Topical Reviews

Directly observed therapy for the treatment of tuberculosis—evidence based dosage guidelines

R. Bednall*, G. Dean† and N. Bateman‡

*Medical Admissions, †Department of HIV and GU Medicine and ‡Thoracic Medicine, Guy's and St. Thomas' NHS Trust, U.K.

Tuberculosis is a communicable disease with public health implications and effective treatment is essential for control of the disease and prevention of the emergence of drug resistant strains. Drug therapy for this disease is well established and discussion now surrounds frequency of administration, duration of treatment and methods of improving compliance. Directly observed intermittent therapy of tuberculosis is supported by the World Health Authority and has become the standard of care in the U.S.A. Available dosage guidelines for directly observed therapy are only supported by limited data. A literature review of recent studies with clinical outcome measures was conducted. Following this review evidence based guidelines have been produced.

Introduction

Tuberculosis (TB) is a communicable disease that has troubled physicians for thousands of years and has been a leading cause of death in Europe and the U.S.A. for centuries (1). The introduction of effective antibiotics and public health strategies during the 20th century should have resulted in tuberculosis becoming a disease of the past. However, the number of cases of tuberculosis, in both developed countries and world-wide, is rising.

The range of antibiotics available to treat Mycobacterium tuberculosis infections is long established (1,2) and the discussion amongst physicians no longer surrounds which drugs to use, but the frequency and duration with which to use them. Originally treatment courses were for 2 years, but it is now accepted that a six month rifamycin containing regimen is effective (3). However, this still requires patients to take several tablets on a daily basis for a long time and for the greatest part of the course they have no symptoms. Non-compliance with medication for asymptomatic, chronic disease has been demonstrated to be in the region of 30–50% (4,5,6). In tuberculosis this can result in both personal and public health risks and has been associated with the emergence of multi-drug resistant tuberculosis (1,7,8).

Improving compliance is an important aspect of tuberculosis control. This was first highlighted by Wallace Fox, in Madras. His initial work demonstrated the efficacy of daily supervised treatment and, later, that intermittent therapy, that is administration of anti-tubercular drugs twice or three times weekly, was a successful treatment option (9). However, when self administered, intermittent dosing did not promote compliance, but this is ensured by employing directly observed therapy (DOT). Directly observed intermittent therapy requires a responsible individual, who may be a healthcare professional, to give the medication to a patient and to ensure that all doses have been taken. This approach has been employed widely in the U.S.A., where it has emerged as the standard of care (10).

The World Health Organisation (WHO) is convinced of the benefits to be gained by using DOT (11) although their view is not supported by all (12,13).

Both the British (14) and American (15,16) Thoracic Societies have issued guidelines on the dosing regimens that should be employed for DOT based largely on ‘best practice’ and they provide limited references to support the data.

Following a literature review of recent studies, evidence based dosing guidelines have been produced.

Literature review

The Iowa Drug Information Service and Medline databases were searched using the key words: tuberculosis, pulmonary tuberculosis, drug therapy and compliance. Five observational studies were identified which had clinical as opposed to sociological outcomes. One was discarded on the basis that insufficient detail was provided for comparative purposes (17). The four studies considered suitable for the purposes of this review are summarized in Table 1 (18–21).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Frequency of therapy (x week^{-1})</th>
<th>Drugs and doses used</th>
<th>Duration of therapy</th>
<th>Cure rate</th>
<th>Relapse/failure rate</th>
<th>Drop out rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caminero et al. (18)</td>
<td>104</td>
<td>2</td>
<td>I: 15 mg kg^{-1} R: 10 mg kg^{-1} P: 60 mg S: 50 mg kg^{-1} (prev. treat. only)</td>
<td>6 months P &amp; E for 2 months only</td>
<td>84%</td>
<td>3.6%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly doses calculated for 60 kg adult 1.8 g 1.2 g 7.2 g 6 g NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neher et al. (19)</td>
<td>886</td>
<td>3</td>
<td>I: 600 mg R: 600 mg P: 1.5–2 g (larger) 1.6–2 g doses S: 0.5–1 g pts &gt; 50 kg</td>
<td>9 months (4 drugs) S sub for E if s/e or resist</td>
<td>85%</td>
<td>1.3% relapse</td>
<td>1.6% failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly doses calculated for 60 kg adult 1.8 g 1.8 g 6 g 6 g 3 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China tuberculosis control collaboration (20)</td>
<td>112 842 alt. days</td>
<td>600 mg 600 mg 3 g 1.25 g 0.75 g 6 months P &amp; E for 2 months only E/S prev. treat. only</td>
<td></td>
<td>85%</td>
<td>3.2%</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly doses calculated for 60 kg adult 1.8 g 1.8 g 6 g 3.75 g 2.25 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilkinson et al. (21)</td>
<td>109</td>
<td>2</td>
<td>I: 900 mg R: 600 mg P: 3 g S: 2 g N/A</td>
<td>6 months 75% (ITT)</td>
<td>4.8%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly doses calculated for 60 kg adult 1.8 g 1.2 g 6 g 4 g N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Thoracic Society (15)</td>
<td>2</td>
<td>2</td>
<td>I: 15 mg kg^{-1} 10 mg kg^{-1} 50–70 mg kg^{-1} 50 mg kg^{-1} 1.8 g</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly doses calculated for 60 kg adult 1.8 g 1.2 g 6.4 g 6 g 3.6 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I: Isoniazid; R: Rifampicin; P: Pyrazinamide; E: Ethambutol; S: Streptomycin.
Caminero et al. evaluated the treatment of 104 patients in Gran Canaria, who were followed for 2 yr (18). Patients were treated with a three-drug regimen, twice weekly for 6 months. Eighty-seven patients (87%) completed therapy having negative tests for acid-fast bacilli at the end of the treatment course. The WHO standards (1996) require an 85% 'cure' rate for tuberculosis therapy regimens and therefore the results of this study are in the appropriate range (20). Relapse rate was 2-4% at 2 yr and two patients stopped therapy due to adverse drug reactions.

Neher et al. reported on the introduction of DOT for the treatment of tuberculosis in the Kathmandu valley (19). Eight hundred and eighty-six patients were treated with a four-drug regimen, three times a week for a period of 9 months. Streptomycin was substituted for ethambutol if side-effects occurred. Patients were followed for 3 yr. Therapy failure and relapse rates were 1-6% and 1-3% respectively. An 85% cure rate was achieved.

The Chinese Tuberculosis Control Collaboration reported on the first 3.5 yr of the DOT programme (20). They treated 112 842 patients with a standard four-drug regimen on alternate days for 6 months. A fifth drug (ethambutol) was added if patients had previously received therapy. Over the first 3.5 yr 85-3% of patients were cured and a further 2-6% 'completed treatment'. In those patients who have been followed up for 2 yr a 3-2% relapse rate has been noted. Failure rates of 5-7% were noted. This study represents a huge success for DOT, as previously only 50% of patients with TB were cured and the disease was responsible for 300 000 deaths in China in 1990.

Wilkinson et al. (21) reported on a retrospective study of the treatment of 109 patients who had undergone DOT in the KwaZulu/Natal region of South Africa. A 95% success rate is stated. However the limitations to the follow-up process should be noted. The study population included transient workers for whom objective follow-up was not possible. Data for these patients is based on third party reports of good health. When the objective data is analysed on an intention to treat basis, the cure rate is 75%. All patients completed therapy and the relapse rate was 4%.

**Discussion**

The dosage regimens for each study were based on varying mg kg\(^{-1}\) doses and frequencies. If simplified by calculating the total weekly doses for a 60 kg adult, it becomes clear that all the studies used similar regimens.

It is therefore suggested that doses for directly observed therapy for tuberculosis should be based on maximum weekly doses and divided into the appropriate frequency for the individual patient. Evidence based dosage guidelines for directly observed therapy, are shown in Table 2. Standard prescription/administration cards are recommended for clear documentation of therapy.

**Conclusion**

Tuberculosis has public health implications and effective treatment is essential for control of spread of disease and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum weekly dose</th>
<th>Doses for twice weekly regimen</th>
<th>Doses for three weekly regimen</th>
<th>Preparations available</th>
<th>Monitoring required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>1-8 g</td>
<td>15 mg kg(^{-1}) max. 900 mg</td>
<td>10 mg kg(^{-1}) max. 600 mg</td>
<td>Tablets 100 mg</td>
<td>LFT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syrup 50 mg ml(^{-1})</td>
<td>FBC</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1-8 g</td>
<td>10 mg kg(^{-1}) max. 600 mg</td>
<td>10 mg kg(^{-1}) max. 600 mg</td>
<td>Capsules 150 mg &amp; 300 mg</td>
<td>LFT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elixir 100 mg ml(^{-1})</td>
<td>FBC</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>6 g</td>
<td>60 mg kg(^{-1}) max. 3 g</td>
<td>40 mg kg(^{-1}) max. 2 g</td>
<td>Tablets 500 mg</td>
<td>LFT</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>6 g</td>
<td>50 mg kg(^{-1}) max. 3 g</td>
<td>30 mg kg(^{-1}) max. 2 g</td>
<td>Tablets 400 mg &amp; 100 mg</td>
<td>U&amp;E</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>3 g</td>
<td>max. 1-5 g</td>
<td>max. 1 g</td>
<td>IM injection 1 g</td>
<td>U&amp;E</td>
</tr>
</tbody>
</table>

Notes: The maximum dose of Rifampicin (600 mg dose\(^{-1}\)) produces plasma concentrations in excess of the mean inhibitory concentration for *M. tuberculosis*. Larger doses are therefore unnecessary and would be associated with an increased incidence of side-effects.

The dosage frequency of streptomycin should be decreased in patients with renal failure; doses should be tailored to the individual patient.

Baseline monitoring should be done before therapy is commenced.

---

**Table 2. Dosage guidelines for DOT of tuberculosis**

**Notes:**
- The maximum dose of Rifampicin (600 mg dose\(^{-1}\)) produces plasma concentrations in excess of the mean inhibitory concentration for *M. tuberculosis*. Larger doses are therefore unnecessary and would be associated with an increased incidence of side-effects.
- The dosage frequency of streptomycin should be decreased in patients with renal failure; doses should be tailored to the individual patient.
- Baseline monitoring should be done before therapy is commenced.
prevention of the emergence of drug resistant strains. Directly observed therapy can increase the rate of course completion and appropriate doses of drugs and careful documentation should be used.

References