 10–12.5 years of continuous dapsone chemotherapy. There was good clinical improvement in all of the cases; nine patients had become smear negative but three were still smear positive. In another study ([13]), continuous rifampin therapy (600 mg daily) was administered, and it was observed that even after 5 years of therapy persisting bacilli were found in the skin, striated muscle, nerve, and smooth muscle.

Even with the present-day multidrug therapy, Levy, *et al.* ([11]) reported persisting

M. leprae in about 10% of patients after 1–2 years of treatment. Jopling ([10]) reported a follow-up study in patients who received MDT consisting of rifampin 600 mg daily, prothionamide 350 mg daily, isoniazid 300 mg daily, and dapsone 100 mg daily. Out of 116 patients, 10 patients had solid-staining bacilli in their skin smears 56–130 months after starting the above treatment. All of these studies clearly show that persister *M. leprae* can be detected in sizable populations of treated multibacillary patients even after prolonged multidrug chemotherapy.

Pyrazinamide has specific action in the intracellular environment of macrophages, and we have tried this with the presumption that by the addition of an antimycobacterial agent which acts by killing intracellularly, we may possibly cut short the duration of treatment and be able to get rid of persisters. Although Shepard and Chang ([14]) did not observe any inhibition of *M. leprae* multiplication in the mouse foot pad by pyrazinamide, these results cannot be directly extrapolated to the human situation. Firstly, pyrazinamide was administered alone and, secondly, the results of the mouse model and human disease do not always correlate, as has been observed in the case of the effect of clofazimine (B663) on *M. tuberculosis* infections in mice and in humans ([2, 17]).

In the present study, pyrazinamide has been used with different drug combinations for the initial 2 months of chemotherapy. This was based on the then prevalent idea that 2 months of intensive therapy with multiple drugs would kill most of the *M. leprae.* The remaining *M. leprae* would be taken care of by the continuing dapsone therapy. At the end of 1 year of therapy (Table 4), it was observed that only 1 patient on regimen II (D + C + P) had solid-staining bacilli in the skin smears as compared to 2 patients on regimen VI (D + C) and 5 patients on regimen VIII (D alone). By the end of 2 years (Table 5), none of the patients who received pyrazinamide had solid-staining bacilli in their skin smears, while two patients who did not receive pyrazinamide had solid-staining bacilli in their skin smears. A comparison of the mouse foot pad inoculation results at the end of 2 years showed growth in 1 patient each on regimens I (D + R + P) and V (D + R), 2 patients on regimen VI (D + C), 2 patients on regimen VII (D + I + T), and 4 patients on regimen VIII (dapsone monotherapy). As mentioned earlier, intake for regimens VII and VIII began earlier than intake into the other regimens. The viability results of regimen VIII reflect the earlier known trends ([17]), and do not appear to have introduced any bias in the comparison.

Since the corresponding regimens with pyrazinamide did not show any growth in the mouse foot pad, it may be inferred that pyrazinamide has some effect. The limitations of our present study are that the numbers of patients on each of the regimens were small and a smooth muscle biopsy could not be obtained from all of the patients at the end of 2 and 5 years. Also, thymectomized irradiated mice were not available to us at that time. In tuberculosis, pyrazinamide has a definite sterilizing effect, and when combined with potent bactericidal drugs like rifampin and isoniazid, it has to be given for 2 months out of the total duration of treatment of 6–9 months. In leprosy, we envisage that untreated lepromatous patients will require 2–4 years of MDT. Extrapolating the experience gained in treating tuberculosis to leprosy, it would probably require at least 9–12 months of treatment with pyrazinamide to attain the maximum sterilizing effect as obtained in tuberculosis.

From the results of our study, it can tentatively be concluded that pyrazinamide appears to have some effect against persisters in multibacillary leprosy. It needs to be tried along with the presently recommended MDT and for a sufficient duration in order to evaluate its exact role in eradicating persisters.

SUMMARY

Pyrazinamide in a dose of 1500 mg was given to 63 borderline lepromatous (BL) and lepromatous (LL) leprosy patients on different drug regimens for the initial 2 months of therapy. Fifty-one BL and LL patients were put on the same drug regimens without pyrazinamide. There was a rapid and good clinical improvement in the patients in both

of the groups. At the end of 2 years, the patients who received pyrazinamide had a morphological index (MI) of zero as compared to those patients who did not receive pyrazinamide, some of whom still had solidly staining bacilli. One out of 20 (5%) scrotal (smooth muscle) biopsies of the patients who received pyrazinamide had growth in the mouse foot pad as compared to 9 out of 38 (23.7%) smooth muscle biopsies of the patients who did not receive pyrazinamide. At the end of 5 years, the patients who received pyrazinamide had slightly better results compared with the non-pyrazinamide group. Pyrazinamide appears to have some effect against persisters in multibacillary leprosy. A well-controlled, randomized trial with longer duration of pyrazinamide therapy in a larger group of patients needs to be carried out to unequivocally determine the exact role of pyrazinamide in leprosy.

RESUMEN

Durante los primeros dos meses de tratamiento se administró pirazinamida (1500 mg) a 63 pacientes con lepra lepromatosa intermedia (BL) o lepromatosa polar (LLp) tratados con diferentes esquemas terapéuticos. Cincuenta y un pacientes BL y LL, recibieron un tratamiento similar pero sin pirazinamida. En ambos grupos hubo una buena y rápida mejoría clínica de los pacientes. Al final de 2 años de tratamiento, los pacientes tratados con pirazinamida tuvieron un índice morfológico de cero mientras que algunos de los pacientes no tratados con la droga aún tuvieron bacilos teñidos solidamente. Cuando se intentó el crecimiento de *M. leprae* en las almohadillas plantares del ratón, esto se logró sólo en el 5% de las biopsias (1 de 20) de músculo liso escrotal tomadas de los pacientes que recibieron pirazinamida y hasta en el 23.7% (9 de 38) de las biopsias de músculo liso de los pacientes que no recibieron la droga. Al final de 5 años de tratamiento, los pacientes que recibieron pirazinamida mostraron resultados ligeramente mejores que los pacientes del grupo sin pirazinamida. La pirazinamida parece tener un cierto efecto contra los bacilos persistentes en la lepra multibacilar. Sin embargo, para establecer el papel exacto de la pirazinamida en la lepra, se requiere hacer un estudio controlado donde se utilicen periodos más largos de tratamiento y grupos más grandes de pacientes.

RÉSUMÉ

On a administré de la pyrazinamide à la dose 1500 mg à 63 malades atteints de lèpre lépromateuse dimorphe (BL) ou de lèpre lépromateuse (LL), selon différents schémas thérapeutiques, au cours des 2 premiers mois du traitement. Cinquante et un malades BL et LL ont été soumis au même schéma thérapeutique, mais sans pyrazinamide. On a observé une amélioration clinique rapide et excellente chez les malades de l'un et de l'autre groupes. Après 2 ans, les malades qui avaient reçu de la pyrazinamide présentaient un index morphologique (MI) de zéro, alors que chez les malades qui n'avaient pas reçu de pyrazinamide, certains livraient encore des bacilles fortement colorables. Sur 20 biopsies du scrotum, (prélevées au niveau des muscles lisses) chez des malades ayant reçu de la pyrazinamide, une seule (5%), a entraîné une croissance bacillaire dans le coussinet plantaire de la souris, contre 9 sur 38 (23, 7%) chez les malades n'ayant pas reçu de pyrazinamide. Après une observation poursuivie pendant 5 années, les malades ayant reçu de la pyrazinamide présentaient des résultats légèrement meilleurs que les malades témoins. La pyrazinamide semble avoir un certain effet contre les bacilles persistant dans la lèpre multibacillaire. Il serait nécessaire de mener une étude clinique randomisée, avec témoins, et de plus longue durée, dans un échantillon plus large de malades, afin de déterminer de manière certaine le rôle exact de la pyrazinamide dans la lèpre.

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