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Drug–drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB

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Objectives: Bedaquiline is a new anti-TB drug, which is metabolized by cytochrome P450 (CYP) 3A4. Concomitant ART is important for all HIV-infected patients treated for TB, but several antiretrovirals inhibit or induce CYP3A4. Single-dose drug–drug interaction studies found no significant interactions with nevirapine or lopinavir/ritonavir, but these findings could be misleading, especially because of bedaquiline's long terminal $t_{1/2}$. We evaluated the effect of nevirapine and lopinavir/ritonavir on bedaquiline exposure.

Methods: We conducted a parallel-group pharmacokinetic study of three groups of participants who were on bedaquiline as part of therapy for drug-resistant TB: no ART (HIV seronegative); nevirapine-based ART; and lopinavir/ritonavir-based ART. Non-compartmental analyses were done and exposure of bedaquiline and its M2 metabolite compared between the no-ART group and the two ART groups.

Results: We enrolled 48 participants: 17 in the no-ART group, 17 in the nevirapine group and 14 in the lopinavir/ritonavir group. The following median bedaquiline pharmacokinetic parameters were significantly higher in the lopinavir/ritonavir group than in the no-ART group: AUC_{0-48} (67 002 versus 34 730 ng·h/mL; $P=0.003$); T_{max} (6 versus 4 h; $P=0.003$); and $t_{1/2}$ (55 versus 31 h; $P=0.004$). On multivariate analysis, bedaquiline exposure was increased by lopinavir/ritonavir, male sex and time on bedaquiline. Bedaquiline exposure was not significantly different between the nevirapine group and the no-ART group. M2 metabolite exposure was not significantly different in either of the antiretroviral groups compared with the no-ART group.

Conclusions: Lopinavir/ritonavir significantly increased bedaquiline exposure. The clinical significance of this interaction remains to be determined.

Introduction

Bedaquiline, which has recently been approved for the treatment of drug-resistant TB, is a diarylquinoline antimycobacterial with the novel mechanism of action of selectively inhibiting mycobacterial ATP synthase.[1] Bedaquiline is primarily metabolized in the liver by the cytochrome P450 (CYP) isoenzyme 3A4 to a less active *N*-monodesmethyl metabolite (M2).[1] Coadministered drugs that induce CYP3A4 could result in reduced bedaquiline concentrations, which could reduce efficacy and select for resistant mutants, while drugs that inhibit CYP3A4 could result in increased bedaquiline concentrations, which could increase the risk of toxicity, notably QT prolongation.[2] TB and HIV coinfection is common and their concurrent treatment has become the standard of care following studies showing reduced mortality when ART is initiated soon after starting TB therapy.[3] The WHO's recommended first- and second-line ART regimens include drugs that may affect bedaquiline exposure by inducing and/or inhibiting CYP3A4.[4]

The NNRTI nevirapine is a moderate inducer of CYP3A4,[5] while the PI lopinavir/ritonavir is a potent inhibitor of CYP3A4.[6] Drug–drug interaction (DDI) studies found only modest effects of nevirapine and lopinavir/ritonavir on bedaquiline exposure.[1] However, both DDI studies used single doses of bedaquiline in participants at steady-state on lopinavir/ritonavir or nevirapine, which may underestimate the magnitude of the DDIs when bedaquiline reaches steady-state following chronic administration. Non-linear mixed-effects modelling estimated 3- and 2-fold increases in average concentrations at steady-state for bedaquiline and M2, respectively, when bedaquiline is coadministered with lopinavir/ritonavir and no significant effect when coadministered with nevirapine.[7]

There are currently no data on bedaquiline pharmacokinetics when coadministered long term in patients on nevirapine- or lopinavir/ritonavir-based ART.

We conducted an observational pharmacokinetic study in patients with drug-resistant TB during the maintenance dose phase of their bedaquiline therapy and compared bedaquiline pharmacokinetic parameters in HIV-infected patients on nevirapine or lopinavir/ritonavir with HIV-uninfected patients not on ART.

Methods

Adults (≥18 years) with drug-resistant TB receiving bedaquiline from the South African national access programme[8] were approached for enrolment into the study. We enrolled consenting participants into three groups: no ART (HIV uninfected); on nevirapine-based ART; and on lopinavir/ritonavir-based ART. Participants on ART must have been on nevirapine for ≥2 weeks and on lopinavir/ritonavir for ≥3 days. Exclusion criteria were other drugs known to inhibit or induce CYP3A4, pregnancy or gastrointestinal diseases that may interfere with pharmacokinetics.

Intensive pharmacokinetic sampling was performed once participants had completed the 2 week loading dose phase (400 mg daily) and ≥1 week of the maintenance dose phase (200 mg on Monday, Wednesday and Friday) of bedaquiline treatment. Pharmacokinetic samples were collected before and at 1, 3, 4, 5, 6, 8, 24 and 48 h after a 200 mg dose of bedaquiline (administered after a meal). Plasma was separated by centrifugation within 1 h of sampling and then stored at −70°C.

Bedaquiline and M2 concentrations were determined using an LC-MS/MS assay validated according to FDA and EMA guidelines.[9,10] Plasma samples (20 μL) were processed by precipitation with acetonitrile containing the isotope-labelled internal standards di(methyl-D3) amine bedaquiline and 4-methyl(^{13}C)-D3 amino M2. The supernatant was concentrated and reconstituted in injection solution consisting of equal parts of acetonitrile and 0.1% formic acid in water. Chromatographic separation was achieved on a Phenomenex Gemini NX-C18, 5 μm, 110Å (50×2.0 mm) analytical column using acetonitrile and 0.1% formic acid (37:63, v/v) as the mobile phase, delivered at a constant flow rate of 500 μL/min. An AB Sciex API 4000 mass spectrometer was operated at unit resolution in the multiple reaction monitoring mode, monitoring the transition of the protonated molecular ion at *m/z* 555.2 to the product ion at *m/z* 58.1 for bedaquiline and the protonated molecular ion at *m/z* 541.1 to the product ion at *m/z* 480.1 for M2. The internal standard transitions monitored were the protonated molecular ion at *m/z* 561.1 to the product ion at *m/z* 64.3 for di(methyl-D3) amine bedaquiline and the protonated molecular ion at *m/z* 545.3 to the product ion at *m/z* 480.1 for 4-methyl-(^{13}C)-D3 amino M2. Electrospray ionization was used for ion production. The assay was validated over the concentration range of 0.00977–5 μg/mL for bedaquiline and 0.00313–0.2 μg/mL for M2. During interday sample analysis, the accuracies (%Nom) for bedaquiline were 97.2%, 96.9% and 104.1% at the high (3.75 μg/mL), medium (1.75 μg/mL) and low (0.0293 μg/mL)

Table 1. Participant characteristics and plasma pharmacokinetic parameters of bedaquiline and the M2 metabolite

	No ART (*N*=17)	Nevirapine (*N*=17)	Lopinavir/ritonavir (*N*=14)
Participant characteristics			
male sex, *n* (%)	13 (77)	10 (59)	9 (64)
age, years	25 (22–38)	37 (21–46)	32 (26–40)
weight, kg	56.7 (52.5–64.7)	58.7 (54.6–69.2)	53.8 (48–60)
days on bedaquiline at PK sampling	43 (34–79)	70 (35–79)	95 (43–114)
Bedaquiline			
AUC_{0-48}, ng·h/mL	34730 (27466–52862)	35174 (28372–64158)	67002 (51862–88255)
P[a]	reference	*P*=0.502	*P*=0.003
C_{max}, ng/mL	1970 (1100–2640)	2000 (1420–2450)	2235 (1670–2850)
P[a]	reference	*P*=0.642	*P*=0.234
T_{max}, h	4 (3–5)	5 (4–6)	6 (5–8)
P[a]	reference	*P*=0.197	*P*=0.003
$t_{1/2}$, h[b]	31 (24–37)	33 (26–44)	55 (44–93)
P[a]	reference	*P*=0.564	*P*=0.004
M2 metabolite			
AUC_{0-48}, ng·h/mL	7449 (6064–9060)	8358 (4943–9537)	6561 (3846–10626)
P[a]	reference	*P*=0.617	*P*=0.606
C_{max}, ng/mL	169 (140–244)	185 (128–281)	172 (103–258)
P[a]	reference	*P*=0.705	*P*=0.921
T_{max}, h	8 (5–8)	6 (0–8)	8 (3–24)
P[a]	reference	*P*=0.391	*P*=0.587
$t_{1/2}$, h[c]	208 (120–447)	240 (124–477)	243 (72–1233)
P[a]	reference	*P*=0.5056	*P*=0.9379

PK, pharmacokinetic.
Unless otherwise stated, values are presented as median (IQR).
[a]*P* values are the difference between the no-ART group and either the nevirapine group or the lopinavir/ritonavir group.
[b]The $t_{1/2}$ of bedaquiline for one patient in the nevirapine group could not be estimated.
[c]The $t_{1/2}$ of M2 could not be estimated in two, seven and eight of the participants from the no-ART, nevirapine and lopinavir/ritonavir groups, respectively.

quality control levels, respectively, with precision <10% across all three levels. The accuracies for M2 were 97.5%, 101.4% and 99.9% at the high (0.150 μg/mL), medium (0.075 μg/mL) and low (0.00938 μg/mL) quality control levels, respectively, with precision <7%.

A sample size of 14 participants in each group was required to detect a 50% difference in the bedaquiline steady-state AUC between the no-ART group and on-ART groups, with 80% power and 5% significance based on the variance calculated from the steady-state concentrations at week 8 reported in the Phase 2 study.[11] As we would likely be using non-parametric statistical testing, we increased the sample size by 15% to 16 participants in each of three groups. Pharmacokinetic parameters were derived from non-compartmental analysis. The Mann–Whitney *U*-test was used to compare pharmacokinetic parameters in parallel groups of participants on nevirapine or lopinavir/ritonavir versus participants not on ART. Multivariate linear regression was used to estimate the impact of covariates on log-transformed bedaquiline AUC_{0-48}. Our sampling times were done when the increase in bedaquiline and M2 metabolite concentrations is approximately linear,[7] which allowed us to use multivariable linear regression for analyses.

The study protocol was approved by the University of Cape Town's Human Research Ethics Committee (reference number 444/2013). All enrolled participants signed informed consent.

Results

The participants' characteristics and the pharmacokinetic parameters of the three groups are shown in Table 1. There were no significant differences in participant characteristics between either the nevirapine group or the lopinavir/ritonavir group and the no-ART group, but duration on bedaquiline at the time of sampling was longer in participants on lopinavir/ritonavir ($P=0.06$). There were no significant differences in the bedaquiline and M2 pharmacokinetic parameters between the nevirapine group and the no-ART group. By contrast, the bedaquiline AUC, T_{max} and $t_{1/2}$ were significantly higher in the lopinavir/ritonavir group than in the no-ART group. There were no significant differences in M2 pharmacokinetic parameters between the lopinavir/ritonavir group and the no-ART group.

Multivariable linear regression modelling controlling for covariate effects (Table 2) showed lopinavir/ritonavir and male sex were associated with a significant increase in bedaquiline AUC_{0-48} of 62% and 47%, respectively. Time on bedaquiline was also associated with increased bedaquiline AUC_{0-48}, but this just failed to reach statistical significance.

Table 2. Multivariable linear regression on covariate effects on bedaquiline AUC_{0-48} (no ART is the reference group)

	Change in AUC_{0-48}	95% CI	*P*
Nevirapine	17% increase	−17%–65%	0.340
Lopinavir/ritonavir	62% increase	13%–132%	0.010
Male sex	47% increase	8%–98%	0.014
Time on bedaquiline (per week increase)	2% increase	−1%–5%	0.060
Weight (per 10 kg increase)	11% decrease	−32%–0.2%	0.107
Age (per year increase)	0.9% increase	−1%–24%	0.186

Discussion

We found that bedaquiline exposure was almost twice as high in the lopinavir/ritonavir group as in the no-ART group. Variables associated with higher plasma bedaquiline exposure on multivariate analysis were lopinavir/ritonavir coadministration, male sex (presumably due to less body fat than women) and time on bedaquiline (of borderline significance). Nevirapine did not significantly affect bedaquiline exposure and neither antiretroviral affected M2 exposure.

Our findings are similar to the estimates of a non-linear mixed-effects model derived from single-dose interaction studies.[7] Svensson *et al.*[7] estimated no significant effect of nevirapine on bedaquiline exposure, but an ∼3-fold increase in bedaquiline and a 2-fold increase in M2 average steady-state concentrations, reached at 6 months, when coadministered with lopinavir/ritonavir. However, the magnitude of the interaction at ∼3 months, which is when we sampled our participants, was simulated to be no effect on M2 and an ∼2-fold increase in bedaquiline exposure.[7]

The clinical implications of the interaction between lopinavir/ritonavir and bedaquiline that we found are unclear, but the toxicity of bedaquiline could be enhanced. Notably, QT prolongation, which correlates with M2 concentrations,[12] could occur at 6 months when the increase in M2 concentrations is maximal.[7] We concur with the WHO's view that coadministration of lopinavir/ritonavir with bedaquiline 'should be used with extreme caution and only in a closely monitored setting when other options are not available'.[13]

Our study has a number of limitations. First, we just failed to achieve the desired sample size in the lopinavir/ritonavir group (14 instead of 16 participants) due to the small proportion of patients on second-line ART in the bedaquiline access programme. Second, pharmacokinetic sampling was not done when participants were at steady-state, when the inhibitory effects of lopinavir/ritonavir on both bedaquiline and its M2 metabolite are predicted to be maximal.[7] Third, our control group was HIV uninfected while the two antiretroviral groups were HIV infected; therefore, we could not control for possible effects of HIV on the pharmacokinetic parameters of bedaquiline. However, it will be difficult to study this possible disease effect as all HIV-infected patients with TB qualify for ART. A strength of our study is that it was conducted in the diseased populations of interest.

In conclusion, we found that concomitant lopinavir/ritonavir almost doubled the plasma bedaquiline exposure. Future studies should explore the effect of lopinavir/ritonavir and other ritonavir-boosted PIs on M2 and bedaquiline pharmacokinetic parameters, and on toxicity, at steady-state. The clinical implications of this DDI remain to be determined.

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Transparency declarations

G. M. served on the data safety and monitoring board for Janssen for the TMC207 (bedaquiline) C208 and C207 Phase 2 trials in patients with MDR TB, 2007–12. All other authors: none to declare.

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