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 infusion¹. 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 breakpoints².

Methods:
Blood samples were taken from ICU patients prior to (t=0) and after (t=1, 2, 3, 6, 12 h) a 30 min infusion of 2 g TMO (n=16) or after 48 h during CoInf with 4g/24h (n=16), 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 WinNonlin including the covariance matrix. Methyl233 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 agreement with a bias of less than 1%.

Discussion:
Temocillin showed a relatively long half-life compared 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 temocillin during continuous infusion were slightly above 16 mg/L and compared well with the prediction based on parameters estimated after intermittent 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 more conservative breakpoint estimate. On the other hand, results from this and other pharmacokinetic studies indicate a much larger interindividual variation in patients than in volunteers³; and the conclusions therefore less biased.

Conclusions:

1. The mean half-life of temocillin was 4.03 h in ICU patients
2. The mean concentration of unbound temocillin during continuous infusion was 17.0 mg/L
3. The Monte Carlo Simulations suggest a clinical susceptible breakpoint of ≤ 8 mg/L based on a dosing regimen of 2000 mg q12h

References:

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