Pharmacokinetics of Temocillin in Intensive Care Patients and Monte Carlo Simulations to Evaluate Breakpoints

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Introduction:

Temocillin (TMO) is a narrow spectrum penicillin with good activity against Gram negative micro-organisms including ESBL and AmpC producers. Little pharmacokinetic data are available however. We performed a pharmacokinetic study in 6 ICU patients receiving TMO 2g q12h and 6 other ICU patients receiving the same daily dose as a continuous infusion[1]. Continuous infusion has been argued to be a more optimal form of administration because of its Pk/Pd characteristics. The parameter estimates found during intermittent infusion were used to perform Monte Carlo Simulations (MCS) to determine Probabilities of Target Attainment (PTAs) for pharmacodynamic indices (PDI) in order to evaluate and suggest clinical breakpoints[2].

Methods:

Blood samples were taken from ICU patients prior to (t=0) and after (t=1, 2, 3, 6, 12 h) a 30 m infusion of 2 g TMO (n=6) or after 48 h during CoInf with 4g/24h (n=6), and then cooled, centrifuged and stored at -70C until analysis by HPLC. Protein binding was determined using an ultrafiltration method. Results were used to estimate population pharmacokinetic parameters by Winnonmix including the covariance matrix. Miclab233 was used to perform simulations for CoInf as well as to perform MCS (10000 cycles) and obtain PTAs for the unbound fraction including 95% and 99% confidence intervals (CI) for the target concentrations. fT>MIC was chosen as the PDI because of the pharmacodynamic properties of TMO.

Results:

Protein binding was 75%. A one-compartment model best fitted to the data, with estimates (se) of Vc =14.3 (0.87) L and k10 = 0.172 (0.059) 1/h corresponding to a mean half-life of 4.03 h. Figure 1 shows the model predicted concentrations versus measured concentrations, indicating a good model fit. Subsequently, the parameter estimates were used to predict the concentrations of temocillin during continuous infusion to further validate the model. The predicted unbound concentration during continuous infusion was 16.9 mg/L, while the actual values measured in 6 patients was 17.0 mg/L, showing good agreemen with a bias of less than 1%.

Figure 2 (left panel) Shows the results of simulations using mean parameter values and for three different dosing regimens. The breakpoint MIC for a mean fT>MIC of 50% is 16 mg/L. However, MCS indicate that for this population of ICU patients the variation is significant. A PTA of at least 95% is obtained for MIC values of 8 mg/L or lower. This indicates Pk/Pd susceptibility breakpoint S ≤ 8 mg/L.
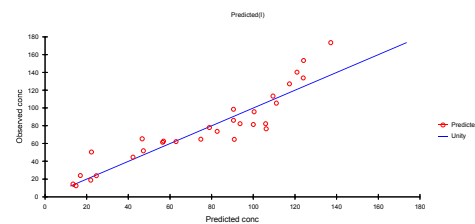

Figure 1. predicted concentrations versus measured concentrations of temocillin during intermittent infusion.The blue line represents the line of identity.
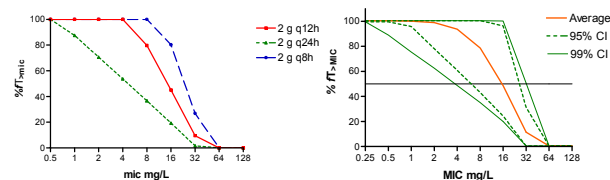

Figure 2. Left panel : mean fT>MIC as a function of MIC for three different dosing regimens. Right panel : mean fT>MIC and 95% and 99% CIas a function of MIC for 2g q12h. The CI represent PTAs of 95 and ((%, respectively.

Discussion:

Temocillin showed a relatively long halflife acompared to other broad-spectrum penicillins such as piperacillin and ticarcillin. This is probably due to the relatively high proteinbinding, in this study 75% resulting in a lower renal clearance. Concentrations of the unbound rtemocillin during continuous infusion were slightly above 16 mg/L and compared well with the prediction based on parameters estimated after interittent infusion. This indicates that there is no rate limiting excretion process within the concentration range studied.

Monte Carlo simulations indicate a susceptibility breakpoint of ≤ 8 mg/L, provided administration of a 2000 mg q12h dosing regimen. This is based on pharmacokinetics of ICU patients rather than volunteers, and there is therefore no leeway. It is often assumed that MCS using data from volunteers yield a conservative breakpoint estimate. On the other hand , results from this and other pharmacokinetic studies indicate a much larger interindividual variation in patients than in voluntreers[3] ;and the conclusions therefore less biased. .

Conclusions:

• The mean half-life of temocillin was 4.03 h in ICU patients

• The mean concentration of unbound temocillin during continuous infusion was 17.0 mg/L

• The Monte Carlo Simulations suggest a clinical susceptible breakpoint of ≤ 8 mg/L based on a dosing regimen of 2000 mg q12h

1. Mouton JW, Vinks AA. Is continuous infusion of beta-lactam antibiotics worthwhile?--efficacy and pharmacokinetic considerations. *J Antimicrob Chemother*. 1996;38(1):5-15.   2. Mouton JW. Impact of pharmacodynamics on breakpoint selection for susceptibility testing. *Infect Dis Clin North Am*. Sep 2003;17(3):579-598.
3. Mouton JW, Punt N, Vinks AA. A retrospective analysis using Monte Carlo simulation to evaluate recommended ceftazidime dosing regimens in healthy volunteers, patients with cystic fibrosis, and patients in the intensive care unit. Clin Ther. 2005 Jun;27(6):762-72