Lack of Relationship between Hepatic Toxicity and Acetylator Phenotype in Three Thousand South Indian Patients during Treatment with Isoniazid for Tuberculosis\textsuperscript{1,2}

PREMA GURUMURTHY, M. S. KRISHNAMURTHY, Q. NAZARETH, R. PARTHASARATHY, G. RAGHUPATI SARMA, P. R. SOMASUNDARAM, S. P. TRIPATHY, and G. A. ELLARD

**Introduction**

Mitchell and colleagues (1, 2) have suggested that isoniazid may be more hepatotoxic for rapid than for slow acetylators because rapid acetylators might be expected to form monoacetylhydrazine from isoniazid more rapidly than do slow acetylators, and monoacetylhydrazine can be converted by p-450-dependent hepatic microsomal enzymes to a potent acylating agent capable of causing hepatic necrosis. This hypothesis has been questioned on the grounds that rapid acetylators acetylate monoacetylhydrazine more rapidly than do slow acetylators to the nontoxic diacetylhydrazine, and that the exposure of rapid acetylators to monoacylhydrazine is, in consequence, similar to that of slow acetylators (3-7).

There is evidence that the results of liver function tests are similar for rapid and slow acetylators during treatment with isoniazid-containing regimens (3, 4, 8-11); however, very few studies have provided evidence on the possible influence of acetylator phenotype on the incidence of frank hepatitis. In their original report on a large study of chemotherapy in the United States, Mitchell and colleagues (1) concluded that of 21 patients considered to have recovered from hepatitis that was probably isoniazid-induced, 18 (86%) were rapid acetylators, in contrast to an expected proportion of 45% rapid acetylators in the population at risk.

We report here the results of serum aspartate (AST) and alanine aminotransferase (ALT) activities in 489 slow and 358 rapid acetylators, and the incidence of hepatitis with jaundice in 1,757 slow and 1,238 rapid acetylators treated with isoniazid-containing regimens in 8 controlled clinical trials in Madras. The data were analyzed retrospectively from studies of which were published from 1960 onwards. In all the studies, the acetylator phenotypes of the patients were determined before treatment was started, with the original intention of evaluating the effect of the acetylation rate on the therapeutic efficacy of the regimen.

**Methods**

All the patients had pulmonary tuberculosis with sputum cultures positive for *Mycobacterium tuberculosis*, and were studied in 8 controlled clinical trials of antituberculosis chemotherapy. They were allocated at random to receive the following regimens:

**Study 1** (12). (1) HP: isoniazid 5 mg/kg and sulphamethazine 0.2 g/kg daily, half in the morning and half in the evening, for 12 months; (2) HP 400 (1): isoniazid alone, 9 mg/kg daily as a single dose, for 12 months; (3) H 400 (2): isoniazid alone, 9 mg/kg daily, half in the morning and half in the evening, for 12 months; (4) H 200: isoniazid alone, 5 mg/kg daily, half in the morning and half in the evening, for 12 months.

**Study 2** (13). (1) HP: the same as in Study 1; (2) HT: isoniazid 7 mg/kg and thioacetzone 3 mg/kg, daily as a single dose, for 12 months; (3) HP/H: isoniazid 200 mg and sodium PAS 6 g, daily as a single dose for 6 months, followed by isoniazid 7 mg/kg, daily as a single dose for 6 months.

**Study 3** (14). (1) SH1: streptomycin 1 or 0.75 g and isoniazid 15 mg/kg as a single dose twice a week, for 12 months; (2) SH2: the same drugs and dosage as SH1, but given once a week; (3) SH3: the same as SH1, but with pyrazinamide 90 mg/kg with each dose; (4) SH4: the same as SH3, for 48 weeks, but preceded by streptomycin 1 or 0.75 g and isoniazid 400 mg as a single dose each day for 4 wk.

**Study 4** (15). (1) SH/SH: the same as in Study 3, except that 2 once-weekly isoniazid dosages were studied, 13 and 17 mg/kg; (2) SH/SHP: the same as SH/SH, but with sodium PAS 6 g in addition with each dose.

**Study 5** (16). (1) SH/HP: streptomycin 1 g, isoniazid 400 mg, and sodium PAS 6 g daily for 2 wk, followed by isoniazid 15 mg/kg and sodium PAS 0.2 g/kg twice a week, for 50 wk; (2) SH/HP: the same initial phase of SHP for 2 wk, followed by isoniazid 5 mg/kg, and sodium PAS 0.2 g/kg daily, for 50 wk.

**Study 6** (17). (1) SHE/HE: streptomycin 1 g, isoniazid 400 mg, and ethambutol 25 mg/kg daily for 2 wk, followed by isoniazid 400 mg and ethambutol 15 mg/kg in a single daily dose for 50 wk; (2) SHE/HE: SHE for 2 wk, followed by isoniazid 15 mg/kg and ethambutol 45 mg/kg in a single dose twice a week, for 50 wk; (3) SHE/HE: SHE for 2 wk, followed by isoniazid 15 mg/kg twice a week and ethambutol 90 mg/kg once a week, for 50 wk; (4) SHE/HE: SHE for 2 wk, followed by isoniazid 15 mg/kg and ethambutol 90 mg/kg in a single dose once a week, for 90 wk.

**Study 7** (18). (1) SH/SH: the same as in Study 3, except that the streptomycin dosage was 0.75 g in all patients; (2) SH/SM(90): the same as SH/SH, but with

(Received in original form February 7, 1983 and in revised form July 20, 1983)

\footnotetext{1}{From the Tuberculosis Research Centre (Indian Council of Medical Research), Madras, India, and the National Institute for Medical Research, London, England.}

\footnotetext{2}{Requests for reprints should be addressed to Dr. S. P. Tripathy, Director, Tuberculosis Research Centre, Madras 600 031, India.}
ACETOYLTRANSFER PHENOTYPE AND HEPATIC TOXICITY

matrix isoniazid, a slow-release formulation (Smith and Nephew HS 82) 30 mg/kg instead of ordinary isoniazid in the once-weekly phase; (3) SH/SM(40): the same regimen as (2) above, but with matrix isoniazid 40 mg/kg instead of 30 mg/kg. Study 8 (19). (1) 2SHRZ/3SHZ: streptomycin 0.75 g, isoniazid 400 mg, rifampin 12 mg/kg, and pyrazinamide 40 mg/kg daily for 2 months, followed by streptomycin 0.75 g, isoniazid 15 mg/kg, and pyrazinamide 70 mg/kg twice a wk, for 5 months; (2) 2SHRZ/3SHZ: the same regimen as (1) above, but with the twice-weekly phase given for 5 months; (3) 2SHZ/3SHZ: the same regimen as (2) above, but without rifampin.

In studies 3 to 8 inclusive, pyridoxine 60 mg was given each dose of isoniazid.

Acetylator phenotypes of the patients were determined in Studies 1 through 6 from the serum isoniazid concentrations 4.5 h after an intramuscularly administered dose of 3 mg/kg of isoniazid using microbiologic (20, 21) or chemical (22) methods. In the remaining 2 studies, classification was based on the ratio of acetylsalicylic acid to isoniazid in urine excreted 3 to 4 h after the intramuscularly administered dosage with 3 mg/kg of isoniazid (23, 24) or 25 to 26 h after an orally given dosage with 30 mg/kg of a slow-release isoniazid formulation (25).

The serum AST and ALT activities (26) were determined on admission, during treatment and at the end of treatment in Studies 7 and 8.

All the patients were under close supervision in controlled clinical trials; it is, therefore, most unlikely that any episode of clinically evident hepatitis with jaundice was missed.

A total of 67 patients took their discharge against medical advice during the course of these 8 studies; of these, 60 withdrew because of reasons unconnected with the treatment, such as moving away from the city; 1 patient had jaundice at the time of his discharge and 6 others dropped out possibly because of adverse reactions other than hepatitis, such as giddiness and joint pains.

Results

The geometric mean serum AST activities determined on admission, during, and at the end of treatment in Studies 7 and 8 are shown separately for the slow and rapid acetylators in table 1. The means for the slow and rapid acetylators were similar at all 3 time points. The serum ALT levels (not tabulated) were also similar in 2 acetylator phenotypes at all 3 time points. In Study 7, serum AST levels of 40 Karman units or more were encountered during treatment in 5 of 192 slow acetylators and 5 of 133 rapid acetylators, and similarly elevated ALT levels were observed in 2 slow and 2 rapid acetylators. In Study 8, elevated AST values were encountered in 29 of 297 slow acetylators and 11 of 225 rapid acetylators (p = 0.06), whereas 10 slow acetylators and 1 rapid acetylator had elevated ALT levels (p = 0.03).

The incidence of clinically evident hepatitis with jaundice in all 8 controlled trials is shown separately for the slow and rapid acetylators in table 2. The incidence is similar in the 2 phenotypes in Studies 5 and 7, slightly higher for the slow acetylators in Studies 1, 2, 3, 4, 5, 6, and 8.
TABLE 3
INCIDENCE OF JAUNDICE ACCORDING TO DRUG COMBINATIONS

<table>
<thead>
<tr>
<th>Drug Combination*</th>
<th>Slow Acetylators</th>
<th>Rapid Acetylators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Jaundice (n) (%)</td>
<td>With Jaundice (n) (%)</td>
</tr>
<tr>
<td>Isoniazid alone</td>
<td>638 9 1.4</td>
<td>444 2 0.5</td>
</tr>
<tr>
<td>PAS and Isoniazid</td>
<td>399 9 2.3</td>
<td>225 3 1.3</td>
</tr>
<tr>
<td>Thioacetazone and Isoniazid</td>
<td>38 1 0.8</td>
<td>39 1 0.6</td>
</tr>
<tr>
<td>Ethambutol and Isoniazid</td>
<td>220 5 2.2</td>
<td>196 1 0.5</td>
</tr>
<tr>
<td>Pyrazinamide and Isoniazid</td>
<td>260 3 1.1</td>
<td>184 3 1.6</td>
</tr>
<tr>
<td>Rifampin, pyrazinamide, and Isoniazid</td>
<td>186 7 3.7</td>
<td>150 5 3.3</td>
</tr>
<tr>
<td>Total patients</td>
<td>1,757 34 1.9</td>
<td>1,238 15 1.2</td>
</tr>
</tbody>
</table>

A substantial majority received streptomycin as well.

3, 4, and 6, and slightly higher for the rapid acetylators in Study 8; none of the differences were significant. In all, 34 (1.9%) of 1,757 slow and 15 (1.2%) of 1,238 rapid acetylators had jaundice (p = 0.2).

In table 3, the findings are expressed according to the drug combinations given. There was no evidence that the companion drugs toisoniazid influ-
enced the relative proportions of slow and rapid acetylators who had hepatitis with jaundice (p = 0.1, by Cochran's test). Separate analyses also showed that the proportions were not influenced by the rhythm of drug adminis-
tration. The overall incidence of jaun-
dice was 1.6%, but there was a strong suggestion (p < 0.01) that the incidence was higher on isoniazid regimes containing rifampin plus pyrazinamide (3.6%) than on isoniazid alone or combinations of isoniazid with PAS, thioacetazone, ethambutol, or pyrazin-
amide (1.4%).

Discussion

The similarity in the two acetylator phenotypes of the serum AST and ALT activities on admission, during, and at the end of treatment indicates that rapid acetylators are no more prone to asymptomatic hepatic damage than are slow acetylators. These findings con-
firm the results of previous studies carried out among patients with tuberculosis in Singapore (3), the United States (8), Hong Kong (4, 11), Finland (9), and Argentina (10). Indeed, as Brown has pointed out (27), in one of the original studies carried out by Mit-
chell and colleagues (28), there was a suggestion that when isoniazid was used prophylactically, raised serum aminotransferase levels were more common in slow than in rapid acetylators.

It is, however, of much greater im-
portance to determine whether the in-

cidence of clinically significant hepatic damage is influenced by the isoniazid acetylator phenotype. The results pre-

sented in this report show conclusively that rapid acetylators are at no greater risk of developing jaundice than are slow acetylators during treatment with isoniazid-containing regimens, the inci-
dence among the 2 phenotypes being 1.2 and 1.9%, respectively. It is unlikely that any episode of jaundice in these studies was missed, as all the patients were under close supervision. Patients who took their discharge against medical advice were few in number, and in only 1 of 67 of these patients could jaundice have been the possible cause for the premature discharge. However, it cannot be assumed that all the cases of hepatitis were isoniazid-induced, particularly in view of the fact that the Madras region in South India is endemic for infective hepatitis. No reliable estimates of the incidence of jaundice in the general population in Madras city are available. Patients admitted to our studies and, however, followed for as long as 5 years after ceasing treatment. In a recent 4-year follow-up of 661 pa-

tients who did not receive any anti-

tuberculosis treatment, the annual inci-
dence of jaundice, presumably caused by infective hepatitis, was 0.9%. This suggests that the additional risk of hepatitis caused by isoniazid treatment is probably of the order of 1% in our population.

Pharmacologic studies undertaken earlier (4, 29) have shown that slow and rapid acetylators excreted similar proportions (approximately 2%) of doses of 5 to 15 mg/kg ordinary isoniazid or 30 mg/kg of a slow-release isoniazid formulation (Smith and Nephew HS 82 "matrix isoniazid") in the urine as monoacetylisoniazid. These results suggest that exposure to monoacetyl-


References

5. Girling DJ. The hepatic toxicity of antituberculos is regimens containing isoniazid, rifampin and pyrazinamide. Tubercle 1978; 59:12-3.
10. Pilbruu JA, De Salvo MC, Manchiu I, De Negroni NR, Szemzo J. Incidencia de las altera-
ACETILATOR PHENOTYPE AND HEPATIC TOXICITY
