Continuous versus Intermittent Infusion of Temocillin in Intensive Care Patients

V. Basma, R. de Jongh, F. Van Bambeke, M.P. Mingeot-Leclercq, P.M. Tulkens
(Unité de pharmacologie cellulaire et moléculaire, Université catholique de Louvain, Bruxelles; Dienst voor intensieve zorgen, Ziekenhuis Oost-Limburg, Genk; Belgium

Abstract:
Objectives: (i) to define conditions for safe use of TMO by CI; (ii) obtain preliminary pharmacokinetics data of TMO admnistered by CI vs. BID in IC patients.
Methods: (i) mimicking the conditions of clinical storage (daily dose of up to 4 g in 48 ml water; 37°C for up to 24 h (stability studies); (ii) mixing TMO with drugs commonly used in IC (mass ratios as if TMO and companion drug are administered through the same infusion line (compatibility studies) (iii) 5 patients without renal insufficiency but with nosocomial infection (> 4 days hospitalisation) without suspicion of the presence of P. aeruginosa or other temocillin-resistent bacteria randomly assigned to TMO CI (2 g / 50 ml infused over 12 hours twice a day) or BID (2 g / 50ml administered as a 30 min bolus) (iv) determination of TMO serum concentrations by HPLC.
Results: TMO was stable for 24 h up to 37°C (meropenem was unstable above 4°C; AAC 2002,46:2327) and ceftazidime or cefepime above 25°C; AAC 2001,45:2643; JAC 2003,51:651). TMO was compatible with amikacin (borderline), gentamicin, tobramycin, clindamycin, flucloxacillin, erythromycin, moxifloxacin, ceftazidime, cefuroxime and fluconazole, as well as with adrenaline, dopamine, dobutamine, nimodipine, enoxaparine, isosorbide dinitrate, furosemide, uradipil, theophylline, omeprazole, insulin, methylprednisolone, ketamine, morphine, sufentanyl, phenytoin, tramadol, penthotal, paracetamol, valproic acid, N-acetyl-cysteine, and aminoacid solutions. Clarithromycin, ciprofloxacin, meropenem, imipenem, piperacillin/tazobactam, vancomycin, amoxicillin/acid clavulanic acid, propofol, midazolam, piritramide, nicardipine, milrinone, and ranitidine were incompatible. 24h serum levels in the CI group (n=3) were 67.5 +/- 13.9 mg/L (disregarding the alpha phase) with minimum 39.7 (thus largely exceeding the breakpoint [16 mg/L]) vs. peaks at 140.3 and 113.3 (day 1), trough at 16.99 and 19.40 (day 5) and mid-interval (50 % of time between 2 dosings) at 39.83 and 63.44 mg/L for BID patients (n=2; mean serum values)
Conclusion: This work shows that TMO can safely be used by CI as far as stability and compatibility are concerned. The pilot pharmacokinetic study suggests that effective and largely stable serum levels can be obtained with CI.

INTRODUCTION

β-lactams are time-dependent antibiotics and show little gain in activity once their concentration exceeds about 4 fold the MIC, which suggests to promote their administration by continuous infusion (Craig & Ebert, 1992).

In the present study, we have examined the feasibility and safety of this approach for temocillin, a narrow spectrum anti-Gram(-) β-lactam commonly used in combination with an anti-Gram (+) agent in the treatment of nosocomial pneumonia. We followed for temocillin the same approach as for ceftazidime, i.e.
(i) performing *in vitro* studies aimed at assessing the drug stability and compatibility under conditions pertinent of its projected clinical use (Servais & Tulkens, AAC 2001);
(ii) examining which serum levels can be obtained in patients receiving standard daily doses of temocillin (Laterre et al., ICAAC 2003).

METHODS

In vitro studies

Stability studies: Temocillin was prepared in aqueous solutions (4 g in 48 ml) and left at temperatures for up to 37°C. Results were compared with those of other β-lactams obtained previously in our laboratory (Vaene et al., AAC 2002). A limit of 90% intactness was used as criterion (as per the provisions of the European Pharmacopeia)

Compatibility studies: Temocillin and each of the other drugs of interest (see Results) were mixed at a mass ratio similar to what would take place in a common line if the two drugs were administered as foreseen (i.e. 4 g temocillin in 48 ml in 24 h; the companion drug following its own administration scheme [see Results]).

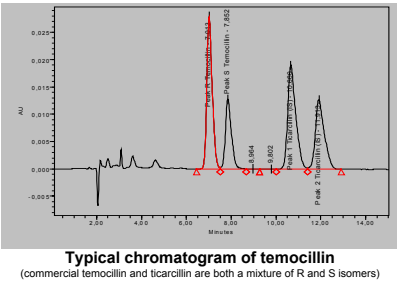
Analyses: All solutions were first examined visually for color changes and appearance of precipitates (using an ad-hoc viewing cabinet). If no change was seen, temocillin was positively identified and quantitatively assayed by HPLC (isocratic elution with Na acetate buffer/acetonitrile [95:5] with ticarcillin as internal standard)

Clinical study

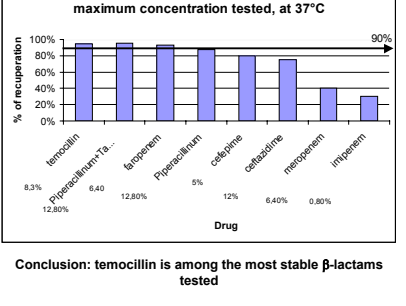
Patients and treatments: 5 patients without renal insufficiency but with nosocomial infection (> 4 days hospitalisation) without suspicion of the presence of *P. aeruginosa* or other temocillin-resistant bacteria were randomly assigned to receive temocillin by continuous infusion (2g/50ml infused over 12 hours twice a day) or BID (2g/50ml administered as a 30 min bolus). Plasma was sampled several times for pharmacokinetic evaluation during the first five days of administration

Analyses: Extraction by filtration through OASIS ® HLB cartridges (eluted with methanol) followed by HPLC as described above. Each chromatogram was visually inspected for absence of interfering product. All assays were performed in triplicate.

IN VITRO STUDIES



Typical chromatogram of temocillin
(commercial temocillin and ticarcillin are both a mixture of R and S isomers)



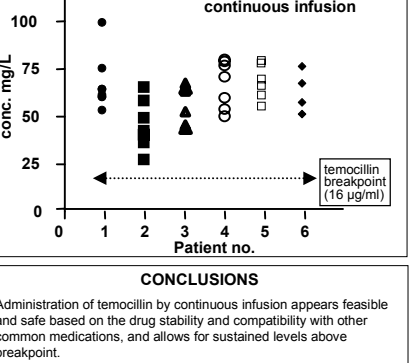
Conclusion: temocillin is among the most stable β-lactams tested

Compatibility studies:

• **compatible drugs:** anti-infectives: gentamicin (amikacin was borderline), tobramycin, clindamycin, flucloxacillin, erythromycin, moxifloxacin, ceftazidime, cefuroxime and fluconazole; other drugs: adrenaline, dopamine, dobutamine, nimodipine, enoxaparine, isosorbide dinitrate, furosemide, uradipil, theophylline, omeprazole, insulin, methylprednisolone, ketamine, morphine, sufentanyl, phenytoin, tramadol, penthotal, paracetamol, valproic acid, N-acetyl-cysteine, and aminoacid solutions.

• **incompatible drugs**: Clarithromycin, ciprofloxacin, meropenem, imipenem, piperacillin/tazobactam, vancomycin, amoxicillin/clavulanic acid, propofol, midazolam, piritramide, nicardipine, milrinone, and ranitidine.

CLINICAL STUDY



CONCLUSIONS

Administration of temocillin by continuous infusion appears feasible and safe based on the drug stability and compatibility with other common medications, and allows for sustained levels above breakpoint.

Address for contact: Paul M. Tulkens - UCL 7370 avenue E. Mounier 73, B-1200 Bruxelles, Belgium
E-mail: tulkens@facm.ucl.ac.be - Web: http://www.facm.ucl.ac.be