ORIGINAL ARTICLE

Clinically relevant enantiomer specific R- and S-praziquantel pharmacokinetic drug-drug interactions with efavirenz and ritonavir

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Abstract

We conducted a clinical study to determine the effect of efavirenz and ritonavir on the pharmacokinetics of R- and S-PZQ in healthy male participants. This was toward evaluating the risk of drug-drug interactions, which may occur after PZQ administration to HIV patients on efavirenz or ritonavir containing regimens. A non-randomized, open-label, single-dose, one sequence crossover study with 2 arms was conducted. We gave 26 healthy volunteers a single oral dose of 40 mg/kg PZQ followed by a daily oral dose of either 400 mg efavirenz or 100 mg ritonavir for 14 consecutive days. On day 14, they ingested a single 40 mg/kg dose of PZQ. We measured plasma levels up to 12 h on day 1 and day 14. Samples were analyzed by LC-MS. Pharmacokinetic analysis was conducted in WinNonlin to determine the primary endpoints (plasma $T_{1/2}$, C_{min}, and AUC). Efavirenz had a significant effect on the pharmacokinetics of PZQ ($p < .05$), reducing the AUC by 4-fold (1213.15 vs. 281.35 h·ng/ml for R-PZQ and 5669 vs. 871.84 h·ng/ml for S-PZQ). Ritonavir had no significant effect on R-PZQ but increased the AUC 2-fold for S-PZQ ($p < .05$) (4154.79 vs. 7291.05 h·ng/ml). Using PZQ in HIV patients needs investigation, as there is a risk of both treatment failure and adverse effects because of induction and inhibition, respectively.

KEYWORDS
drug-drug interaction, enantiomer specific, pharmacokinetics, praziquantel

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Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; MEC, minimum effective concentration; PZQ, praziquantel.

1 | INTRODUCTION

Schistosomiasis is one of the leading neglected tropical diseases that affect over 218 million people worldwide, with the greatest burden being in children of school-going age.[1] Praziquantel (PZQ) is currently the WHO-recommended drug for both treatment and preventive chemotherapy of schistosomiasis due to its effectiveness across all schistosome species. The drug is administered as a racemic mixture of R and S enantiomers in equal proportions. Of the enantiomers, R is believed to be the main effector molecule, while S does not have a significant role but contributes to the bitter taste of the tablet.[2]

HIV and schistosomiasis are the most widespread infections in the world.[3] The two diseases share the same epidemiological space, especially in poor regions where endemicity is high such as Zimbabwe, Zambia, Ethiopia, and Nigeria.[3,4] The prevalence of HIV/AIDS and schistosomiasis ranges from 15–18% to 50%, respectively, with the situation estimated to be worse in data-deficient countries.[4] Over 10 million people are on antiretroviral (ARV) treatment in the sub-Saharan African region.[5] In Zimbabwe, about 1.3 million people are living with HIV/AIDS [6] with 89% and 76% of adults and children on antiretroviral therapy, respectively.[7] Of those patients, about 800 000 are on efavirenz-based regimen.[7] Efavirenz-based ART is the WHO-recommended alternative first-line treatment for HIV/AIDS in both adults and children older than 3 years, while ritonavir is part of the first-line and second-line recommendations.[8]

There have been reports of drug-drug interactions involving PZQ when given concomitantly with albendazole,[9] ketoconazole,[10,11] rifampicin,[12] dexamethasone,[13] and carbamazepine.[13] These interactions can impact on the safety and efficacy of PZQ. For example, PZQ levels are significantly reduced to sub therapeutic levels when co-administered with rifampicin, dexamethasone and carbamazepine.[12-14] Inhibition of enzymes involved in PZQ metabolism on the other hand may result in elevated drug levels which presents risk for drug-drug interactions, adverse events, discomfort, and poor treatment compliance.

PZQ undergoes extensive first-pass metabolism by cytochrome P450 (CYP) enzymes with less than 0.01% of the drug being excreted unchanged in urine.[15] Additionally, the compound is highly protein-bound with approximately 80% bound to albumin. CYPs 1A2, 2C9, 2C19, and 3A are important metabolizing enzymes in vitro.[16,17] These enzymes are modulated by inducers and inhibitors. Among the ARVs, efavirenz is a known inducer of CYP3A and CYP2C19[18] and inhibitor of CYP1A2[19] and CYP2C19.[20] Protease inhibitors are known potent inhibitors of CYP3A and CYP2C19.[21] This, therefore, presents a mechanistic basis for the likely effects of ARVs on PZQ pharmacokinetics (PK), which could affect the efficacy and safety of the PZQ. While the risk for drug-drug interactions can be bidirectional, it is the effect of ARVs on PZQ that is most likely. This is because previous studies have shown that while PZQ is rapidly metabolized by CYP450 s, it does not have inhibitory or induction effects on the CYP enzymes.[22] ARVs such as non-nucleoside analogue inhibitors (NNRTI) and protease inhibitors are however potent inhibitors or inducers of drug-metabolizing enzymes.

Our studies in vitro have shown PZQ metabolism to be enantiomer specific with R-PZQ being mainly metabolized by CYP1A2 and CYP2C19 whereas S-PZQ is metabolized by CYP2C19 and CYP3A4.[23] We, therefore, hypothesize that there will be a greater inhibitory and induction effect on S-PZQ as compared to the R-isoform since efavirenz and ritonavir have been shown to induce and inhibit CYP3A. Efavirenz also has an inhibitory effect on CYP2C19 and CYP1A2.[19] We therefore evaluated the extent and nature of the risk of drug-drug interactions in the co-treatment of HIV and schistosomiasis in this study. The aim is to increase knowledge towards the safe and efficacious use of PZQ especially in cases of coinfection and in mass drug treatment programs where the HIV status of an individual and concomitant drugs have not been taken into consideration before PZQ administration.

2 | MATERIALS AND METHODS

2.1 | Study drugs

Biltricide (PZQ brand) scored 600 mg tablets were obtained from Merck-Bayer, efavirenz 200 mg tablets were obtained from Strides (Bangalore and India), 100 mg Norvir (ritonavir brand) tablets were obtained from Abbvie.

2.2 | Chemicals and reagents

R-PZQ and S-PZQ were a generous gift from Merck Serono. Racemic PZQ, Diazepam (IS), Acetonitrile and formic acid were obtained from Sigma Chemical Co. All other reagents were of the highest obtainable grade.

2.3 | Study population, participant recruitment and ethical considerations

Forty-one volunteers had their full medical history and physical examination. We included study participants in the trial if they met the following criteria: Age of 18–40 years with a body mass index between 18 and 35 kg/m^2 and were deemed healthy as determined by the physician after a medical history, normal electrocardiogram, and physical examination. They also needed to have full blood count, urea and electrolytes, liver function and urinalysis results within acceptable ranges and being seronegative for hepatitis B and C and HIV. Participants were not allowed to smoke, take alcohol, caffeine-containing beverages, prescribed or over the counter medication, grapefruit, or recreational drugs for 2 weeks before starting the study until completion. The study excluded individuals with a history of drug or alcohol abuse, smokers, and those on any herbal or prescription medication.

We informed participants willing to participate about the nature, relevance, and consequences of the study. Recruitment was only after the completion of a written informed consent form. Study approvals were obtained from the Medical Research Council of Zimbabwe (registration number A/2318), University of Zimbabwe Joint Research Ethics Committee (registration number 188/19), and from the Medicines Control Authority of Zimbabwe (registration number CT171/2018). The participants were identified according to the inclusion and exclusion criteria set for the study. Twenty-six young male volunteers met the study inclusion criteria and enrolled in the study.

2.4 | Study design

The two studies were non-randomized open-label, single-dose, single-sequence cross-over (e.g., PZQ followed by PZQ + ARV) to evaluate the effect of efavirenz and ritonavir on PZQ pharmacokinetics (Figure 1). Each participant served as their control. Participants who met the inclusion criteria were divided into arm 1 and 2. Both arms were given oral doses of 40 mg/kg PZQ (dosed per weight) followed by either 400 mg efavirenz (arm 1 for 13 consecutive days) or 100 mg ritonavir (arm 2 for 14 consecutive days). Participant compliance was followed by daily directly observed treatment. Venous blood samples (3 ml) were collected in EDTA tubes PZQ post-dosing on day 1 and day 14. Sampling for PZQ pharmacokinetics was conducted at time points 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h. Samples were centrifuged at 1300 RCF for 5 min. Plasma was collected and aliquoted into a cryotube for storage at −20°C until analysis.

2.5 | Clinical safety assessments

Participants remained inpatient at the AiBST Clinical Trial Unit at Chitungwiza Central Hospital for at least 24 h before and after receiving PZQ on days 1 to 3 and days 15 to 17. Safety assessments including physical examination, vital signs, serum biochemistry, hematology, urinalysis, and ECG were completed during screening. During admission, participants were assessed for vital signs and monitored for any adverse events or symptoms.

2.6 | Measurements of R- and S-PZQ in plasma

Plasma samples were extracted using protein precipitation with acetonitrile as the extraction solvent. Briefly, 100 µl of plasma was spiked with 10 µl of 200 ng/ml diazepam (internal standard) followed by the addition of 290 µl of ice-cold acetonitrile. The mixture was vortexed for 30 seconds before centrifugation at 1300 RCF for
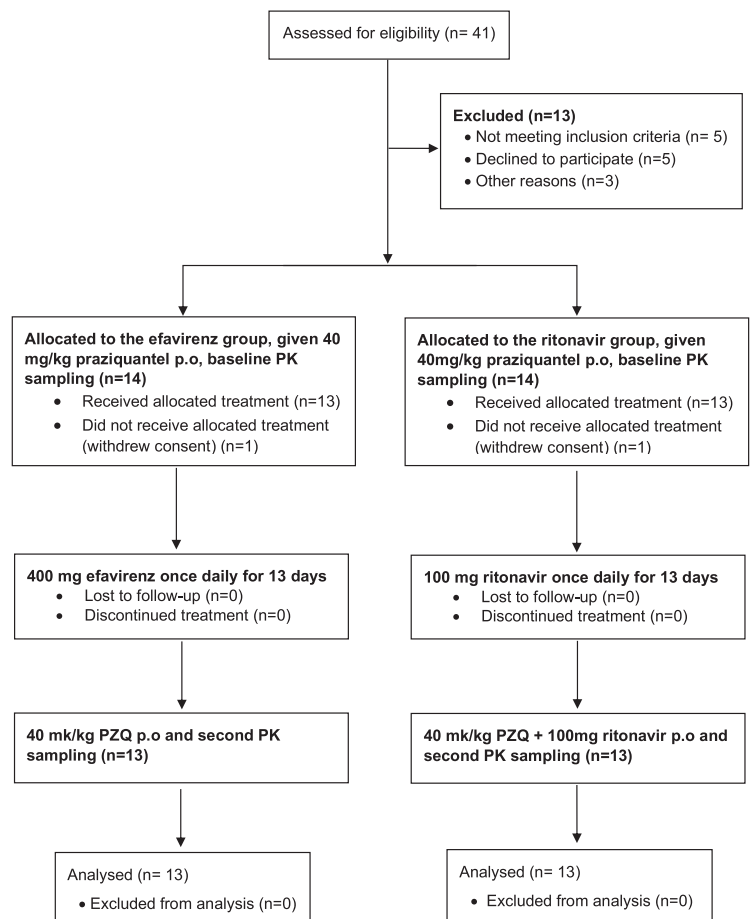

FIGURE 1 Study design and basic method

10 minutes. A volume of 350 µl of the supernatant was collected and was evaporated to dryness under a gentle stream of nitrogen. The dried residue was reconstituted in 50 µl of mobile phase and 5 µl was injected into the LC/MS-MS for analysis.

R- and S-PZQ levels were determined on a mass spectrometer using a validated method.[24] A 3200 Q TRAP Series triple quadrupole (AB Sciex) liquid chromatography-mass spectrometry MS/MS system was used to carry out the analysis. The LC module consisted of an Agilent 1100 series HPLC system. MS/MS analyses were performed in positive ionization mode. Analyst software (AB Sciex) served to operate the instrument and analyze the data. The compounds of interest were separated by chiral chromatography using an astec cellulose DMP column (150 × 4.6 mm, 5 µm, Supelco). The mobile phase consisted of 0.1% formic acid in acetonitrile delivered at a flow rate of 0.8 mL/min. The column was maintained at a temperature of 35°C. Analytes were followed by multiple reaction monitoring at m/z 313.3/203.2 (quantifier ion), 313.3/83.2 (qualifier ion) and 313.3/174.2 (qualifier ion) for both R- and S-PZQ. Diazepam was followed at m/z 285/193 (quantifier ion) and 285/154 (qualifier ion).

2.7 | Pharmacokinetic analysis

Pharmacokinetic parameters were estimated from plasma concentrations using non-compartmental analysis in WinNonlin software version 8.2 (Certara). The area under the curve (AUC) from time of dosing to the last quantifiable concentration (AUC_{last}) and infinity (AUC_∞) was estimated using the linear and logarithmic trapezoidal rule. The linear up and log down method was used. The elimination rate constant (K_{el}) was determined by the program using nonlinear regression of the natural logarithm of concentration values in the elimination phase. The terminal half-life ($T_{1/2}$) was calculated using the equation $T_{1/2} = \ln2/\lambda$. The apparent clearance, CL/F was determined from the equation CL/F = Dose/AUCinf. PK profiles were plotted as graphs of R-PZQ and S-PZQ concentrations vs time.

2.8 | Statistical analysis

Statistical analysis was performed using GraFit software (version 3.0, Erithacus Software Limited). The analysis included descriptive statistics, paired t-tests, and the computation of the 90% confidence interval. The null hypothesis assumed no significant difference between the test and reference treatments. Analysis of variance (ANOVA) was performed on the AUC and C_{max} after transformation of the data to their natural logarithmic (ln) values. The 90% confidence intervals (CIs) were calculated using the error variance obtained from ANOVA. The following equation was used:

$$90\% \, \text{CI} = (\overline{X}_T - \overline{X}_R) \pm t_v^{0.1} \sqrt{S^2 x \frac{2}{n}}$$

where $\overline{X}_T$ and $\overline{X}_R$ are the geometric means of the ln transformed values for the test treatment (T) and the reference treatment (R); S^2 is the error variance obtained from the ANOVA; n is the number of participants, t is the t-value for 90% of the t-distribution, and v is the degree of freedom of the error variance from the ANOVA. The anti-ln of the above CI values was then computed to give the 90% CIs of the ratio of the test to the reference treatment geometric means.

3 | RESULTS

3.1 | Baseline characteristics

A total of 28 black males were enrolled with 26 completing the pharmacokinetic study. Out of the initial 41 participants screened, 5 participants did not meet the inclusion criteria, and 10 dropped out of the study (Figure 1). Baseline characteristics are summarized in Table 1. PZQ and ritonavir were generally well tolerated by the participants. In the efavirenz group, 33% of the participants had mild dizziness with symptoms disappearing by day 5. No other symptoms or abnormal vital signs were reported during the study or post-study follow-up period.

3.2 | Analysis of R- and S-PZQ in plasma

The lower limit of quantitation for both R- and S-PZQ was 6.24 ng/ml with a signal to noise ratio of 5:1. The linearity range was 6.24 ng/ml to 1026 ng/ml (r^2 = .999) with accuracy, precision, and recovery within the acceptable bioanalytical method validation range for the low, middle and high-quality control levels assessed. The analyte signal did not change upon assessing short-term stability, benchtop at 28°C for 24 h and over 3 freeze-thaw cycles. Autosampler stability was acceptable as the extracted samples' signal intensity did not change. Chromatographic separation was achieved with a good resolution for the analytes. The retention time was 3.88 min for diazepam (IS), 4.68 min for R-PZQ and 5.04 min for S-PZQ.

3.3 | Pharmacokinetic analysis

R-PZQ was more extensively metabolized as compared to S-PZQ when the drug was given alone, with R-PZQ being cleared up to six times

TABLE 1 Baseline characteristics of participants enrolled in the study (n = 28)

Characteristic	Mean (SD)	Range
Age: y	23.01 (3.87)	20.33–24.48
Weight: kg	61.14 (7.00)	55.00–65.25
Height: cm	173.68 (6.55)	168.75–178.25
Body mass index: kg/m^2	20.33 (1.95)	18.40–21.93

faster than S-PZQ. The C_{max} and AUC of S-PZQ in plasma were 2–3 times more than that of R-PZQ (Table 2 and Table 3). Efavirenz significantly reduced the plasma concentrations of R- and S-PZQ (Figure 2). This significant inductive effect was characterized by a 4-fold reduction in AUC_{inf} (1213.15 vs. 281.35 h·ng/ml, $p < .05$ for R-PZQ and 5669 vs. 871.84 h·ng/mL, $p < .001$ for S-PZQ) (Table 2). The C_{max} reduced significantly for S-PZQ (1991.32 vs. 329.98 ng/ml, $p < .001$) and with a less significant effect for R-PZQ (491.78 vs. 104.32 ng/ml, $p > .05$). The clearance was, however, significant in both cases ($p < .05$) with a 6-fold and 10-fold increase for R and S-PZQ, respectively.

The relative bioavailability of PZQ was increased when the drug was given concomitantly with ritonavir (Figure 3). Ritonavir had a significant effect on S-PZQ which was characterized by a 2-fold increase in the AUC (4154.79 vs. 7291.05 h·ng/ml), $p < .05$) with a decrease in the clearance (570.54 vs. 325.12 L/h, $p < .01$), and an increase in the C_{max} (1174 vs. 2336 ng/ml, $p < .01$). The effect was however not significant ($p > .05$) on R-PZQ with an AUC of 1012 versus 1057 h·ng/ml, C_{max} of 308.44 versus 354.34 ng/ml and mean clearance of 2340 versus 2241 L/h (Table 3).

4 | DISCUSSION

PZQ is the only WHO-recommended drug which has a good safety profile and is effective against all species of schistosome. This study aimed to evaluate the risk of drug-drug interactions which may occur when PZQ is administered to HIV patients on antiretroviral therapy containing efavirenz or ritonavir. This has a potential impact on the effectiveness of PZQ mass drug administration programs and treatment of schistosomiasis in HIV patients.

Results of this study demonstrate a significant risk of drug-drug interactions (DDI) if PZQ is administered to patients on efavirenz-based antiretroviral therapy (ART). Concomitant administration of PZQ and efavirenz resulted in a 4-fold reduction in the exposure level of R- and S-PZQ. This is consistent with other studies where efavirenz has been shown to significantly reduce drug exposure of concomitantly administered drugs.[25] This inductive effect presents a significant risk for treatment failure because of sub therapeutic levels of PZQ in patients on efavirenz containing regimens. This has a confounding effect as efavirenz-based highly active antiretroviral therapy is widely

TABLE 2 Effect of efavirenz on the pharmacokinetics of R- and S-PZQ following single-dose administration of 40 mg/kg racemic PZQ alone (reference) and together with 400 mg efavirenz (treatment)

PK parameter	PZQ alone		PZQ + Efavirenz		Treatment/reference (%)			
	Geo Mean	95% CI	Geo Mean	95% CI	GMR	95% CI	Difference observed (%)	p value
R-Praziquantel								
AUC_{inf} (h·ng/ml)	1213.15	660.07–2229.67	281.43	119.18–664.57	23.20	8.60–62.17	−74.36	.0480
$AUC_{t0-tlast}$ (h·ng/ml)	1140.41	609.42–2134.03	248.02	108.28–568.08	21.75	8.22–57.52	−76.90	.0469
C_{max} (ng/ml)	491.78	227.61–1062.58	104.32	48.52–224.31	21.21	7.67–58.64	−82.52	.0430
T_{max} (h)	1.88	1.13–3.15	1.64	1.13–2.38	—		−18.22	.0947
Half-Life (h)	2.66	1.95–3.67	2.76	1.76–4.32	—		17.63	.2965
Clearance/F (L/h)	1960.10	1089.02–3527.92	8449.32	3572.69–19982.44	—		546.74	.0304
V_d/F (L)	7507.98	3396.67–16595.57	33637.78	16540.20–68409.14	—		280.92	.0264
Elimination rate constant (1/h)	0.26	0.19–0.36	0.25	0.16–0.39	—		3.45	.4495
S-Praziquantel								
AUC_{inf} (h·ng/ml)	5669.77	4344.86–7398.70	871.84	398.47–1907.55	16.57	7.09–33.35	−75.26	.00001
$AUC_{t0-tlast}$ (h·ng/ml)	5413.80	4179.61–7012.43	826.17	375.05–1819.89	15.26	7.01–33.22	−75.16	.00002
C_{max} (ng/ml)	1991.32	1394.32–2843.95	329.98	164.65–661.33	15.37	7.97–33.43	−76.85	.0009
T_{max} (h)	2.42	1.84–3.18	1.81	1.39–2.36	—		−25.48	.0320
Half-Life (h)	2.27	1.62–3.18	2.00	1.48–2.72	—		−15.83	.1639
Clearance/F (L/h)	419.40	319.77–550.08	2727.44	1218.61–6104.45	—		950.27	.0048
V_d/F (L)	1373.82	926.52–2037.07	7887.36	3593.34–17312.70	—		757.72	.0062
Elimination rate constant (1/h)	0.31	0.22–0.43	0.35	0.35–0.47	—		11.76	.1866

Note: We based statistical calculations for AUC and C_{max} on ln-transformed data. A single-tailed, paired student *t*-test was used to test for the differences between the means of the critical PK parameters: AUC, C_{max}, T_{max}, clearance, elimination rate constant (Kel) and the apparent volume of distribution. We set the significance at $\alpha = .05$.

Abbreviations: AUC_{inf}, AUC from time zero to infinity; AUCt0–tlast,, area under the plasma concentration-time curve from time zero to the last sampled time point; CI, confidence interval; Cmax, peak plasma concentration of the drug; GMR, Geometric men ratio; T_{max}, time needed to achieve Cmax.

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TABLE 3 Effect of ritonavir on the pharmacokinetics of R- and S-PZQ following single-dose administration of 40 mg/kg racemic PZQ alone (reference) and together with 100 mg ritonavir (treatment)

PK Parameter	PZQ alone Geo Mean	95% CI	PZQ + Ritonavir Geo Mean	95% CI	Treatment/reference (%) GMR	95% CI	Difference observed (%)	p value
R-Praziquantel								
AUC_{inf} (h·ng/ml)	1012.96	850.81–1206.03	1057.66	748.26–1495.00	104.41	72.33–150.72	17.62	0.2528
$AUC_{t0-tlast}$ (h·ng/ml)	888.02	718.08–1098.19	950.73	644.30–1402.88	107.06	70.35–162.92	22.8	0.2264
C_{max} (ng/ml)	308.44	220.74–430.99	354.34	248.34–505.558	114.88	72.35–182.41	13.70	0.3462
T_{max} (h)	1.69	1.19–2.41	1.53	1.22–1.92	—		−15.46	0.1875
Half-Life (h)	3.57	2.37–5.37	2.71	1.95–3.77	—		−28.64	0.1337
Clearance/F (L/h)	2340.12	1943.27–2818.01	2241.23	1626.29–3088.71	—		4.36	0.4138
V_d/F (L)	12034.61	8020.60–18057.48	8772.21	5165.68–14896.73	—		−15.74	0.3488
Elimination rate constant (1/h)	0.19	0.13–0.29	0.26	0.18–0.35	—		26.08	0.0917
S-Praziquantel								
AUC_{inf} (h·ng/ml)	4154.79	3187.12–5416.25	7291.05	5879.52–9041.47	175.49	126.99–242.50	69.84	0.0027
$AUC_{t0-tlast}$ (h·ng/ml)	3972.89	3016.52–5232.47	7083.71	5677.68–8837.92	178.30	127.59–249.16	71.88	0.0030
C_{max} (ng/ml)	1174.93	893.11–1545.68	2336.96	1929.43–2830.57	198.19	144.88–273.07	88.41	0.0002
T_{max} (h)	2.20	1.66–2.91	1.60	1.16–2.20	—		−24.58	0.0510
Half-Life (h)	2.25	1.82–2.76	1.81	1.40–2.33	—		−19.25	0.0860
Clearance/F (L/h)	570.54	442.78–735.16	325.12	264.96–398.93	—		−44.37	0.0009
V_d/F (L)	1847.59	1256.81–2716.06	847.06	593.38–1209.20	—		−55.79	0.0053
Elimination rate constant (1/h)	0.31	0.25–0.38	0.38	0.30–0.50	—		34.38	0.0958

Note: We based the statistical calculations for AUC and C_{max} on ln-transformed data. A single-tailed, paired student t-test was used to test for the differences between the means of the critical PK parameters: AUC, C_{max}, T_{max}, clearance, elimination rate constant (Kel) and the apparent volume of distribution. We set the significance at α = 0.05.

Abbreviations: AUC_{inf}, AUC from time zero to infinity; $AU_{Ct0-tlast}$, area under the plasma concentration-time curve from time zero to the last sampled time point; CI, confidence interval; Cmax, peak plasma concentration of the drug; GMR, Geometric men ratio; SD, standard deviation; T_{max}, time needed to achieve Cmax.
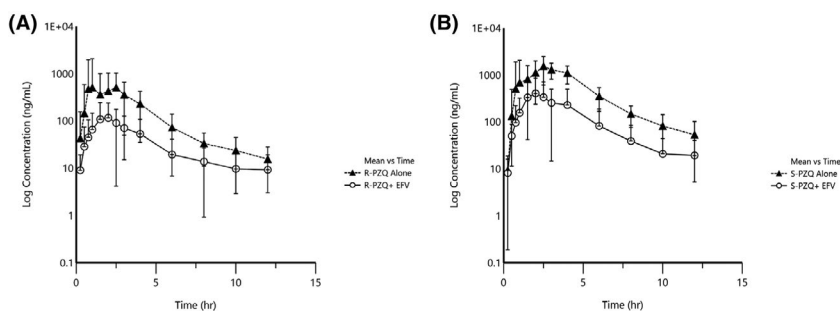

FIGURE 2 Plasma concentration versus time curves obtained for (A) R- and (B) S PZQ after administration of 40 mg/kg racemic PZQ alone and after exposure to 400 mg efavirenz/day for 13 days. We report data as mean ± SD (n = 13)
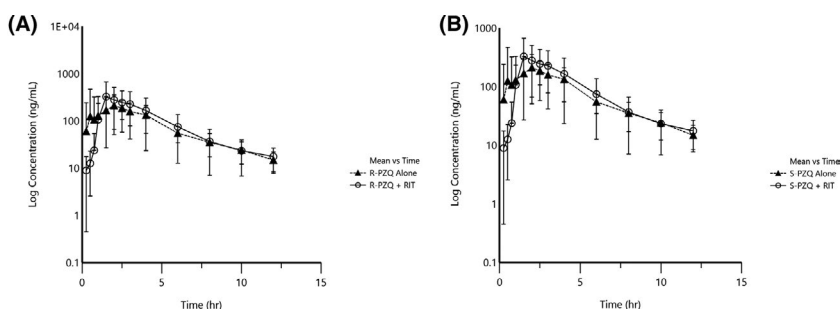

FIGURE 3 Plasma concentration versus time curves obtained for (A) R- and (B) S PZQ after administration of 40 mg/kg racemic PZQ alone and after exposure to 100 mg ritonavir/day for 14 days. We report data as mean ± SD (n = 13)

prescribed and is the preferred first-line therapy in drug-naive HIV patients in Zimbabwe and other sub-Saharan African countries. This also has an impact in the sub-Saharan African clinical setting where annual PZQ mass drug administrations are conducted in children populations among whom some will be on efavirenz-based ART. The risk of poor treatment outcomes in these children is high and should be taken into consideration during the deployment of these programs.

Ritonavir did not have a significant inhibitory effect on R-PZQ and caused a 2-fold AUC increase for S-PZQ. Administration of PZQ in patients taking ritonavir-based ART is therefore predicted to have a minimal increase in R-PZQ exposure and relatively higher exposure levels of S-PZQ. Ritonavir is a potent inhibitor of CYP3A4[26,27] which has been demonstrated to enhance the levels of other protease inhibitors in plasma.[28] There was however a 25% decrease in T_{max} for S-PZQ. The difference was less significant for R-praziquantel. This could suggest an effect on gut metabolism rather than hepatic metabolism. There was no change in the T_{max} for R-PZQ when co-administered with efavirenz, suggesting a role of hepatic metabolism.

Both efavirenz and ritonavir affected the C_{max} and AUC, with no significant change in half-life. This could be explained by an altered absorption phase because of inhibited CYP3A4-mediated drug metabolism in the small intestine. Efavirenz is a known inducer and inhibitor of CYP3A4 and CYP2C19 in humans[29] with induction having a dominant effect especially when the drug is repeatedly dosed. However, the induction is liver specific with no effect on intestinal CYP3A4 or P-gp.[30,31] It, however, inhibits both intestinal and hepatic CYP3A4. Ritonavir is a known CYP3A4 inhibitor.[26,32] Inhibition of both CYP3A4-mediated hepatic and gut metabolism could explain the increased bioavailability. As expected, the effect was more pronounced with S-PZQ as compared to R-PZQ. A similar result has been observed when grapefruit was co-administered with praziquantel.[33] This could also affect transporters such as P-gp. The role of transporters in PZQ metabolism is however not well characterized.

PZQ is given as a racemate administered at 40 mg/kg of scored 600 mg tablets. It is a high clearance drug due to first-pass hepatic metabolism resulting in a low bioavailability of less than 20%. For efficacy, a minimum effective concentration (MEC) of 1 μg/mL should be maintained for at least 4 h.[34] This makes PZQ sensitive to metabolism-based DDI via induction or inhibition. Efavirenz reduced the exposure of both R- and S-PZQ 4-fold and all participants failed to attain the MEC for more than the minimum 4 h. This is predictive of treatment failure. A similar observation was reported in patients pre-exposed to a strong CYP3A inducer, rifampicin, where 7 out of 10 participants did not have detectable levels of racemic PZQ due to DDI.[12] The data on rifampicin is now captured on the PZQ product label. Our findings should therefore add to information which guides the safe and efficacious use of PZQ, including being part of the drug label. This will be useful in regions where both HIV and schistosomiasis are endemic, such as sub-Saharan Africa.

The inhibition of CYP3A mediated PZQ metabolism was stereoselective, where ritonavir only inhibited S-PZQ metabolism but did not cause significant inhibition of R-PZQ metabolism. This is in agreement with our previous findings where we demonstrated that S-PZQ is mainly metabolized by CYP3A4, whereas R-PZQ is mainly metabolized by CYP1A2 and CYP2C19.[23] This stereoselectivity is consistent with a CYP3A4/5 study which showed a difference in Km between R- and S-PZQ, which was at least 2.5 fold indicating S-PZQ had a stronger binding affinity for CYP3A4.[16] The same study also showed the aromatic ring of PZQ in more proximity to CYP 3A4 than R-PZQ, suggesting that the aromatic ring could be metabolized easily by CYP 3A4 in S-PZQ than R-PZQ.

In conclusion, our study shows clinically significant findings concerning DDI involving PZQ and efavirenz that should be considered in the treatment of schistosomiasis in regions where efavirenz-based ART is also common. Strategies to avoid this detrimental DDI should be explored. One approach would be treatment staggering as was suggested in the treatment of PZQ and the anti-TB drug, rifampicin, to avoid DDI.[35] Further studies also need to be done to evaluate the extrapolation of our findings from adults to children, as some pharmacokinetics studies have shown different pharmacokinetic results between adults and children.[36]

DISCLOSURE

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Roslyn Thelingwani, Collen Masimirembwa, Charles Nhachi, James Hakim, Julia Stingl, and Nadina Stadler participated in research design. Roslyn Thelingwani, Chenai Mutiti, Nyasha Kapungu, and Comfort Kanji conducted experiments. Roslyn Thelingwani, Nyasha Kapungu, and Comfort Kanji performed data analysis. Chenai Mutiti, Nyasha Kapungu, Comfort Kanji, Charles Nhachi, Nadina Stadler, Julia Stingl, James Hakim, Roslyn Thelingwani, and Collen Masimirembwa wrote or contributed to the writing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study is available on request from the corresponding author (RT). The data are not publicly available due to privacy or ethical restrictions.

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