Poster

[P25-3] P25-3: Anti-infective drugs (3): TB drugs

Chair: Masahiro Kobayashi, Japan

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[P25-3-3] Adequacy of isoniazid and rifampicin in anti-tuberculosis treatment in children; a pharmacometric approach

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Background

The burden of tuberculosis is still great with an annual global incidence of 9.6 million and especially in India with an estimated incidence figure of 2.2 million cases. Inadequate treatment due to, for example inadequate drug exposure, may lead to relapse in patients and development of antimicrobial resistance. Isoniazid and rifampicin are still the most important drugs in anti-tuberculosis treatment and is combined with other drugs in a combination therapy. There are today two mainly used treatment regimens in India for tuberculosis; a daily regimen recommended by the World Health Organisation and an intermittent regimen provided free of cost by the Indian government.

This study aimed (i) to develop pharmacometric models of isoniazid and rifampicin in Indian children and (ii) to investigate the adequacy of the current dosing of isoniazid and rifampicin in children.

Methods

The study was conducted at the Christian Medical College and Hospital in Vellore, India. A total of 41 children diagnosed with tuberculosis were included in the analysis. Isoniazid and rifampicin concentrations were determined at steady state, 2 months after initiation of therapy. The pharmacokinetic data were analysed using a nonlinear mixed effect model approach in NONMEM (v7.3) using FOCE method with interactions.

Results

The pharmacokinetics of both isoniazid and rifampicin were described by one compartment disposition models. A flexible transit compartment model was used to describe the absorption phase, with 5 transit compartments for isoniazid and 9 transit compartments for rifampicin. A mixture model was successfully added to the isoniazid model, to describe the known polymorphisms in NAT, resulting in slow and fast acetylators identifying two subgroups with different elimination clearances. In the isoniazid model body weight were added allometrically on volume of distribution and elimination clearance. Model validation indicates a good fit of the model to the data. Eighteen percent of the patients on isoniazid and ninety percent of the patients on rifampicin exhibited a decreased maximum concentration compared to the accepted therapeutic range.

Conclusions

Pharmacokinetic models were successfully constructed for both isoniazid and rifampicin. These models can be used to determine if the current dosing guidelines in children are adequate and be used to simulate alternative treatment schedules.

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