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Gatifloxacin Exposure in Maxillary Sinus and Middle Ear – All Sites of Infection Are Not Created Equal

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ABSTRACT

Background. Due to the similar physiology of maxillary sinus (MS) and middle ear (ME), it is often assumed that antimicrobial penetration is similar into MS and ME fluids. Traditional methods for assessing drug penetration into these closed compartments (single point estimates of concentration ratio) often support this assumption. Here, we present results from two analyses, each comparing drug exposure in a closed infection space with that in plasma. **Methods.** Separate population pharmacokinetic (PK) models were developed from clinical trials. MS data was obtained from seven patients enrolled in a clinical study evaluating serial sinus aspirates. Each patient had six matched pairs of gatifloxacin (GAT) plasma and MS samples at steady-state. ME data came from two trials (n=95): a multiple dose, open-label, double-tympanocentesis study and a single dose PK study in children post-tympanostomy tube placement. Each patient contributed one pair of matched GAT plasma and ME samples. In both analyses, GAT PK was evaluated by simultaneous modeling of closed compartment (ME or MS) and plasma concentrations for each patient. Due to differences in the study populations (adult sinusitis vs. pediatric otitis media), the ratio between the exposure in the closed compartment and plasma was used for comparisons rather than absolute exposure values. **Results.** The mean (%CV) predicted 24 hr AUC (mg*hr/L) in plasma and MS was 30 (18) and 46 (38), respectively. Despite the fact that point estimates of MS:plasma concentration ratios from other GAT studies average ~1.8, the mean 24 hr AUC MS:plasma ratio was 1.49 (range 0.88, 2.23). The mean (%CV) 24 hr AUC in plasma and ME was 33 (69) and 33 (79), respectively. The mean 24 hr AUC ME:plasma ratio was 1.00 (range 0.99, 1.01), in contrast to the mean ME:plasma concentration ratio of ~1.3. **Conclusion.** Point estimates of the MS or ME to plasma concentration ratio may not be predictive of actual exposure ratios and are not necessarily useful in pharmacodynamic analyses. These results suggest that PK from one closed compartment may not be extrapolated to other closed compartments, even those with similar physiology.

INTRODUCTION

- Due to the similar physiology of maxillary sinus and middle ear, it is often assumed that antimicrobial penetration is similar into maxillary sinus and middle ear fluids.
- Traditional methods for assessing drug penetration into these closed compartments (single point estimates of concentration ratio) often support this assumption.
- Here, we present results from two analyses, each comparing drug exposure in a closed infection space with that in plasma.

METHODS

Study Design

- For the sinus aspirate analysis, data were obtained from a single-center, open-label study evaluating the pharmacokinetics and pharmacodynamics of gatifloxacin in adult patients with acute maxillary sinusitis which enrolled men and women ≤ 18 years old with a diagnosis of acute maxillary sinusitis based upon clinical and radiographic findings.
- For the middle ear fluid analysis, data were pooled from two studies:
  - *Single-dose TP Study*: multicenter, open-label, two-part, single-dose, dose-escalation trial of oral gatifloxacin in pediatric subjects (ages three months to seven years) scheduled for tympanostomy tube placement (TP); and
  - *ROM/AOM-TF Study*: open-label, single-center, non-comparative Phase II clinical trial designed to evaluate gatifloxacin treatment in infants/children (ages three months to four years) diagnosed with otitis media (ROM) or acute otitis media treatment failures (AOM-TF).

Gatifloxacin Treatment

- Adults received 400 mg PO daily for five days. Children received single or multiple doses of 10 mg/kg PO daily.

Pharmacokinetic Sampling Strategy

Table 1: Pharmacokinetic Sampling.

Sample Type	Sinusitis Study	Single Dose TP Study	ROM/AOM-TF Study
Plasma	Six serial samples: Day 3 or 4, before, 0.5, 1, 2, 4, and 6 hours after gatifloxacin dosing	Two samples: first at time of MEF sampling and second +2 hours after MEF	One sample at the during-treatment visits on Days 4, 5, or 6; approximately 6-10 hours postdose; no sample was to be collected less than 2 hours postdose
Sinus Samples	Six serial samples: Day 3 or 4, before, 0.5, 1, 2, 4, and 6 hours after gatifloxacin dosing	Not applicable	Not applicable
Middle Ear Fluid (MEF)	Not applicable	One sample: 0.5, 1, 2, 4, 12, or 24 hours after drug administration	At time of plasma sample at the during-treatment visit

All samples were analyzed using a validated HPLC method

Pharmacokinetic Analysis – Sinus Aspirates

- Individual patient plasma concentrations were described using a one-compartment model with first-order absorption and elimination using NONMEM® Version 5.1 Level 1.1. Sinus aspirate concentrations were simultaneously described using a variation of the biophase model. The transfer rate constant from the plasma to the sinus compartment (K1s) and the elimination rate constant from the sinus compartment (Kso) were modeled independently. Residual variability was described using separate additive error models for sinus and plasma concentrations.
- Individual parameter estimates were used to create predicted concentration time profiles with samples every half hour from 0 to 24 hours. From these predicted profiles, AUC was calculated using the trapezoidal rule, C_{max} was defined as the maximum predicted concentration, and the time at which that concentration occurred was the T_{max}.

METHODS, continued

Pharmacokinetic Analysis – Middle Ear Fluid Aspirates

- Pharmacokinetic analyses were conducted using the computer program NONMEM®, Version 5.1.1 (First Order method).
- Model used to predict plasma population pharmacokinetic parameters had been developed previously using dense pharmacokinetic data obtained in a single-dose study of gatifloxacin suspension in children aged 6 months to 16 years (ICAAC 2001 Abstract #38).
- The pharmacokinetic parameters and inter- and intra-individual variability were fixed to the population mean estimates and Bayesian parameter estimation within NONMEM® was then used to obtain individual predictions and parameter estimates.
- Due to the sparse nature of the middle ear fluid data, simplified "effect-compartment" models were attempted to describe the pharmacokinetics of gatifloxacin in middle ear fluid. The pharmacokinetic parameters describing the disposition of gatifloxacin in plasma were fixed to the individual Bayesian estimates obtained as described above.
- Several permutations of the effect-compartment model were attempted to describe the middle ear fluid disposition through simple rate constants in and out of the middle ear fluid compartment. The modified effect compartment model was simplified to one with an equilibrium constant between plasma and middle ear fluid. This model allowed the two rates, K_{2e} (rate in) and K_{e0} (rate out), to be set equal (renamed as K_e); eliminating one parameter from the model.
- Once an appropriate model was chosen, predicted plasma and middle ear fluid simulated concentration-time profiles were generated for each subject; the trapezoidal rule was then used to calculate estimates of plasma area under the plasma concentration-time curve ($AUC_{0\text{-}24}$).

RESULTS

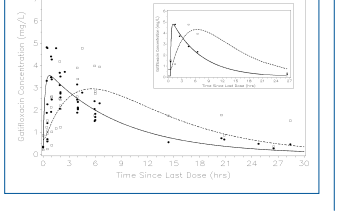
Data

- Sinusitis Study - Of the 12 patients enrolled in the sinusitis study, 7 had sufficient pharmacokinetic data for inclusion in the analysis. Approximately 42 plasma and 42 sinus aspirate samples were available for analysis.
- Middle Ear Fluid Studies - A combined total of 320 gatifloxacin plasma concentrations and 95 gatifloxacin middle ear fluid concentrations collected from 236 of the 301 (78%) subjects enrolled in the single-dose (199 plasma concentrations and 55 middle ear fluid concentrations collected from 115 subjects) and ROM/AOM-TF (121 plasma concentrations and 40 middle ear fluid concentrations collected from 121) studies were available for development of the pharmacokinetic model for gatifloxacin in middle ear fluid.

Pharmacokinetic Analysis

- Sinus Aspirate Pharmacokinetics - Median predicted steady-state gatifloxacin concentration versus time profile in plasma and sinus aspirate with a representative patient insert are presented in **Figure 1**. Median (range) predicted pharmacokinetic parameter estimates in plasma and sinus aspirate are presented in **Table 2**.
- Middle Ear Fluid Pharmacokinetics - Median predicted steady-state gatifloxacin concentration versus time profile in plasma and sinus aspirate with a representative patient insert are presented in **Figure 2**. Median (range) predicted pharmacokinetic parameter estimates in plasma and sinus aspirate are presented in **Table 2**.

Figure 1: Median predicted steady-state gatifloxacin concentration versus time profile in plasma and sinus aspirate with a representative patient insert. The solid line (—) in the figure represents predicted plasma concentrations; the dashed line (--) represents predicted sinus concentrations; the filled symbols (●) represent observed plasma concentrations and; the empty symbols (□) represent observed sinus concentrations.



RESULTS, continued

Figure 2: Median predicted steady-state gatifloxacin concentration versus time profile in plasma and middle ear fluid aspirate. The solid line (—) in the figure represents predicted plasma concentrations; the dashed line (--) represents predicted middle ear fluid concentrations; the filled symbols (●) represent observed plasma concentrations and; the empty symbols (□) represent observed middle ear fluid concentrations.

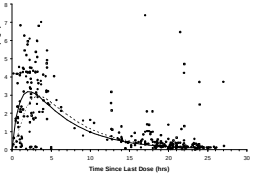


Table 2: Median (Range) Predicted $AUC_{0\text{-}24}$ Estimates and Their Ratio.

	Sinusitis Study	MEF Studies
$AUC_{0\text{-}24}$ (Plasma)		
n	7	378
Median (Min – Max)	30.1 (22.6 – 38.4)	29.8 (8.35 – 190)
$AUC_{0\text{-}24}$ (Sinus)		
n	7	------
Median (Min – Max)	54.7 (27.2 – 67.6)	
$AUC_{0\text{-}24}$ (MEF)		
n	------	70
Median (Min – Max)		29.0 (8.42 – 126)
Ratio		
n	7	95[b]
Median (Min – Max)	1.51 (0.88 – 2.23)	1.00 (0.988 – 1.01)

CONCLUSIONS

- Point estimates of the maxillary sinus or middle ear to plasma concentration ratio may not be predictive of actual exposure ratios and are not necessarily useful in pharmacodynamics analyses.
- These results suggest that pharmacokinetic from one closed compartment may not always be extrapolated to other closed compartments, even those with similar physiology.

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