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Original Article

Influence of blood concentration monitoring of isoniazid on liver damage in patients with pulmonary tuberculosis complicated with liver dysfunction

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Abstract: Objective: The aim of this study was to investigate the influence of blood concentration monitoring (BCM) of isoniazid on liver damage in patients with pulmonary tuberculosis complicated with liver dysfunction (PTCLD). Methods: A total of 82 patients with PTCLD, admitted to Ji'nan Infectious Diseases Hospital, were selected and randomly divided into 2 groups, a control group (n = 41) and BCM group (n = 41). Both groups of patients were treated with 2HRZE/4HR chemotherapy and liver protection treatment. BCM of isoniazid was conducted once a month in the blood concentration group and dosage of isoniazid was adjusted based on monitoring results. Therapeutic effects of pulmonary tuberculosis were evaluated after treatment. Adverse reactions during treatment were observed. Liver function indexes were detected before and after treatment. Liver biopsies were performed and Ishak's integral system was used for histological evaluation. Results: There were no statistical differences in general data between the two groups (all P > 0.05). Compared with the control group, there were no statistical differences in treatment effects of pulmonary tuberculosis in the BCM group (Wilcoxon W = 1,672.000, P = 0.744). Compared with the control group, the BCM group could reduce the content of alanine aminotransferase (t = 2.508, P = 0.014), aspartate aminotransferase (t = 4.196, P = 0.000), total bilirubin (t = 3.013, P = 0.004), direct bilirubin (t = 3.123, P = 0.003), and indirect bilirubin (t = 3.583, P = 0.001) after treatment, but there were no statistical differences in albumin (t = 0.339, P = 0.735) and prothrombin time (t = 0.354, P = 0.724). Scores of focal necrosis (t = 2.251, P = 0.027) and portal inflammation (t = 2.042, P = 0.045) were also reduced but there were no statistically significant differences in fusion necrosis (t = 0.556, P = 0.580), pylephlebitis (t = 0.136, P = 0.892), and hepatic fibrosis (t = 1.078, P = 0.284). Incidence of total adverse reactions could be reduced (χ^2 = 4.100, P = 0.043), but there were no statistical differences in specific indexes of gastrointestinal reaction (χ^2 = 2.877, P = 0.090), peripheral neuritis (χ^2 = 0.346, P = 0.556), and hematological symptoms (χ^2 = 1.012, P = 0.314). Conclusion: BCM of isoniazid reduces liver damage in patients with PTCLD.

Keywords: Isoniazid, blood concentration monitoring, pulmonary tuberculosis, liver dysfunction, liver damage

Introduction

Pulmonary tuberculosis is a pulmonary chronic infectious disease caused by mycobacterium tuberculosis. It can be transmitted through the respiratory tract and is a major controlled infectious disease in China [1, 2]. One third of the world's population has been infected with mycobacterium tuberculosis and more than 9 million new cases of tuberculosis are added annually [3]. At present, anti-tuberculosis drugs mainly include isoniazid, rifampicin, pyrazinamide, ethambutol, and other drugs. Isoniazid is often used as a first-line drug for its high selectivity and strong penetration to mycobacterium tuberculosis. However, isoniazid has strong hepatotoxicity, which can cause focal necrosis, portal inflammation, fusion necrosis, pylephlebitis, hepatic fibrosis, and other hepatic histological changes. These are manifested with increase of patient liver function indexes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBiL), especially when isoniazid is used in combination with rifampicin. Rifampicin can accelerate the metabolism of isoniazid into hepato-

toxic substances by inducing the production of hepatic drug enzymes, significantly enhancing hepatotoxicity [4-7].

Compared to pulmonary tuberculosis alone, patients with pulmonary tuberculosis complicated with liver dysfunction (PTCLD) have poor pharmacokinetics in the liver. Anti-tuberculosis treatment is more likely to cause toxic side effects. It is difficult to conduct effective standardized treatment clinically [8, 9]. Saito et al. studied 44 cases of pulmonary tuberculosis complicated with cirrhosis. They found that patients showed higher mortality and incidence of adverse reactions in anti-tuberculosis chemotherapy significantly increased [10]. With the popularization of individual medicine in recent years, monitoring of blood drug concentrations has solved the problem of high heterogeneity of drug pharmacokinetics and reduced damage to patients from drugs with more and severe adverse reactions [11, 12]. For example, Cai et al. found that maintaining blood concentration at 25.6-37.4 mg/L could reduce adverse reactions, such as bone marrow transplantation, and prolong the survival time of patients by monitoring the blood concentration of fluorouracil in gastric cancer patients [13]. Therefore, this research investigated whether monitoring of blood concentration of isoniazid could reduce liver damage in patients with PTCLD.

Materials and methods

General information

A total of 82 cases of PTCLD patients, admitted to the Department of Respiratory in Ji'nan Infectious Diseases Hospital, from March 2015 to June 2017, were selected as research subjects. Patients were randomly divided into 2 groups, with 41 cases in each group, the control group and blood concentration monitoring (BCM) group. All patients signed informed consent and the Ethics Committee of Ji'nan Infectious Diseases Hospital approved this study.

Inclusion criteria and exclusion criteria

Inclusion criteria: 1) Patients diagnosed with pulmonary tuberculosis in accordance with the diagnostic standards of pulmonary tuberculosis (WS288-2008), details as follows. Sputum smear microscopy: Acid-fast bacillus was positive. Clinical manifestations: Cough and expectoration ≥ 2 weeks or associated by hemoptysis. Chest imaging examination: Plaque or infiltration shadows were shown in the apex pulmonis or infraclavicula. Mycobacterium culture was positive. A comprehensive analysis was carried out mainly based on results of sputum smear microscopy, combined with clinical manifestations, results of chest imaging examination, and mycobacterium culture; and 2) Mild liver dysfunction: High normal value ≤ ALT, AST, TBiL ≤ 2 times the high normal value. Normal value of ALT: 5-40 U/L; normal value of AST: 8-40 U/L; normal value of TBiL: 3.4-17.1 μmol/L.

Exclusion criteria: 1) Severe liver dysfunction: ALT, AST or TBL > 2 times the high normal value and to determine combined with other clinical indicators; 2) Patients with drug allergies; and 3) Patients complicated with malignant tumors, hematological diseases, rheumatic immunity diseases, cardiovascular diseases, nervous system diseases, and mental disorders.

Treatment methods

Both groups of patients were treated with 2HRZE/4HR chemotherapy and liver protection treatment, including isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) for 2 months of intensive treatment. Isoniazid (H) and rifampicin (R) were included for 4 months of maintenance treatment. Patients in the control group received oral doses of isoniazid 0.30 g, rifampicin 0.45 g, pyrazinamide 1.50 g, and ethambutol 0.75 g daily. BCM of isoniazid was conducted once a month in the BCM group. If blood concentration was greater than 6 mg/L at 1 hour after medication, the dosage would be reduced by 0.05 g on the second day until blood concentration remained lower than 6 mg/L at 1 hour after medication. The reduced dosage would be taken at 12 hours after medication. Dosage of the other three types of drugs was the same as that in the control group. Isoniazid, rifampicin, pyrazinamide, and ethambutol were produced by Shenyang Hongqi Pharmaceutical Co. Ltd.

Evaluation of therapeutic effects of pulmonary tuberculosis

After completion of anti-tuberculosis treatment, therapeutic effects of the two groups of

Table 1. Comparison of general data between the two groups of patients

Clinical data	Control group (n = 41)	Blood concentration monitoring group (n = 41)	t/χ^2	P
Age (year)	46.32 ± 10.22	45.98 ± 10.86	0.146	0.884
Male (case)	27 (65.85)	29 (70.73)	0.225	0.635
Course of diseases (year)	3.83 ± 0.88	3.61 ± 0.79	1.191	0.237
ALT (U/L)	52.44 ± 8.08	55.01 ± 9.20	1.344	0.183
AST (U/L)	48.56 ± 6.90	50.71 ± 7.07	1.394	0.167
TBiL (μmol /L)	24.33 ± 5.71	22.58 ± 4.29	1.569	0.121
DBiL (μmol/L)	13.52 ± 3.22	12.89 ± 3.11	0.901	0.370
IBiL (μmol/L)	10.81 ± 2.96	9.69 ± 2.91	1.728	0.088
ALB (g/L)	41.50 ± 5.26	41.72 ± 5.20	0.191	0.849
PT (s)	14.06 ± 2.13	14.01 ± 2.08	0.108	0.915
Focal necrosis (point)	2.09 ± 0.87	2.01 ± 0.83	0.426	0.671
Fusion necrosis (point)	2.55 ± 1.17	2.68 ± 1.09	0.521	0.604
Portal inflammation (point)	2.24 ± 0.96	2.16 ± 0.90	0.389	0.698
Pylephlebitis (point)	2.38 ± 1.18	2.29 ± 1.20	0.342	0.733
Hepatic fibrosis (point)	2.36 ± 1.27	2.49 ± 1.36	0.447	0.656

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin; DBiL, direct bilirubin; IBiL, indirect bilirubin; ALB, albumin; PT, prothrombin time.

patients were evaluated and divided into three levels, including significantly effective, effective, and ineffective. Significantly effective: Cough, expectoration, hemoptysis, and other symptoms of tuberculosis disappeared; Pulmonary plaque shadow disappeared; Sputum smear microscopy showed negative. Effective: Pulmonary tuberculosis symptoms and pulmonary plaque shadow improved. Ineffective: Pulmonary tuberculosis symptoms and pulmonary plaque shadow did not improve and were even aggravated. Total effective rate = Number of cases (significantly effective + effective)/total number of cases*100%.

Observation index

An automatic biochemical analyzer was used to detect liver function, before and after treatment, including ALT, AST, TBiL, direct bilirubin (DBiL), indirect bilirubin (IBiL), and albumin (ALB). An automatic coagulometer was used to detect prothrombin time (PT) before and after treatment. Adverse reactions during treatment, including gastrointestinal reactions, peripheral neuritis, and hematological symptoms, were observed. All patients underwent liver biopsies before and at the end of treatment. Ishak's integral system was used for histological evaluation: focal necrosis (0-4 points), fusion necrosis (0-6 points), portal inflammation (0-4 points), pylephlebitis (0-4 points), and hepatic fibrosis (0-6 points) [14, 15].

Statistical analysis

SPSS13.0 software was used for statistical analysis. Measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). The two groups of data were compared via t-test. Count data were compared using χ^2 test. The two groups of rank data were compared via Wilcoxon signed rank sum test. $P < 0.05$ represents a statistical difference. $P < 0.01$ represents a significant statistical difference.

Results

Comparison of general data between two groups of patients

General data between the two groups of patients were compared. Results in **Table 1** show that, compared with the control group, the BCM group had no statistical differences in age ($t = 0.146$, $P = 0.884$), gender ($\chi^2 = 0.225$, $P = 0.635$), course of disease ($t = 1.191$, $P = 0.237$), ALT ($t = 1.344$, $P = 0.183$), AST ($t = 1.394$, $P = 0.167$), TBiL ($t = 1.569$, $P = 0.121$), DBiL ($t = 0.901$, $P = 0.370$), IBiL ($t = 1.728$, $P = 0.088$), ALB ($t = 0.191$, $P = 0.849$), PT ($t = 0.108$, $P = 0.915$), focal necrosis ($t = 0.426$, $P = 0.671$), fusion necrosis ($t = 0.521$, $P = 0.604$), portal inflammation ($t = 0.389$, $P = 0.698$), pylephlebitis ($t = 0.342$, $P = 0.733$), and hepatic fibrosis ($t = 0.447$, $P = 0.656$), but were comparable.

Table 2. Comparison of therapeutic effects of pulmonary tuberculosis between the two groups of patients (n, %)

Results of treatment	Control group (n = 41)	Blood concentration monitoring group (n = 41)	Wilcoxon W	P
Significantly effective	28 (68.29)	26 (63.41)	1,672.000	0.744
Efficiency	8 (19.51)	11 (26.83)		
Ineffectiveness	5 (12.20)	4 (9.76)		
Total effective rate	36 (87.80)	37 (90.24)		

Table 3. Comparison of liver function after treatment between the two groups of patients

Liver function index	Control group (n = 41)	Blood concentration monitoring group (n = 41)	t	P
ALT (U/L, $\bar{x}$ ± sd)	101.86 ± 25.17	89.55 ± 18.82	2.508	0.014*
AST (U/L, $\bar{x}$ ± sd)	94.61 ± 21.39	76.88 ± 16.57	4.196	< 0.001**
TBiL (μmol/L)	37.15 ± 9.46	31.08 ± 8.77	3.013	0.004**
DBiL (μmol/L)	20.64 ± 4.56	17.56 ± 4.37	3.123	0.003**
IBiL (μmol/L)	16.51 ± 3.94	13.52 ± 3.61	3.583	0.001**
ALB (g/L)	38.93 ± 5.04	39.31 ± 5.10	0.339	0.735
PT (s)	14.28 ± 2.20	14.11 ± 2.15	0.354	0.724

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin; DBiL, direct bilirubin; IBiL, indirect bilirubin; ALB, albumin; PT, prothrombin time. *P < 0.05, **P < 0.01.

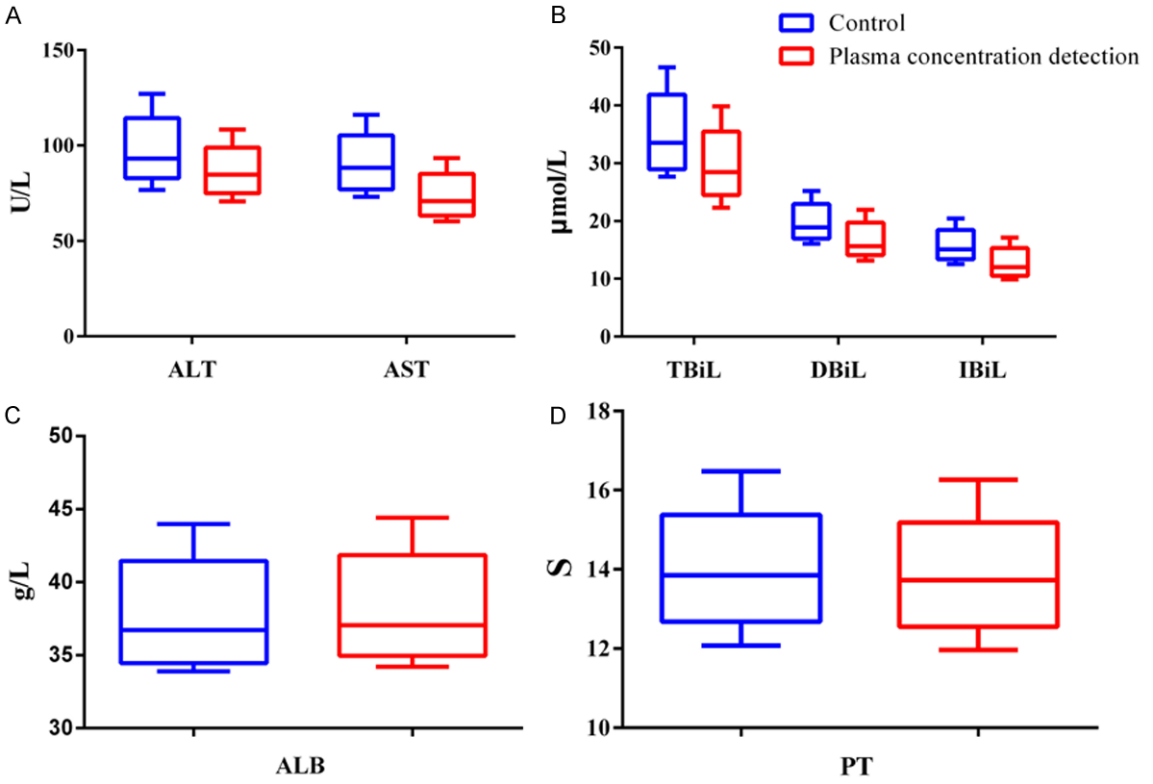

Figure 1. Distribution of liver function indicators after treatment between the two groups of patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin; DBiL, direct bilirubin; IBiL, indirect bilirubin; ALB, albumin; PT, prothrombin time.

Table 4. Comparison of liver histology after treatment between the two groups of patients (point, $\bar{x}$ ± sd)

Liver histology index	Control group (n = 41)	Blood concentration monitoring group (n = 41)	t	P
Focal necrosis	2.96 ± 1.03	2.42 ± 1.14	2.251	0.027*
Fusion necrosis	2.81 ± 1.10	2.95 ± 1.18	0.556	0.580
Portal inflammation	2.91 ± 1.03	2.45 ± 1.01	2.042	0.045*
Pylephlebitis	2.41 ± 1.30	2.37 ± 1.36	0.136	0.892
Hepatic fibrosis	3.28 ± 1.72	2.88 ± 1.64	1.078	0.284

Note: *P < 0.05.

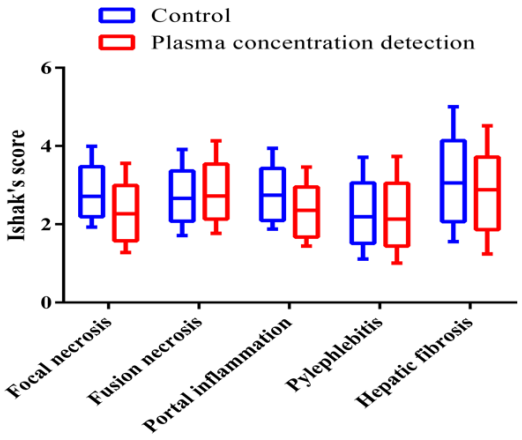

Figure 2. Distribution of Ishak's grade after treatment between the two groups of patients.

Comparison of therapeutic effects of pulmonary tuberculosis between the two groups of patients

After completion of anti-tuberculosis treatment, results of treatment of the two groups were evaluated. Results in **Table 2** show that there were no statistical differences in therapeutic effects of pulmonary tuberculosis in the BCM group, compared with the control group (Wilcoxon W = 1,672.000, P = 0.744).

Comparison of liver function after treatment between the two groups of patients

After completion of anti-tuberculosis treatment, liver function of the two groups was detected. Results in **Table 3** and **Figure 1** show that, compared with the control group, the BCM group significantly reduced the post-treatment content of ALT (t = 2.508, P = 0.014), AST (t = 4.196, P = 0.000), TBiL (t = 3.013, P = 0.004), DBiL (t = 3.123, P = 0.003), and IBiL (t = 3.583, P = 0.001). There were no statistical differences in ALB (t = 0.339, P = 0.735) and PT (t = 0.354, P = 0.724).

Comparison of liver histology after treatment between the two groups of patients

After completion of treatment, the liver histology of the two groups was assessed for Ishak scores of liver biopsies. Results in **Table 4** and **Figure 2** show that, compared with the control group, the BCM group reduced scores of focal necrosis (t = 2.251, P = 0.027) and portal inflammatory (t = 2.042, P = 0.045), but there were no significant differences in fusion necrosis (t = 0.556, P = 0.580), pylephlebitis (t = 0.136, P = 0.892), and hepatic fibrosis (t = 1.078, P = 0.284).

Comparison of other adverse reactions between the two groups of patients

Adverse reactions during treatment were compared between the two groups of patients. Results in **Table 5** show that, compared with the control group, the BCM group reduced occurrence of total adverse reactions (χ^2 = 4.100, P = 0.043). Regarding gastrointestinal reaction (χ^2 = 2.877, P = 0.090), peripheral neuritis (χ^2 = 0.346, P = 0.556), hematological symptoms (χ^2 = 1.012, P = 0.314), and other specific indicators, there were no statistical differences.

Discussion

Isoniazid is often used as a first-line anti-tuberculosis drug due to its characteristics of high selectivity and strong penetration over mycobacterium tuberculosis. However, isoniazid has a strong hepatotoxicity which can cause histopathological changes in the liver and an increase of hepatic function enzyme spectrum [16, 17]. Mechanisms of isoniazid-induced liver damage may be related to oxidative stress injuries, inducing hepatocyte apoptosis, stimulation of inflammatory reactions, and other pathological processes [18]. For example, Verma et

Table 5. Comparison of other adverse reactions between the two groups of patients (case)

Index	Control group (n = 41)	Blood concentration monitoring group (n = 41)	χ^2	P
Gastrointestinal reaction	5	1	2.877	0.090
Peripheral neuritis	2	1	0.346	0.556
Hematological symptoms	1	0	1.012	0.314
Total	8	2	4.100	0.043*

Note: *P < 0.05.

al. performed genome-wide expression analysis on Hep3B cells after isoniazid treatment. They found that isoniazid could reduce the phosphorylation of extracellular regulated protein kinases 1 and prevent the transfer of nuclear factor erythroid 2-related factor 2 from cytoplasm to the nucleus so that it could not play a protective role in nucleus, thereby resulting in cell apoptosis due to oxidative stress such as reactive oxygen species [19].

Patients with pulmonary tuberculosis are often associated with other liver diseases, such as chronic hepatitis B, viral hepatitis C, steatohepatitis, cirrhosis, alcoholic liver disease, autoimmune hepatitis, and so forth. If liver function is poor, the excretion of anti-tuberculosis drugs slows down, easily leading to accumulation of drugs in the body, thereby causing serious adverse reactions [20-22]. Therefore, it is of great clinical significance to monitor the blood concentration of anti-tuberculosis drugs in patients with PTCLD.

In this research study, 82 patients with PTCLD were randomly divided into 2 groups, a control group and BCM group. There were no statistical differences in age, gender, and course of disease between the two groups of patients. Liver function examinations and liver biopsies were performed before tuberculosis chemotherapy. It was found that liver function indexes of ALT, AST, and TBiL and liver histological scores of focal necrosis, portal inflammation, fusion necrosis, pylephlebitis, and hepatic fibrosis in both groups of patients were higher than normal values. However, there were no statistical differences between the two groups, which were comparable. Both groups of patients were treated with a 2HRZE/4HR chemotherapy regimen and liver protection treatment. The BCM group conducted BCM of isoniazid once a month and the dosage of isoniazid was adjusted based on monitoring results. Dosage of the other three types of drugs was the same as that of control group. Therapeutic effects of the two groups of patients after treatment were evaluated. It was found that when conducting monitoring of blood concentration of isoniazid for patients with poor pharmacokinetics, clinical effects of conventional treatment could still be achieved and total effective rates were even slightly higher than that of the control group in the case of reducing the dosage of isoniazid or taking a small amount with multiple times. However, there were no statistical differences, possibly related to the small sample size. In addition, compared with the control group, the BCM group reduced liver function indexes of ALT, AST, and TBiL after treatment, reduced scores of focal necrosis and portal inflammation, and reduced incidence of total adverse reactions, including gastrointestinal reactions, peripheral neuritis, and hematological symptoms. Therefore, isoniazid blood concentrations in patients with PTCLD should be monitored and medication dosage and duration of isoniazid should be adjusted. This will ensure that the blood concentration of isoniazid remains below the toxic dose, avoiding adverse reactions.

Although multiple BCM is more effective for clinical guidance, considering the time, labor, and other cost constraints, the frequency of BCM was set to once a month. Each monitoring was carried out until the blood concentration of 1 hour after isoniazid treatment was controlled below 6 mg/L. According to the above experimental results, once a month monitoring frequency can achieve the purpose of controlling occurrence of adverse events. For actual clinical practice, monitoring frequency can be increased correspondingly during early anti-tuberculosis treatment to explore the regularity of the pharmacokinetics of patients. In the later period of treatment, monitoring frequency can be reduced accordingly to save medical resources.

Although this study preliminarily investigated the protective effects of BCM of isoniazid on

patients with pulmonary tuberculosis and liver dysfunction, there remains many unsolved scientific issues: 1) Whether there is a difference in BCM for patients with liver dysfunction caused by different liver diseases; 2) In this research, the blood concentration of 1 hour after isoniazid treatment was controlled at below 6 mg/L, then what was the most appropriate range of concentration control; and 3) Whether the monitoring of blood concentrations of multiple anti-tuberculosis drugs simultaneously could continue to reduce incidence of adverse events. Therefore, the next step will be to continue to study the following three aspects: 1) BCM is carried out in patients with pulmonary tuberculosis complicated with different liver diseases to compare whether there are statistical differences in occurrence of adverse events; 2) Carry out comprehensive BCM of a series of anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, etc.) to further reduce incidence of adverse events in patients with pulmonary tuberculosis and liver dysfunction; and 3) Investigate how to determine the dosage and frequency of drug treatment according to different levels of blood concentrations, avoiding the empirical treatment of clinicians and forming a reference treatment program.

In summary, this present study conducted the BCM of isoniazid in patients with PTCLD, comparing the effects of treatment, liver function, liver histology, and occurrence of other adverse events. Results confirmed the clinical significance of carrying out monitoring of isoniazid blood concentration. This study lays a theoretical foundation for the development of individual medicine in the future.

Disclosure of conflict of interest

None.

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