Pharmacokinetic Analysis of Gatifloxin in Plasma and Sinus Aspirate During Treatment of Acute Maxillary Sinusitis

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INTRODUCTION

Gatifloxin (GAT) is an atypical quinolone antibiotic approved for use in the treatment of community-acquired respiratory tract infections (CARTIs) and community-acquired skin and skin structure infections (CA-SSIs).

The traditional paradigm for evaluating antimicrobial agents in the treatment of CARTIs includes measuring the peak plasma concentration at steady-state that was previously unavailable.

Unfortunately, this paradigm provides no information concerning the time-course regarding the time course of antimicrobial exposure at the site of infection. A critical paradigm that reflects such information is the potential for the development of drug resistance. This study was designed to address these limitations.

A pilot study was conducted in a novel technique, involving the insertion of the sinus catheter to loosen the mucosal contents of the sinus cavity at each dosing interval. This was performed on Study Day 3 or 4. However, two of these patients were not enrolled into the pharmacokinetic analysis.

RESULTS

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Pharmacokinetic Analysis

The pharmacokinetics of GAT were studied simultaneously in plasma and sinus aspirate for each patient individually using NONMEM® Versions 5.1.1 as shown in Figure 3. A non-compartment model with 2 Linstra absorption and elimination was used to describe the steady-state plasma concentration-time profile of GAT in each subject.

Bioavailability

The gatifloxin concentrations were adequately described for each individual using a 3-compartment distribution model as described in the methods. Although Cmax, t1/2, and AUC0-24 were modeled individually, these parameters were estimated with a large degree of uncertainty (20%–30% for 3 patients). In addition, there was a strong correlation of t1/2 between t1/2 and AUC0-24 for 3 patients. These initial estimates indicate that the model may be over-parameterized and likely result from having collected limited sinus aspirate data during the elimination phase. Therefore, despite accuracy in the model predicted concentration, the individual estimates for Cmax, AUC0-24, and t1/2 should be interpreted with caution.

The median results for the median predicted pharmacokinetic parameters (Table 3) were used to generate a median steady-state concentration versus time profile in plasma and sinus aspirate. A subset of the observed concentration versus time data, along with the median predicted steady-state concentration versus time profile, is shown in Figure 4.

CONCLUSIONS

The steady-state pharmacokinetics of GAT in plasma for the pilot population following an oral 400 mg dose were more similar to those reported in healthy volunteers (Cmax=19.6 mg/L; AUC0-24=54.7 mg·hr/L) than has been reported in patients with community-acquired respiratory tract infections (Cmax=19.6 mg/L; AUC0-24=54.7 mg·hr/L).

Previous studies in which a single sinus sample was collected in patients at various times during the 24-hour dosing interval provided limited information regarding the time-course of GAT on the tissue at steady-state. The advantage of all the individual rates of GAT in sinus mucosa to serum was observed for t1/2 and AUC0-24 (17.1–24.5).

In this pilot study, sinus aspirate samples were collected after GAT was dosed to steady-state. The median values of the individual ratio for Cmax and AUC0-24 were approximately 1.10 and 1.09, respectively. Based upon these ratios and examination of the median predicted concentration versus time curves in plasma and sinus aspirate, it can be seen that the tissue/plasma ratios are not constant over time.

Individual predicted concentration-time profiles indicate that peak GAT concentrations occur around 8 hours following a dose. In order to attain more reliable pharmacokinetic parameter estimation and subsequently more accurate GAT exposure measures in future studies conducted in a larger patient population, this would reduce the number of samples that need to be collected per patient, provided that the data is consistently collected using the same process of the plasma and sinus aspirate concentration versus time profiles.

REFERENCES


Gatifloxin package insert.