

Model-based extrapolation of the early bacterial activity (EBA) of bedaquiline and pretomanid for the treatment of pulmonary tuberculosis

AUTHORS

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BACKGROUND

Model-based approaches offer a method of discriminating whether the dose and exposure to an anti-tubercular compound is appropriate to ensure efficacy (i.e., bactericidal and sterilizing activity). Recently, a semi-mechanistic two-state model was developed [1] to include fast-(F) and slow-(S) growing subpopulations which represent the log-growth and stable phase of *Mycobacterium tuberculosis* infection. This approach was successfully applied for the prediction of the early bactericidal activity (EBA) of rifampicin in humans. Here we attempt to assess the predictive performance of the model to describe the EBA of pretomanid (PMD) and bedaquiline (BDQ).

METHODS

Compartmental PK models were developed using concentration-time data generated by GlaxoSmithKline (GSK) in non-infected C57BL/6J mice using different dose levels (mg/kg) for PMD. PK data in BALB/c mice following single doses of BDQ were extracted from a publication by Tasneen *et al.* [2]. These models were used to predict the steady-state concentration in both acute and chronic experimental murine protocols. Subsequently, antibacterial activity was assessed in terms of drug potency (EC_{50}), under the assumption of a theoretical maximum killing rate for both compounds (E_{MAX} was fixed to 0.0671 h^{-1}). For PMD, two studies were conducted on 122 patients tested doses of 50, 100, 200, 600, 1000, or 1,200 mg/day. The average observed EBA in the two clinical studies was $0.15 \pm 0.01 \log_{10} \text{ CFU/mL/day}$ for PMD [6]. For BDQ, four arms were tested (100, 200, 300, 400 mg/day). The observed mean fall in $\log_{10} \text{ CFU/mL/day}$ were 0.040, 0.056, 0.077, and 0.104 per respective arm [4]. Exposure to PMD in humans was estimated using a 1-compartment model and a 2-compartment PK model for BDQ [5]. Whilst the active metabolites of BDQ may play a role in the overall antibacterial effect, we have not incorporated it in the extrapolation of the effects. Instead, comparable formation rate was assumed across species and consequently similar apparent potencies. The data analysis was implemented in NONMEM v.7.3. All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

RESULTS

Our analysis shows that the potency estimates of PMD against F and S subpopulations are 1.77 mg/L and 123 mg/L, respectively. These figures are approximately one order of magnitude higher than those observed for BDQ, which had potency estimates for the F and S subpopulations of 0.192 mg/L and 3.04 mg/L, respectively. Based on the dosing regimens tested in the EBA studies, the average predicted steady state concentrations in humans on day 14 were 1.28 mg/L for PMD and 1.68 mg/L for BDQ, which corresponds to values comparable (PMD) or 8-fold higher (BDQ) than the potency estimates for the fast-growing subpopulation. Visual predictive checks (VPCs) describing model-based extrapolation of the antibacterial activity after correction for PK differences in humans showed good agreement between the model-predicted and observed CFU count over time profiles.

CONCLUSIONS

We have assessed the performance of an *in vivo* PKPD modelling framework for the extrapolation of the antibacterial effects of antitubercular drugs in humans. Our examples provide insight into the bactericidal activity of compounds on F and S growing subpopulations of *M. tuberculosis*, but also the challenges when dealing with interspecies differences in PK and overall bactericidal activity, particularly when active metabolites are formed. Whilst EBA has been considered a standard step in the clinical evaluation of antitubercular drugs, these protocols are not optimal for the selection of doses to be tested in subsequent clinical studies when drugs with high potency also show prolonged elimination half-life, as in the case of BDQ.

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