Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes

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Background:

- In African countries the 2-month sputum culture conversion rate is only 50%–70%
- In vitro → microbial kill + ADR are associated with AUC/MIC and Peak/MIC
- Is there a link between drug concentrations and therapy failure?

Methods:

Goal of the study: identification of pharmacokinetic parameters of first-line anti-tuberculosis drugs and subsequent outcomes in patients

- 3 hospitals, from 08/1999-02/2002, hospitalized for 2 month
- Inclusion criteria: (+) sputum microscopy/culture, ≥16 years, no evidence of drug resistance
- 1st two month: isoniazid, rifampicin, pyrazinamide, ethambutol→ sputum ad Microscopy/culture → sputum-negative patients were treated with rifampin and isoniazid for 4 more month
- Follow up for 2 years after hospital discharge
- Primary outcome → treatment failure, or relapse, or death, up to 2 years
- Secondary outcome → 2-month sputum culture conversion

Results:

- 142 patients were enrolled (table 1)
- Each of the 142 patients had a unique concentration–time profile for each of the 3 drugs (Fig 1)
- 15 (11%) didn't convert sputum cultures to negative after 2 months of treatment
- Highest predictor for 2-month sputum conversion was pyrazinamide peak concentration (Fig 2)
- Patients failing sputum conversion→93% (CI 70–99) had a low pyrazinamide Cmax
- 25% of 142 patients had poor long-term outcomes (Fig 3)
- Drug concentration thresholds predictive of this outcome were a 24-hour AUC of 363 mg·h/L for pyrazinamide, 13 mg·h/L for rifampin, and 52 mg·h/L for isoniazid
- ≥91% of patients with poor long-term outcomes received at least 1 drug with a low AUC
- The lower the cumulative number of drugs above the cutoff AUC threshold, the higher the odds of poor long-term outcomes (P = .001) (table 3)
- 2.11% (CI, .72-6.00) developed ADR + 0.7% (CI, .12-3.87) developed ADR prior to the third month of therapy→patients had suboptimal rifampin and isoniazid drug concentrations prior to developing ADR (table 4)

Discussion:

- Suboptimal drug concentrations is associated with poor 2-month sputum conversion rates, higher relapse and ADR
- Drug concentration rates in patients are not predictable→check during therapy necessary?
- Determined AUC concentration cutoff values that predict >91% of long-term clinical outcomes→ needs external validation in other studies
- Pyrazinamide concentrations were the most important predictor of both sputum conversion and sterilizing activity
- Monotherapy pyrazinamide → lowest microbial kill rates compared with rifampin and isoniazid, but pyrazinamide is the dominant drug in combination therapy with these 2 drugs
- ADR was preceded in time by low rifampin and isoniazid concentrations
- AUC and peak concentration (indexed to MIC) are associated with both efficacy and suppression of ADR for first-line anti-tuberculosis compounds

Limitations:

- 64% of patients had a recurrent tuberculosis episode
- Low rate of HIV-infected patients→ results should not be generalized to patients with AIDS
- Results were for pulmonary tuberculosis patients→ other organs might need different drug concentrations
- Sputum was not collected from all patients after discharge
- Study design did not capture the quantitative sputum bacillary burden, which is known to predict microbiologic outcomes