Elevated gatifloxacin and reduced rifampicin concentrations in a single-dose interaction study amongst healthy volunteers

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Objectives: Pharmacokinetic drug–drug interactions were investigated between the fluoroquinolone gatifloxacin and a fixed dose combination (FDC) of rifampicin, isoniazid and pyrazinamide.

Patients and methods: The single-dose pharmacokinetics of the four drugs was evaluated in an open-label three-way cross-over study amongst 22 healthy volunteers following administration of gatifloxacin, the FDC or the two products together.

Results: Modest but potentially important drug–drug interactions affecting gatifloxacin and rifampicin concentrations were detected. The elimination rate of gatifloxacin was reduced such that the AUC from 0 h to infinity was increased with a geometric mean ratio (GMR) [90% confidence interval (CI)] of 1.14 (1.10, 1.18). Conversely, the AUC from 0 h to infinity for rifampicin was reduced (GMR: 0.81, 90% CI: 0.81, 0.96) when rifampicin, isoniazid and pyrazinamide were given together with gatifloxacin.

Conclusions: Studies in patients including pharmacokinetic evaluation at steady state, efficacy and toxicity are required to determine the importance of the interactions for use of the combination of gatifloxacin, rifampicin, isoniazid and pyrazinamide in the treatment of tuberculosis.

Keywords: pharmacokinetics, pyrazinamide, isoniazid, Mycobacterium tuberculosis

Introduction

More effective antitubercular regimens that will allow reduced treatment durations are urgently needed. Promising activities have been demonstrated for moxifloxacin and gatifloxacin in vitro in murine models and in extended bactericidal studies.1–3 Four month regimens including gatifloxacin or moxifloxacin in combination with rifampicin, pyrazinamide and isoniazid or ethambutol are currently being evaluated in patients. Pharmacokinetic interactions within these treatment regimens have the potential to compromise their efficacy or safety. Identification of a pharmacokinetic basis for altered drug activity may facilitate the rational development of drug combinations and doses. We investigated the single-dose pharmacokinetic interactions between gatifloxacin and a fixed dose combination (FDC) comprising rifampicin, isoniazid and pyrazinamide in healthy volunteers.

Materials and methods

The study was approved by the University of Cape Town Research Ethics Committee (REC REF: 005/2004) and the Secretariat Committee on Research Involving Human Subjects of the World Health Organization (RPC 077). Twenty-four volunteers were enrolled after giving their written informed consent to participate. They had normal findings upon medical history, physical examination and laboratory testing (full blood count, serum chemistry; hepatitis B surface antigen; urinary pH, protein, glucose, blood and screen for drugs of abuse). They had not taken prescribed medication in the 2 weeks before the study, or over-the-counter preparations (except paracetamol) in the week before the study, or smoked or donated blood in the 2 months before the study, or consumed >6 U alcohol/day. The women were using contraception measures. Pregnant or breast-feeding women were not enrolled.
Gatifloxacin interaction with TB drugs

Single doses of each of three treatments (gatifloxacin 400 mg in one Gatispan $400^\circledR$ tablet; rifampicin 600 mg, isoniazid 300 mg and pyrazinamide 1600 mg as four FDC tablets of AkuriT-Z$^{\circledR}$; and Gatispan$^\circledR$ together with the FDC in the same doses; both products manufactured and supplied by Lupin Ltd, India) were given with 240 mL of water under fasting conditions. The treatments were separated by 2 weeks. The sequence of treatments was randomized. Venous samples collected in heparinized tubes before and at 0.5, 1, 1.5, 2, 2.5, 3.5, 5, 8, 12, 24, 36 and 48 h after dosing were placed in crushed ice before separation of the plasma by centrifugation (750 g for 10 min). Within 1 h of sampling, plasma was stored at $\sim$80°C until analysis.

Plasma drug concentrations were quantified by tandem HPLC mass spectrometry (Applied Biosystems API 2000). A $20 \times 2.1$ mm Hypersil Gold C18 column (Thermo, MA, USA) was used for rifampicin and the racemic mixture of gatifloxacin and a $20 \times 2.1$ mm Betasil silica column (Thermo) for isoniazid and pyrazinamide. The mobile phase for gatifloxacin and rifampicin comprised a gradient from 10% to 90% acetonitrile in 0.1% formic acid with a 5 min run time. For isoniazid and pyrazinamide, an isocratic elution using 80% acetonitrile in 0.1% formic acid was used. The flow rate was 0.3 mL/min and the injection volume was 5 μL. Moxifloxacin served as internal standard for gatifloxacin, rifapentine for rifampicin and sulfamethoxazole for isoniazid and pyrazinamide. Selected reaction monitoring transitions of [M-H]$^-$ to product ions were gatifloxacin $m/z$ 845.3; isoniazid $m/z$ 138.0–121.4; rifampicin $m/z$ 823.5–791.4; rifapentine $m/z$ 877.2–845.3; isoniazid $m/z$ 138.0–121.2; pyrazinamide $m/z$ 124.1–81.1 and sulfamethoxazole $m/z$ 254.0–92.2. Plasma protein was precipitated with 3 vol of acetonitrile containing the internal standard. Samples were vortexed and centrifuged for 5 min at 750 g. Supernatant (5 μL) was injected into the column. Standard curves were linear in the ranges 0.1–30 mg/L for rifampicin, 0.1–15 mg/L for gatifloxacin and isoniazid and 0.2–70 mg/L for pyrazinamide. Quality control samples covering the ranges were included with each run. Inter- and intra-day coefficients of variation were below 10%. The lower limit of quantification was set at 0.2 mg/L for pyrazinamide and 0.1 mg/L for rifampicin, gatifloxacin and isoniazid.

Drug concentrations below the validated ranges were treated as missing data. Non-compartmental analysis using WinNonlin version 3.3 (Pharsight Corp., Mountain View, CA, USA) described maximum observed drug concentration ($C_{\text{max}}$), time to $C_{\text{max}}$ ($T_{\text{max}}$), plasma half-life ($t_{1/2}$) associated with the terminal slope of the semi-logarithmic concentration–time curve and AUC extrapolated to infinity ($AUC_{0-\infty}$). Stata version 8.2 (Stata Corp., College Station, TX, USA) was used for statistical tests and to summarize results. Wilcoxon matched pairs sign-rank test was used to detect significant differences between untransformed pharmacokinetic measures. Geometric mean ratios [90% confidence intervals (CIs)] were calculated to compare $C_{\text{max}}$ and $AUC_{0-\infty}$ for the combined treatments with those for the gatifloxacin tablet and the FDC when given alone.

| Table 1. Median (IQR) for $C_{\text{max}}$ and $AUC_{0-\infty}$ after oral administration of a single dose of gatifloxacin (400 mg) given alone, after a single dose of rifampicin (600 mg), isoniazid (300 mg) and pyrazinamide (1500 mg) in FDC given alone, and after oral administration of the two products together [the GMR with 90% CI is given for comparison of the combined treatment values with those of gatifloxacin and the FDC (rifampicin, isoniazid plus pyrazinamide)] |
|---|---|---|
| | Gatifloxacin plus FDC | GMR (90% CI) |
| Gatifloxacin $C_{\text{max}}$ (mg/L) | 3.62 (3.13, 4.05) | 3.39 (3.07, 3.59) | 0.98 (0.90, 1.07) |
| Gatifloxacin $AUC_{0-\infty}$ (mg.h/L)$^a$ | 32.89 (29.79, 35.27) | 36.27 (31.92, 43.61) | 1.14 (1.10, 1.18) |
| Rifampicin $C_{\text{max}}$ (mg/L)$^a$ | 13.90 (11.70, 15.20) | 10.20 (9.28, 12.60) | 0.80 (0.71, 0.90) |
| Rifampicin $AUC_{0-\infty}$ (mg.h/L)$^a$ | 95.59 (83.18, 114.44) | 82.38 (68.45, 113.47) | 0.88 (0.81, 0.96) |
| Isoniazid $C_{\text{max}}$ (mg/L) | 3.75 (3.09, 4.98) | 3.63 (2.81, 4.40) | 0.86 (0.74, 1.00) |
| Isoniazid $AUC_{0-\infty}$ (mg.h/L) | 10.73 (8.61, 25.27) | 9.67 (7.47, 25.79) | 0.95 (0.89, 1.02) |
| Pyrazinamide $C_{\text{max}}$ (mg/L) | 38.10 (32.10, 40.00) | 35.70 (31.00, 38.60) | 0.98 (0.93, 1.05) |
| Pyrazinamide $AUC_{0-\infty}$ (mg.h/L) | 538.88 (461.13, 580.69) | 550.17 (480.96, 593.07) | 1.03 (1.00, 1.07) |

$^a$P < 0.05 using Wilcoxon matched pairs sign-rank test.
2.00 h (IQR: 1.42, 2.50); \( P = 0.010 \), and rifampicin concentrations were reduced (Table 1). AUC\(_{0-\infty}\) was 12% lower on average, but the individual reductions varied; three participants had reductions of more than 35% (Figure 1b). The \( t_{1/2} \) of rifampicin was similar with or without concomitant gatifloxacin [median 3.63 h (IQR: 3.10, 4.18) versus 3.91 h (IQR: 3.57, 4.10); \( P = 0.789 \)].

Although isoniazid concentrations tended to be marginally lower (Table 1), and the \( t_{1/2} \) slightly reduced when the FDC and gatifloxacin were co-administered [median 1.66 h (IQR: 1.31, 4.37) versus 1.71 h (IQR: 1.35, 4.09); \( P = 0.047 \)], the \( C_{\text{max}} \) and AUC\(_{0-\infty}\) values were not significantly different.

Pyrazinamide concentrations were less variable than those of the other drugs. \( C_{\text{max}} \) and AUC\(_{0-\infty}\) were not affected when the two products were given together (Table 1), although \( t_{1/2} \) was modestly increased [median 8.61 h (IQR: 7.48, 10.29) versus 7.24 h (IQR: 6.54, 10.31); \( P = 0.027 \)].

Discussion

The pharmacokinetic interactions between the FDC (containing rifampicin, isoniazid and pyrazinamide) and the tablet formulation of gatifloxacin were not anticipated.

The pharmacokinetics of gatifloxacin following a single 400 mg dose was similar to that reported previously.\(^4,5\) Gatifloxacin concentrations were modestly increased when it was given with the FDC. As 80% to 95% of the gatifloxacin dose is excreted unchanged in the urine, metabolically based drug–drug interactions are unlikely.\(^5\) The prolonged \( t_{1/2} \), therefore, suggests a renal mechanism. Probenecid has the potential to reduce renal excretion of gatifloxacin, suggesting that tubular secretion contributes to its elimination.\(^5\) This secretory mechanism is shared by many weak acids. Thus, the acid metabolites of pyrazinamide or isoniazid might compete with gatifloxacin for renal tubular secretion, accounting for the retarded elimination of gatifloxacin observed. That the change in gatifloxacin and pyrazinamide concentrations were correlated supports this hypothesis; the difference between the AUC\(_{0-\infty}\) for gatifloxacin with the FDC and the AUC\(_{0-\infty}\) for gatifloxacin without the FDC and the difference between the AUC\(_{0-\infty}\) for pyrazinamide with gatifloxacin and the AUC\(_{0-\infty}\) without gatifloxacin were associated (Spearman’s \( r = 0.451; \ P = 0.035 \)). The AUC was increased by only 14% in this study. However, adverse effects of gatifloxacin might be more frequent with higher gatifloxacin concentrations,\(^6\) and it is a concern that accumulation of gatifloxacin may occur more readily in patients at risk (e.g. those with renal impairment). Whether modestly increased concentrations of gatifloxacin will enhance the activity of a multidrug antitubercular treatment regimen is not known. However, an early bactericidal activity study amongst tuberculosis patients treated with 400 mg daily found a correlation between the decline in bacilli during the first 2 days and the AUC to 24h/MIC.\(^3\)

The concentrations of rifampicin were in keeping with other single-dose studies in healthy volunteers and higher than those reported in patients. This can be attributed, in part, to autoinduction of metabolizing enzymes and P-glycoprotein with repeated doses. The modest reduction in rifampicin concentrations with gatifloxacin co-administration appears to be a result of reduced absorption as the \( t_{1/2} \) was not affected. The importance of the interaction needs to be assessed in the context of a growing consensus that the currently used doses of rifampicin are at the bottom of its effective range. Although the optimum range for rifampicin concentrations in tuberculosis patients has not been defined, higher doses are associated with improved early bactericidal activity and better treatment results.\(^7,8\) Wide inter-patient variability in rifampicin concentrations and the low rifampicin concentrations reported in several patient studies add to concerns that an average reduction of 12% in the AUC might result in critically low rifampicin concentrations in some patients.\(^9–11\)

Gatifloxacin and rifampicin have important sterilizing activities against Mycobacterium tuberculosis and the potential to shorten the time to eradication of the pathogen. It is not known whether increased concentrations of gatifloxacin could...
compensate for reduced rifampicin exposure in a combined treatment regimen.

Steady-state conditions and the effects of enzyme induction and inhibition with multiple daily doses were not studied. Volunteers given consecutive doses of rifampicin for 4 days had reduced concentrations of moxifloxacin, probably largely a result of increased expression of phase II metabolic enzymes. As gatifloxacin is almost completely eliminated in the urine unchanged, repeated doses of rifampicin are unlikely to decrease its concentrations by those mechanisms. Other important limitations in the application of the findings of this study to tuberculosis patients include the study population, which does not reflect heterogeneous patient populations or the effects of disease and nutritional status, and the design, which does not allow discrimination between the effects of rifampicin, isoniazid and pyrazinamide on gatifloxacin concentrations. Moreover, the pharmacodynamic consequences of the altered drug concentrations could not be evaluated. It is therefore necessary to evaluate the pharmacokinetic interactions and the relationship of the drug concentrations to their effects in patient studies.

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Transparency declarations

None to declare.

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