Evaluation of the physicians’ approach to the diagnosis and treatment of patients with antituberculosis drug-induced hepatotoxicity

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Abstract

Objectives To describe the practices of physicians on the diagnosis and treatment of antituberculosis drug-induced hepatotoxicity (ATH), and to evaluate the concordance between these practices and the American Thoracic Society (ATS) 2006 guidelines.

Methods Information was reviewed on 670 new cases of tuberculosis patients aged not less than 15 years and registered at the outpatient clinics of a large hospital in southern Thailand during October 2006 to September 2009. The patient was identified as having ATH if: (1) he/she was diagnosed as transaminitis, hepatitis or hepatotoxicity from antituberculosis (anti-TB) drugs; (2) their treatment regimen was subsequently modified by their attending physicians; and (3) their liver enzyme decreased after withdrawal of the suspected anti-TB drugs. Compliance with the ATS guidelines was considered on diagnosis, initial management, selection of alternative regimens, and a reintroduction strategy.

Results The prevalence of ATH was 6.7%. The proportion of patients diagnosed as ATH in accordance with the ATS 2006 guidelines was 73.8%. For the initial management, isoniazid, rifampicin and pyrazinamide were concurrently stopped in 55.0% of patients. While waiting for normalization of liver enzymes, 28 patients (70.0%) were treated with alternative regimens and 12 patients (30.0%) took no drug. Only 47.5% of the ATH patients received a regimen in accordance with ATS guidelines, including three less hepatotoxic drugs (ethambutol, ofloxacin and streptomycin). Of 34 patients who discontinued the treatment, anti-TB drugs were reintroduced sequentially in 30 patients (88.2%). Of these, only 23.4% were firstly rechallenged with rifampicin as suggested by the ATS guidelines.

Conclusions The practice of physicians on the diagnosis and management of ATH varied. The practices of physicians on the diagnosis and rechallenged method were in high compliance with the ATS guidelines. For the initial management and selection of alternative regimens, the physicians’ compliance was not good.

Introduction

Tuberculosis (TB) is one of the major causes of death from curable infectious diseases. In 2009, about 9.4 million new TB cases occurred and 1.7 million people died from TB [1]. At least four first-line antituberculosis (anti-TB) drugs such as isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) are required to cure TB patients [2]. These are well tolerated and safe drugs with few side effects [3]. However, the incidence of antituberculosis drug-induced hepatotoxicity (ATH) during TB treatment has been variably reported between 3% and 20% [4–8]. Two of these four agents (H and Z) are major hepatotoxins [9,10]. Hepatotoxicity will increase when H and R are combined [11] because rifampicin, which is a powerful enzyme (CYP 3A4) inducer, may increase the hepatotoxic metabolite of isoniazid [12]. This side effect often results in discontinuation of the most effective first-line drugs. It also has a negative impact on patient compliance, decreases treatment success rates and may eventually enhance treatment failure, relapse or emergence of drug resistance [13,14].
There is a broad range of guidelines on the monitoring of liver function during TB treatment, diagnosis of ATH and reintroduction of anti-TB treatment. These have been set by various countries and scientific institutions, such as the American Thoracic Society (ATS) [15], the US Centers of Disease Control [16] and the British Thoracic Society [17]. These recommendations are based on evidence from expert committee reviews, opinions and/or clinical experience; therefore they have many variations and are inconsistent about details. Although these guidelines have been established, there are no data on how the physicians actually managed TB patients who developed hepatotoxicity, and how practices were in accordance with the ATS 2006 guidelines.

This study aimed to: determine the prevalence and clinical course of ATH; describe the physicians’ practice on the diagnosis and treatment of ATH; and evaluate the concordance between these practices and the ATS 2006 guidelines.

Methods

Study design, study setting and sample selection

A cross-sectional descriptive study was used. It was carried out at a large hospital in southern Thailand. Information was reviewed on patients who received first-line treatment for active TB registered at the outpatient clinics during October 2006 to September 2009 (3 years). Patients who were aged less than 15 years, had previous TB treatment and had undergone tests for abnormal baseline liver functions were excluded.

The patients who were identified as having ATH were as follows: (1) patients diagnosed by their attending physicians as having transaminitis, hepatitis or hepatotoxic from anti-TB regardless of their liver enzyme levels; (2) patients whose treatment regimen was modified by their attending physicians; and (3) patients whose liver enzyme decreased after withdrawal of the suspected anti-TB drugs.

Data collection

Patients’ information from the computerized database was reviewed by three senior pharmacy students. This information included: patient demographics (age, sex); clinical data (site of infection, TB treatment regimens and HIV status); symptoms of hepatotoxicity (nausea/vomiting, anorexia, abdominal pain, fatigue and jaundice); and duration of time from starting the treatment up to developing hepatotoxicity. Laboratory data associated with hepatotoxicity were also recorded including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin and alkaline phosphatase (ALP).

Moreover, the practices of the physician related to the diagnosis and management of ATH were recorded. These included: (1) the diagnosis for ATH; (2) initial management; (3) selection of alternative TB regimen; and (4) reintroduction of anti-TB drugs. In addition, the outcomes of the anti-TB rechallenge were also reviewed. The information on these practices was excluded if the patients with ATH had concomitant severe adverse drug reactions including severe cutaneous reactions, blurred visions and/or were referred to another hospital. The official statement of the ATS 2006 on hepatotoxicity of anti-TB therapy [15] was used as standard guidelines when evaluating the compliance of physicians’ practices.

Ethical considerations

The study protocol was approved by the Ethical Review Committee for Research in Human Subjects of the Faculty of Medicine, Prince of Songkla University.

Statistical analysis

All statistical analyses were carried out using R-program version 2.0.1 [18]. Categorical variables, such as patients’ gender, sites of infection, treatment regimens and physicians’ practices, were expressed in frequency and percentage. Numerical variables such as patients’ age and duration of hepatotoxicity development were expressed in means and standard deviation.

Results

Characteristics and clinical courses of ATH patients (Table 1)

During the 3-year study period, a total of 670 new TB patients, of not less than 15 years and receiving first-line treatment for active TB, were registered at outpatient clinics. Of these, 45 patients had abnormal baseline liver function tests. Finally, only 625 TB patients were included in this study. Among these, 42 patients (6.7%) fulfilled the above criteria for ATH. There were 29 female
(69.1%) and 13 male (30.9%) patients. The mean age was 51.7 years (SD = 18.6, range = 19–84 years). A total of 28 (66.7%) were pulmonary TB patients, 13 (30.9%) were extra-pulmonary TB and one patient (2.4%) of was both types. Three patients (7.1%) were HIV-positive. Thirty-seven patients (88.1%) received HRZE regimen while the hepatotoxicity developed.

The mean time from the start of treatment to onset of ATH was 32.5 days (SD = 22.1, range = 7–92 days) and 40 patients (80.9%) developed ATH within the first 2 months. The percentage of patients with each hepatotoxicity symptom and the mean levels of transaminase enzymes, total bilirubin, direct bilirubin and ALP are shown in Table 1.

**Physicians’ practices on the management of ATH**

**Practices relating to the diagnosis of ATH (Fig. 1)**

There were 42 patients who were initially identified as having ATH by their attending physicians. Of these, 27 patients (64.3%) had ALT or AST levels more than five times the upper limit normal (ULN) regardless of their symptoms. Four patients (9.5%) had ALT or AST levels of more than three times but less than or equal to five times of the ULN without jaundice. Five patients (11.9%) had both ALT and AST levels less than or equal to three times of the ULN. Therefore, 31 patients (73.8%) were diagnosed by using criteria that complied with the ATS 2006 guidelines. Table 2 shows the details of 11 patients (26.2%) who were diagnosed by the criteria that did not comply with the ATS 2006 guidelines. However, all of six patients whose ALT and AST were not more than three times the ULN had abnormal levels of total bilirubin and/or direct bilirubin.

**Practices on selection of alternative TB regimens**

After the suspected anti-TB drugs were discontinued, liver enzyme measurements were taken in 39 (97.5%) patients. The duration from anti-TB discontinuation to the first liver enzyme measurement was 3–19 days (mean ± SD = 9.1 ± 3.7 days). While waiting for the normalization of liver enzymes, 28 patients (70.0%) received less hepatotoxic drugs (alternative regimens) and 12 patients (30.0%) took no drugs. However, only 47.5% (19/40) received at least three less hepatotoxic drugs including ethambutol (E), ofloxacin (O) and streptomycin (S) that adhered to the ATS guidelines. Other alternative regimens were EO (12.5%), OS (12.5%), HZEO (2.5%) and HRE (2.5%). For each alternative drug, ofloxacin, ethambutol, streptomycin, isoniazid, pyrazinamide, rifampicin were prescribed in 27 (96.4%), 26 (92.9%), 21 (75.0%), 2 (7.1%), 1 (3.6%), 1 (3.6%) patients respectively.

**Figure 1**: Diagnosis of antituberculosis drug-induced hepatotoxicity (ATH). *Diagnosis complied with the Guidelines of the American Thoracic Society 2006. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit normal.

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Practices relating to the reintroducing of anti-TB drugs

Among the 40 patients who stopped anti-TB drugs, five (12.5%) patients did not follow up their treatment. Of the 35 patients, 34 (97.1%) were reintroduced by anti-TB drugs. Twenty-nine patients (85.3%) were treated in accordance with the ATS guidelines by reintroducing anti-TB drugs while the ALT levels were less than two times the ULN, regardless of other values. Isoniazid was reintroduced for all patients, but rifampicin, ethambutol and pyrazinamide were reintroduced for 91.2%, 53.8% and 48.3% of the patients respectively.

For 34 patients, anti-TB drugs were reintroduced simultaneously at full dosage in four (11.8%) patients. Anti-TB drugs were rechallenged sequentially that complied with the ATS guidelines in 30 patients (88.2%). Among these, 28 patients (93.3%) received full doses. Of the patients who were rechallenged sequentially, 22 patients (63.3%) were firstly rechallenged with isoniazid, and one patient (3.3%) with pyrazinamide. Only seven (23.4%) patients who complied with the ATS 2006 guidelines were reintroduced with rifampicin as the first drug.

Outcomes of reintroduction anti-TB drugs

Among 34 patients who were reintroduced with anti-TB drugs, their liver function enzymes were increased in eight (23.5%) patients. The liver enzyme increased after taking rifampicin in six

Table 2: Clinical presentations of patients whose antituberculosis drug-induced hepatotoxicity diagnosis was not complied with the American Thoracic Society 2006 Guidelines

<table>
<thead>
<tr>
<th>Type of patients</th>
<th>Patients no.</th>
<th>ALT (U L⁻¹)</th>
<th>AST (U L⁻¹)</th>
<th>Total bilirubin (mg%)</th>
<th>Direct bilirubin (mg%)</th>
<th>ALP (U L⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with both ALT and AST ≤3 times of the ULN regardless of hepatitis symptoms</td>
<td>1</td>
<td>9</td>
<td>40</td>
<td>16.35</td>
<td>13.98</td>
<td>133</td>
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<tr>
<td></td>
<td>2</td>
<td>98</td>
<td>93</td>
<td>8.67</td>
<td>7.46</td>
<td>193</td>
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<td></td>
<td>3</td>
<td>45</td>
<td>42</td>
<td>2.44</td>
<td>1.51</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>42</td>
<td>69</td>
<td>4.14</td>
<td>4.04</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>85</td>
<td>55</td>
<td>3.42</td>
<td>2.58</td>
<td>167</td>
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<tr>
<td></td>
<td>6</td>
<td>98</td>
<td>78</td>
<td>4.75</td>
<td>4.15</td>
<td>142</td>
</tr>
<tr>
<td>Patients with ALT or AST ≤5 times and &gt;3 times of ULN without jaundice</td>
<td>1</td>
<td>145</td>
<td>131</td>
<td>0.14</td>
<td>0.08</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>89</td>
<td>184</td>
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<td></td>
<td>3</td>
<td>165</td>
<td>145</td>
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<td>57</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>180</td>
<td>120</td>
<td>0.74</td>
<td>0.63</td>
<td>74</td>
</tr>
</tbody>
</table>

*Normal value for each laboratory data: ALT 0–41 U L⁻¹, AST 0–40 U L⁻¹, total bilirubin 0.2–1 mg%, direct bilirubin 0–0.2 mg%, ALP 39–117 U L⁻¹. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ULN, upper limit normal.
patients and pyrazinamide in two patients. The details of the rechallenged patterns among eight patients with recurrent hepatotoxicity and their liver function tests after rechallenging are shown in Table 3.

**Discussion**

In this study, about 7% of the patients were identified with hepatotoxicity from anti-TB drugs. Most of them were female patients and pulmonary TB. More than three-quarters developed ATH while receiving the regimen of four drugs (HRZE). Most occurred within the first 2 months from starting the treatment. About three-quarters of them were diagnosed as ATH in accordance with the ATS guidelines. When hepatotoxicity developed, all patients discontinued all or some anti-TB drugs. Isoniazid (H), rifampicin (R) and pyrazinamide (Z) were concurrently stopped in about two-thirds of the patients as recommended by the ATS. While waiting for normalization of liver enzymes, almost a half of the patients were substituted with at least three less hepatotoxic drugs as suggested by the ATS. These included ethambutol (E), ofloxacin (O) and streptomycin (S). Thirty per cent of the patients took no drug. Almost 90% of the patients were rechallenged when the liver enzymes decreased to less than two times the ULN. Isoniazid was reintroduced in all patients in contrast to pyrazinamide, which was rechallenged in only a half of the patients. Sequential reintroduction was done with nearly 90% of the patients. Isoniazid was also selected as the first drug for reintroduction for most patients. About one-fourth of patients increased some of their liver enzymes after anti-TB reintroduction. The last drugs given to these patients were rifampicin or pyrazinamide.

The prevalence of hepatotoxicity during TB treatment in this study was similar to previous studies that have reported variations between 3% and 20% [4–8]. The difference may be due to the data collection methods (study design), the investigators’ definition of hepatotoxicity and the population studied. Therefore, a comparison of the reported ATH incidences across different settings should not be undertaken. Isoniazid, rifampicin and pyrazinamide were each reported as causing hepatotoxicity [19] and a combination of these drugs increased the risk. In the present study, ATH usually occurred with most patients receiving a regimen of four drugs (HRZE) and occurred during the intensive phase (within the first 2 months).

The criteria for diagnosis of ATH recommended by the ATS 2006 [15] were that the serum transaminase levels should be: (1) more than three times the ULN with jaundice and/or hepatitis symptoms; or (2) more than five times the ULN (with or without symptoms). Data from this study showed that nearly 30% of the patients did not meet the ATS 2006 diagnosis criteria. However, among patients whose transaminase enzymes were not more than three times of the ULN, their bilirubin levels and/or ALP were higher than the normal value. This indicated impaired liver function. Isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic drugs. Acetyl hydrazine, a metabolite of isoniazid, is responsible for liver damage [20]. Additionally, the combination of isoniazid and rifampicin, a potent enzyme inducer, increases the formation of isoniazid toxic metabolite [12,21]. Moreover, rifampicin alone inhibits the re-uptake of bilirubin, leading to an increase in the bilirubin level [22]. Therefore, the bilirubin and/or ALP level should also be included in the criteria for considering ATH. Furthermore, the guidelines for the management of ATH should recommend how to deal with the patient who has abnormal bilirubin and/or ALP levels.

When a patient is suspected as having hepatotoxicity, potentially hepatotoxic drugs should be withdrawn immediately until there is normalization of liver enzymes [15]. However, the ATS statement did not specify which drugs should be withheld. In this study, pyrazinamide, isoniazid and rifampicin were discontinued in almost all patients. This was in contrast to ethambutol, which was stopped in less than a half of the patients. This may be due to the low hepatotoxicity incidence from ethambutol compared with that from isoniazid, rifampicin or pyrazinamide [20]. When the causative drugs have been discontinued, patients should be treated using at least three alternative anti-TB agents [15,16], such as ethambutol, streptomycin and fluoroquinolones [17,23]. The safety of alternative regimens, including fluoroquinolones, has been indicated by many studies [23–25]. In this study, ofloxacin and ethambutol were selected as alternative drugs in most cases. However, potential hepatotoxic drugs such as pyrazinamide, rifampicin and isoniazid were not withheld in about 5% of patients. Moreover, 12 patients took no anti-TB drugs during the normalization period, which may lead to drug-resistant TB [13].
After the discontinuation of potentially hepatotoxic drugs, the reintroduction should be done when the ALT return to a level that is less than twice the ULN [15]. The present study showed that almost all patients were reintroduced by anti-TB drugs in agreement with ATS guidelines. Drug reintroduction is a method for indicating the causative drug and selecting the appropriate future regimen. Although reintroduction may lead to hepatotoxicity, the first-line anti-TB drugs such as H, R, and Z are essential to cure the disease and treatment without R and H may be prolonged [26]. A sequential rechallenge was suggested by the ATS statements [15] and this method is easier to identify the causative drug. Moreover, there was no difference in the rate of recurrent hepatotoxicity among the patients who underwent simultaneous challenge or sequential challenge [27]. However, this study showed that simultaneous rechallenge was used in about 10% of patients.

The ATS guidelines recommended reintroducing rifampicin as the first drug. This may due to the lower incidence for hepatotoxicity of rifampicin (1.1%) compared with isoniazid (1.6%) [11]. Pyrazinamide causes the highest incidence of hepatotoxicity among the first-line anti-TB drugs. The incidence of hepatotoxicity attributed to pyrazinamide has been reported to range from 0.30 to 0.52 per 100 person-months [6,28]. Pyrazinamide in combination with ethambutol caused the high incidence of hepatotoxicity ranging up to 58% [10]. Therefore, it should not be reintroduced as the first agent. However, in our study, most patients were reintroduced with isoniazid as the first drug and one patient started with pyrazinamide.

Most patients with ATH recovered completely after the reintroduction of anti-TB drugs. However, the liver laboratory values of almost one-fourth increased after rechallenging. Rifampicin (six cases) and pyrazinamide (two cases) were used as the last anti-TB drug before the increment of liver enzymes. This may not be attributed to rifampicin alone because liver enzymes increased while rifampicin was used in combination with isoniazid.

To our knowledge, this is the first study describing the actual practice of physicians on the management of ATH in Thailand. Furthermore, all aspects of the important steps in ATH management, including diagnosis, initial management, selection of alternative regimens, and rechallenge methods, were evaluated. The major limitation was that it was retrospective and the researcher had to rely on the data available in its current form. Moreover, this study comprised a small number of patients with hepatotoxicity. It may not be representative of all ATH cases. Further prospective studies should be conducted with more TB patients.

Conclusions
In conclusion, the practices of physicians related to the diagnosis and management of hepatotoxicity varied considerably and also deviated from the ATS 2006 guidelines. These results suggest that physicians treating TB patients should have additional training on the management of ATH. Furthermore, the guidelines for ATH management should be distributed more widely. Moreover, more details should be provided in the guidelines. These should include: (1) whether bilirubin levels should be considered for diagnosis of ATH; (2) what should be the dosage of anti-TB when rechallenging; and (3) how should patients with abnormal bilirubin but normal transaminase levels be managed.

Acknowledgement
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References


