Population PK/PD of Ampicillin/Sulbactam in Patients with Moderate or Severe Community-Acquired Pneumonia

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Introduction

Unasyn® (injectable combination of sulbactam sodium and ampicillin sodium, dose ratio 1:2) has been marketed over 60 countries in the world, and prescribed for the treatment of various types of infections. It is currently used in doses up to 12 g/day however in Japan approved doses are up to 6 g/day (3 g BID).

The aim of this analysis was to study the pharmacokinetics (PK) of ampicillin and sulbactam after doses of 12g/day divided in 4 doses (i.e. 3 g QID) in Japanese patients with moderate or severe community-acquired pneumonia. The PK model was then used to explore the efficacy of the drug through the calculation of the expected time above the minimum inhibitory concentration (MIC) for the different pathogens identified in the patients.

Methods

The population PK analysis was performed using NONMEM 6.2 based on log-transformed plasma concentration samples. Simultaneous fit of the concentration data of both drugs was evaluated by the use of the L2 item in NONMEM. L2 item acts grouping observations within individual records and allows for two types of observations (ampicillin and sulbactam concentrations) to be considered as two elements of a multivariate observation [1].

The MIC for ampicillin/sulbactam was reported as ampicillin concentration. The time above MIC (TAM) during the treatment duration period for all the patients for which the MIC value was available was integrated using the following equation:

$$\frac{\partial A}{\partial t} = \frac{C(t)^{GAM}}{C(t)^{GAM} + MIC^{GAM}}$$

Where C is ampicillin concentration at each time point, MIC is the MIC value for each patient, GAM is a factor fixed to 99, in order to create a function which gives an all or nothing response. When divided by the duration of the treatment (hrs), the fraction time above MIC was obtained.

Results: PK Model

In total, 222 plasma concentration observations for both sulbactam and ampicillin coming from 47 patients were available for the analysis. A two-compartment model described both the ampicillin and the sulbactam PK, where inter-patient variability was estimated for clearance and for peripheral volume. Creatinine clearance and body weight were included in the final model. Final PK parameters (**Table 1**) were similar between the two compounds and similar to previously reported values [2 - 4]. A visual predictive check was performed for the final combined model (**Figure 1**).

Results: PK-PD Analysis

The percentage of time above the MIC value established for each identified pathogen ranged from 55 to 100% (**Table 2**). **Figure 2** shows simulation results for predicted percentage of time above different MIC values for BID, TID and QID schedules.

Conclusions

A PK model that described both ampicillin and sulbactam plasma concentration data was established. This model was used to make inferences on the efficacy of the drug through the calculation of TAM for different pathogens and different dosing schedules.

Table 1. Parameter estimates for the combined final model

Parameter	Ampicillin Estimate	(RSE%)	Sulbactam Estimate	(RSE%)
CL (l h⁻¹)	10.7	(3.39)	10.4	(3.40)
CLCR on CL	0.701	(7.65)	0.701	(7.65)
V1 (l)	9.97	(6.07)	10.2	(7.04)
Q (l h⁻¹)	4.14	(21.8)	4.58	(28.2)
V2 (l)	4.48	(9.91)	4.04	(12.1)
BWT on V2	1.00	Fix	1.00	Fix
CV% [CL]	14.8	(15.5)*	15.2	(15.2)*
CV%[V2]	15.2	(36.2)*	14.8	(28.3)*
Res variability %	24.2	(26.9)	23.3	(28.8)
$\rho[\varepsilon_{ij,ampr}, \varepsilon_{ij,sulb}]$	0.946	(29.5)		
$\rho[\eta_{CL,ampr}, \eta_{CL,sulb}]$	0.858	(34.8)		

*RSE% for CV

Table 2. Summary of Identified MICs and the Time Above MIC by Subject

Bacteria	N	MIC (µg/mL)*	Time above MIC (%)**
S. Pneumonia	11	0.06 [0.06-2.00]	98.88 [3.71]
H. Influenza	8	0.50 [0.12-4.00]	87.48 [20.06]
M. Catarrhalis	8	0.12 [0.06-0.12]	100.00 [0.00]
E. Coli	1	4.00 [NA]	99.99 [NA]
K. Oxytoca	1	16.00 [NA]	54.56 [NA]
S. Aureus	1	0.12 [NA]	100.00 [NA]
K. Pneumonia	1	4.00 [NA]	99.99 [NA]
E. Aerogenes	1	4.00 [NA]	89.84 [NA]

* Median [range] as ampicillin concentration. ** Percent of QID dosage regimen calculated with total plasma ampicillin concentrations; mean [sd] (n>1). NA = not applicable.
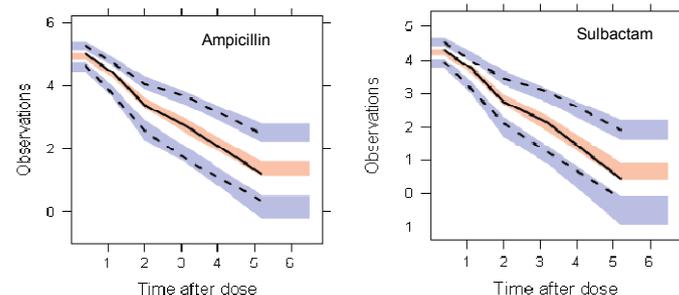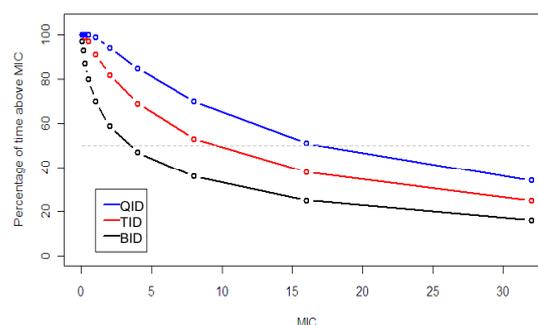

Fig 1. VPC for Ampicillin and Sulbactam PK

Fig 2. Predicted percentage of time above different MIC values for BID, TID and QID schedules

References

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