Pharmacokinetic interaction between bedaquiline and clofazimine in patients with drug-resistant tuberculosis

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SUMMARY

BACKGROUND: Bedaquiline (BDQ) and clofazimine (CFZ) are both recommended for treating drug-resistant tuberculosis (DR-TB). As CFZ is an inhibitor of the cytochrome P450 isoenzyme 3A4 (CYP3A4) in vitro, and BDQ a substrate of CYP3A4, there is a potential for pharmacokinetic (PK) drug-drug interaction that may result in increased BDQ exposure when co-administered with CFZ, which could increase the toxicity of BDQ.

METHODS: We assessed the effect of co-administered CFZ on BDQ bioavailability, or on clearance of BDQ and its N-monodesmethyl metabolite (M2), in patients with DR-TB using a population PK model developed from data of patients with DR-TB. This was a secondary analysis of a study designed to explore drug-drug interactions between BDQ and antiretrovirals.

RESULTS: Of 46 participants, 30 were on concomitant CFZ when intensive PK sampling of BDQ was done. CFZ did not have a statistically significant effect on BDQ bioavailability (\(9.1\%, 90\%CI = 22.8 \text{ to } +7.1; P = 0.19\)) or on BDQ and M2 clearance (\(+12.2\%, 90\%CI = -13.7 \text{ to } +38; P = 0.32\)).

CONCLUSION: We did not find a statistically significant PK drug-drug interaction between BDQ and CFZ, but cannot exclude a potentially clinically relevant interaction due to the wide confidence intervals of the estimated interaction effects.

KEY WORDS: population pharmacokinetics; drug-drug interaction; BDQ; CFZ; TB

BEDAQUILINE (BDQ) IS A RECENTLY approved antimycobacterial drug used in the treatment of drug-resistant tuberculosis (DR-TB). BDQ is predominantly metabolised by cytochrome P450 isoenzyme 3A4 (CYP3A4) to its N-monodesmethyl metabolite (M2), which is less active but more toxic than BDQ. Co-administration with drugs that inhibit CYP3A4 results in increased exposure to BDQ, which could increase the risk of toxicity, notably QT prolongation.

The anti-leprosy drug, clofazimine (CFZ), has been repurposed as an anti-tuberculosis drug and is the cornerstone of the short-course multidrug-resistant tuberculosis regimen recommended by the World Health Organization (WHO). It is also widely used in other types of DR-TB. CFZ inhibits CYP3A4 in vitro, but also weakly induces CYP3A4. There are no published clinical data on pharmacokinetic (PK) drug-drug interactions between CFZ and substrates of CYP3A4 such as BDQ. Co-administration of BDQ and CFZ will become increasingly common as access to BDQ increases.

We assessed the effect of co-administered CFZ on exposure to BDQ and its M2 metabolite in patients with DR-TB using a population PK model. This approach has been shown to predict drug-drug interactions well for drugs such as BDQ that have long half-lives.

METHODS

We conducted a secondary analysis of an observational study of the drug-drug interactions between BDQ and antiretroviral drugs nevirapine (NVP) and lopinavir/ritonavir (LPV/r) in South African adults with DR-TB, which has been reported previously. BDQ was dosed at 400 mg daily for 2 weeks, followed by 200 mg three times weekly for 22 weeks. Anti-tuberculosis drugs were administered as directly observed therapy in almost all participants. Participants were from three groups: human immunodeficiency virus (HIV) negative (control group), and HIV-infected on NVP-based or LPV/r-based antiretroviral therapy (ART) (NVP and LPV/r groups). During the BDQ maintenance dosing period (between weeks 3 and 24), all participants...
had intense PK sampling (pre-dose and 1, 3, 5, 6, 8, 24 and 48 h after dosing) and 28 patients also had sparse sampling done (at 24 and 48 h post-dose) on several occasions.

The study protocol was approved by the Human Research Ethics Committee of the University of Cape Town, Cape Town, South Africa. All participants provided written informed consent.

To account for PK sampling at differing durations on BDQ treatment in the observational study, a population PK analysis was conducted using a published model of BDQ and M2 developed from data on patients with DR-TB.8,9 The model was implemented in NONMEM version 7.3 (Icon Development Solutions, Ellicott City, MD, USA), and the NWPRI prior functionality was used.

For the present study, this analysis was extended to investigate a potential effect of concomitant CFZ (dosed at 100 mg daily) administration on BDQ bioavailability, or on the clearance of BDQ and M2. The model used included priors, i.e., existing information on the parameter values, on all absorption and disposition parameters, but not on parameters quantifying interaction effects. Information on the concomitant use of CFZ was obtained by reviewing prescription charts and clinical notes. An additional parameter affecting BDQ and M2 clearance or oral bioavailability in patients receiving concomitant CFZ was evaluated.

The statistical significance of the added parameters was tested using the likelihood ratio test (α = 0.05). The 90% confidence intervals (90%CI) of the effect estimates were derived using sampling importance resampling (SIR) methodology,10 implemented with the Perl-speaks-NONMEM software (Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden).11 Data were managed and plotted using R (R Foundation for Statistical Computing, Vienna, Austria). As BDQ and M2 exposure depend on the duration on BDQ treatment and type of ART, the estimated variability in BDQ exposure in participants with and without CFZ was visualised by plotting the model-derived individual area under the concentration curve over 48 h (AUC0–48h) relative to the typically expected AUC0–48h at the corresponding time point, based on the participant’s dosing history, body weight and ART use.

RESULTS

We enrolled 46 participants on BDQ as part of the treatment for DR-TB: 17 controls, 17 in the NVP group and 14 in the LPV/r group. Two participants (one with and one without CFZ) were switched from NVP- to LPV/r-based ART and were intensively sampled on two separate occasions. Baseline characteristics of the 46 participants were as follows: median age 36 years (range 19–62), median weight 57.4 kg (range 44.0–86.0), 14 females and 29 HIV-infected. Of the 46 participants, 30 were receiving concomitant CFZ at the time of PK sampling. Concomitant CFZ use was similar among the groups: 12/17 in the HIV-negative group, 10/17 in the NVP group and 9/14 in the LPV/r group. A total of 488 BDQ and 486 M2 plasma concentration observations were included in the analysis.

The Figure shows the distribution of relative individual BDQ exposure in patients with and without concomitant CFZ, showing no obvious differences between the groups. The magnitude of the estimated interaction effects and their uncertainty are presented in the Table. CFZ did not have a statistically significant effect on BDQ bioavailability, or on BDQ and M2 clearance. Alternative parameterisations of the CFZ effect on clearance, assuming impact only on BDQ and not on M2, or allowing the magnitude and direction of the effect on BDQ and M2 to be different, also did not yield any statistically significant effects (P = 0.11 and P = 0.09, respectively).

DISCUSSION

We found a slight increase in the clearance of BDQ and M2 when CFZ was co-administered in a population PK model, but this effect was not statistically significant. We also found no statistically significant effect of CFZ co-administration on the bioavailability of BDQ. Our findings suggest that there is no major PK drug-drug interaction between BDQ and CFZ. However, a potentially clinically relevant interaction (defined as a ≥20% change in a
BDQ and M2 clearance.

Second, in vitro studies are known to poorly predict clinical drug-drug interactions for drugs that are highly protein-bound, such as CFZ. Third, the regimen. Our findings suggest that the increase to 31.9 ms when CFZ was included in the regimen. The in vitro studies used liver microsomes or a liver cell line, which are not as good as recombinant P450 enzymes in predicting clinical drug-drug interactions.

In a Phase II study of BDQ in participants with multidrug-resistant TB, the mean change in QTcF from baseline was 12.3 ms in participants on BDQ, increasing to 31.9 ms when CFZ was included in the regimen. Our findings suggest that the additive QT prolongation of BDQ and CFZ is due to a pharmacodynamic rather than a PK interaction; this is supported by a linear increase in QTcB of >15 ms from baseline observed over 2 weeks (long before CFZ steady-state concentrations are reached) of an early bactericidal activity study.

Our study has several limitations. First, it was not designed to assess the drug-drug interaction between BDQ and CFZ, but was a secondary analysis of a drug-drug interaction study of BDQ and ART drugs. Second, administration of CFZ was not observed on the day of PK sampling. Third, the confidence intervals of the estimated CFZ interaction effects were wide, a consequence of the limited sample size and the random inter-individual variability.

In conclusion, we found no major PK drug-drug interaction between BDQ and CFZ. A prospective, adequately powered drug-drug interaction study should be conducted to confirm our findings.

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References


CONTEXTE : La bédaquiline (BDQ) et la clofazimine (CFZ) sont toutes deux recommandées pour le traitement de la tuberculose pharmacorésistante (TB-DR). La CFZ est un inhibiteur de l’isoenzyme P450 cytochrome (CYP3A4) in vitro et la BDQ est un substrat de CYP3A4. C’est pourquoi il y a une interaction pharmacocinétique (PK) potentielle entre les deux médicaments qui peut aboutir à une exposition accrue à la BDQ quand elle est co-administrée avec la CFZ, ce qui augmenterait la toxicité de la BDQ.

MÉTHODES : Nous avons évalué l’effet de l’administration simultanée de la CFZ sur la biodisponibilité de la BDQ ou sur la clairance de la BDQ et de son métabolite N-monodesmethyl (M2), chez les patients atteints de TB-DR ; nous avons pour cela utilisé un modèle de PK en population élabore`e à partir des données de patients atteints de TB-DR. Ceci a été une analyse secondaire d’une étude conçue pour explorer les interactions médicamenteuses entre la BDQ et des antirétroviraux.

RÉSULTATS : De 46 participants, 30 ont été concomitamment sous CFZ quand l’échantillonnage intensif de PK de la BDQ a été réalisé. La CFZ n’a pas eu d’effet statistiquement significatif sur la biodisponibilité de la BDQ (–9,1% ; IC90% –22,8 à + 7,1 ; P = 0,19) ou sur la clairance de la BDQ et du M2 (±12,2% ; IC90% –13,7 à + 38 ; P = 0,32).

CONCLUSION : Nous n’avons pas trouvé d’interaction statistiquement significative en terme de PK entre la BDQ et la CFZ, mais nous ne pouvons pas exclure une interaction potentiellement pertinente sur le plan clinique en raison des larges intervalles de confiance des effets estimés de l’interaction.