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Pharmacokinetics (PK) of Ampicillin-Sulbactam (SAM) during Orthotopic Liver Transplantation (OLT)

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ABSTRACT

Background: SAM is used as surgical prophylaxis during OLT due to its broad spectrum activity against Gram-positive,-negative and anaerobic pathogens. SAM resistance among Gram-negatives is rising, making dosage selection paramount to preventing surgical site infections. Current guidelines recommend a 3g dose, consisting of 2g ampicillin (AMP) and 1g sulbactam (SUL), every 2h. There are no data; however, describing SAM PK during OLT to support an optimized dosing regimen.

Methods: This was a single-center PK study of OLT patients receiving SAM for surgical prophylaxis at a dose selected by the anesthesiologist. Patients were excluded if they were undergoing simultaneous liver and kidney transplantation and had a CrCL < 30 mL/min at start of surgery. Up to 24 blood samples, along with times of pertinent events, were collected throughout the OLT. AMP and SUL plasma concentrations were determined. Population PK analyses were conducted in Pmetrics using R. Akaike information criterion (AIC) and visual inspection determined best model fit. Individual PK parameters were simulated to describe free AMP time above the MIC_{90} ($fT>MIC_{90}$) of 32 mg/L.

Results: Five patients were enrolled. Participants had a mean ± SD age of 64 ± 8 years, body weight 82 ± 9 kg, CrCL of 75 ± 35 mL/min, and received various SAM doses (1.5-3g q2-3h). A 2 compartment model fitted the data better than a 1 compartment model for both AMP (AIC: 396 vs. 423) and SUL (AIC: 334 vs. 347). Final models included fractional clearance (CL_f) terms on typical total body clearance (CL_B) to account for the placement of the portal vein clamp. AMP PK parameters (AIC: 372) were: CL_B, 9.7 ± 2.6 L/h; CL_f, 0.73 ± 0.49; volume of central compartment (Vc), 7.2 ± 1.4 L; intercompartment constants (k12 and k21), 4.08 ± 3.28 and 2.63 ± 2.9 h^{-1}, respectively. Final SUL PK parameters (AIC: 314) were: CL_B, 8.3 ± 2.5 L/h; CL_f 0.92 ± 0.55; Vc, 7.3 ± 1.6 L; k12, 4.60 ± 4.41 h^{-1}, and k21, 4.07 ± 3.31 h^{-1}. Exposures ranged from 58-98% with only 3g q2h providing nearly 100% $fT>MIC_{90}$.

Conclusion: This is the first study to describe intra-operative SAM PK in OLT recipients and the effect of portal vein clamp on AMP and SUL clearance. These data will help guide optimized SAM dosing regimens for OLT surgery based on local MIC distributions for targeted pathogens.

INTRODUCTION

- Infection is the most common cause of 30-day post-operative mortality in patients undergoing OLT[1-5]
- Antibiotics are given as prophylaxis to mitigate surgical infection risk[6]
- Ampicillin-sulbactam is an appropriate choice for antibiotic prophylaxis in OLT due to its broad-spectrum coverage
- Due to rising ampicillin-sulbactam resistance in Gram-negative organisms, optimal choice of dosage and frequency is paramount
- There are no data describing ampicillin-sulbactam intra-operative pharmacokinetics in patients undergoing OLT

OBJECTIVE

The objective of this study was to describe ampicillin and sulbactam intra-operative pharmacokinetics during OLT

METHODS

Study Design

- Single-center pharmacokinetic study
- Approved by the local IRB
- Written consent was provided by all patients

Patients

- Inclusion criteria:
  - Age 18 years or older
  - Scheduled for OLT at Hartford Hospital
  - Receiving ampicillin-sulbactam for surgical prophylaxis
- Exclusion criteria:
  - History of moderate or severe penicillin or β-lactam antibiotic
  - Simultaneous liver-kidney transplant
  - Creatinine clearance (CrCL) less than 30 mL/min
- Ampicillin-sulbactam dose and frequency was selected by anesthesiologist

Sample Collection and Processing

- Up to 24 blood samples per patient were collected during the OLT procedure
  - Centrifuged for 15 minutes at 25 °C at 3,000 rpm to separate plasma
- Protein binding assessed at first dose peak
  - Transferred into 3 ultrafiltration devices and centrifuged for 40 minutes at 25 °C at 2,000 g to separate protein free filtrate (PFF)
- Plasma and PFF frozen at -80 C until analysis

Concentration Determination

- Ampicillin and sulbactam plasma and PFFconcentrations were determined using high performance liquid chromatography in plasma and saline matrices

Pharmacokinetic Analysis

- Population pharmacokinetic modeling was performed using Pmetrics for R
- 1- and 2- compartment models were differentiated based on Akaike information criterion (AIC) and visual fit
- Covariates weight, CrCL, and placement of portal vein clamp were examined as covariates

Pharmacokinetic Analysis, cont'd

- To assess exposure, the model-derived % of the dosing interval that free ampicillin concentrations remained above the MIC was simulated for each patient using an ampicillin-sulbactam MIC_{90} from contemporary *Escherichia coli* of 32mg/L[7]

RESULTS

Table 1. Baseline participant characteristics

Characteristic	Total Patients (N=5)
Age (years); mean ± SD (range)	64 ± 8 (52 – 73)
Female sex; n (%)	2 (40%)
Weight (kg); mean ± SD (range)	83 ± 9 (73 – 96)
Height (cm); mean ± SD (range)	168 ± 11 (156 – 178)
BMI (kg/m^2); mean ± SD (range)	29 ± 3 (26 – 34)
CrCL (mL/min); mean ± SD (range)	75 ± 39 (30 – 130)
Ampicillin/Sulbactam Regimen	
1.5g q2h	1
3g q3h	2
3g q2h	2

Sample Collection and Processing

- Forty-three total plasma samples were collected during procedures and available for pharmacokinetic analyses
- A range of 4-12 samples were collected for each patient

Protein Binding

- Protein binding ranged from 8-25% and 11-43% for ampicillin and sulbactam, respectively

Pharmacokinetic Analysis

- A 2-compartment model fitted the data better than a 1-compartment model for ampicillin (AIC: 396 vs. 423) and sulbactam (AIC: 334 vs. 347)
- Weight and CrCL did not significantly improve model fit
- Incorporation of clamp placement as a fraction (CL_f) of typical baseline clearance (CL_B) improved model fit for ampicillin (AIC: 372) and sulbactam (AIC: 314)

$$\text{Clearance} = (CL_B)*Cl_f^{clmp}, \text{ where clmp=0 prior to clamp and 1 when clamp in place}$$

- Observed versus predicted fits are displayed in Fig1
- Final population model parameter estimates are provided in Table 2

Figure 1. Observed vs. predicted ampicillin (**top**) and sulbactam (**bottom**) concentrations based on the final 2-compartment population PK model. Left: Population predicted; Right: maximum *a posteriori* Bayesian individual predicted

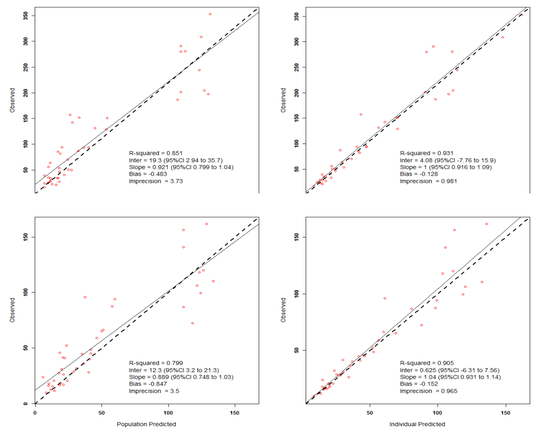
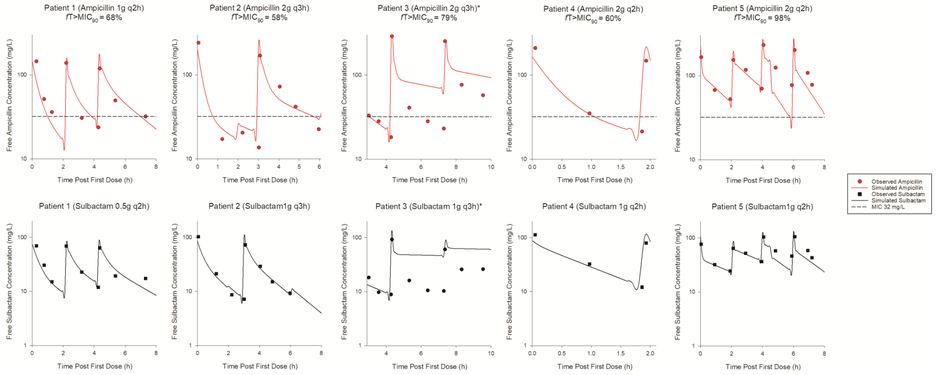


Figure 2. Observed versus simulated free ampicillin (**top**) and sulbactam (**bottom**) concentrations for each patient relative to MIC_{90}



*Patient received an ampicillin-sulbactam 3g over 1 hour infusion followed by a 3g bolus dose. Sampling started 3 hours after the end of bolus, which was time of incision. Massive blood transfusion received circa 5 hours.

Table 2. Ampicillin and sulbactam population pharmacokinetic parameter estimates for 5 adult patients undergoing OLT

PK Parameter	Ampicillin			Sulbactam		
	Mean± SD	Median	IQR	Mean± SD	Median	IQR
CL_B (L/h)	9.74 ± 2.89	10.22	7.51-12.17	8.30 ± 2.85	2.85	5.85-9.42
CL_f	0.73 ± 0.55	0.62	0.48-0.64	1.14 ± 0.44	0.94	0.92-1.16
V_c (L)	7.20 ± 1.57	7.25	6.34-8.25	7.33 ± 1.61	8.19	6.51-8.44
k_{12} (h^{-1})	4.08 ± 3.67	2.20	1.23-6.92	4.60 ± 4.93	1.00	1.00-10.00
k_{21} (h^{-1})	2.63 ± 3.25	1.21	1.00-1.49	4.07 ± 3.35	2.43	1.67-6.71

CL_B typical baseline clearance, CL_f, fractional clearance; V_c, volume of central compartment, k_{12} and k_{21}, intercompartmental transfer constants

DISCUSSION & CONCLUSION

- These are the first data to describe ampicillin and sulbactam intra-operative pharmacokinetics in patients undergoing OLT
- A 2-compartment model with adjusted clearance after portal clamp placement predicted ampicillin and sulbactam exposures best
- Significant intraoperative blood loss occurring during certain surgeries (e.g., Patient 3) may explain discordance between observed and simulated concentrations
- These data can help optimize ampicillin-sulbactam surgical prophylaxis regimens to meet local resistance patterns
- Although several different regimens were prescribed here, an ampicillin-sulbactam 3g q2h regimen should provide the greatest likelihood of maintaining ampicillin concentrations above 32 mg/L
- Further studies exploring the impact of major bleeding events and massive transfusion during OLT on the pharmacokinetics of ampicillin and sulbactam are warranted

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