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• *BRIEF REPORTS* •

Effect of anti-tuberculosis therapy on liver function of pulmonary tuberculosis patients infected with hepatitis B virus

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Abstract

AIM: To observe the effect of anti-tuberculosis therapy on liver function of pulmonary tuberculosis patients with hepatitis B virus (HBV) infection, and to compare the differences of liver function by two treatments of anti-tuberculosis.

METHODS: Forty-seven TB patients with HBV infection and 170 TB patients without HBV infection were divided into HPBE(S) and HLAMKO treatment groups. Liver function tests before and after the treatments were performed once in 2 wk or monthly, and their clinical manifestations were recorded.

RESULTS: The rate of hepatotoxicity occurred in 26 (59%) TB patients with HBV during anti-TB treatment, higher than that in 40 (24%) TB patients without HBV. Hepatotoxicity occurred in 66 out of 217 patients, and the incidence of liver dysfunction was 46.1% in HPBE(S) group, significantly higher than that in HLAMKO group (12.7%) ($P<0.01$).

CONCLUSION: TB patients with HBV should choose HLAMKO treatment because of fewer hepatotoxicity.

Key words: Anti-tuberculosis; HBV

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INTRODUCTION

In recent years, the occurrence of tuberculosis has been increasing obviously[1,2], and many tubercle bacilli are resistant to anti-tuberculosis drugs, so the combination of anti-tuberculosis drugs has become essential. At present, most commonly used anti-TB drugs are more or less hepatotoxic, especially when several anti-TB drugs are used in combination. Liver dysfunction caused by anti-TB drugs often results in interruption of anti-TB therapy and acute hepatic failure, which even threatens patient's life[3,4]. In China, a large number of people are carrying hepatitis B virus (HBV), so tuberculosis patients are very commonly infected with HBV. When these patients are treated by anti-TB medicines, is it easier to show liver dysfunction because of infection with HBV[5-9]? We analyzed the effect of anti-TB therapy on liver function of patients with pulmonary tuberculosis infected with HBV and compared the hepatotoxicity of an anti-TB plan (HPBES, including isonicazide, rifampicin, pyrazinamide, ethambutol, streptomycin) with that of another anti-TB plan-HLAMKO (including isonicazide, rifabutin, amikacin, ofloxacin, levofloxacin). We suggest that physicians should be careful to use anti-TB medicines for pulmonary tuberculosis patients with HBV infection and choose anti-TB medicines, which cause less liver damage.

MATERIALS AND METHODS

Subjects

Forty-seven patients carrying HBV for 3-15 years were all inpatients (1996-2001). Of them 28 were men and 19 were women aged 20-67 years. Their liver function was normal when they suffered from pulmonary tuberculosis. We also analyzed 170 outpatients and inpatients (including 108 men and 62 women) with pulmonary tuberculosis, but without carrying HBV. All patients were diagnosed as pulmonary tuberculosis by chest X-ray, medical history, antacid bacillus in phlegm and TB-PCR[10]. All patients were not infected with other hepatitis viruses and had no alcoholic liver ailment or other chronic liver ailment. The values of ALT were all below 60 U/L before anti-TB therapy, and these patients did not drink alcohol during the period of therapy. All patients were matched with the diagnostic standard set up in 1988[11], including 118 cases of pulmonary TB types II and III, 83 cases of tuberculosis pleurisy (type IV), 4 cases of tuberculosis pericarditis (type V), 7 cases of tracheal-bronchial TB, 5 cases of thoracic wall TB.

Methods of treatment

Patients were divided into two groups, HPBES group: isonicazide 0.3 g, once a day; rifampicin 0.45 g once a day, pyrazinamide 1.0 g once a day, ethambutol 1.0 g once a day and/or streptomycin 0.75 g once a day; and HLAMKO

group: isonicazide 0.3 g once a day, rifabutin 0.6 g once a week, amikacin 0.2 g VD, twice a day, ofloxacin 0.2 g VD, twice a day or levofloxacin 0.2 g VD, twice a day. The general conditions of the two groups were not distinguishable ($P>0.05$). All patients were treated till the disappearance of symptoms, smaller focal lesions on breast X-ray film, negative antacid bacilli in phlegm. The curative effects were graded as effectiveness: disappearance or improvement of symptoms and smaller focal lesions on breast X-ray film, remission: improved symptoms and unchanged focal lesions on breast X-ray film, inefficiency-without improvement of clinical symptoms and breast X-ray film.

Parameters detected

Patients' liver functions were detected by automatic biochemical analytic apparatus when the patients had empty stomachs. Anti-HAV, anti-HBV, anti-HCV, anti-HDV, anti-HEV were detected by ELISA. Liver function of the patients was examined repeatedly every 2 wk till 2 months after therapy, then every month. When ALT was above 1 336 IU/L 2-3 mo after therapy, we defined it as liver dysfunction. However, if it was below 3 340 IU/L, we still continued the anti-TB therapy and added some liver protecting and ALT decreasing medicines including febuprol, biphenydimethylesterate, *etc*. But if liver dysfunction was serious (ALT >3 340 IU/L) and the patients had clinical symptoms and the effect of treatment was not good, then we stopped using anti-TB drugs.

Statistical analysis

Data were expressed as mean±SD and the comparison between groups was analyzed by χ^2 test or t test.

RESULTS

Clinical characteristics of patients with hepatic damage

Of the 217 patients, ALT kept abnormal (>1 336 IU/L) in 66 patients (30%) for more than 4 wk during the course of anti-TB therapy. Abnormal ALT appeared 2 mo after anti-TB therapy in 48 patients, and 17 patients had symptoms including fatigue, decreased appetite, dizziness, nausea, *etc*. Of the 115 patients using HPBES therapy plan, 53 patients (46%) had abnormal liver function. Of the 102 patients using HLAMKO therapy plan, 13 patients (13%) had hepatic damage ($P<0.01$, Table 1). One 48-year-old male patient had acute hepatic necrosis 1 wk after the HPBES therapy plan and died.

Table 1 Liver dysfunction of 66 patients after anti-TB treatment (mean±SD)

	HPBE (S) (n = 53)	HLAMKO (n = 13)	Total (n = 66)
Age (yr)	43±10	46±13	44±12
Sex (M/F)	38/15	9/4	47/19
T-Bil (μmol/L)	26 (6–202)	22 (8–112)	25 (6–202)
Albumin (g/L)	41±5.2	44±6.4	41±6.1
Globulin (g/L)	30±4.8	31±6.2	30±5.7
AST (IU/L)	2 271±37	2 134±42	2 204±41
ALT (IU/L)	2 538±64	2 688±79	2 622±75

Changes of liver function in HBV carriers

Of the 47 HBV carriers without symptoms and physical signs of hepatitis, 20 patients were positive for HBeAg, and 26 patients (59%) had liver dysfunction after anti-TB treatment, only 24% (40/170) of non-HBV carriers had liver dysfunction ($P<0.01$), but there was no significant difference in liver dysfunction between the positive and negative HBeAg groups. In the 47 pulmonary tuberculosis patients carrying HBV, the percent of the HPBES group with hepatic damage was 80% (8/10), but that of the HLAMKO group with hepatic damage was 30.4% (3/10) ($P<0.01$). The percent of liver dysfunction in non-HBV carriers receiving HLAMKO plan was 7.6% (Table 2).

Table 2 Effect of HBV on liver function after anti-TB treatment (%)

Group	HPBE(S) (%)	HLAMKO (%)
HBV carriers	19/24 (79.2)[b]	7/23 (30)[b]
$HBeAg^+$	8/10 (80)[d]	3/10 (30)
$HBeAg^-$	11/14 (79)	4/13 (31)
Noncarriers	34/91 (37)	6/79 (8)

[b]$P<0.01$ *vs* noncarriers, [d]$P<0.01$ *vs* HPBE(S).

Comparison between the two therapy plans

One hundred and fifteen patients used the HPBES plan. The time of treatment was 32±10 d. The treatment was effective for 64% (74/115), alleviative for 28% (32/115), inefficient for 7% (9/115) patients. Fifty-nine patients had serious side effects (hepatic damage mainly), and 15 (25%) stopped the therapy because of it.

One hundred and two patients used the HLAMKO plan. The time of treatment was 35±10 d. The treatment was effective for 63% (65/102), alleviative for 36% (37/102), inefficient for 3% (3/102) patients. Seventeen patients had side effects, 2 (11%) stopped the therapy because of rash, and 13 had liver dysfunction, but completed anti-TB treatment.

The time of treatment and the curative effect between the two plans were not significantly different ($P>0.05$). The number of patients stopping anti-TB treatment because of side effects in HPBES group was much more than that in HLAMKO group. Most of the side effects were hepatic damage.

DISCUSSION

Hepatic damage caused by drugs is a common side effect of anti-TB treatment. One reason is hepatotoxicity of drugs. Enzymes for drug metabolism in hepatocyte microsomes may have congenital defect, malformation, low activity, or be inhibited by drugs, so drugs or drug metabolites are very toxic to hepatocytes. The other reason is hypersensitivity by drugs. The drugs as a hapten cause allergic reaction by immune mechanism leading to the single ALT increase in clinical situation. Commonly used anti-TB drugs, such as isonicazide, rifampicin, pyrazinamide, ethambutol, *etc*., are all hepatotoxic, especially when rifampicin and pyrazinamide

are used in combination[12]. Isonicazide causes hepatic damage either by the toxicity of or hypersensitivity induced by its metabolite-acehydrazide. Rifampicin may accelerate the metabolism of isonicazide as a strong enzyme inducer resulting in the increase of acehydrazide. Acehydrazide combines with biomacromolecules in liver leading to hepatocellular damage usually seen in aged patients with excessive drinking, malnutrition or a liver ailment. Pyrazinamide's hepatotoxicity is dose-dependent and the general dose rarely causes hepatic damage. Isonicazide and rifampicin are the first line anti-TB medicines because of their strong bactericidal effects. However, rifabutin, amikacin, ofloxacin, levofloxacin, *etc.*, in the HLAMKO treatment plan have not been reported with obvious hepatotoxicity[13,14]. We found that the incidence of liver dysfunction was significantly higher in regimen HPBE(S) (46.1%) compared with HLAMKO (12.7%) ($P<0.01$). We think that HLAMKO treatment plan is superior regarding its fewer hepatotoxicities.

There are many risk factors of hepatic damage during the course of anti-TB treatment, such as the type of tuberculosis, recurred tuberculosis, HBV infection, alcohol drinking, age, nutrition status, heredity, individual difference and immune status, *etc.* Scholars outside China reported that most of hepatocytes in HBV carriers without clinical symptoms had changes in histology and spot necrosis in some hepatocytes. One researcher took liver biopsy from 25 pulmonary tuberculosis patients with HBV infection during the course of anti-TB treatment and discovered that all the patients with liver dysfunction suffered from viral hepatitis, even liver cirrhosis. Hepatic damage of the patients with pulmonary tuberculosis during the course of anti-TB treatment was related to HBV infection and pre-existing pathologic changes in liver. Anti-TB medicines only aggravated pre-existing hepatic damage[15,16]. So, HBV infection or pre-existing liver ailment might be an important risk factor[17,18]. Hepatotoxicity caused by anti-TB medicines was liable to happen in the first 2-3 mo of aggressive anti-TB treatment. Hepatic damage of the patients with positive HBV was caused by viral damage overlapped by medicine damage[4]. In our study, the rate of hepatotoxicity in 26 (59%) TB patients with HBV infection during anti-TB treatment was higher than that in 40 (24%) patients without HBV, and the incidence of liver dysfunction was significantly higher in regimen HPBE(S) (80%) with HBV infection compared with HLAMKO (30%) ($P<0.01$). However, the percent of liver dysfunction in non-HBV carriers accepting HLAMKO plan was 7.6%. So, TB patients with HBV infection should choose HLAMKO with fewer liver hepatotoxicity, and we should pay great attention to associated risk factors of hepatic damage.

Hepatotoxicity caused by anti-TB medicines usually happened in the first 2-3 mo of anti-TB treatment. In our study, 66 out of 217 patients had hepatic damage which happened in 21 patients within 1 mo, in 45 patients within 2 mo. We should inform the patients the possible side effects and get co-operation of the patients and choose the treatment plan with efficiency and the least side effects. Furthermore, we should monitor liver function of the patients. If the patients suffered from hepatic damage during the course of anti-TB treatment, it should be stopped, but some scholars did not agree with drug withdrawal[8], as it could increase the tolerance of TB. Some data demonstrated that tuberculosis patients with HBV receiving anti-TB treatment and liver protecting treatment simultaneously did not suffer from hepatic damage and jaundice. So, we used liver protectors when the patients' ALT was above 80 IU/L because the liver protecting drugs could relieve the liver dysfunction caused by anti-TB medicines by getting rid of the toxin in liver and improving the repair and regeneration of liver cell membranes. After using liver protecting drugs, we monitored liver function every week. If liver function did not improve, we adjusted liver protecting drugs and continued to observe the patients for 2-3 wk, if still liver function did not improve, we might stop isonicazide, rifampicin or pyrazinamide.

Pulmonary tuberculosis patients with HBV were more sensitive to hepatotoxic drugs because of pre-existing hepatic damage and liver function of these patients improved more slowly. The hepatitis induced by hepatotoxic drugs still kept for some time after anti-TB treatment ended, we should still monitor liver function and give proper treatment after completion of anti-TB treatment.

It is important to pay attention to the risk factors, such as liver disease family history, excessive drinking, age, HBV-HCV carrier, *etc.*, and prevent the hepatic damage caused by anti-TB medicines. We should observe the patients more carefully and monitor liver function every 1-2 wk in the early course of anti-TB treatment. We must adjust anti-TB treatment plan and choose slight hepatotoxic drugs and use liver protecting drugs in patients with HBV infection, therefore, we may decrease the incidence of hepatitis induced by drugs and increase the cure rate of tuberculosis.

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