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Hepatitis in Leprosy Patients Treated by a Daily Combination of Dapsone, Rifampin, and a Thioamide[1]

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Since January 1980, each active case of leprosy registered at the Hansen Clinic of Pointe-à-Pitre, Guadeloupe, is treated daily by a combination of drugs. Paucibacillary cases are prescribed a daily combination of dapsone (DDS) and rifampin (RMP) for six months. Multibacillary cases are prescribed a daily combination of DDS, RMP, and a thioamide (TH) (ethionamide or prothionamide) for the first year, followed by a combination of DDS and RMP for the second year. TH was chosen instead of clofazimine as the third drug in combination with DDS plus RMP because TH is a bactericidal drug ([17]), and is more readily accepted by light-skinned patients. This paper reports the high incidence (13%) of hepatitis observed in multibacillary cases and its possible relationship to the administration of TH with RMP.

PATIENTS AND METHODS

Patients

From January 1980 to September 1982, from a population of 350,000 inhabitants, the Hansen Clinic of Guadeloupe registered 178 new cases of leprosy: 146 paucibacillary and 32 multibacillary. To these cases should be added 22 relapses that occurred among the 515 multibacillary cases already treated for more than five years. On the other hand, responsibility for treatment of 37 of the new paucibacillary cases was assumed by private physicians. Thus, this study reports the incidence of hepatitis under chemotherapy of 109 paucibacillary cases and 54 multibacillary cases.

Methods

To be considered as multibacillary leprosy cases, patients had to fulfill two of the following four criteria: a) presence of acid-fast bacilli in the nasal smear; b) Bacteriologic Index equal to or greater than 2+ in at least one lesion; c) negativity of the Mitsuda test, and d) the presence of globi in histopathological specimens. Patients not demonstrating two of these criteria were considered as paucibacillary cases.

Standard drug regimens for adult paucibacillary patients were DDS 100 mg plus RMP 600 mg daily for six months, and for adult multibacillary patients, DDS 100 mg plus RMP 600 mg daily for two years supplemented during the first year with TH (either ethionamide or prothionamide in tablets of 250 mg) 500 mg daily. For younger patients, each drug was usually given in half the adult dosage. The drugs were deliv-

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ered monthly, free of charge, at the clinic and prescribed for self-administration. The percentage of prescribed therapy actually received by the patients was assessed from the clinical records of attendance. Patients with at least 90% attendance were considered as regular; those with 50%–90% attendance, as irregular; and patients with less than 50% attendance, as very irregular.

All patients had a complete clinical examination at the beginning of chemotherapy and every six months thereafter. At each monthly delivery of drugs, patients were questioned for new symptoms, and if any were reported, a complete clinical and laboratory assessment was done. In addition to the monthly visit to the clinic, patients were requested to come whenever they noticed any abnormal symptom.

Systematic laboratory assessments were made at the beginning of chemotherapy, every six months during chemotherapy, and whenever requested for clinical symptoms. The tests included measurement of the transaminases (TGO/TGP Kit standardisé SFBC, Biomerieux, France), bilirubin and alkaline phosphatase, and search for hepatitis B antigen (passive hemagglutination test, Wellcome HA Screening Kit). In case of hepatic disturbances during chemotherapy, liver function tests were repeated every two weeks. The diagnosis of hepatitis was made either clinically, when jaundice occurred, or based only on laboratory evidence when, in the absence of jaundice, transaminase values were at least six times higher than normal.

RESULTS

Incidence and nature of hepatitis

Although no patients had clinical or laboratory evidence of hepatic abnormality at the beginning of chemotherapy, five cases of jaundice and two cases of laboratory-diagnosed hepatitis with nausea and vomiting were observed during chemotherapy among the 54 multibacillary patients; whereas no evidence of hepatitis was observed among the 109 paucibacillary patients. In every case, hepatitis was associated with significant increases of transaminase and bilirubin levels, but not with increases in the level of alkaline phosphatase. A viral etiology of the hepatitis was unlikely in the first six patients; they were hepatitis-B-antigen negative at the beginning of chemotherapy and remained negative at the onset of the hepatitis. A viral etiology was not impossible in the seventh patient who was hepatitis-B-antigen positive at the onset of the hepatitis; the hepatitis-B-antigen test had not been done at the beginning of chemotherapy (Table 1).

Hepatitis is not related to the longer course of chemotherapy received by the multibacillary patients because the delay between the begining of chemotherapy and the diagnosis of hepatitis was 1 month in one patient, between 1 and 2 months in four patients, and between 4 and 10 months in the last two patients. These last two patients were irregular in their monthly clinic attendance.

Finally, discontinuing treatment with RMP or TH but not DDS was rapidly followed by clinical and laboratory recovery. Jaundice disappeared within two months. When RMP was resumed without TH, there was no recurrence of the hepatitis. Therefore, TH appears responsible for the toxicity.

Possible causes of hepatitis other than TH

To determine whether or not factors other than TH might explain the occurrence of hepatitis in multibacillary patients, the main characteristics of the multibacillary and paucibacillary populations were analyzed. As shown in Table 2, the percentage of children (less than 15 years old) is 45% among paucibacillary and only 10% among multibacillary patients. Therefore, older age might be thought to contribute to the higher level of drug hepatotoxicity among multibacillary patients. However there were 61 adult patients (more than 15 years old) among the paucibacillary patients and 49 among the multibacillary patients; therefore, the number of adult paucibacillary patients at risk was not smaller than the number of adult multibacillary patients at risk of drug hepatotoxicity. Moreover, the median age was similar among adult patients of both categories. Therefore, older age does not appear to contribute to the excessive

TABLE 1. *Main characteristics of seven cases of hepatitis among 54 patients with multibacillary leprosy treated daily with 100 mg dapsone, 600 mg rifampin, and 500 mg thioamide (prothionamide or ethionamide).*

Register no.	Type of case	Sex	Age (yr)	Weight (kg)	Regularity of attendance (%)	Time from start of chemotherapy to onset of hepatitis (days)	Hepatitis B-antigen	
							Before chemotherapy	At onset of hepatitis
1251	Relapse	M	55	75	50	120	0	0
2451	Relapse	M	45	72	50	300	0	0
3036	New case	M	32	75	>90	30	0	0
2906	New case	M	62	73	50–90	60	0	0
2939	New case	M	55	66	50–90	60	0	0
3024	New case	F	32	42	>90	40	Not done	+
3925	New case	F	23	50	50–90	60	0	0

incidence of hepatitis among adult multibacillary patients. Furthermore, no significant differences in sex and weight were noticed between adult multibacillary and paucibacillary patients. Thus the only difference between the two adult populations was in the intake of TH by the multibacillary patients.

A similar analysis was made among the multibacillary patients to determine whether or not some other factors might be related to the occurrence of hepatitis. Neither sex, age, weight, nor the fact that the patient was a new case or a relapse case appeared to be a contributing factor.

DISCUSSION

The seven cases of hepatitis observed among the 54 multibacillary patients treated daily with the combination DDS, RMP, and TH were related to the administration of TH. Actually TH, either ethionamide or prothionamide, is well known as a drug potentially toxic to the liver ([1–8, 10–12, 14–17, 19–27, 29]). However, when TH was used in the 1960s for the chemotherapy of relapsed cases of tuberculosis, its use was accompanied by a mean rate of gastrointestinal disturbances as high as 45%, but the mean rate of hepatitis was not higher than 2% (35 hepatitis cases among 1806 patients). The TH-containing regimens used for tuberculosis during the 1960s did not include RMP; whereas it is included in the TH regimens now used for leprosy in Guadeloupe. Therefore, the high rate of hepatotoxicity observed in Guadeloupe appears to be a consequence of the concurrent administration of TH and RMP. As early as 1969, a high incidence of hepatotoxicity was observed in Paris,

TABLE 2. *Incidence of hepatitis according to sex and age of patients and type of leprosy.*

Type of leprosy	Total	Male		Female	
		<15 years	≥15 years	<15 years	≥15 years
Paucibacillary	0/109	0/24	0/29	0/24	0/32
Multibacillary					
Relapses	2/22	0/0	2/18	0/0	0/4
New cases	5/32	0/5	3/19	0/0	2/8
Total	7/163	0/29	5/66	0/24	2/44

France, by Lesobre and coworkers ([13]) when TH and RMP were combined in the treatment of tuberculosis: of 23 patients, 4 developed jaundice and 3, laboratory abnormalities. More recently, several cases of severe hepatitis were observed among patients receiving TH and RMP in a trial in Bamako, Mali ([28]).

The mechanism of toxicity is not known. It is possible that RMP, which is a strong inducer of hepatic drug-metabolizing enzymes ([9]), potentiates the direct toxicity of TH. Because hepatitis was observed in patients without any predisposing factor having been identified, it is tempting to relate toxicity to individual susceptibility. In practice, this means that regular laboratory surveillance of liver function should be carried out when a combination of TH and RMP is to be prescribed, and that TH should be terminated whenever significant disturbances occur.

Finally, it should be emphasized that in this study, as in those carried out in France ([13]) and in Mali ([28]), the daily dose of TH was at least 500 mg for adult patients, i.e., 7–10 mg/kg. It is thus possible that reducing the daily dose of TH to 5 mg/kg would reduce the risk of toxicity without altering the antibacterial effectiveness of the drug.

SUMMARY

A 13% incidence of hepatitis was observed among 54 cases of multibacillary leprosy treated daily with the three-drug combination of dapsone, rifampin, and a thioamide (ethionamide or prothionamide). No hepatitis was observed among 109 cases of paucibacillary leprosy treated daily with the two-drug combination of dapsone and rifampin. Symptoms were jaundice in five cases and nausea plus vomiting associated with a significant increase of transaminase levels in two cases. In five cases, the symptoms appeared during the first two months of therapy and in two cases, later. Discontinuing treatment with rifampin and the thioamide but not dapsone resulted in recovery. When rifampin was resumed without the thioamide, the hepatitis did not recur. Viral etiology could be eliminated in six cases. Neither sex, age, weight nor the fact that the patient was a new case or a relapse case appeared to be a contributing factor. Hepatotoxicity caused by administration of a thioamide might have been potentiated by the concurrent administration of rifampin.

RESUMEN

Se observó una incidencia de hepatitis del 13% en un grupo de 54 pacientes con lepra multibacilar tratados diariamente con una combinación de las drogas dapsona, rifampina y una tioamida (etionamida o protionamida). En un grupo de 109 pacientes con lepra paucibacilar tratados diariamente con la combinación de las drogas dapsona y rifampina no se encontraron casos de hepatitis. Los síntomas de la hepatitis fueron ictericia en 5 casos, y náusea y vómitos asociados con un aumento importante de las transaminasas en 2 casos. En 5 casos los síntomas aparecieron durante los primeros 2 meses de terápia, en tanto que en 2 casos éstos aparecieron después. La suspensión del tratamiento con rifampina y la tioamida (sin retirar la dapsona) resultó en recuperación del paciente. Cuando se reimplantó el tratamiento con rifampina sin la tioamida, la hepatitis no reapareció. En 6 casos se pudo eliminar la etiología viral. La edad, el sexo, el peso y el hecho de que el paciente fuera un caso nuevo o una recaída, no parecieron ser factores contribuyentes. La hepatotoxicidad causada por administración de una tioamida pudo haber sido potenciada por la admistración simultánea de la rifampina.

RÉSUMÉ

Chez 54 malades atteints de lèpre multibacillaire, traités quotidiennement par une combinaison de trois médicaments, à savoir la dapsone, la rifampicine, et une thioamide (ethionamide ou prothionamide), on a observé une incidence d'hépatite s'élevant à 13%. Aucune hépatite n'a été observée parmi 109 cas de lèpre paucibacillaire traités quotidiennement par une combinaison de deux médicaments, c'est-à-dire la dapsone et la rifampicine. Les symptômes observés ont consisté en jaunisse dans cinq cas, et en nausées et vomissements associés avec une élévation significative des taux de transaminase chez deux cas. Chez 5 malades, les symptômes sont apparus au cours des deux premiers mois du traitement, et chez deux autres cas, plus tardivement. L'interruption du traitement par la rifampicine et la thioamide, tout en maintenant la dapsone, a entraîné la guérison. Lorsque la rifampicine était administrée à nouveau, sans être accompagnée de thioamide, l'hépatite n'est pas réapparue. L'étiologie virale a pu être éliminée dans 6 cas. Il n'est pas apparu que le sexe, l'âge, le poids, non plus que le fait que le malade soit un nouveau cas ou une récidive, constituent un facteur contribuant à ce phénomène. La toxicité hépatique de la thioamide peut avoir été potentialisée par l'administration concommittente de rifampicine.

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