Deleterious Influence of Pyrazinamide on the Outcome of Patients With Fulminant or Subfulminant Liver Failure During Antituberculous Treatment Including Isoniazid

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Isoniazid and pyrazinamide are well-known hepatotoxic drugs, often used in combination. The aim of this study was to assess the prognostic influence of pyrazinamide on the outcome of fulminant or subfulminant liver failure caused by antituberculous therapy. Eighteen patients with fulminant or subfulminant liver failure due to antituberculous therapy were studied. Nine patients received isoniazid and rifampicin without pyrazinamide (group 1), and nine patients received isoniazid and rifampicin together with pyrazinamide (group 2). The severity of fulminant and subfulminant liver failure, as judged by the prevalence of coma and the lowest level of factor V, was similar in the two groups. Spontaneous survival was greater in group 1 (eight of nine) than in group 2 (two of nine) ($P < .02$). The authors conclude that pyrazinamide co-administration was associated with an increased mortality in patients with fulminant or subfulminant hepatitis occurring during antituberculous therapy. In these patients, pyrazinamide administration and an interval of more than 15 days between the onset of antituberculous treatment and jaundice, combined with grade III encephalopathy and factor V below 20%, predicted death without liver transplantation. (HEPATOLOGY 1995;21:929-932.)

The recent increase in the incidence of tuberculosis in developed countries has led to a widespread use of antituberculous agents, often in combination.[1,2] Fulminant and subfulminant liver failure (as defined by a jaundice to encephalopathy time interval of less than 15 days, and from 16 days to 3 months, respectively)[3] is a well-known, although uncommon, complication of isoniazid administration.[4,5] Pyrazinamide is also known to be hepatotoxic and can cause lethal hepatic failure.[6]

The influence of combined isoniazid and pyrazinamide use on the outcome of patients developing fulminant or subfulminant liver failure is not known. The aim of this study was: (1) to assess the influence of pyrazinamide co-administration on the outcome of patients with fulminant or subfulminant liver failure due to antituberculous treatment, and (2) to determine criteria for emergency liver transplantation in such patients.

PATIENTS AND METHODS

From April 1972 to June 1991, 18 patients with fulminant or subfulminant liver failure occurring as a result of antituberculous treatment were identified in this study. Seventeen were admitted to the Liver Intensive Care Unit of Hôpital Beaujon. One patient was admitted to the Liver Unit of Liège Hospital.

Nine were men or boys and nine were women or girls. Their mean age was 42 years (range, 15 to 69 years). All other causes of acute liver injury were ruled out in each. Specifically, (1) there was no history of blood transfusions or illicit parenteral drug use; (2) no detectable IgM against hepatitis B core antigen and hepatitis A virus was found; (3) a panel of anti-organelle antibodies was negative in each; and (4) no exposure to hepatotoxic substances other than the antituberculous therapy was identified in each. Patient 14 was a hepatitis B virus chronic carrier. Patient 17 was positive for human immunodeficiency virus. None of the patients had previous history of alcohol abuse.

The antituberculous drugs administered to these 18 patients are listed in Table 1. The indications for antituberculous treatment were pulmonary tuberculosis in 5, pleural tuberculosis in 4, tuberculous peritonitis in 3, tuberculous adenitis in 3, and tuberculous spondylitis, urinary tuberculosis, and gastrointestinal tuberculosis in 1 patient each.

All of the patients developed manifestations of encephalopathy that progressed to grade III (i.e., coma; see Table 1 for encephalopathy grading) in 14 (78%). Immunologic manifestations such as fever, hypereosinophilia, or cutaneous rash were absent in all 18. A liver biopsy was performed in 13 (72%). Massive necrosis and cholestasis without fibrosis were observed in all 13. Supportive therapy included dextrose infu-

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TABLE 1. Main Characteristics of the Patients

Patient No.	Year	Age (y)	Isoniazid Dosage (mg/kg/d)	Pyrazinamide Dosage (mg/kg/d)	Other Drugs	Onset of Jaundice* (d)	Maximal Grade of Encephalopathy†	Maximal ALAT Activity (× normal)	Factor V/ Prothrombin Time‡ (% of normal)	Serum Creatinine on Admission (μmol/L)	Outcome
1	1972	26	6.5	0	R, S	6	III	66	10/10	94	Alive
2	1972	32	11	0	E, R	6	II	45	30/28	77	Alive
3	1973	24	6	0	E, R	10	III	110	10/10	85	Alive
4	1973	67	17	0	E, R	7	III	72	15/10	126	Alive
5	1975	15	19	0	E, R	6	III	46	10/10	175	Alive
6	1975	65	9.5	0	R, S	9	III	30	15/12	95	Alive
7	1975	69	9.5	0	E, R	5	II	42	23/21	90	Alive
8	1975	27	10	0	E, R, S	10	III	41	10/10	70	Alive
9	1977	69	5.5	0	E, R	85	II	57	24/27	115	Dead
10	1980	37	5	27	E	244	III	34	10/10	110	Dead
11	1986	68	5	25	E, R	52	III	42	10/10	73	Dead
12	1989	20	3.5	18	R, S	25	III	50	16/15	230	LT Alive
13	1990	40	5	29	R	100	III	85	10/10	524	LT Dead
14	1990	25	5	33	E, R	98	III	53	15/15	60	LT Alive
15	1990	41	9.5	37	E, R	7	III	180	10/10	130	Alive
16	1990	52	5	28	E, R	7	I	80	30/28	57	Alive
17§	1991	31	3	30	E, R	51	III	51	11/10	82	Dead
18	1991	53	3	26	E, R	18	III	60	15/14	50	LT Dead

Abbreviations: E, ethambutol; R, rifampicin; S, streptomycin; LT, liver transplantation.
* Time interval between the onset of treatment and the onset of jaundice.
† Grade I, asterixis; grade II, confusion; grade III, coma.
‡ Lowest value.
§ HIV-positive patient.

sion (200 g daily), phosphorous supplementation, and mechanical ventilation in 14. Sedative drugs, diuretics, and fresh frozen plasma were not administered. Specific data are presented in Table 1.

Based on the use of pyrazinamide, the study population could be divided into two groups. Group 1 consisted of nine patients who were not given pyrazinamide. Group 2 consisted of nine patients who were. Six[4] of the nine patients of group 1 and one patient (number 10) of group 2 (Danan, Lancet 1981;2:1056, Letter) were previously reported.

RESULTS

Clinical and Biochemical Features. Groups 1 and 2 were comparable regarding age and sex. The mean daily dosage of isoniazid was significantly higher in group 1 than in group 2 (Table 2). The mean daily dosage of rifampicin did not differ between the two groups. Seven patients in each group were given ethambutol. The mean time interval between the onset of antituberculous treatment and the onset of jaundice was shorter, albeit not significantly, in group 1 (16 days; range, 6 to 85 days) than in group 2 (67 days; range, 7 to 244 days).

The prevalence of coma and the lowest level of factor V obtained by the subjects in each group did not differ between the two groups (Table 2). The mean maximal serum bilirubin level was lower, albeit not significantly, in group 1 (255 μmol/L) than in group 2 (419 μmol/L). The mean interval between the onset of jaundice and the onset of encephalopathy in group 1, 3.7 ± 6.2 days, did not differ significantly from that in group 2, 6.4 ± 4.7 days. This interval was significantly shorter in the 10 patients who survived spontaneously (2.2 ± 2 days) than in the eight patients who either died or received transplants (8.7 ± 6.5 days, $P < .01$). None of the patients had known preexisting renal failure. An increased serum creatinine value (>100 μmol/L) was observed at admission in three patients in group 1 and in four others in group 2 (Table 1). Because pyrazina-

TABLE 2. Comparison of Groups 1 and 2

	Group 1 Without Pyrazinamide (n = 9)	Group 2 With Pyrazinamide (n = 9)	P
Age (y) (mean ± SD)	44 (±22.9)	41 (±15)	NS
Sex ratio (M/F)	3/6	6/3	NS
Isoniazide dosage (mg/kg/d) (mean ± SD)	10 (±4.7)	5 (±1.9)	<.05
Rifampicin dosage (mg/kg/d) (mean ± SD)	10 (±1.9)	10 (±2)	NS
Interval between the onset of treatment and the onset of jaundice (d) (mean ± SD)	16 (±25.9)	67 (±75.2)	NS
Prevalence of coma	6/9	8/9	NS
Minimal factor V (% of normal) (mean ± SD)	16 (±7.5)	14 (±6.5)	NS
Spontaneous survival	8/9	2/9	<.02

mide is mainly excreted by the kidney, associated impairment of renal function may conceivably have led to higher pyrazinamide levels and toxicity.

Liver Transplantation. Our emergency liver transplantation program began in 1986.[7] To define criteria for liver transplantation in patients admitted for liver failure due to antituberculous treatment, we compared the eight patients who survived (patients 1 to 8) with the three patients who died (patients 9 to 11) before the end of 1986. Two of the three patients who died had received pyrazinamide, but none of the eight survivors had. The time interval between the onset of antituberculous treatment and the onset of jaundice was greater than 15 days in the three patients who died, whereas it was always less than 15 days in the eight who survived.

In accordance with these results, the combination of the following four criteria was used to decide emergency liver transplantation in patients admitted for liver failure due to antituberculous treatment: pyrazinamide co-administration; time interval between the onset of antituberculous treatment and the onset of jaundice greater than 15 days; grade III encephalopathy; and factor V below 20% of normal. The combination of the latter two factors has been used to identify nonsurvivors of fulminant and subfulminant liver failure for several years at our institution.[7,8]

The combination of these four criteria was prospectively applied to the remaining seven patients observed between 1989 and 1991. During this period, five patients met the criteria for liver transplantation; four received transplants (two at Hôpital Paul Brousse, one at Liège hospital, and one at Hôpital Beaujon), with two survivors. At the time of transplant decision, these five patients all were comatose and had factor V between 10% and 16% of normal. The fifth patient, in whom liver transplantation was not used because of a co-existent human immunodeficiency virus infection, died of subfulminant liver failure. The two patients who did not meet these criteria (one of them, patient 15, with coma and factor V at 10% of normal) did not receive transplants, and both survived.

Overall Survival. Among the nine patients who were receiving isoniazid but not pyrazinamide, eight survived and one died. Among the nine patients who were given both isoniazid and pyrazinamide, two survived, three died, and four received transplants, with two surviving. If one assumes that the four patients who received transplants would not have survived spontaneously, the proportion of patients who survived was reduced significantly in group 2 (two of nine) as compared with group 1 (eight of nine) ($P < .02$) (Table 2).

DISCUSSION

As a consequence of the development of multiple drug resistance, combinations of three or more major antituberculous agents are often prescribed in patients with active tuberculosis.[2,8] Thus, patients developing fulminant or subfulminant hepatitis occurring as a result of antituberculous therapy often have been receiving a combination of agents.

The major finding of this study was the striking difference in the spontaneous survival rate of patients who had received isoniazid and rifampicin as compared with those receiving isoniazid and rifampicin plus pyrazinamide. The former group had a surprisingly high (88%) spontaneous recovery rate. In contrast, the latter group had a spontaneous recovery rate of only 22%, similar to that observed in fulminant drug-induced hepatitis taken globally.[3,9,10] Importantly, the maximal severity of encephalopathy and the lowest factor V value obtained by each group did not differ.

Rifampicin is very seldom hepatotoxic when given alone.[4] However, it is a potent microsomal enzyme inducer.[11] Isoniazid is metabolized by cytochrome P450 enzymes to a reactive metabolite that is toxic to the liver.[11] Fulminant hepatitis in patients receiving isoniazid and rifampicin is thought to be due to the toxic effects of isoniazid, possibly enhanced by the concomitant administration of rifampicin.[4] As previously reported,[4] and confirmed by three additional patients in the current study, isoniazid-rifampicin fulminant hepatitis usually occurs within 10 days of the initiation of the antituberculous treatment.

Pyrazinamide given alone may produce fulminant or, more often, subfulminant hepatitis.[6] The liver failure due to pyrazinamide usually occurs after long periods of treatment.[6,12,13] To our knowledge, the mechanism of pyrazinamide hepatotoxicity remains unknown.

In patients receiving both isoniazid and pyrazinamide (plus or minus rifampicin), fulminant or subfulminant liver failure may be caused by either isoniazid or pyrazinamide or both. The current study does not provide an answer to this question. It is noteworthy, however, that in the two patients who spontaneously survived after administration of both isoniazid and pyrazinamide (patients 15 and 16), manifestations of hepatitis occurred 7 days after the onset of the treatment, a time interval similar to that seen in patients experiencing isoniazid-rifampicin fulminant hepatitis (Table 1). It is therefore tempting to speculate that these two patients, who had an early onset of fulminant liver failure and a good prognosis, may have had isoniazid-mediated hepatic injury. The seven remaining patients treated with both isoniazid and pyrazinamide exhibited a long interval before the onset of jaundice (similar to that observed in pyrazinamide hepatitis) and either died or received transplants (Table 1). We speculate that these patients may have had pyrazinamide-induced fulminant hepatitis as a form of hepatic injury caused by pyrazinamide possibly confounded by isoniazid hepatitis, resulting in a lethal outcome.

Although pyrazinamide-induced hepatitis was initially reported in patients receiving a daily dose greater than 30 mg/kg,[13] it is noteworthy that 7 of our nine cases of pyrazinamide-associated fulminant hepatitis occurred in patients given a daily dose $\leq$30 mg/kg (Table 1). Similar cases of fatal hepatitis with a long inter-

val between the onset of antituberculous therapy and the onset of hepatitis have been observed in patients on antituberculous regimen, including low doses of pyrazinamide, and were reported more than 35 years ago in the United States[14] and more recently in the Netherlands[15] and in the United Kingdom.[16] Several prospective studies suggest that the incidence of hepatic disturbances may be higher in tuberculous patients given pyrazinamide than in those not given this drug (reference 17 and references therein).

These observations should serve as a reminder for the need to respect the following therapeutic guidelines, as recommended by the French Health authorities[18]: (1) perform liver and renal function tests before starting the drug and, if possible, avoid pyrazinamide in patients with abnormal test results; (2) monitor serum alanine aminotransferase activity every week for the 2 months of pyrazinamide administration and monitor serum creatinine every month; (3) stop the administration of pyrazinamide as soon as serum alanine aminotransferase activity is more than three times elevated; (4) usually stop the administration of the drug after 2 months of treatment.

It is concluded that the fulminant or subfulminant liver failure seen in patients receiving isoniazid and rifampicin without pyrazinamide usually occurs within 15 days of the onset of treatment (eight of nine patients) and has a good prognosis (eight survivors among nine patients). In contrast, fulminant or subfulminant hepatitis occurring in patients receiving isoniazid and rifampicin plus pyrazinamide may be divided into two subtypes: (1) in the first one, hepatitis occurs early, has a fulminant course and a good prognosis similar to those of isoniazid-induced hepatitis (suggesting that this first subtype of hepatitis may be due to isoniazid); (2) in the second one, hepatitis occurs 15 days or more after the initiation of treatment, has a subfulminant course (suggesting that this second subtype of hepatitis may be due to pyrazinamide), and has a bad prognosis. Accordingly, the patients in this latter subgroup may be reasonably considered as candidates for emergency liver transplantation when grade III encephalopathy and factor V below 20% are present.

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