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Serial Sinus Aspirate Sampling (SSAS): A Novel Technique for Evaluating Antimicrobial Therapy of Acute Maxillary Sinusitis (AMS)

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REVISED ABSTRACT

Context. The relationship between drug exposure and the time course of antimicrobial effect at the primary infection site for acute maxillary sinusitis has not previously been explored. **Purpose.** To quantify the time course of sinus sterilization, describe gatifloxacin exposure at the infection site, and to pose the hypothesis that the use of continuous and quantitative time-related endpoints would allow for better characterization of drug effect. **Methods.** Single-center, open-label pilot study. **Patients.** 12 patients with a radiologically-confirmed clinical diagnosis of acute maxillary sinusitis. **Main Outcome Measures.** Time to microbiological eradication of pathogenic organisms from the sinus. **Results.** Sinus catheters were inserted into the maxillary sinus with minimal discomfort and were well tolerated. Of the 12 enrolled patients, 10 were clinically evaluable, from whom 7 pathogens were isolated: *S. pneumoniae* (4), staphylococci (2), and *E. aerogenes* (1). The median predicted 24-hour AUC (mg*hr/L) in plasma and sinus aspirate was 30.1 and 54.7, respectively. The median 24-hr AUC sinus:plasma ratio was 1.51 (range 0.88, 2.23). The median time to sinus sterilization was 53 hours (95% CI 43, 91). The median time to resolution of each sign and symptom of infection ranged between 1 and 3 days with 87% (69/79) of total signs and symptoms resolving by the end of 5 days of therapy. **Conclusions.** Exposure of organisms to gatifloxacin was associated with rapid sinus sterilization. The serial sinus aspirate sampling approach for quantifying the time course of sinus sterilization and describing drug exposure at the infection site provides more robust information than standard approaches used for evaluating antimicrobial therapies of acute maxillary sinusitis. The collection of pharmacokinetic data from the site of infection may allow for better pharmacodynamic characterization of antimicrobial agents for the treatment of acute maxillary sinusitis. This model may be useful to evaluate the efficacy of antimicrobial agents with fewer patients.

INTRODUCTION

- Clinical trials leading to the FDA approval of antimicrobial agents are typically equivalence studies and involve several hundreds of patients.
- In the traditional paradigm for evaluating antimicrobial regimens for the treatment of acute maxillary sinusitis, clinical and/or microbiological response determination generally occurs 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 documentation of drug effect with relatively few patients compared with traditional clinical trial approaches,
  - Allow for the development of drug exposure-response relationships with data specific to the infection site, and
  - Allow greater resources for studying the safety of antimicrobial agents.
- We used a new technique to determine the time course of gatifloxacin effect in the treatment of acute maxillary sinusitis. This approach involved the insertion of an indwelling catheter into the maxillary sinus, which allowed for serial sinus aspirate sampling.

METHODS

Study Design

- Single-center, open-label study evaluating the pharmacokinetics and pharmacodynamics of gatifloxacin in adult patients with acute maxillary sinusitis.

METHODS, continued

Patients

- Enrolled men and women ≥ 18 years old with a diagnosis of acute maxillary sinusitis based upon clinical and radiographic findings.
  - Primary inclusion criteria: 1) facial pain/tenderness over one or both maxillary areas and either purulent discharge from the maxillary sinus orifice or purulent discharge from the nose or purulent discharge present in the back of the throat; and
  - Radiological documentation, i.e., at least one of the following: opacification or an air/fluid level or mucosal thickening of ≥ 5 mm.

Treatment

- Gatifloxacin 400 mg PO daily for 5 days.

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).

Microbiological Assessments

- Sinus aspirate specimens were obtained daily via the sinus catheter for microbiological assessment. Susceptibility of isolates to gatifloxacin was determined by broth microdilution methods.

Pharmacokinetic Sampling

- 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 gatifloxacin dosing.

Clinical Assessments

- Clinical evaluations were carried out daily during therapy and 7 to 14 days after the completion of therapy.

Primary Outcome Measure

- Time to microbiological eradication of pathogenic organisms from the sinus was the primary outcome measure. Microbiological response was evaluated daily for the 5 days of therapy and was classified as either eradicated or persisted.
  - *"Eradicated"* was defined as the absence of the initial pathogen from all subsequent sinus aspirate cultures.
  - *"Persistent"* was defined as the presence of the initial pathogen in the final culture.

Pharmacokinetic Analysis

- 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}.

Statistical Methods

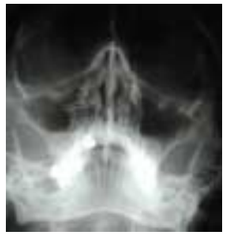
- Estimates of the resolution rates were obtained using the Kaplan-Meier product-limit method, and 95 percent confidence intervals for these estimates were obtained.
- To gain insight into potential sample sizes for comparative clinical trials using time to eradication rather than clinical success/failure as the primary endpoint, we estimated the power to detect clinically important differences with a Type I error (α) of 0.05 for various sample sizes.

RESULTS

Patients, Clinical Response to Therapy, and Adverse Events

- A total of 12 patients were enrolled into the study, 6 Caucasian males and 6 Caucasian females. The mean (± SD) age was 48.3 ±15.3 years. Of the 12 patients enrolled, 10 were available for clinical response evaluation.
- 7 pathogens were isolated from the clinically evaluable patients, *S. pneumoniae* (4), staphylococci (2), and *E. aerogenes* (1).
- Sinus catheters were inserted with minimal discomfort (**Figure 1**).
- Adverse events were mild and transient in nature. No serious adverse events occurred during the study.

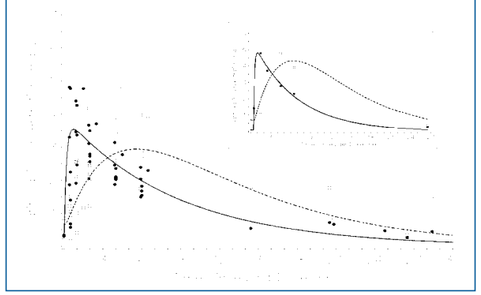
Figure 1: Waters-view radiograph with sinus catheter.



Pharmacokinetic Analyses

- Of the 10 clinically evaluable patients, 7 had sufficient pharmacokinetic data for analysis.
- Median predicted steady-state gatifloxacin concentrations versus time profile in plasma and sinus aspirate with a representative patient insert is presented in **Figure 2**.
- Median (range) predicted pharmacokinetic parameter estimates in plasma and sinus aspirate are presented in **Table 1**.

Figure 2: 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

Table 1: Median (range) predicted pharmacokinetic parameter estimates in plasma and sinus aspirate.

Parameter	Plasma	Sinus aspirate
C_{max} (mg/L)	3.77 (2.52-4.80)	3.14 (2.18-4.32)
T_{max} (hr)	1.00 (0.3-1.5)	5.50 (2.2 – 7.8)
$AUC_{0\text{-}24hr}$ (mg*hr/L)	30.1 (22.6-38.4)	54.7 (27.2-67.6)
k_{01} (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 C_{max} (sinus:plasma)	0.90 (0.56-1.32)	
Ratio of $AUC_{0\text{-}24hr}$ (sinus:plasma)	1.51 (0.88-2.23)	

C_{max}= Maximal concentration; T_{max}= Time to C_{max}; $AUC_{0\text{-}24hr}$= 24 hour area under the concentration-time curve; k_{01} = Absorption rate constant; k_{10} = Elimination rate constant; k_{1s} = transfer rate from plasma to sinus compartment; k_{so} = elimination rate constant from sinus.

Pharmacodynamic Analyses

- **Figure 3** shows an inverted Kaplan-Meier plot of the time course of sinus sterilization.
- Inverted Kaplan-Meier plots of the time course of resolution of signs and symptoms of infection are presented in **Figure 4**.

Power Calculations

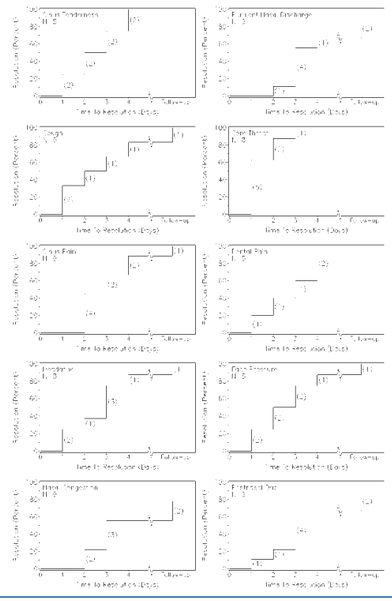
- Sample sizes for detecting differences in median time to sinus sterilization in hours with α = 0.05 and 80 or 90% power are shown in **Table 2**.
- Using cure or failure as the primary endpoint and assuming an 85% clinical cure rate for gatifloxacin and a cure rate of 95% for clinical superiority, 200 patients per group would be required.

Figure 3: Inverted Kaplan-Meier plot of the time course of sinus sterilization. The time to median and to 75% sinus sterilization was 53 and 91 hours, respectively.

Table 2: Sample sizes for detecting differences in median time to sinus sterilization in hours with α = 0.05 and 80 or 90% power.

Group 1 (hours)	53	53	53	53
Group 2 (hours)	23	29	35	41
Difference (hours)	30	24	18	12
n per group (90% power)	31	59	123	322
n per group (80% power)	26	44	92	241

Figure 4: Inverted Kaplan-Meier plots of the time course of resolution of signs and symptoms of infection.



DISCUSSION AND CONCLUSIONS

- The objectives of this study were to quantify the time course of sinus sterilization and to describe organism exposure to gatifloxacin at the infection site with the hypothesis that the use of a continuous and quantitative endpoint would allow for better characterization of drug effect.
- We successfully used time to sterilization as an endpoint and characterized organism exposure to gatifloxacin in maxillary sinus fluid.
- The use of a continuous and specific measure of drug effect had a significant effect on clinical trial sample size calculations.
- Collection of these types of data in larger sinusitis trials and, when technically feasible, in other indications, will allow for the development of drug exposure-response relationships with data specific to the infection site.
- Studies encompassing these design elements hold the promise of reducing the total number of patients required to demonstrate efficacy.
- Given that the FDA is encouraging the development of valid pharmacodynamic models during drug development in return for a reduction in the total number of clinical trials for registration, efficacy may be established with fewer patients and greater resources can be applied to study the safety of antimicrobial agents.