Plasma concentrations of first-line antituberculosis drugs in a random sample of tuberculosis patients in Denmark

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Background

Tuberculosis (TB) is a pandemic, with 9 million new cases of TB disease and approximately 2 million deaths each year [1].

Treatment failure is associated with delayed disease detection or treatment, HIV infection, noncompliance and other co-morbidities [2,3,4].

Lower than expected plasma levels of one or more of the first-line antituberculosis drugs isoniazid, rifampicin, ethambutol and pyrazinamide have frequently been observed, and in small studies without controls low plasma levels have been associated with ineffective treatment [5,6,7]. Still the clinical significance of low plasma concentrations of one or more of the first-line TB drugs remains to be determined.

Ineffective TB treatment could be a consequence of low plasma levels of one or more of the first-line TB drugs possibly caused by malabsorption, inaccurate dosing, altered metabolism, drug-drug interaction etc.

Aim

- To assess the prevalence of lower than expected plasma concentrations of first-line antituberculosis drugs in TB patients in Denmark.
- To investigate possible risk factors for and consequences of low plasma concentrations.

Material & Methods

32 adult patients with active TB (pulmonary and extra pulmonary) and 3 adult patients receiving prophylactic treatment were included in the present study and 2 h blood samples were collected.

Plasma concentrations of first-line antituberculosis drugs were determined using HPLC MS-MS (High Performance Liquid Chromatography and Tandem Mass Spectrometry). Normal limits were obtained from Ref [8].

The clinical charts were reviewed for baseline characteristics and clinical status at 2, 4 and 6 months after initiation of treatment.

Results

Plasma concentrations below lower normal limit of rifampicin were observed in 19/33 (58%), of isoniazid in 25/35 (71%), of ethambutol in 13/28 (46%), of pyrazinamid in 3/29 (10%) and of both isoniazid and rifampicin in 15/33 (45%).

Distribution of plasma concentrations of each of the four TB drugs are presented in figure 1.

Plasma concentrations of isoniazid were correlated inversely with CRP both at baseline (p=0.007) and at time of sampling (p<0.005), and positively with treatment duration (p=0.014).

Plasma concentrations of rifampicin decreased with increasing age (p=0.006), and were significantly lower among patients with low hemoglobin at baseline compared to patients with normal hemoglobin at baseline (p=0.003).

During 1 year follow up 3 patients died and 2 had relapse. Death or relapse was observed more frequently in patients with below median values of rifampicin (p=0.044), of isoniazid (p=0.041) or of both drugs (p=0.005).

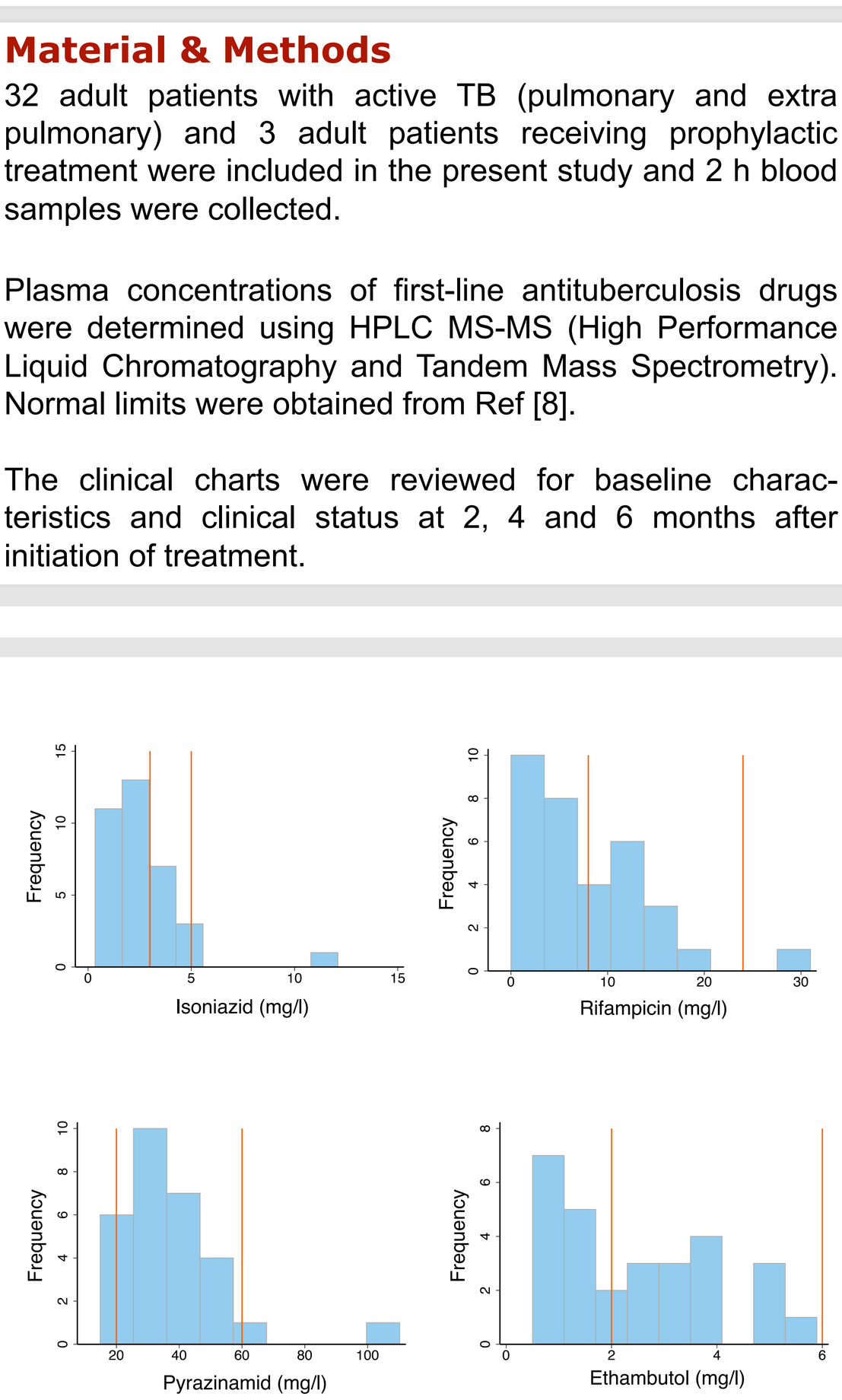

Figure 1. Distributions of plasma concentrations of first-line TB drugs.

Vertical lines show the lower and upper normal limit for each drug.

Conclusion and perspectives

Plasma concentrations of rifampicin and isoniazid below the lower normal limit are frequently observed in adult TB patients in Denmark.

Lower plasma concentrations of isoniazid and/or rifampicin is associated with poorer clinical outcome.

The present study is limited by the small sample size and a future large scale study are needed to investigate the clinical significance of plasma concentrations below the lower normal limit.

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