Journal of Antimicrobial Chemotherapy (2009) **63**, 243–245
doi:10.1093/jac/dkn511
Advance Access publication 18 December 2008

JAC

Temocillin revived

David M. Livermore[1]* and Paul M. Tulkens[2]

[1]Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK; [2]Unité de Pharmacologie Cellulaire et Moléculaire & Centre de Pharmacie Clinique, Université Catholique de Louvain, Bruxelles, Belgium

Resistance in Gram-negative pathogens is an increasing concern, with carbapenems often appearing as the only acceptable treatment option in serious infections. Reviving older compounds that have fallen into disuse may help to alleviate this burden. Temocillin (6-α-methoxy-ticarcillin) is resistant to most if not all classical and extended-spectrum β-lactamases and to AmpC enzymes. It is also chemically stable, allowing administration by continuous infusion. Pharmacokinetic/pharmacodynamic analysis, aided by Monte-Carlo simulations, suggests a breakpoint of 8 mg/L for the registered maximum dosage of 4 g daily. Temocillin's weaknesses, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas*. In settings where these are unlikely or are covered by other agents, temocillin may be useful, potentially 'sparing' carbapenems and having little apparent potential to select for *Clostridium difficile*.

Keywords: ESBLs, AmpC, α-methoxy penicillins

Accumulating resistance among Gram-negative pathogens has spurred the search for novel targets, but the results are disappointing to date, with no anti-Gram-negative drug possessing a truly novel mode of action submitted for registration in more than 30 years.[1] To meet present challenges, it is therefore important to re-examine older 'forgotten' compounds that may prove useful. Reviving temocillin is one example of this approach; others include renewed interest in polymyxins[2] and intravenous fosfomycin.[3]

Developed and first marketed in the UK by Beecham Pharmaceuticals in the 1980s, temocillin was quickly abandoned because of what were then perceived as major drawbacks, namely a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas aeruginosa*.[4,5] What was not taken into account—although appreciated at the time by clinical microbiologists—was temocillin's remarkable β-lactamase stability.[5] Specifically, temocillin is resilient to all classical and extended-spectrum TEM, SHV and CTX-M enzymes and to AmpC β-lactamase.[6–8] It is labile to the chromosomal metallo-β-lactamase of *Chryseobacterium meningosepticum*,[9] but relatively stable to some (maybe not all) acquired metalloenzymes.[10] Its stability to KPC and OXA carbapenemases remains to be assessed.

Temocillin is the 6-α-methoxy derivative of ticarcillin and so has the same relationship to its parent compound as cefoxitin does to cefalotin, although the modification is arguably more advantageous for temocillin. Molecular modelling and biochemical studies have elucidated the role played by this α-methoxy moiety:[11] specifically, it blocks the entry of a water molecule into the β-lactamase active site cavity, preventing activation of the serine and the chemical events leading to hydrolysis. The price is that temocillin's binding to many penicillin-binding proteins (PBPs) is also impaired, explaining its lack of activity against Gram-positive bacteria. Moreover, although PBP-3 remains temocillin's primary target in *Escherichia coli*—as revealed by low-temperature labelling studies and by the filamentation response of exposed cells—the PBP-3–antibiotic complex formed is unstable, a trait that leads to temocillin's affinity for this target being underestimated in conventional PBP competition experiments.[12]

The MICs of temocillin for Enterobacteriaceae are between 2 and 32 mg/L, with modes of 4–8 mg/L[4,5,13] and with more than 90% of isolates susceptible at 16 mg/L.[7,14] Some authors find MICs for *Serratia* spp. to be higher than those for other Enterobacteriaceae, but values are still mostly ≤16 mg/L and the finding is not universal. Temocillin MICs are not significantly raised by the expression of common β-lactamases, including AmpC and extended-spectrum β-lactamase (ESBL) types.[6–8,15] Moreover, unlike cephalosporins, temocillin does not select derepressed mutants of AmpC-inducible species.[16] MICs for *Bacteroides* spp. are high: the reasons are unknown but probably relate to low PBP avidity as temocillin is stable to the chromosomal β-lactamases of these organisms.[4] MICs for *P. aeruginosa* are high too, typically 128–256 mg/L,[4,5] compared with

*Corresponding author. Tel: +44-20-8327-7223; Fax: +44-20-8327-6264; E-mail: david.livermore@hpa.org.uk

ticarcillin MICs of 16–32 mg/L. Once again the reasons are unclear, but may relate to poor permeation, efficient efflux or reduced PBP binding. Paradoxically, *Burkholderia cepacia* is more susceptible to temocillin than to other β-lactams except meropenem and ceftazidime, with an MIC_{90} of 32 mg/L reported for isolates from cystic fibrosis patients.[17]

Longitudinal studies in Belgium, where temocillin has remained in use since the 1980s, indicate that MIC distributions for Enterobacteriaceae have remained stable, at least over the past 6 years.[7,13,14]

The MICs of an antibiotic must, of course, be viewed together with its pharmacokinetics and safety profile. Temocillin is from a chemical class well known for its excellent tolerability, except among patients with specific allergy, and there is no evidence that it behaves differently from other widely used penicillins in this context. Its pharmacokinetics are also straightforward, with a V of ~0.2 L/kg,[18] similar to most other β-lactams, but with relatively slower clearance (~40–45 mL/min)[19,20] related to strong protein binding (70% to 85%).[21–23] Based on the maximum registered dosage of 2 g twice daily, the peak and trough total concentrations are 150–200 and 15–30 mg/L, respectively,[19,22,23] with free concentrations at ~15% to 30% of these values. Like all β-lactams, temocillin has 'time-dependent' microbiological activity, related to the fraction of the dosage interval during which the free concentration exceeds the MIC ($fT > MIC$). In discontinuous administration, an $fT > MIC$ of 29% to 34% achieves bacteriostasis for penicillins against Gram-negative target organisms.[24] Taking a value of 40%, for the sake of caution, along with median pharmacokinetic values, Monte-Carlo simulations for intensive care patients suggest a clinical breakpoint of 16 mg/L, as originally proposed as epidemiological cut-off,[25] whereas a breakpoint of 8 mg/L allows for 95% confidence intervals of the pharmacodynamic parameters.[23] The latter value was adopted for systemic infections by the BSAC Working Party on Susceptibility Testing, with a 32 mg/L breakpoint for lower urinary tract infection (UTI), to allow for the high concentrations reached in urine.[26]

An improved pharmacokinetic/pharmacodynamic profile is obtained by administering temocillin as a continuous infusion. The compound remains un-degraded for several days in aqueous solution, facilitating this approach and permitting stable free-drug concentrations above 16 mg/L.[23] Based on general experience with penicillins, these levels should achieve stasis against organisms with MICs of 16 mg/L and maximal cidality rates against those with MICs of ≤4 mg/L.[27] Recent investigators have used larger dosages (2 g thrice daily, or 6 g/day by continuous infusion) without adverse effect,[28] implying that there may be scope to increase both the dose and the breakpoint.

Registered indications of temocillin in the UK and in Belgium as noted in the Specification of Product Characteristics are septicaemia, UTIs and lower respiratory tract infections, 'where susceptible Gram-negative bacteria are suspected or confirmed'. Based on temocillin's relatively narrow spectrum, we view it as potentially most appropriate as microbiologically directed therapy, particularly for the UTIs due to confirmed ESBL producers. The spread of *E. coli* with ESBLs, principally CTX-M types, is a growing problem in both Europe and Asia, especially among 'complicated' patients with recent antibiotics and healthcare exposure.[29] Empirical use in urinary infection might be considered if the local epidemiology and the patient's risk factors suggest that ESBL-producing Enterobacteriaceae are likely. In this setting, temocillin might be an alternative to carbapenems, which are the only other β-lactams with comparable β-lactamase stability. It is understood that the manufacturer is undertaking an outcome analysis for temocillin in complicated UTIs due to ESBL producers in the UK, and we welcome this. It is plausible that, as a narrow-spectrum antibiotic, temocillin may be ecologically benign: certainly, old studies suggest little or no propensity to select for resistant pathogens or for overgrowth by *Clostridium difficile*.[30,31]

Published clinical data on temocillin's use in severe sepsis or nosocomial pneumonia remain scanty and date from nearly a quarter of a century ago.[23,28,32–34] Allowing for the complexity of many of the patients who have non-urinary infections with ESBL producers, meaningful comparative trials will be difficult to initiate in these settings. Nevertheless, Belgian experience suggests that temocillin is safe and effective in, for example, ventilator-associated pneumonia so long as the organism appears susceptible *in vitro* or, in empirical use, so long as anti-Gram-positive agents are also given and *Pseudomonas* is considered unlikely.

Temocillin is likely to remain a niche product, yet its prudent use, along the lines suggested here, may help clinicians to cope with difficult situations while sparing other agents.

Funding

No funding was used for the production of this article. The laboratory work and pharmacokinetic/pharmacodynamic investigations of P. M. T. on β-lactams, including temocillin, are supported by the Belgian Programme of Interuniversity Poles of Attraction initiated by the Federal Office for Scientific Technical and Cultural Affairs (research projects IAP5/33 and IAP6/19), the Belgian *Fonds de la Recherche Scientifique Médicale* (grant numbers 3.4549.00 and 3.4542.02) and the *Direction générale de la recherche et des technologies* of the *Région Wallonne* (FIRST-Entreprise Programme).

Transparency declarations

None to declare.

References

1. O'Neill AJ. New antibacterial agents for treating infections caused by multi-drug resistant Gram-negative bacteria. *Expert Opin Investig Drugs* 2008; **17**: 297–302.

2. Landman D, Georgescu C, Martin DA *et al.* Polymyxins revisited. *Clin Microbiol Rev* 2008; **21**: 449–65.

3. Falagas ME, Giannopoulou KP, Kokolakis GN *et al.* Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008; **46**: 1069–77.

4. Slocombe B, Basker MJ, Bentley PH *et al.* BRL 17421, a novel β-lactam antibiotic, highly resistant to β-lactamases, giving high and prolonged serum levels in humans. *Antimicrob Agents Chemother* 1981; **20**: 38–46.

5. Jules K, Neu HC. Antibacterial activity and β-lactamase stability of temocillin. *Antimicrob Agents Chemother* 1982; **22**: 453–60.

6. Rodriguez-Villalobos H, Malaviolle V, Frankard J *et al*. *In vitro* activity of temocillin against extended spectrum β-lactamase-producing Escherichia coli. *J Antimicrob Chemother* 2006; **57**: 771–4.

7. Glupczynski Y, Huang TD, Berhin C *et al*. In vitro activity of temocillin against prevalent extended-spectrum β-lactamases producing *Enterobacteriaceae* from Belgian intensive care units. *Eur J Clin Microbiol Infect Dis* 2007; **26**: 777–83.

8. Livermore DM, Hope R, Fagan EJ *et al*. Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteria-ceae from south-east England. *J Antimicrob Chemother* 2006; **57**: 1012–4.

9. Vessillier S, Docquier JD, Rival S *et al*. Overproduction and biochemical characterization of the *Chryseobacterium meningosepticum* BlaB metallo-β-lactamase. *Antimicrob Agents Chemother* 2002; **46**: 1921–7.

10. Docquier JD, Riccio ML, Mugnaioli C *et al*. IMP-12, a new plasmid-encoded metallo-β-lactamase from a *Pseudomonas putida* clinical isolate. *Antimicrob Agents Chemother* 2003; **47**: 1522–8.

11. Matagne A, Lamotte-Brasseur J, Dive G *et al*. Interactions between active-site-serine β-lactamases and compounds bearing a methoxy side chain on the α-face of the β-lactam ring: kinetic and molecular modelling studies. *Biochem J* 1993; **293**: 607–11.

12. Labia R, Baron P, Masson JM *et al*. Affinity of temocillin for *Escherichia coli* K-12 penicillin-binding proteins. *Antimicrob Agents Chemother* 1984; **26**: 335–8.

13. Glupczynski Y, McGlillavry G, Yourassowsky E. Temocillin: comparative *in vitro* activity against Gram-negative clinical isolates. *Acta Clin Belg* 1988; **43**: 194–8.

14. Vanhoof R, Berin C, Carpentier M *et al*. Comparative *in vitro* activity of temocillin and other antimicrobial agents against Enterobacteriaceae isolated from patients admitted to five Belgian hospitals. *Acta Clin Belg* 2001; **56**: 354–9.

15. Yang Y, Livermore DM. Activity of temocillin and other penicillins against β-lactamase-inducible and -stably derepressed enterobacteria. *J Antimicrob Chemother* 1988; **22**: 299–306.

16. Stapleton P, Shannon K, Phillips I. The ability of β-lactam antibiotics to select mutants with derepressed β-lactamase synthesis from *Citrobacter freundii*. *J Antimicrob Chemother* 1995; **36**: 483–96.

17. Bonacorsi S, Fitoussi F, Lhopital S *et al*. Comparative *in vitro* activities of meropenem, imipenem, temocillin, piperacillin, and ceftazidime in combination with tobramycin, rifampin, or ciprofloxacin against *Burkholderia cepacia* isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 1999; **43**: 213–7.

18. Hampel B, Feike M, Koeppe P *et al*. Pharmacokinetics of temocillin in volunteers. *Drugs* 1985; **29** Suppl 5: 99–102.

19. Hoffler D, Koeppe P. Temocillin pharmacokinetics in normal and impaired renal function. *Drugs* 1985; **29** Suppl 5: 135–9.

20. Boelaert J, Daneels R, Schurgers M *et al*. The pharmacokinetics of temocillin in patients with normal and impaired renal function. *J Antimicrob Chemother* 1983; **11**: 349–56.

21. Overbosch D, van Gulpen C, Mattie H. Renal clearance of temocillin in volunteers. *Drugs* 1985; **29** Suppl 5: 128–34.

22. Lockley MR, Brown RM, Wise R. Pharmacokinetics and tissue penetration of temocillin. *Drugs* 1985; **29** Suppl 5: 106–8.

23. De Jongh R, Hens R, Basma V *et al*. Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection. *J Antimicrob Chemother* 2008; **61**: 382–8.

24. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am* 2003; **17**: 479–501.

25. Fuchs PC, Barry AL, Thornsberry C *et al*. Interpretive criteria for temocillin disk diffusion susceptibility testing. *Eur J Clin Microbiol* 1985; **4**: 30–3.

26. Andrews JM. BSAC standardized disc susceptibility testing method (version 7). *J Antimicrob Chemother* 2008; **62**: 256–78.

27. Mouton JW, Punt N, Vinks AA. Concentration–effect relationship of ceftazidime explains why the time above the MIC is 40 percent for a static effect *in vivo*. *Antimicrob Agents Chemother* 2007; **51**: 3449–51.

28. Laterre PF, Dugernier T, Wittebole X *et al*. Temocillin 6g daily in critically ill patients: continuous infusion vs. conventional administration. In: *Abstracts of the Eighteenth European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, 2008*. Abstract O150. http://www.blackwellpublishing.com/eccmid18/abstract.asp?id=68167 (31 October 2008, date last accessed).

29. Livermore DM, Canton R, Gniadkowski M *et al*. CTX-M: changing the face of ESBLs in Europe. *J Antimicrob Chemother* 2007; **59**: 165–74.

30. Boon RJ, Beale AS. Studies with temocillin in a hamster model of antibiotic-associated colitis. *Antimicrob Agents Chemother* 1985; **27**: 980–1.

31. Mittermayer HW. Influence of temocillin on human bowel flora. *Drugs* 1985; **29** Suppl 5: 43–8.

32. Legge JS, Reid TM, Palmer JB. Clinical efficacy, tolerance and pharmacokinetics of temocillin in patients with respiratory tract infections. *Drugs* 1985; **29** Suppl 5: 118–21.

33. Schulze B, Heilmann HD. Treatment of severe infections with temocillin. Clinical and bacteriological evaluation. *Drugs* 1985; **29** Suppl 5: 207–9.

34. Offenstadt G, Lesage D, Hericord P *et al*. Temocillin treatment of serious infections due to Gram-negative bacilli in an intensive care unit. *Drugs* 1985; **29** Suppl 5: 213–20.