# Hepatotoxicity of the Daily Combination of 5 mg/kg Prothionamide + 10 mg/kg Rifampin[1]

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In a previous study ([1]), a 13% incidence of hepatitis was observed in patients with multibacillary leprosy treated during the first year with a daily three-drug combination of dapsone (DDS), rifampin (RMP), and a thioamide, either ethionamide (ETH) or prothionamide (PTH). Discontinuing treatment with rifampin and the thioamide, but not dapsone, resulted in recovery. Because the majority of the patients remained hepatitis B-antigen negative, and because no cases of hepatitis were observed in paucibacillary patients treated with rifampin and dapsone without a thioamide, the hepatitis appeared toxic in nature and related to the administration of the thioamide in combination with rifampin.

However, all adult patients received a daily dose of 500 mg of thioamide, irrespective of their body weight. Although we found no difference in the incidence of hepatitis according to the body weight of the patients, the prescription of a standard daily dose of 500 mg PTH could have contributed to the high incidence of the hepatitis. Therefore, a second study began in October 1982 in which the daily dose of thioamide was reduced to 5 mg/kg, a dosage which still gives active blood levels ([3]). In this study, monthly assessments of liver function were performed in order to detect early hepatic disturbances and to be able to stop the treatment before the onset of jaundice. The aim of the present paper is to report the incidence and the gravity of the hepatitis observed in the second study and to discuss the place of thioamide in the chemotherapy of leprosy.

## PATIENTS AND METHODS

**Patients.** From October 1982 to July 1984, 110 multibacillary (MB) patients were treated with the three-drug regimen under study: 10 were newly diagnosed, previously untreated patients; 8 were newly diagnosed relapse patients who had been under long-term dapsone monotherapy; and 92 were inactive, smear-negative patients who had been under long-term dapsone monotherapy. The rationale for giving the three-drug regimen to the latter group was to offer them an alternative to life-long dapsone monotherapy.

During the same period of time, 103 paucibacillary (PB) patients were put on the two-drug standard regimen: 59 were newly diagnosed, previously untreated patients; 1 was a relapse patient who had been taken out of the register in 1972 after long-term dapsone monotherapy; and 43 were inactive patients on dapsone monotherapy to whom six-month chemotherapy was offered in order to complete their treatment more rapidly.

**Methods.** As in the previous report ([1]), to be considered as multibacillary cases of leprosy, patients had to fulfill two of the following criteria: a) presence of acid-fast bacilli in the nasal smear, b) bacterial index equal to or greater than 2+ in at least one lesion, c) negativity of the Mitsuda test, and d) presence of globi in histopathological specimens. Other patients were considered as paucibacillary cases.

Standard drug regimens were DDS 100 mg plus RMP 10 mg/kg body weight daily for six months for paucibacillary patients and, for multibacillary patients, DDS 100 mg plus RMP 10 mg/kg body weight daily

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for two years, supplemented during the first year with daily PTH 5 mg/kg body weight. PTH was preferred to ETH because it was available in 250 mg and 125 mg tablets which permitted a more precise adaptation of the drug dosage to the body weight of the patients.

The drugs were delivered 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 clinic attendance records: 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 month during the first three months of chemotherapy, and then every three months or whenever clinical symptoms dictated. The laboratory tests included the measurement of the transaminases (TGO/TGP Kit standardisé SFBC, Biomérieux, France), bilirubin, and alkaline phosphatase, and search for hepatitis B-antigen (passive hemagglutination test, Wellcome HA screening kit). During chemotherapy, when the transaminases levels were two to five times higher than normal, laboratory tests were repeated every two weeks without any change in the chemotherapy. When the transaminases were at least six times higher than normal, the diagnosis of hepatitis was made and RMP and PTH were stopped, but not dapsone. As soon as the laboratory tests returned to normal, RMP was resumed and PTH was replaced by 100 mg clofazimine daily.

## RESULTS

No patients had clinical or laboratory evidence of liver function abnormality at the beginning of chemotherapy. During chemotherapy, no cases of hepatitis were observed among the 103 paucibacillary cases, but 18 cases occurred among the 110 multibacillary patients, an incidence of 16.5%. In 2 cases there was jaundice, in 5 cases there was laboratory-diagnosed hepatitis with nausea and vomiting, and in 11 cases, laboratory-diagnosed hepatitis without any clinical symptoms. Hepatitis was associated neither with an increase of the levels of alkaline phosphatases nor with a positive hepatitis B-antigen. Actually all 18 patients with hepatitis were hepatitis B-antigen negative at the beginning of chemotherapy and remained so at the onset of hepatitis. The delay between the beginning of chemotherapy and the diagnosis of hepatitis was three months or less in ten patients and between four and six months in the remaining eight patients. Five of these eight patients were irregular in their monthly attendance but the three others were regular (The Table).

In every case, stopping RMP and PTH but not DDS was followed by complete clinical and laboratory recovery. Jaundice disappeared within two weeks, and the transaminase levels returned to normal within two months. When RMP was resumed without PTH there were no recurrences of hepatitis. Finally, as shown in The Table, no factors other than the intake of PTH with RMP appeared to be contributing to hepatitis in the multibacillary patients.

## DISCUSSION

The results of our studies demonstrate that decreasing the daily dosage of PTH from about 10 mg/kg to 5 mg/kg did not decrease the incidence of hepatitis in multibacillary leprosy patients treated daily by the three-drug regimen DDS, RMP, and PTH. Actually, the incidence of hepatitis was 7 out of 54 patients receiving 10 mg/kg PTH in the first study ([1]), and 18 out of 110 patients receiving 5 mg/kg PTH in the present study. The difference is not statistically significant ($p > 0.05$). Between both studies there was no more significant difference in the length of time from the start of chemotherapy and the onset of hepatitis. The length of time was three months or less in 5 out of 7 patients treated with 10 mg/kg PTH and in 10 out of 18 patients treated with 5 mg/kg PTH. The only obvious difference was in the clinical symptoms. In the first study with 10

THE TABLE. *Main characteristics of the 18 cases of hepatitis among 110 MB patients treated daily with 100 mg dapsone, 10 mg/kg rifampin, and 5 mg/kg prothionamide.*

| Type of case | Sex | Age (yr) | Body weight (kg) | Daily dose of PTH (mg) | Regularity of attendance (%) | Time from start of chemotherapy to onset of hepatitis (days) |
|---|---|---|---|---|---|---|
| New case | F | 53 | 68 | 250 | 90 | 60 |
| New case | M | 59 | 80 | 375 | 50–90 | 180 |
| New case | F | 61 | 50 | 250 | 90 | 130 |
| Inactive | M | 36 | 68 | 250 | 90 | 60 |
| Inactive | F | 35 | 50 | 250 | 90 | 83 |
| Inactive | F | 64 | 60 | 250 | 90 | 84 |
| Inactive | M | 55 | 64 | 250 | 50–90 | 180 |
| Inactive | F | 47 | 70 | 375 | 90 | 150 |
| Inactive | F | 66 | 64 | 250 | 90 | 80 |
| Inactive | M | 48 | 60 | 250 | 90 | 90 |
| Inactive | M | 18 | 75 | 375 | 90 | 90 |
| Inactive | F | 49 | 64 | 250 | 90 | 90 |
| Inactive | M | 30 | 63 | 250 | 90 | 150 |
| Inactive | M | 60 | 65 | 250 | 50–90 | 150 |
| Inactive | M | 55 | 70 | 250 | 50–90 | 180 |
| Inactive | M | 83 | 75 | 375 | 50–90 | 180 |
| Relapse | M | 22 | 90 | 500 | 90 | 70 |
| New case | M | 46 | 70 | 250 | 90 | 30 |

mg/kg PTH, jaundice was observed in 5 out of 7 patients with hepatitis; whereas in the second study with 5 mg/kg PTH, jaundice was observed in 2 out of 18 patients with hepatitis ($p < 0.05$). Of course, the monthly assessments of liver function in the second study permitted earlier detection of hepatitis and, therefore, led to the stopping of RMP and PTH before the onset of jaundice.

The high incidence of the hepatitis and its regularly favorable outcome in both our studies are in disagreement with the findings of Pattyn, *et al.* [5], who recently reported a 4.5% incidence of hepatitis with a 26% mortality in patients receiving the combination RMP and PTH. But, in their study, the daily dose of PTH was 500 mg and the diagnosis of hepatitis was mainly on clinical grounds.

Although PTH is, after RMP, the most powerful bactericidal drug currently available for the treatment of *Mycobacterium leprae* infections [5] the high incidence of hepatitis observed in patients receiving the daily combination 5 mg/kg PTH plus 10 mg/kg RMP raises serious questions of whether such a combination should be used. From our findings and those of others [4, 5], daily PTH may be given with daily RMP only when its daily dose does not exceed 5 mg/kg and monthly assessments of the liver function, at least transaminase tests, are routinely performed. The monthly laboratory assessments should be continued as long as the daily combination RMP + PTH is given, and not only during the first three months of chemotherapy as was done in our second study, because a significant proportion of PTH-associated hepatitis occurred between the third and the sixth month of chemotherapy. As soon as the transaminase levels are increased significantly (six times higher than normal), PTH and RMP should be stopped but not DDS. After recovery, only RMP should be resumed and combined with clofazimine. Despite its less bactericidal activity against *M. leprae* than PTH, clofazimine is therefore the drug of choice [6] to be given with DDS and RMP when monthly assessments of the liver function are not available, or in case of PTH hepatotoxicity.

## SUMMARY

Because a 13% incidence of hepatotoxicity was observed in a first study of multibacillary leprosy patients treated daily with dapsone, rifampin, and 10 mg/kg thioamide, the patients were treated in a second study with 5 mg/kg thioamide in daily combination with dapsone and rifampin. In this

study, monthly assessments of liver function were performed in order to detect early hepatic disturbances. Despite the reduced dosage of thioamide, a 16.5% incidence of hepatotoxicity was observed among 110 multibacillary patients. However, jaundice was observed in only 2 out of 18 cases of hepatotoxicity (11%); whereas it was observed in 5 out of the 7 cases of hepatotoxicity (71%) in the first study ($p < 0.05$).

The decrease in the thioamide dosage and the performance of monthly assessments of liver function did not decrease the incidence of hepatotoxicity but did decrease its severity. It is concluded that thioamide should not be used in daily combination with rifampin unless the daily dose is 5 mg/kg and monthly assessments of liver function are routinely performed.


## RESUMEN

Debido a que se observó una incidencia de hepatotoxicidad del 13% en un primer estudio con pacientes con lepra multibacilar tratados diariamente con dapsona, rifampina y tioamida en dosis de 10 mg/kg, los pacientes se trataron en un segundo estudio con 5 mg/kg de tioamida en combinación diaria con dapsona y rifampina. En este estudio, se hicieron determinaciones mensuales de la función hepática para poder descubrir las alteraciones tempranas en este órgano. No obstante la dosis reducida de tioamida, se observó una incidencia de hepatotoxicidad del 16.5% en una población de 110 pacientes multibacilares. Sin embargo, mientras que en el primer estudio, 5 de 7 casos de hepatotoxicidad (71%) mostraron ictericia, en el segundo estudio sólo 2 de 18 casos de hepatotoxicidad (11%) presentaron ictericia ($p < 0.05$).

La disminución en la dosis de tioamida y la práctica mensual de las pruebas de función hepática no disminuyeron la incidencia de hepatotoxicidad pero sí disminuyeron su severidad. Se concluye que la tioamida no debe usarse en combinación diaria con rifampina a menos que se use la dosis de 5 mg/kg y que se valore la función hepática de manera rutinaria.

## RÉSUMÉ

Lors d'une étude antérieure, on a observé une incidence de 13% de manifestation toxique au niveau du foie chez des malades atteints de lèpre multibacillaire traités quotidiennement par la dapsone, la rifampine, et 10 mg/kg de thioamide. Ces malades ont été traités, dans une seconde étude, avec 5 mg/kg de thioamide, en combinaison journalière avec de la dapsone et de la rifampine. Dans cette étude, on a procédé à des évaluations mensuelles de la fonction hépatique, en vue de déceler des lésions hépatiques précoces. Malgré la dose réduite de thioamide, on a observé une incidence de 16,5% de toxicité hépatique chez les 110 malades multibacillaires. Toutefois, une jaunisse n'a été relevé que chez 2 des 18 cas présentant des manifestations d'hépatotoxicité (11%). Par contre, de telles manifestations de jaunisse ont été observées chez 5 des 7 cas avec manifestations toxiques au niveau du foie (71%), qui ont été étudiées au cours de la première étude ($p < 0,05$).

Une diminution des doses de thioamide, de même que les évaluations mensuelles de la fonction hépatique, n'ont pas permis de diminuer l'incidence de manifestations toxiques au niveau du foie; elles en ont cependant diminué la gravité. On en conclut qua la thioamine ne devrait pas être utilisée en combinaison quotidienne avec la rifampycine, à moins que la dose ne dépasse pas 5 mg/kg et par jour, et que des évaluations périodiques de la fonction hépatique soient régulièrement pratiquées.


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