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Hepatotoxicity of the Combination of Rifampin-ethionamide in the Treatment of Multibacillary Leprosy[1]

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For treatment of multibacillary leprosy combined chemotherapy must be administered to prevent the selection of drug resistant mutants and possibly to improve results in terms of relapse rates. It has been our opinion ([5, 7]) that a definite cure of multibacillary leprosy can only be obtained by the combined administration of powerful bactericidal drugs against *Mycobacterium leprae,* of which only two are presently known—rifampin and ethionamide or prothionamide ([3, 6]).

During prospective trials of combined regimens including the combination of rifampin with ethionamide or prothionamide, we unexpectedly observed cases of hepatitis which can only be interpreted as the result of drug toxicity. These are discussed in the present report.

PATIENTS AND DRUG REGIMENS

Ethionamide and prothionamide are considered equivalent as far as antibacterial activity is concerned. We use here only the term prothionamide (PRO), although in some areas ethionamide (ETH) has been used.

Previously treated and untreated multibacillary patients [Bacterial Index (BI) >2 at any of at least three skin sites] were included in the trials. After appropriate clinical, neurological, bacteriological and generally histopathological evaluation, patients were hospitalized and treated with a combination of rifampin (RMP), prothionamide (PRO), and either dapsone (DDS) or

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clofazimine (CLO). Previously untreated patients and patients treated previously for a maximum of five years with dapsone (monotherapy) received a combination of RMP+PRO+DDS. Patients previously treated for more than five years with DDS, because they were at risk of having secondary DDS resistance, were given CLO instead of DDS. In Zaire and Rwanda, all female patients were treated with CLO-containing regimens. Treatment regimens varied in different countries but, during the introductory phase, they always included the triple combination.

Since hepatitis was only very rarely observed after more than six months of treatment, only the first six months of the treatment regimens are given here.

Zaire-Rwanda

Regimen A: (26w RMP 600 7/7, PRO 500 7/7, DDS 100 7/7). During 26 weeks: RMP 600 mg, PRO 500 mg and DDS 100 mg, daily.

Regimen B: same as A but DDS replaced by CLO.

Burundi-Comore Islands

Regimen C: (8w RMP 600 7/7, PRO 500 7/7, DDS 100 7/7 + 18w R 600 1/7, PRO 500 7/7, DDS 100 7/7). Eight weeks: RMP 600 mg, PRO 500 mg and DDS 100 mg daily, followed during 18 weeks by RMP 600 mg once a week, with daily PRO 500 mg and DDS 100 mg.

Regimen D: (8w RMP 600 7/7, PRO 500 7/7, CLO 100 7/7 + 18w RMP 600 1/7, PRO 500 7/7, CLO 100 7/7). Same as C but DDS replaced by CLO.

Since in Burundi a prevalence survey of DDS resistance had been performed ([1]), patients who had been treated for more than five years with DDS, but were shown not to be DDS resistant, were also given Regimen C.

Turkey-Nigeria

Regimen E: (2w RMP 600 7/7, PRO 500 7/7, DDS 100 7/7 + 24w RMP 600 1/7, PRO 500 7/7, DDS 100 7/7). Two weeks: RMP 600 mg, PRO 500 and DDS 100 mg daily, followed by 24 weeks: RMP 600 mg once weekly, PRO 500 mg and DDS 100 mg daily.

Regimen F: identical to Regimen E but DDS replaced by CLO first two weeks 100 mg daily, next 24 weeks 300 mg once weekly.

Bamako

Regimen G: (90d RMP 600 2/7, PRO 500 7/7, DDS 100 7/7). Ninety days: RMP 600 mg twice a week, PRO 500 mg daily and DDS 100 mg daily.

Regimen H: same as Regimen G but DDS replaced by CLO.

RESULTS

Diagnosis of hepatitis was almost always clinical since most observations were done in rural hospitals. A few centers had laboratory facilities and based their diagnoses on increased ALAT (alanine-aminotransferase) tests and bilirubin levels. When icterus or hepatitis were diagnosed, antileprosy treatment was stopped. In some cases treatment was restarted after the hepatitis had subsided. In most cases, however, treatment was continued with dapsone or clofazimine in monotherapy.

There were 105 patients in Regimen A (with four cases of hepatitis, 4%) and 184 patients in Regimen B (with 11 cases of hepatitis, 5.9%).

Since these differences are not significant (Fisher's exact test $p = 0.11$), patients on Regimens A and B are discussed as a single group—Regimen A/B. The overall incidence of hepatitis in Regimen A/B was 5%. Table 1 shows the age distribution of the patients, the duration of previous dapsone monotherapy at the start of combined treatment, and the incidence of hepatitis. The latter increased with age—from less than 5% under age 49, it reached 11.6% in patients aged 50 years or older. The difference was highly significant. There was also an increase in hepatitis in those patients treated previously for longer periods of time, but the difference between the groups treated in the past for 0–9 years and more than 10 years was not significant.

The mean incubation time for hepatitis was 88 days; median = 76 days (Table 2). Four patients in this group died (27%). Their mean age was 48 years, not significantly different from the mean age (45.6 years) of those who developed hepatitis and recovered, but ten years higher than the mean age of all patients treated with Regimen A/

TABLE 1. *Age of patients, incidence of hepatitis, and duration of previous treatment in patients on Regimens A/B, C/D, E/F and G/H.*

Age	Regimen A/B		Regimen C/D		Regimen E/F		Regimen G/H
	No.	No. with hepatitis (%)	No.	No. with hepatitis (%)	No.	No. with hepatitis (%)	No.
<10	4		11				
10–19	14		37	3 (8)	6		1
20–29	48	2 (4.1)	55	3 (5.4)	15	1	17
30–39	84	3 (3.5)	49	1 (2)[a]	11	4	26
40–49	79	3 (4)	31		3		4
>50	60	7 (11.6)	43	1 (2.3)	5		5
Adults					41		
Total	289	15 (5)	226	8 (3.5)	81	5 (6.2)	53
Duration previous treatment (yr)							
0	119	3 (2.5)	118	2 (1.6)	37	2	3
1–4	28	2 (11)	65	5 (7.6)	16		41
5–9	33	1 (3)	12		2	2	6
10–14	26	2 (7.6)	8	1[a]	1		3
15–20	40	2 (5)	17		3		1
>20	43	4 (9.3)	6		2	1	
Unknown[b]					20		

[a] Patient treated with Regimen D.
[b] Unknown, but for many years.

B. In two patients treatment was restarted; hepatitis reappeared within a month in one patient, while in the second treatment had to be stopped because of gastrointestinal complications.

There were 205 patients in Regimen C with seven cases of hepatitis (3.4%) and 21 patients in Regimen D with one case of hepatitis (4.7%). Since these incidences were not significantly different ($p = 0.36$), patients in Regimens C and D are discussed as one group (Regimen C/D). The 3.5% overall incidence of hepatitis in this group was not significantly different from the incidence in Regimen A/B ($p = 0.13$). An increase of hepatitis with increasing age was not observed, although this may have been due to the smaller number of older patients included in this regimen. The mean age for group A/B was 38.8 years compared with 27.6 years for group C/D; the 50% percentile for Regimen A/B was nearly 40 years, while it was nearly 30 years for Regimen C/D. Hepatitis in group A/B appeared after a mean incubation time of 108 days; median = 118–152 days (Table 2). The mean age of these patients was 24 years, not significantly different from the mean of all those treated with Regimen C/D. There were two deaths. The mortality of hepatitis in Regimen C/D was 25%.

Treatment was restarted cautiously in three patients by the administration for two weeks of the combination DDS+RMP; when results of alkaline phosphatase and ALAT tests remained normal, ETH was added at a reduced dose of 375 mg without any recurrence of hepatitis.

There were only 81 patients in Regimen E/F with five cases of hepatitis (one was subclinical); one patient died. There was no clear correlation with age or duration of previous treatment, probably because the groups were too small (Table 1). The mean incubation time for hepatitis in this group was 80 days (Table 2).

No cases of hepatitis were observed among the 47 patients included in Regimen G or the six patients in Regimen H (Table 1). The majority of these patients were young; their mean age was 32 years and the 50% percentile was between 30 and 34 years. The great majority had been previously (irregularly) treated for periods not exceeding five years.

Acute phase serum from seven hepatitis cases was examined for the presence of hepatitis B virus markers. In no instance was

TABLE 2. *Sex, age, and mean Bacterial Index (BI) at start of treatment and incubation time for hepatitis during different regimens.*

No.	Sex	Age	BI	Regimen	Incub. time (days)
1	M	21	3	A	51
2	M	42	3	A	64
3	M	44	2	A	72
4	M	33	4	A	142
5	F	50	4	B	8
6	F	50	2.5	B	66
7	M	62	4.5	B	72[b]
8	M	61	4.5	B	72
9	F	53	3	B	76
10	M	56	5	B	77–109[a]
11	F	65	2.5	B	102[b]
12	F	61		B	106
13		29	3.5	B	121
14	F	30	2	B	142[b]
15	F	36	3	B	150[b]
16	M	50	2	C	36
17	F	16	3.5	C	46
18	M	11	3.5	C	118[b]
19	M	22	2	C	152
20	M	20	2.5	C	159
21	F	17	4.5	C	167
22	M	25	2	C	186[b]
23	M	30	2	D	5
24	F	20	2	E	72
25	M	30	3.5	F	48[b]
26	M	34	5	F	67
27	M	26	3	F	80
28	M	34	5	F	134

[a] Relapse on retreatment.
[b] Died.

B antigen detected but antibodies against the surface antigen were present in all sera.

DISCUSSION

Hepatitis, mostly with jaundice, appeared in 4.5% of a group of 596 multibacillary leprosy patients treated for six months with a combination of RMP 600 mg, ETH 500 mg, and either DDS or CLO 100 mg. Incubation time was 5–186 days, with a mean of 93 and a median of 76 days. Mortality from this hepatitis was 26%.

Hepatitis does occur rarely in leprosy patients in the absence of combined therapy; in our studies, hepatitis was observed in some patients several months after therapy had been stopped, and in others taking DDS, many months after they had taken a single dose of RMP of 25 mg/kg body weight. The etiology of this low-incidence hepatitis, which could be identical to that occurring in the nonleprosy population, remains unknown.

The hepatitis cases described in this paper are probably not caused by the hepatitis B virus, since the hepatitis B virus antigen was not found in any of the acute phase sera examined. Hepatitis virus surface antibodies were present in all sera. (This is a common observation in Africans, particularly in multibacillary leprosy patients [4].) Therefore the hepatitis cases observed must be interpreted as the result of drug toxicity.

In all of the regimens used, ETH was given daily in a 500 mg dose. RMP, 600 mg, was given either daily (Regimen A/B) or daily during the first eight weeks followed by a once-weekly dose (Regimen C/D), or daily during the first two weeks only, also followed by a once-weekly dose (Regimen E/F). There was no difference in the incidence of hepatitis for these alternatives of RMP administration. Whether DDS or CLO were included in the regimens did not affect the incidence of hepatitis.

Cases of icterus were described during the treatment of tuberculosis with RMP. It was later discovered that these were not due to RMP per se, but that RMP increased the toxicity of isoniazid (INH) administered simultaneously. There were only exceptional cases of jaundice when RMP was administered in monotherapy ([11]). ETH has been claimed to induce liver damage, but the incidence of this is difficult to evaluate because it was generally given in association with other drugs, particularly INH. From several series of observations, the incidence varies from 0–5% ([2, 10]). Rollier and Rollier ([8]) reported one case of hepatitis among 102 multibacillary leprosy patients treated with ETH 500 mg daily in monotherapy. Many reports from leprosy treatment centers mention that they administer the combination RMP+DDS or RMP+CLO or even RMP+DDS+CLO for periods of from 1–3 months, but hepatitis is never mentioned. The combinations ETH+DDS and ETH+CLO are also not hepatotoxic because during a second "continuation" phase of treatment, we have administered either DDS or CLO or DDS+ETH or CLO+ETH, without RMP, to most of the above-mentioned patients (for six months). Only two cases of hepatitis appeared among them

(both on the combination ETH+CLO) which might not be different from the low incidence hepatitis in the nonleprosy population (unpublished data).

It, therefore, seems that in our observations the combination of RMP and ETH—in the dosages and frequencies used—is the etiologic factor for the hepatic toxicity. It could be that in analogy with what occurs for INH, RMP induces the synthesis of host enzymes resulting in the production of toxic metabolites of ETH.

The correlation of hepatitis with the older age group in Regimen A/B may be the result of pre-existing liver damage, either through the longstanding leprosy infection with concurrent amyloidosis, or liver damage from other causes.

There are four possible reasons for the absence of hepatitis in Regimen G/H: 1) the patients in this regimen were considerably younger than those in Regimen A/B, although they were of comparable age to those in Regimen C/D; 2) since in all regimens approximately 50% of hepatitis cases appear during the first trimester, shortening the period of administration of the combination RMP+ETH should reduce the incidence of hepatitis by about one half; 3) the number of patients in Regimen G/H was small; and 4) it is also possible that RMP administered twice a week instead of daily (in combination with daily ETH) avoids hepatotoxicity.

In five cases treatment was restarted. In one patient retreated with RMP 600 mg and ETH 500 mg hepatitis recurred; in a second, treatment had to be abandoned because of gastric intolerance. In three other cases no harm was done when the drugs were reintroduced cautiously with a lower dose of 375 mg ETH.

When this high incidence of hepatitis was observed, the dosage of ETH in the regimens was lowered to 5 mg/kg body weight. Since then about 40 patients have been treated with this reduced ETH dosage, and no further cases of hepatitis have been observed.

This measure might not avoid entirely the appearance of hepatitis. For example, Stingl and Stingl ([9]) observed one case of hepatitis among 18 patients treated with the combination RMP 600 mg, ETH 175 mg, DDS 50 mg, and INH 175 mg daily; however, they did not present details on the age of the patients or the length of their previous treatment, although "50% of [the group] had received DDS treatment for varying duration and regularity."

If a definite cure for multibacillary leprosy can only be obtained by the administration of an association of bactericidal drugs, our observations illustrate once more the great need for new, potent bactericidal drugs against *M. leprae,* since the combination of the only two powerful bactericidals presently known ([3]) gives rise to 5–10% hepatotoxicity.

Ongoing studies will have to show if a reduction in the dosage of ETH or a reduction in the duration of the treatment with combination RMP+ETH will be able to reduce the hepatotoxicity while keeping its antibacterial effect.

SUMMARY

During treatment of multibacillary leprosy with the combination rifampin (RMP) 600 mg, ethionamide (ETH) 500 mg, and either dapsone (DDS) or clofazimine (CLO) 100 mg, hepatotoxicity was observed in 4.5% of 596 patients. Hepatitis appeared after 5–186 days, with a mean of 93 days and a median of 76 days. Mortality was 26%. ETH and DDS or CLO were administered daily in all regimens in which hepatitis occurred. RMP was given either daily or daily during the first two weeks or eight weeks, followed by a once-weekly dose. It is concluded that the combination RMP+ETH is the toxic component. In some patient groups there was a high correlation of toxicity with age. A regimen in which RMP was administered only twice a week during three months was not accompanied by hepatotoxicity. Future studies should show if reduction of the daily dose of ETH or reduction of the duration of the administration of RMP+ETH might reduce the incidence of hepatotoxicity while conserving the efficacy.

RESUMEN

Se observó que durante el tratamiento de 596 pacientes con lepra multibacilar con una combinación de 600 mg de rifampicina (RMP), 500 mg de etionamida (ETH) y 100 mg de dapsona (DDS) o clofazimina (CLO), el 4.5% de ellos mostraron hepatotoxicidad. La hepatitis apareció después de 5 a 186 días, con una media

de 93 días y una mediana de 76 días. La mortalidad fue de 26%. En los casos en los que hubo hepatitis, la ETH y la DDS o la CLO se administraron diariamente. La RMP se administró diariamente, o diariamente sólo durante las primeras 2 a 8 semanas continuando después con una dosis una vez cada semana. Se concluyó que la combinación RMP+ETH fue el componente tóxico. En algunos grupos de pacientes hubo una alta correlación entre la toxicidad y la edad. Cuando la RMP se administró solamente 2 veces por semana durante 3 meses, no ocurrió la hepatotoxicidad. Los estudios futuros demostrarán si la reducción de la dosis diaria de ETH o la reducción en el tiempo de administración de RMP+ETH pueden reducir la incidencia de hepatotoxicidad sin disminuir la eficacia observada.

RÉSUMÉ

Au cours du traitement de la lèpre multibacillaire par une combinaison rifampicine (RMP) 600 mg, ethionamide (ETH) 500 mg, complété par la dapsone (DDS) ou la clofazimine (CLO), 100 mg, on a observé une toxicité hépatique chez 4.5% de 596 malades. L'hépatite est apparue après 5–186 jours, avec une moyenne de 93 jours et une médiane de 76 jours. La mortalité a été de 26%. L'ETH et la DDS ou la CLO avaient été administrées quotidiennement dans toutes les posologies à la suite desquelles une hépatite est survenue. La rifampicine était administrée soit quotidiennement, ou bien quotidiennement initialement seulement durant deux semaines, ou durant huit semaines, suivie ensuite par une dose hebdomadaire. On en conclut que la combinaison RMP+ETH constitue l'élément toxique. Dans certains groupes de malades, on a relevé une corrélation élevée de la toxicité avec l'âge. Une posologie faisant appel à l'administration de RMP uniquement deux fois par semaine au cours des trois premiers mois, n'a pas été accompagnée de toxicité hépatique. Des études ultérieures pourraient montrer si la réduction de la dose quotidienne d'ETH, ou la réduction de la durée d'administration de la combinaison RMP+ETH est susceptible de réduire l'incidence de la toxicité hépatique, tout en conservant son efficacité thérapeutique.

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REFERENCES

1. Bourland, J., Van Loo, G. and Pattyn, S. R. Dapsone resistant leprosy in Burundi. Lepr. Rev. **54** (1983) 239–242.
2. Chambatte, C., Kermarec, J., Haguenauer, G., Page, G. and Bach, J. F. Essais cliniques du thiamide de l'acide-alpha-prophylisonicotinique (1321 Th) dans le traitement de la tuberculose humaine. Tolérance, toxicité viscérale comparées à celles du 1314 Th. Rev. Tuberc. Pneumol. **29** (1965) 33–48.
3. Colston, M. J., Ellard, G. A. and Gammon, P. T. Drugs for combined therapy: Experimental studies on the antileprosy activity of ethionamide and prothionamide and a general review. Lepr. Rev. **49** (1978) 115–126.
4. Maupas, P., Chiron, J. P., Goudeau, A., Coursaget, P., Perrin, J., Barin, F., Yvonnet, B., Dubois, F., Duflo, B., Duflo-Moreau, B., Sidibe, S. and Diallo, A. N. Epidémiologie et conséquences pathologiques du portage chronique du virus de l'hépatite B au Mali. Bull. Soc. Pathol. Exot. Filiales **74** (1981) 722–732.
5. Pattyn, S. R. Comments on the chemotherapy of leprosy as influenced by the present knowledge on *Mycobacterium leprae*. Lepr. Rev. **43** (1972) 126–136.
6. Pattyn, S. R. Further data on the effect of ethionamide and prothionamide in experimental leprosy. Lepr. Rev. **49** (1978) 199–202.
7. Pattyn, S. R. The strategy of leprosy treatment: A personal view. Ann. Soc. Belg. Med. Trop. **60** (1980) 253–262.
8. Rollier, R. and Rollier, M. Traitement de lèpre lépromateuse par l'éthionamide. Maroc. Med. **52** (1972) 148–166.
9. Stingl, P. and Stingl, M. Results of a combined leprosy therapy in Sierra Leone. Castellanica **3** (1977) 53–54.
10. Zankl, I. and Weichert, E. Tolérance hépatique du prothionamide. Prax. Pneumol. **26** (1972) 450–454.
11. Zimmerman, H. J. *Hepatotoxicity. The Adverse Effects of Drugs and Other Chemicals on the Liver.* New York: Appleton-Century-Crofts, 1978.