

## Pharmacokinetics of intravenous azithromycin and ceftriaxone when administered alone and concurrently to healthy volunteers

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**This study was conducted to identify whether or not a pharmacokinetic interaction existed when azithromycin and ceftriaxone were administered concurrently. This randomized, open-label, three-way crossover study in 12 healthy volunteers characterized the plasma pharmacokinetic parameter profiles of both drugs, as well as the white blood cell uptake and exposure to azithromycin, when the drugs were administered alone and together. The plasma pharmacokinetic parameters for azithromycin and ceftriaxone did not differ significantly either after a single dose or at steady state when the two were co-administered as opposed to being administered alone. Moreover, the neutrophil and monocyte/lymphocyte peak azithromycin concentrations and sampling period exposures also did not differ significantly between the study arm and the control arm. This study confirms that there is no interaction between azithromycin and ceftriaxone when they are administered concurrently.**

Keywords: azithromycin, ceftriaxone, pharmacokinetics

### Introduction

Of the 2–3 million cases of community-acquired pneumonia (CAP) that occur in the United States each year it is estimated that ~258 patients for each 100 000 population will have illness that is serious enough to warrant hospital admission.<sup>1</sup> For those patients admitted to a general medical ward, current treatment guidelines suggest that the combination of a third-generation cephalosporin with a macrolide is an appropriate regimen.<sup>1,2</sup> Owing to the spectrum of activity, convenience of once-daily dosing and good tolerance profiles, the combination of intravenous ceftriaxone and azithromycin has become a common choice for the initial treatment of inpatient CAP.<sup>1–3</sup> Although currently there is no literature to suggest a pharmacokinetic interaction between azithromycin and ceftriaxone, the fact that they are used concurrently so frequently generates the need to assure that no interaction exists.<sup>3</sup> As a result, a study was conducted to identify whether single or 'steady-state' dosing of ceftriaxone and azithromycin resulted in significant changes to one or the other's plasma pharmacokinetic profiles. In addition, because of the importance of white blood cell (WBC) uptake of azithromycin both in terms of infection site drug delivery and pathogen

clearance, peak phagocyte concentrations and total regimen exposures were also evaluated to ensure that ceftriaxone did not alter WBC uptake of azithromycin.<sup>4,5</sup>

### Materials and methods

This randomized, open-label, three-way crossover study was approved by the Institutional Review Board of Bassett Healthcare. Twelve healthy volunteers at least 18 years of age and within 30% of their ideal body weight for their sex, height and frame were recruited to the study. After providing written informed consent, subjects were deemed healthy by medical history, physical examination, vital signs (including heart rate, blood pressure and temperature) and laboratory screening [a complete blood count, alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, total protein, serum creatinine and urine pregnancy for women of childbearing potential (repeated before each study arm)]. Women of childbearing potential were to be surgically sterile (ovaries intact) or utilizing a non-hormonal barrier method of birth control. All subjects were required to be free of any drug exposure known to interfere with the pharmaco-

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kinetics or assays of azithromycin or ceftriaxone for at least 10 days before the study. Subjects with clinically significant abnormal physical exams, medical histories or laboratory results were excluded from participation in the study. Other exclusion criteria included: a history of serious intolerance/allergy/sensitivity to macrolides and/or  $\beta$ -lactams; history of drug or alcohol abuse within the past year; an intention to donate blood (during, or 8 weeks before or after, the study); the use of nicotine delivery devices within the past year; inability to tolerate venipuncture and multiple blood samplings; and those who, in the opinion of the investigator, could not follow instructions.

A computer-generated randomization scheme was used to assign subjects to the following dosing regimens in random order: (i) ceftriaxone 1 g (Rocephin Lot: U6231, exp. 6/04) intravenous (iv) in 100 mL of 5% dextrose in water every 24 h for three consecutive days; (ii) azithromycin 500 mg iv (Zithromax Lot: 203617, exp. 9/1/02) in 500 mL of 5% dextrose in water every 24 h for three consecutive days; and (iii) ceftriaxone 1 g iv in 100 mL of 5% dextrose in water every 24 h for 10 days with azithromycin 500 mg iv in 500 mL of 5% dextrose in water every 24 h for the first 3 days of ceftriaxone dosing. Ceftriaxone and azithromycin doses were infused by gravity over ~30 and 60 min, respectively. During the combination regimen, ceftriaxone was administered first followed immediately by the azithromycin infusion.

Subjects were required to fast for at least 8 h before each dose and to remain fasting for the 4 h subsequent to study drug administration for the first and third day of each study arm. Additionally, subjects avoided caffeinated and alcoholic beverages for 48 h before and for the duration of each study arm. Dosing periods of any arms containing azithromycin were separated by at least 30 days, whereas the period consisting of only ceftriaxone was spaced by at least a 7 day period from the last ceftriaxone dose.

Plasma samples were collected before the first doses of both medications and then repeatedly over the next four (0.5, 1, 2, 4, 8, 12, 24, 24.5, 25, 36, 48, 48.5, 49, 50, 52, 56, 60, 72, 84 and 96 h) and 10 days (0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 24.5, 25, 25.5, 26, 36, 48, 48.5, 49, 49.5, 50, 51, 52, 54, 56, 60, 72, 96, 120, 144, 168, 192, 216 and 240 h) for ceftriaxone and azithromycin, respectively. Intense plasma sampling occurred for both drugs on days 1 and 3 of dosing during all study arms. In addition to plasma samples, during azithromycin-containing dosing periods, 25–30 mL aliquots of blood were collected in EDTA-containing tubes for the isolation of WBCs at pre-dose, 2, 24, 26, 48, 50, 72, 120, 192 and 240 h. Isolation of polymorphonuclear leucocyte (PMN) and monocyte/lymphocyte (M/L) fractions was conducted as described previously.<sup>6</sup>

All specimens were stored at  $-80^{\circ}\text{C}$  and shipped frozen overnight in a sufficient quantity of dry ice to Emprexe Analytical, LLC (Buffalo, NY, USA) for sample analyses. All

heparinized plasma ceftriaxone samples were quantified using a validated reverse phase, high pressure liquid chromatographic (HPLC) assay with cefuroxime as the internal standard. Linearity was observed over the calibration curve range 1.00–250 mg/L and the assay had a limit of detection of 0.131 mg/L for ceftriaxone in human plasma (signal to noise ratio = 5). The overall precision (percentage relative standard deviation; %RSD) and accuracy (analytical recovery; %AR) of the assay were determined from the plasma quality control samples analysed during the analysis of study samples, and calculated as 4.82% (4.11–5.31%) and 100% (97.8–104%), respectively. Ceftriaxone demonstrated stability in heparinized human plasma for up to 111 days when stored at  $-70^{\circ}\text{C}$ , as well as after three freeze–thaw cycles. Prepared samples were stable on the autosampler for up to 30 h at  $4^{\circ}\text{C}$ .

Azithromycin plasma specimens were assayed using a reverse phase, LC/MS/MS assay that was validated to quantify azithromycin in heparinized human plasma samples using erythromycin as the internal standard. Linearity was observed over the calibration curve range 0.0025–2.0 mg/L with a limit of quantification of 0.0025 mg/L. The overall %RSD and %AR of the assay were 5.53% (4.14–6.96%) and 102% (101–103%), respectively. Azithromycin demonstrated stability in heparinized human plasma for up to 504 days when stored at  $-70^{\circ}\text{C}$ , as well as after three freeze–thaw cycles. Prepared samples were stable on the autosampler for up to 23 h at  $4^{\circ}\text{C}$ . The quantification of azithromycin in PMNs and M/Ls was carried out using a reverse phase, LC/MS/MS assay that was validated to quantify azithromycin in human neutrophils and monocytes using erythromycin as the internal standard. Linearity was observed over the calibration curve range 0.010–2.0 mg/L with a limit of quantification of 0.010 mg/L. Back-calculated concentrations in neutrophils were generated using azithromycin/erythromycin peak area response ratios. For neutrophils, the overall precision and accuracy of the assay were determined from the leucocyte quality control samples analysed during the analysis of study samples, and calculated as 8.75% (3.18–13.7%) and 94.8% (92.5–96.8%), respectively. For monocytes, the overall precision and accuracy of the assay were calculated as 7.92% (5.81–11.4%) and 94.2% (91.7–96.5%), respectively.

All of the assays (more detailed methodology can be found at <http://www.emprexe.com>) were specific for their test compounds and internal standards (when used) in the presence of acetylsalicylic acid, acetaminophen, caffeine, ibuprofen, naproxen, ketoprofen and salicylic acid.

#### *Pharmacokinetic parameter analysis*

All plasma data were analysed by non-compartmental methods with the TopFit Version 2.0 computer program. Weighting was set at  $1/Y^2$ . The single-dose and steady-state (third dose for both) pharmacokinetic parameters that were evaluated for azithromycin and ceftriaxone included: peak

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plasma concentration ( $C_{\max}$ ); terminal elimination half-life ( $T_{1/2}$ ); area under the plasma concentration–time curve from zero to infinity ( $AUC_i$ ) calculated via the linear trapezoidal method; total clearance ( $CL_t$ ); and volume of distribution ( $V_d$ ). PMN and M/L azithromycin concentrations were calculated as described previously.<sup>6</sup> PMN and M/L exposure curves were then calculated by the linear trapezoidal method from time zero to the last sampling time point at 240 h ( $AUC_{240}$ ).

### Statistical analysis

Twelve subjects provided at least a 90% power to detect a 30% difference in the mean AUC and  $C_{\max}$  of azithromycin using a 5% significance level. Summary study subject demographics and pharmacokinetic parameter values were produced with the SigmaStat Version 2.03 computer program (SPSS, Inc.). Plasma azithromycin and ceftriaxone pharmacokinetic parameters and azithromycin PMN and M/L exposure curves were compared between the test arm (ceftriaxone/azithromycin combination) and control arms (azithromycin only, ceftriaxone only) using paired *t*-tests of log-transformed data and the above-mentioned software. Statistical significance was defined as  $P \leq 0.05$ .

## Results

Twelve subjects (six males, mean age  $\pm$  S.D.  $35.5 \pm 12.5$  years, weight  $86.5 \pm 7.89$  kg; six females, age  $40.2 \pm 11.0$  years, weight  $71.1 \pm 13.8$  kg) were enrolled into the study and

11 subjects completed all study phases. One subject was dismissed from the study after becoming pregnant between the last two study arms of her randomization and did not complete the ceftriaxone-only phase of the protocol. Because of this, all her azithromycin data were included in the analyses but her ceftriaxone data were not.

Six subjects reported mild to moderate adverse events that may have been or were related to study therapy. Three subjects reported mild nausea or dyspepsia during the azithromycin–ceftriaxone combination regimen. One subject reported mild diarrhoea during the ceftriaxone-only regimen. Two subjects reported mild to moderate headaches during the combination regimen (both subjects) and during the azithromycin-only regimen (one subject). One person reported mild hand pain during the azithromycin infusion, which may have been temperature related. Between two of the regimens, one subject reported moderate tongue and throat inflammation that was noted to possibly be thrush. No serious adverse events were reported during the study.

As shown in Table 1, when azithromycin was administered concurrently with ceftriaxone, it did not result in any statistically or clinically significant changes in ceftriaxone's pharmacokinetic parameter profile either when it was dosed once or to steady state. When the reverse was examined (Table 2), although there was a statistically significant decrease in steady-state azithromycin exposure, this ~1% change was not considered clinically relevant in the least. The remaining azithromycin plasma pharmacokinetic parameters after both one and three doses did not demonstrate any signi-

**Table 1.** Single-dose and steady-state ceftriaxone plasma pharmacokinetic parameter values (mean  $\pm$  S.D.) when given alone and with azithromycin

Dose	Drug	$C_{\max}$ (mg/L)	$AUC_i$ (mg·h/L)	$T_{1/2}$ (h)	$CL_t$ (L/h)	$V_d$ (L/kg)
Single dose	ceftriaxone	128.7 $\pm$ 14.8	973.12 $\pm$ 120.61	7.4 $\pm$ 1.0	1.0 $\pm$ 0.1	0.13 $\pm$ 0.01
	ceftriaxone + azithromycin	129.4 $\pm$ 16.0	996.35 $\pm$ 132.90	7.8 $\pm$ 1.0	1.0 $\pm$ 0.1	0.13 $\pm$ 0.02
Steady state	ceftriaxone	136.4 $\pm$ 21.2	1075.40 $\pm$ 191.76	7.5 $\pm$ 0.6	0.9 $\pm$ 0.2	0.12 $\pm$ 0.02
	ceftriaxone + azithromycin	134.2 $\pm$ 24.7	1073.44 $\pm$ 156.58	7.2 $\pm$ 0.7	0.9 $\pm$ 0.1	0.11 $\pm$ 0.01

**Table 2.** Single-dose and steady-state azithromycin plasma pharmacokinetic parameter values (mean  $\pm$  S.D.) when given alone and with ceftriaxone

Dose	Drug	$C_{\max}$ (mg/L)	$AUC_i$ (mg·h/L)	$T_{1/2}$ (h)	$CL_t$ (L/h)	$V_d$ (L/kg)
Single dose	azithromycin	3.3 $\pm$ 1.1	6.52 $\pm$ 1.28	14.9 $\pm$ 4.3	79.5 $\pm$ 16.4	13.1 $\pm$ 1.1
	azithromycin + ceftriaxone	3.9 $\pm$ 1.0	6.62 $\pm$ 0.97	14.0 $\pm$ 3.0	77.0 $\pm$ 11.1	11.0 $\pm$ 4.5
Steady state	azithromycin	3.7 $\pm$ 1.1	17.75 $\pm$ 2.89 <sup>a</sup>	76.8 $\pm$ 14.0	28.3 $\pm$ 5.1	30.8 $\pm$ 6.6
	azithromycin + ceftriaxone	4.0 $\pm$ 0.9	17.68 $\pm$ 3.20 <sup>a</sup>	78.7 $\pm$ 11.2	29.2 $\pm$ 5.7	30.0 $\pm$ 4.4

<sup>a</sup> $P = 0.04$ .

**Table 3.** Azithromycin PMN and M/L pharmacokinetic parameters (mean  $\pm$  S.D.) when administered alone and with ceftriaxone

Drug	PMN $C_{\max}$ (mg/L)	PMN AUC <sub>240</sub> (mg·h/L)	M/L $C_{\max}$ (mg/L)	M/L AUC <sub>240</sub> (mg·h/L)
Azithromycin	266.0 $\pm$ 60.6	35 442 $\pm$ 6796	485.5 $\pm$ 262.3	28 639 $\pm$ 11 471
Azithromycin + ceftriaxone	278.3 $\pm$ 128.3	35 669 $\pm$ 9530	596.7 $\pm$ 303.5	32 114 $\pm$ 17 452

ficant changes when ceftriaxone was administered concurrently.

When PMN and M/L peak azithromycin concentrations and exposures were assessed, although there were no significant differences noted when ceftriaxone was added, it was evident that, as has been demonstrated in the past, the WBCs act as a major reservoir of azithromycin in the human body.<sup>6</sup> Comparison of the data in Table 3 with values in Table 2 reveals that peak WBC concentrations were  $\sim$ 2-log-fold higher than those achieved in plasma. In addition, when the WBC concentration–time curves were compared with those of plasma (simulation of the three doses given based on steady-state exposure curve amount) they exceeded them by  $>3$  logs (data not shown).

## Discussion

Current CAP treatment guidelines recommend an advanced generation cephalosporin plus a macrolide as a first-line regimen for patients with CAP whose disease is severe enough to warrant hospital admission.<sup>1,2</sup> Though there are various options for both parts of the combination regimen, ceftriaxone with azithromycin has become a popular choice by many to meet the needs of their patients. The fact that the combination of ceftriaxone and azithromycin is recommended for an indication with such a large incidence/population lends one to believe that the combination is used commonly. Because of this assumption, it is necessary to ensure that there is no adverse interaction between the two drugs in terms of tolerance, pharmacokinetics and pharmacodynamics. In this study, the vast majority of reported adverse events were of a mild nature and none of them required treatment with additional medication. As would be expected, those adverse events that involved the gastrointestinal tract were the most common. Unlike a previous healthy volunteer study with intravenous erythromycin and clarithromycin, in which  $\sim$ 33% had to discontinue erythromycin due to gastrointestinal distress and 50% had to discontinue clarithromycin infusions due to phlebitis, none of the adverse events reported in this study with intravenous azithromycin required subject discontinuation or treatment interruption.<sup>7</sup>

In terms of pharmacokinetics of azithromycin and ceftriaxone, the addition of one drug did not have a significant

adverse effect on the other either when studied after single doses of the two or at steady state. Although there should be no debate over the choice of three doses as being steady state for ceftriaxone, the same cannot be said for azithromycin. In the case of azithromycin, although the drug's half-life is only  $\sim$ 14 h after a single dose, this rapidly increases to at least 70 h within two to three doses of starting a regimen, and steady-state conditions are only achieved after prolonged periods. Consequently, in this study we used three doses as an assumed 'steady-state' as it was the average length of dosing utilized for the treatment of CAP patients during clinical trials with the drug.<sup>8,9</sup> Therefore, the potential for an interaction between the two drugs was studied using clinically relevant regimens, albeit not pharmacokinetically ideal ones. Although there was no pharmacodynamic testing conducted during this study, the lack of a pharmacodynamic interaction between these drugs can be inferred from previous studies. In two past clinical trials, patients initially treated with a combination of a macrolide and a non-pseudomonal third-generation cephalosporin not only had less mortality than patients placed on other antibiotic regimens but also had a significantly shorter length of stay in hospital.<sup>10,11</sup> These results would suggest a possible additive or synergic effect between these drugs rather than any type of antagonism.

In conclusion, the co-administration of ceftriaxone and azithromycin does not result in any clinically significant interactions and is a well tolerated combination.

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