TITLE OF THE ABSTRACT
Comparison of drug concentration of isoniazid and rifampicin between daily and intermittent anti-tubercular (ATT) regimen, in children treated for tuberculosis.

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OBJECTIVES:

- To measure the drug exposure as the area under the concentration time curve to six hours (AUC$_{0-6h}$) for both isoniazid and rifampicin in children treated by either daily or intermittent ATT regimen.

- To determine the inter-patient variability in plasma concentrations, as well to determine the basic pharmacokinetic parameters, for isoniazid and rifampicin in above population.

METHODS
Children aged 2 to 16 years, initiated on either daily or intermittent (thrice weekly) ATT were recruited into the study, after obtaining informed consent. Towards the end of the intensive phase, blood specimens were collected pre-dose, followed by 0.5, 1, 1.5, 2, 2.5, 4 and 6hrs post-dose. The concentrations of isoniazid and rifampicin were analyzed using a validated LC-MS/MS and HPLC assays, respectively. Results were analyzed using non parametric methods with R version 3.1.2.

RESULTS
The median dose (mg/kg) *for isoniazid was 10.13 versus 8.10 (p=0.005) in the intermittent and daily dose regimens respectively. The C$_0$ (μg/mL) * was below the limit of detection versus 0.15
The \( C_{\text{max}} (\mu g/mL) \) * was 6.8 versus 6.86, \( C_2 (\mu g/mL) \) * was 5.1 versus 5.54 and \( C_6 (\mu g/mL) \) * was 2.01 versus 2.18. None of these were significantly different. Median AUC_{0-6h} (mg.hr/L) * was 22.18 versus 24.55 (\( p = 0.879 \)).

The median dose (mg/kg) * for rifampicin was 10.26 versus 10.77. \( C_0 (\mu g/mL) \) * was below the limit of detection, versus 0.01 (\( p = 0.4 \)), \( C_{\text{max}} (\mu g/mL) \) * was 6.19 versus 5.59, \( C_2 (\mu g/mL) \) * was 4.3 versus 4.4 and \( C_6 (\mu g/mL) \) * was 1.01 versus 1.68. However, there was no significant difference. Median AUC_{0-6h} (mg.hr/L) * was 16.87 versus 16.51 (\( p = 0.879 \)).

**CONCLUSION:**

All the patients (except 2) had isoniazid \( C_{\text{max}} \) above 3\( \mu g/mL \) (recommended range: 3-6\( \mu g/mL \)) and 83% of the patients had rifampicin \( C_{\text{max}} \) less than recommended range (8-24\( \mu g/mL \)). 31% of the patients had a very low \( C_{\text{max}} \) for rifampicin, which is <4\( \mu g/mL \). \( C_{\text{max}} \) has a strong correlation with AUC_{0-6h} in both regimens for both isoniazid and rifampicin. (\( r = 0.889 \) and 0.97 for isoniazid; \( r = 0.89 \) and 0.98 for rifampicin).

Only 20% of the patients had \( C_{\text{max}} \) at 2hrs for both isoniazid and rifampicin. Hence, pharmacokinetic studies in children for both drugs should include earlier time points to capture the \( C_{\text{max}} \) accurately. Dose of rifampicin does not appear to have a correlation with the exposure. Also rifampicin has a high interindividual variability (% CV of 54% for AUC and 59% for \( C_{\text{max}} \)). Therefore, we recommend the use of TDM for patients on rifampicin (especially for the patients who do not respond adequately or respond slowly).

**KEYWORDS:** Tuberculosis, isoniazid, rifampicin, regimens, children

*indicates intermittent versus daily regimen respectively.*