Anti-tuberculosis drug induced hepatitis – a Sri Lankan experience

WV Senaratne¹, MJ Pinidiyapathirage², GAMHE Perera¹ and AR Wickremasinghe²

(Index words: Liver function tests, WHO treatment recommendations)

Abstract

Objective To assess the incidence of anti-tuberculosis (TB) drug induced hepatitis (AIH) in Sri Lankan patients, determine risk factors of AIH, and to address management options in AIH.

Design A prospective study.

Setting Chest Hospital, Welisara, Sri Lanka, from April 2001 to April 2002.

Patients Seven hundred and eighty three patients with a confirmed diagnosis of TB and resident in the Colombo and Gampaha districts who presented to Chest Hospital, Welisara, Sri Lanka.

Methods WHO recommended treatment was commenced in all cases. AIH was diagnosed when patients complained of decreased appetite with nausea or vomiting and elevated serum bilirubin (SB; >1.1 mg/dL) or elevated serum alanine transferase (ALT; > 3 times upper limit of normal).

Results Of 783 enrolled patients, 74 (9.5%) developed AIH, the majority (58%) developing AIH within the first 2 weeks of the intensive phase of treatment. AIH was more common among patients over 60 years (p = 0.018), who developed pulmonary TB (p = 0.028), and in patients weighing 33–55 kg (p = 0.004). Age, weight and rifampicin overdosage were significant predictors of AIH. Of the 74 AIH patients, standard treatment was restarted in 60, treatment modified in six, two defaulted and six died.

Conclusions The incidence of AIH in Sri Lanka is 9.5% in treated patients. AIH was associated with age, low body weight and rifampicin overdosage.

Introduction

Anti-tuberculosis (TB) drug induced hepatitis (AIH) is a common complication in the management of TB. Studies in the USA and UK have reported a 3% and 4% incidence of AIH with rifampicin and isoniazid (with or without pyrazinamide in UK) [1,2], and studies from India have reported incidences ranging from 2% to as high as 30% [3–5]. No data are available for Sri Lanka.

Many risk factors for AIH have been described. They include advanced age, high alcohol consumption, extensive disease, hypoalbuminaemia, slow acetylator phenotype, female sex and endemic viral hepatitis [6–8]. The objective of this study was to assess the incidence of AIH in Sri Lankan patients, determine the risk factors of AIH and address management options.

Materials and methods

A prospective study was carried out from April 2001 to April 2002 at Chest Hospital, Welisara, Sri Lanka. Patients with a confirmed diagnosis of TB, resident in the Colombo and Gampaha districts and were under the care of the principal author were recruited after obtaining informed written consent. Diagnosis of TB was made according to WHO case definitions [9,10].

WHO category 1 and 2 treatment was commenced on all new and re-treatment cases respectively [9,10]. Baseline pretreatment serum bilirubin (SB) concentrations by the diazo method (normal range 0.2–1.1 mg/dL) and alanine transaminase (ALT) concentrations by the

References


Reitman and Frankel method (normal range 0–38 U/L) were assayed on all patients. All patients were followed up until the final outcome of that episode. Personal and follow up data were recorded in a pretested questionnaire and data sheet.

Of 893 patients who were enrolled, 110 who defaulted treatment during the intensive phase (first 2 months of category 1, and first 3 months of category 2) were excluded from the study. Eight such defaulters were included in the study as they had developed AIH at the time of defaulting. Patients who defaulted treatment after the intensive phase of either category were included in the study as previous studies have shown that AIH is common during the first few weeks of treatment [11,12].

The dose of anti-TB drugs given to a patient conformed to the recommendations of the National Manual on TB Control [13], which is based on WHO guidelines [9], and operational at the time of the study. SB and ALT concentrations were re-assayed when patients complained of decreased appetite with or without nausea or vomiting, or when the general condition deteriorated. AIH was diagnosed when SB concentration exceeded 1.1 mg/dL or when ALT concentrations exceeded 117 IU or both with decreased appetite and nausea or vomiting. Where severity of the disease did not permit discontinuing all drugs, a combination of streptomycin, ethambutol and ciprofloxacin was given when either ALT or both ALT and SB were elevated, until the concentrations returned to normal. In patients who had elevated SB with normal ALT, and who had to be continued on treatment, a combination of streptomycin, isoniazid and ethambutol was given until SB concentrations returned to normal. All anti-TB drugs were omitted on other patients until liver function tests returned to normal. Isoniazid, rifampicin and pyrazinamide were re-introduced sequentially starting with lower doses [12].

Data were analysed using SPSS [14]. Frequency distributions, Chi-square tests and logistic regression analyses were used.

Approval was obtained from the Ethical Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura. Permission to conduct the study was obtained from the Director, Chest Hospital, Welisara. Informed consent was obtained from all subjects, and subjects developing AIH were treated appropriately.

Results

The 783 patients were between 11 and 84 years of age, with a mean of 45.2 years (SD 15.4). The majority were males (72.2%), employed (57.6%), having a monthly income in excess of Sri Lankan Rupees (SLR) 5000 (69.6%), and having to support five or fewer dependents (87.5%) (Table 1). Regular current smokers comprised 44% and alcohol was consumed on a regular basis by 35% of participants, all of whom were males.

The majority (77.8%) of participants weighed between 33 kg and 55 kg (Table 2). Of the 721 (92.1%) patients with pulmonary tuberculosis, 679 (94.2%) were sputum positive for acid fast bacilli (AFB). In 244 patients (33.8%), more than three zones of the lungs were radiographically involved. Only 26 patients (3.3%) gave a past history of hepatitis. Before anti-TB treatment, 156 (19.9%) and seven (0.9%) patients had elevated ALT and SB concentrations. Of the 74 patients (9.5% of total) who developed AIH, the majority (58%) developed AIH within the first two weeks of the intensive phase of treatment (Table 3).

AIH was not associated with gender, a new or retreatment regimen, sputum positive or not for AFB, extent of chest xray involvement, a history of hepatitis, regular alcohol consumption, administration of potentially hepatotoxic drugs for other illnesses, and elevated ALT or SB concentrations before anti-TB treatment (Table 4).

### Table 1. Details of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
</tr>
<tr>
<td>11–20</td>
<td>44</td>
<td>5.6</td>
</tr>
<tr>
<td>21–30</td>
<td>113</td>
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<td>31–40</td>
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<td>41–50</td>
<td>182</td>
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<td>51–60</td>
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<td>&gt;60</td>
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<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>565</td>
<td>72.2</td>
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<td>Female</td>
<td>218</td>
<td>27.8</td>
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<td>Employment status</td>
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</tr>
<tr>
<td>Employed</td>
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<tr>
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<td>332</td>
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<tr>
<td>Occupation</td>
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<td></td>
</tr>
<tr>
<td>Administrative and managerial</td>
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<td>0.0</td>
</tr>
<tr>
<td>workers</td>
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<td></td>
</tr>
<tr>
<td>Professional, technical and</td>
<td>9</td>
<td>2.0</td>
</tr>
<tr>
<td>related workers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clerical and related workers</td>
<td>24</td>
<td>5.3</td>
</tr>
<tr>
<td>Sales workers</td>
<td>79</td>
<td>17.5</td>
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<tr>
<td>All other workers</td>
<td>30</td>
<td>6.7</td>
</tr>
<tr>
<td>Skilled and semiskilled</td>
<td>172</td>
<td>38.1</td>
</tr>
<tr>
<td>Unskilled</td>
<td>137</td>
<td>30.4</td>
</tr>
<tr>
<td>Income¹</td>
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<td></td>
</tr>
<tr>
<td>&lt; SLR 5000.00</td>
<td>176</td>
<td>30.4</td>
</tr>
<tr>
<td>&gt; SLR 5000.00</td>
<td>403</td>
<td>69.6</td>
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<tr>
<td>Number of dependents²</td>
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<td></td>
</tr>
<tr>
<td>1–5</td>
<td>506</td>
<td>87.5</td>
</tr>
<tr>
<td>≥ 6</td>
<td>72</td>
<td>12.5</td>
</tr>
<tr>
<td>Smoking status</td>
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<tr>
<td>Current regular smokers</td>
<td>343</td>
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<tr>
<td>Others</td>
<td>440</td>
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</tr>
<tr>
<td>Consumption of alcohol</td>
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<td></td>
</tr>
<tr>
<td>Consume alcohol regularly</td>
<td>271</td>
<td>34.6</td>
</tr>
<tr>
<td>Others</td>
<td>512</td>
<td>65.4</td>
</tr>
</tbody>
</table>

¹ In 204 subjects income could not be determined.
² In 205 subjects the exact number of dependents could not be determined.
AIH was more common among patients over 60 years (p = 0.018), those who developed pulmonary TB (p = 0.028), and in patients weighing 33–55 kg (p = 0.004).

Based on present dosing recommendations according to body weight [10] patients were categorised as receiving an ‘overdose’ or getting a dose within recommended limits of each drug. AIH was significantly associated with receiving an ‘overdose’ of rifampicin, isoniazid and pyrazinamide but not ethambutol (Table 4).

Age, low body weight, and rifampicin overdosage were significant predictors of AIH in a logistic regression model (Table 5). A patient less than 60 years old was 0.5 times likely to develop AIH as compared to a patient more than 60 years. A patient getting an overdose of rifampicin was 2.5 times more likely to get AIH as compared to a patient receiving an acceptable dose. Overdoses of isoniazid and pyrazinamide were not significant predictors of AIH after controlling for age, weight and rifampicin overdose.

Of the patients who developed AIH, 34 had elevated SB with normal ALT concentrations, and 40 had either elevation of both SB and ALT, or raised ALT concentrations only. Anti-TB treatment was omitted in 42 patients, and rifampicin, isoniazid and pyrazinamide reintroduced under streptomycin and ethambutol cover. Among these 42 patients, 35 were restarted on standard (category 1 and 2) regimens. In the remaining seven patients, treatment was modified to streptomycin, isoniazid and ethambutol during the intensive phase followed by isoniazid and ethambutol during the continuation phase in two patients. Three died and two defaulted before standard treatment was reintroduced.

Twenty seven patients with AIH who had an elevated SB concentration with normal ALT, and who had to be continued on some form of treatment due to the severity of the illness, were started on a combination of streptomycin, isoniazid and ethambutol. In 25 of them, SB returned to normal on this regimen and ALT remained normal. Standard treatment was recommenced in 22 of these patients. Three had to be continued on streptomycin, isoniazid and ethambutol during the intensive phase of treatment followed by isoniazid and ethambutol during the continuation phase. Two patients died while on streptomycin, isoniazid and ethambutol, among whom SB and ALT were normal in one and SB concentration was 1.3 mg/dL with normal ALT in the other at the time of death. Five patients who were severely ill were managed with a combination of streptomycin, ethambutol and ciprofloxacin among whom standard treatment was recommenced in three, modified treatment continued in one and the other died.

### Table 2. Clinical features of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 33</td>
<td>79</td>
<td>10.2</td>
</tr>
<tr>
<td>33–55</td>
<td>602</td>
<td>77.8</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>93</td>
<td>12.0</td>
</tr>
<tr>
<td>Site of lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>721</td>
<td>92.1</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>62</td>
<td>7.9</td>
</tr>
<tr>
<td>Treatment category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>695</td>
<td>88.8</td>
</tr>
<tr>
<td>Retreatment</td>
<td>88</td>
<td>11.2</td>
</tr>
<tr>
<td>Sputum examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>679</td>
<td>94.2</td>
</tr>
<tr>
<td>Negative</td>
<td>42</td>
<td>5.8</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involvement &lt; 3 zones</td>
<td>471</td>
<td>65.9</td>
</tr>
<tr>
<td>Involvement &gt; 3 zones</td>
<td>244</td>
<td>34.1</td>
</tr>
<tr>
<td>Past history of hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>26</td>
<td>3.3</td>
</tr>
<tr>
<td>Absent</td>
<td>757</td>
<td>96.7</td>
</tr>
<tr>
<td>Presence of other illnesses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(for which the treatment taken could have an effect on liver functions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>90</td>
<td>23.0</td>
</tr>
<tr>
<td>Absent</td>
<td>693</td>
<td>77.0</td>
</tr>
<tr>
<td>Serum ALT levels prior to commencement of anti-TB treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 38 IU (normal)</td>
<td>627</td>
<td>80.1</td>
</tr>
<tr>
<td>≥ 39 IU (abnormal)</td>
<td>156</td>
<td>19.9</td>
</tr>
<tr>
<td>Serum bilirubin levels prior to commencement of anti-TB treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1.1 mg/dL (normal)</td>
<td>776</td>
<td>99.1</td>
</tr>
<tr>
<td>≥ 1.2 mg/dL (abnormal)</td>
<td>7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

1 The weights of nine subjects were not recorded.
2 Sputum examination results are for patients having pulmonary TB.
3 Chest x-rays were not available in six patients with pulmonary TB.

AIH was more common among patients over 60 years (p = 0.018), those who developed pulmonary TB (p = 0.028), and in patients weighing 33–55 kg (p = 0.004).

### Table 3. Incidence of anti-tuberculosis drug induced hepatitis with treatment duration (n = 783)

<table>
<thead>
<tr>
<th>Weeks of treatment</th>
<th>No. of AIH cases (%)</th>
<th>No. of defaulters (/1000)</th>
<th>Incidence (/1000)</th>
<th>95% CI (/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>43 (58.1)</td>
<td>0</td>
<td>54.9</td>
<td>39.0 – 70.9</td>
</tr>
<tr>
<td>3–4</td>
<td>20 (27.0)</td>
<td>3</td>
<td>27.1</td>
<td>15.4 – 38.9</td>
</tr>
<tr>
<td>5–6</td>
<td>9 (12.1)</td>
<td>2</td>
<td>12.6</td>
<td>4.4 – 20.8</td>
</tr>
<tr>
<td>7–8</td>
<td>1 (1.4)</td>
<td>3</td>
<td>1.4</td>
<td>0 – 4.2</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>1 (1.4)</td>
<td>88</td>
<td>1.6</td>
<td>0 – 4.8</td>
</tr>
</tbody>
</table>

### Discussion

Colombo and Gampaha districts comprising both urban and rural sectors are the most populated districts in the country and have a high burden of TB when compared to other districts. In 2002, two of these districts recorded 29% of all TB cases reported in the country [15]. The incidence of AIH in our study was 9.5%, which is high when compared to studies done in the west [1,2], but
### Table 4. Association between AIH and selected variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>AIH</th>
<th>Non-AIH</th>
<th>$X^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
<td>8.7</td>
<td>516</td>
<td>91.3</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>11.5</td>
<td>193</td>
<td>88.5</td>
</tr>
<tr>
<td>Type</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cases</td>
<td>64</td>
<td>9.2</td>
<td>631</td>
<td>90.8</td>
</tr>
<tr>
<td>Retreatment</td>
<td>10</td>
<td>11.4</td>
<td>78</td>
<td>88.6</td>
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<td>Sputum</td>
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<tr>
<td>Positive</td>
<td>69</td>
<td>10.2</td>
<td>610</td>
<td>89.8</td>
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<td>9.5</td>
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<td>90.5</td>
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<td>Pulmonary</td>
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<td>648</td>
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<td>1.6</td>
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<td>Chest xray&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Involvement ≤ 3 zones</td>
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<td>History of hepatitis</td>
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<td>Regular alcohol use</td>
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<td>&lt;60 years</td>
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<td>&gt;60 years</td>
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<td>107</td>
<td>85.0</td>
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<td>&lt;33 kg</td>
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<td>91.1</td>
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<td>537</td>
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<td>6</td>
<td>6.7</td>
<td>84</td>
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<tr>
<td>No</td>
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<td>9.8</td>
<td>625</td>
<td>90.2</td>
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<td>Pre-treatment serum ALT</td>
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<td>≤38 IU</td>
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<td>9.1</td>
<td>570</td>
<td>90.9</td>
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<tr>
<td>≥39 IU</td>
<td>17</td>
<td>10.9</td>
<td>139</td>
<td>89.1</td>
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<td>Pre-treatment serum bilirubin</td>
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<td>≤1.1 mg/dL.</td>
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<td>9.4</td>
<td>704</td>
<td>90.6</td>
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<td>≥1.2 mg/dL.</td>
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<td>16.7</td>
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<td>83.3</td>
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<td>Rifampicin&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Overdose</td>
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<td>88.1</td>
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<td>No</td>
<td>14</td>
<td>4.9</td>
<td>271</td>
<td>95.1</td>
</tr>
<tr>
<td>INAH&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>9.8</td>
<td>663</td>
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<td>0</td>
<td>0.0</td>
<td>39</td>
<td>100.0</td>
</tr>
<tr>
<td>Pyrazinamide&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>71</td>
<td>10.3</td>
<td>616</td>
<td>89.7</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1.1</td>
<td>86</td>
<td>98.9</td>
</tr>
<tr>
<td>Ethambutol&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>72</td>
<td>9.6</td>
<td>680</td>
<td>90.4</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.0</td>
<td>22</td>
<td>100.0</td>
</tr>
</tbody>
</table>

AIH = anti-tuberculosis drug induced hepatitis, * Fisher’s exact test

<sup>1</sup> Chest x-rays were not available in six patients with pulmonary TB

<sup>2</sup> The weights of nine subjects were not recorded

<sup>3</sup> Overdose is more than 10 mg/kg. Weights of nine subjects were not recorded

<sup>4</sup> Overdose is more than 5 mg/kg. Weights of nine subjects were not recorded

<sup>5</sup> Overdose is more than 30 mg/kg. Weights of nine subjects were not recorded

<sup>6</sup> Overdose is more than 15 mg/kg. Weights of nine subjects were not recorded
similar to the incidence reported from India [3,5].

Patients over 60 years, those having pulmonary tuberculosis, and those who weighed between 33 kg and 55 kg, independently had a high risk of developing AIH. Pulmonary TB patients having a high risk of developing AIH may be due to the small sample size of extra-pulmonary TB cases in this series. In the multivariate model, age, weight between 33 kg and 55 kg, and overdose of rifampicin were significant predictors of AIH. In our study, the doses of anti-TB drugs were based on recommended doses for three weight bands [9,13]. When the dose of each drug was calculated per kilogram body weight [10], 489, 735, and 687 patients received a higher dose of rifampicin, isoniazid and pyrazinamide (Table 4). Even if a more stringent p-value of 0.01 is used for significance to account for multiple hypothesis testing, all variables except site, age and isoniazid overdose will still be significant.

Patients in the 33–55 kg category were more likely to get a higher dose of each drug which may explain the higher risk of AIH in this group of patients. Dispensing anti-TB drugs strictly according to body weight is not always possible, and is impractical in a control programme. For example, a patient who weighs 40 kg should ideally receive 400 mg of rifampicin. However, it is not possible to administer this dose with capsules containing 150 mg of rifampicin, and a decision has to be made whether to administer 300 mg or 450 mg. The former is an underdose, which might result in emergence of drug resistant strains, whereas the latter is a higher dose which increases the risk of AIH. Hence, in such a situation calculating the dose of individual drugs according to the body weight becomes a dilemma to the clinician. Overdose of rifampicin being a significant predictor of AIH implies that it is the most important drug in the combination that requires dose modification.

Twenty five patients with AIH who had high SB with normal ALT were successfully managed with a combination of streptomycin, isoniazid and ethambutol until SB returned to normal; 22 were restarted on standard treatment and three were continued on the same combination during the intensive phase followed by isoniazid and ethambutol. In the 74 who developed AIH, standard treatment was restarted in 60 patients. Among the remainder, six patients needed treatment modification with streptomycin, isoniazid and ethambutol during the intensive phase followed by isoniazid and ethambutol.

Of the 74 patients who had AIH, 73 (98.6%) developed AIH within the first 8 weeks of treatment. Screening for HIV and a hepatitis B carrier state to see whether these factors are associated with an increased risk of AIH was not done for logistic reasons. Viral studies to exclude viral hepatitis were also not done as this facility is not available. Although we acknowledge this drawback, we do not feel that this deficiency would have significantly altered the results of the present study; correction of liver dysfunction on withdrawal of incriminating drugs is evidence of its cause.

The British Thoracic Society recommends withdrawal of rifampicin, isoniazid and pyrazinamide when transaminase concentration is elevated more than five times the normal, or serum bilirubin concentration is elevated [12]. Dissing and colleagues [7] suggest to continue treatment even when ALT concentrations are six times the upper limit of normal without symptoms, and SB concentration is less than twice the upper limit of normal. Patients in our series developed symptoms much earlier with ALT concentrations three times above the upper limit of normal or SB elevated above 1.1 mg/dL. The threshold for diagnosis of AIH in Sri Lankan patients is much lower than that of the patients in the west. This probably explains the high rate of AIH in our study. The higher incidence of anti-TB drug induced hepatotoxicity in patients of the Indian sub-continent may also be related to genetic factors such as the acetylator state, as studies have shown a higher risk of AIH in slow acetylators [6,16].

**Acknowledgements**

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Abstract

Introduction Termination of pregnancy is a popular option for pregnancies complicated by lethal congenital malformations (LCMs). In Sri Lanka, where abortion laws are restrictive, this is not available. We studied the psychological responses and coping strategies of women who had to continue their pregnancies knowing the baby had a LCM.

Setting A teaching hospital in Sri Lanka.

Study design Qualitative inquiry.

References


Psychological reactions and coping strategies of Sri Lankan women carrying fetuses with lethal congenital malformations

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(Index words: Need for counselling and legal reform, psychological distress)

Method We conducted a semi-structured interview of 10 women whose fetuses were diagnosed to have a LCM.

Results All women showed a grief reaction on hearing the news and were distressed about having to carry a futile pregnancy. Eight women were grateful they knew of the abnormality because it prepared them for the birth better, while the other two wished they had not known. They all found having to share facilities with ‘normal’ women to be painful. Seven women who received ‘routine’ antenatal care felt that the doctors were ill-equipped to deal with their situation. All felt that abortion should be legalised for LCMs. All engaged in religious rites believed