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

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ABSTRACT

Purpose. A novel approach to collect sinus exudate was utilized and the time course of gatifloxacin (GAT) in the blood and at the primary infection site were assessed during treatment for acute maxillary sinusitis (AMS).

Methods. Twelve patients with AMS received 400 mg of GAT daily for 5 days. The maxillary antrum was punctured and a sinus catheter was inserted into the nasal cavity prior to dosing. Blood and sinus samples were collected after 4 days of therapy pre-dose and at 0.5, 1, 2, 4 and 6 hr. Sinus exudate was loosened using approximately 2 mL of saline and immediately aspirated. HPLC was used to determine GAT concentrations in sinus fluid (LLOQ=0.03 mg/L) and plasma (LLOQ=0.05 mg/L). Endogenous urea concentrations were measured to correct for saline dilution; GAT sinus concentrations were determined as the assayed concentration times the ratio of urea in plasma/sinus. GAT concentrations in plasma and sinus were modeled simultaneously for each subject using NONMEM®.

Results. Seven subjects were available for pharmacokinetic evaluation. A one-compartment model with first-order absorption and elimination adequately described GAT concentrations in plasma. A variation of the biophase model was used to describe sinus GAT concentrations. The transfer rate constant from the plasma to sinus (k_{1S}) and the apparent elimination rate constant from the sinus (k_{S0}) were modeled independently and did not assume steady-state conditions. The median k_{1S} and k_{S0} were 0.34 and 0.17 hr^{-1}, respectively. The model enabled determination of steady-state measures of GAT exposure; the median of the individual ratios of AUC and Cmax between the sinus and plasma were 1.51 and 0.90, respectively.

Conclusions. Techniques to measure drug exposure at the primary infection site may contribute to more accurate assessment of the time course of antimicrobial effect than traditional models that rely upon plasma drug concentrations or hypothetical drug concentrations at the primary infection site.

INTRODUCTION

- Gatifloxacin (GAT) is an FDA approved fluoroquinolone antibiotic shown to be safe and efficacious for the treatment of community-acquired respiratory tract infections, including acute maxillary sinusitis (AMS).
- The traditional paradigm for evaluating antimicrobial regimens for the treatment of AMS involves determination of clinical and/or microbiological response typically during the interval of 7 to 14 days after the end of antimicrobial therapy.
- Unfortunately, this paradigm provides no information concerning the time-course of sinus sterilization or information regarding the extent of microorganism exposure to an antimicrobial agent at the infection site. A clinical trial paradigm that collects such information has the potential to allow for the development of drug exposure-response relationships with data specific to the infection site.
- A pilot study was conducted in which a novel technique, involving the insertion of an indwelling catheter into the maxillary sinus for the collection of sinus aspirate, enabled the determination of the time-course of GAT concentration and bacteriological response at the infection site.

OBJECTIVES

To characterize the GAT concentration versus time profiles at steady-state and to estimate GAT exposure measurements in both plasma and sinus aspirate for patients with AMS.

METHODS

Study Design

This was a single-center, open label study designed to (i) evaluate the pharmacokinetics of GAT in plasma and at the infection site, and (2) examine the time course of sinus sterilization in adult patients with AMS following oral administration of GAT 400 mg once daily for 5 days.

Patients

Twelve adult men and women with a diagnosis of AMS based upon clinical signs and symptoms (e.g., facial pain/tenderness over one or both maxillary areas and purulent discharge from the sinus cavity) and radiographic findings were enrolled.

Catheter Insertion

On Study Day 1, after anesthetizing the inferior meatus of the nose on the diseased side, a polyethylene catheter was then inserted into the maxillary sinus a few centimeters above the sinus floor using a spring activated-puncture device (SinoJect®, Atos Medical, Horby, Sweden).

Pharmacokinetic Sample Collection

On Study Day 3 or 4, six serial blood samples and six serial aspirates of sinus fluid were obtained for pharmacokinetic evaluation immediately before and 0.5, 1, 2, 4, and 6 hours after GAT dosing. Approximately 2 mL of saline was injected through the sinus catheter to loosen the mucosal contents of the sinus cavity at each sample collection time. The contents of the sinus cavity were then aspirated within 30 seconds following the saline wash.

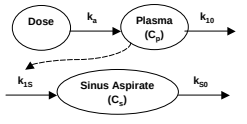
Determination of GAT Concentrations

HPLC was used to determine GAT concentrations in sinus aspirate (LLOQ=0.03 mg/L) and plasma (LLOQ=0.05 mg/L). A urea dilution method was used to correct the assayed sinus aspirate GAT concentration due to the addition of saline during sample collection.[1] Urea concentrations were determined using a commercial diagnostic kit (Urea Nitrogen Quantification, SIGMA, United Kingdom). The corrected GAT concentrations in sinus aspirate were then determined as the product of the assayed concentration and the ratio of urea in blood to sinus.

Pharmacokinetic Analysis

The pharmacokinetics of GAT were modeled simultaneously in plasma and sinus aspirate for each patient individually using NONMEM® Version 5.1.1 as shown in Figure 1. A one-compartment model with first-order absorption and elimination was used to describe the steady-state plasma concentration-time profile of GAT. Inclusion of an absorption lag-time parameter into the model was explored for each individual. GAT sinus concentrations were described using a drug distribution compartment with a transfer rate constant from the plasma to the sinus compartment (k_{1s}) and an apparent elimination rate constant from the sinus compartment (k_{s0}). Separate additive error models were used to describe the residual variability in the sinus and plasma concentrations.

Figure 1: Pharmacokinetic model



In order to estimate plasma and sinus GAT exposure measurements [e.g., Cmax and AUC_{0-24}], the parameter estimates generated as a result of the individual model fits were used to create concentration-time profiles with samples predicted every half-hour from 0 to 24 hours. From this predicted profile, AUC_{0-24} was calculated using the linear trapezoidal rule. Cmax was defined as the maximum predicted concentration and the time at which that concentration occurred was the Tmax. Individual ratios of the GAT exposure measurements in sinus aspirate relative to plasma were also calculated.

RESULTS

Data

- The patient population (n=12) was Caucasian and was equally divided among males and females. Patients ranged in age from 24 to 79 years of age with a median age of 48.5 years. The median patient weight was 73.1 kg and ranged from 51.3 to 90.7 kg.
- Nine patients had pharmacokinetic samples successfully collected from both the blood and the sinus catheter on Study Day 3 or 4. However, two of these subjects had incomplete sinus aspirate data collected and were not included in the pharmacokinetic analysis.
- The actual sample collection times rather than the protocol sampling times were used in the pharmacokinetic analysis for each individual. Those plasma and sinus aspirate GAT concentrations reported as missing, not quantifiable, or below the limit of detection of the assay were excluded from the analysis.
- Examination of the individual observed GAT concentration versus time profiles revealed that distribution into sinus aspirate was slower and more prolonged than the absorption of the oral dose into the plasma; peak concentrations in sinus aspirate appear to approach those measured in the plasma.

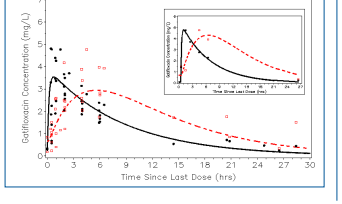
Pharmacokinetic Analysis

- A one-compartment model with first-order absorption and elimination adequately described the steady-state plasma concentration-time profile of gatifloxacin for each patient. An absorption lag-time was evaluated for all patients, however inclusion of this parameter in the model resulted in an improved model fit for only 3 patients (ALAG ~ 0.4 hr).
- Gatifloxacin sinus concentrations were adequately described for each individual using a sinus distribution compartment as described in the methods. Although k_{1s} and k_{s0} were modeled independently, these parameters were estimated with a large degree of uncertainty (SEM > 50% for 3 patients). In addition, there was a strong correlation ($r^2 > 0.8$) between k_{1s} and k_{s0} for 5 patients. These instabilities 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 concentrations, the individual estimates for k_{1S} and k_{S0} should be interpreted with caution.
- The median values for each of the individual model-predicted pharmacokinetic parameters (Table 1) were used to generate a median steady-state concentration versus time profile in plasma and sinus aspirate. A scatterplot of the observed concentration versus time data, along with the median predicted steady-state concentration versus time overlay, is shown in Figure 2.

Table 1: Median (range) of the individual predicted pharmacokinetic parameter estimates for GAT in plasma and sinus aspirate (n=7)

Parameter	Plasma	Sinus aspirate
Cmax (mg/L)	3.77 (2.52-4.80)	3.14 (2.18-4.32)
Tmax (hr)	0.91 (0.3-1.5)	5.50 (2.2 – 7.8)
AUC_{0-24hr} (mg-hr/L)	30.1 (22.6-38.4)	54.7 (27.2-67.6)
k_a(hr^{-1})	6.4 (3.34-18.1)	-
k_{10} (hr^{-1})	0.11 (0.08-0.20)	-
k_{1S} (hr^{-1})	-	0.34 (0.16-1.15)
k_{S0} (hr^{-1})	-	0.17 (0.11-1.31)
Ratio of Cmax	0.90 (0.56-1.32)	
Ratio of AUC_{0-24hr}	1.51 (0.88-2.23)	

Figure 2: Median (n=7) predicted steady-state GAT concentration versus time profile in plasma and sinus aspirate with a representative patient insert. The lines represent the median predicted plasma (—) and sinus (--) concentrations; the symbols represent the observed concentrations in plasma (●) and sinus aspirate (□).



DISCUSSION

- The steady-state pharmacokinetics of GAT in plasma for this patient population following an oral 400 mg dose were more similar to those reported in healthy volunteers (Cmax=3.8 mg/L; AUC_{0-24}=33 mg-hr/L) than to those reported in patients with community-acquired respiratory tract infections (Cmax=4.2 mg/L; AUC_{0-24}=51 mg-hr/L).[2]
- Previous studies in which a single sinus mucosa sample was collected in patients at various times during the 24-hour dosing interval provided limited information regarding the time course of GAT in sinus tissue at steady-state. The average of all of the individual ratios of GAT concentrations in the sinus mucosa to serum was reported to be 1.78 and ranged from 1.17 to 2.49.[2]
- In this pilot study, serial sinus aspirate samples were collected after GAT was dosed to steady-state. The median values of the individual ratios for Cmax and AUC_{0-24} were approximately 1.51 and 0.90, 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 GAT concentration-time profiles indicate that peak sinus concentrations occur around 5.5 hours following a dose. In order to obtain more reliable pharmacokinetic parameter estimates and subsequently more accurate GAT exposure measures, future studies would require additional sampling during the sinus aspirate elimination phase.
- Alternatively, a population-based approach could be utilized to obtain individual 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 are strategically collected during all phases of the plasma and sinus aspirate concentration versus time profile.

CONCLUSIONS

- Serial pharmacokinetic sampling using the indwelling catheter provided extensive information regarding the time course of GAT in sinus tissue at steady-state that was previously unavailable.
- Techniques to measure drug exposure at the primary infection site may contribute to more accurate assessment of the time course of antimicrobial effect than traditional models that rely upon plasma drug concentrations or hypothetical drug concentrations at the effect site.

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