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Temocillin dosage adjustment in a preterm infant with severe renal disease: a case report

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Background: Temocillin is a carboxypenicillin antibiotic indicated in complicated urinary tract infections due to susceptible ESBL-producing Enterobacteriaceae. While temocillin therapeutic schemes for adult patients with normal or impaired renal function are evidence based, little is known in paediatric populations.

Objectives: We report herein the management of temocillin treatment in a preterm infant with end-stage renal disease.

Patients and methods: The patient was a 7-month-old preterm infant born at 35 weeks gestation and treated by temocillin for 10 days for a bacteraemic urinary tract infection due to a susceptible ESBL-producing *Enterobacter cloacae* complex strain. Temocillin was administered by continuous infusion using a loading dose of 25 mg followed by a maintenance dose of 70 mg daily. Determination of MIC and temocillin plasma and urinary concentration was performed.

Results: Clinical improvement was observed 24 h after the initiation of temocillin treatment. Temocillin concentrations ranged between 21.6 and 35.5 mg/L in urine between the first and the sixth day of treatment and between 47.0 and 61.8 mg/L in plasma after 6 and 10 days of treatment, respectively. Temocillin concentrations were found to be above the determined MIC of 6 mg/L. From the measured concentrations, we can postulate that 100%$fT_{>MIC}$ was achieved in urine and at least equal to 40% in plasma.

Conclusions: Temocillin dosing adjustment performed in the present reported case allowed safe and effective treatment. The strategy described herein could be used as a basis for further clinical studies relative to temocillin use in a paediatric population with renal impairment.

Introduction

Temocillin is an old β-lactam antibiotic member of the carboxypenicillins developed in the UK by Beecham Pharmaceuticals in the 1980s.[1] Temocillin is a 6-α-methoxy derivative of ticarcillin, effective on the Ambler classes A and C β-lactamases thanks to the additional α-methoxy group, but imposes no selection pressure on Gram-positive organisms, anaerobes and *Pseudomonas aeruginosa*.[2] In the face of community diffusion of ESBL-producing *Escherichia coli* and the emergence of carbapenemase-producing Enterobacteriaceae, the remarkable β-lactamase stability of temocillin has led to renewed interest over the last decade in its use as a potential carbapenem-sparing agent.[1,2] Nevertheless, the temocillin spectrum seems to be limited to Enterobacteriaceae[3] with MICs stable over the past few years and ranging from 2 to 32 mg/L, with an MIC of 16 mg/L originally proposed as the epidemiological cut-off.[1] Initially, temocillin susceptibility breakpoints proposed by BSAC for Enterobacteriaceae were MIC ≤8 mg/L for systemic infections and ≤32 mg/L for urinary tract infections.[4] Recently, EUCAST set clinical breakpoints of ≤0.001 mg/L for susceptible and >16 mg/L for resistant for *E. coli*, *Klebsiella* spp. (except *Klebsiella aerogenes*) and *Proteus mirabilis*.[5] Temocillin was initially indicated as an orphan drug for the treatment of *Burkholderia cepacia* lung infection in patients with cystic fibrosis. Currently, temocillin is available in France, Belgium, the UK, Luxembourg and Iran for the treatment of urinary and lower respiratory tract infections and bacteraemia caused by susceptible organisms.[2] In France, temocillin obtained marketing authorization for the treatment of urinary tract infections in 2015 at the recommended dosages of 4–6 g per day and 25–50 mg/kg/24 h for adults or

children with normal renal function, respectively. While some studies and data are available to support temocillin dosage in adults,[6–9] only a few case reports can be found for children.[10,11] We report herein a case of bacteraemic ESBL-producing *Enterobacter cloacae* urinary tract infection successfully treated with temocillin in a preterm infant with severe renal failure.

Case report

A 7-month-old preterm infant (male, 62 cm, 6.87 kg) born prematurely at a gestation of 35 weeks and 3 days was admitted to the department of paediatrics of our university hospital 23 days after his birth for a bilateral ureterohydronephrosis due to a posterior urethral valve diagnosed at 24 weeks gestation. Suffering from end-stage renal disease, he underwent circumcision and vesicostomy, despite urethral valve ablation and several urinary catheterizations over the following 2 month period. Renal function was stabilized and serum creatinine levels and glomerular filtration rate (GFR) estimated with the revised Schwartz formula[12] ranged from 141 to 176 μmol/L (normal range: 11–34 μmol/L) and 11 to 17 mL/min/1.73 m^2 (normal range: 55–85 mL/min/1.73 m^2), respectively. Since GFR was above 10 mL/min/1.73 m^2, dialysis was not performed. During the latter 4 months after surgery, many infectious complications occurred including three pyelonephritis episodes caused by MSSA, ESBL-producing *Klebsiella oxytoca* and co-trimoxazole-resistant *E. coli*, respectively. During the last episode of pyelonephritis, co-trimoxazole prophylaxis was stopped after 1 month of treatment and the patient was treated for 2 days by intramuscular ceftriaxone (300 mg daily) and thereafter by oral cefixime (4 mg/kg/24 h) since the *E. coli* isolate was susceptible to third-generation cephalosporins. A transient clinical improvement was observed and prophylactic cefixime therapy was initiated. A few days afterwards, more serious infectious symptoms including diarrhoea, fever, dehydration and loss of weight appeared and urine culture revealed the presence of an ESBL-producing *E. cloacae* complex (ECC) strain. Finally, the cefixime treatment was switched to temocillin owing to a new episode of high fever (39°C/102.2°F) and the persistence of ESBL-producing ECC in urine culture and haemoculture. Indeed, the strain was susceptible to temocillin and the MIC value determined by Etest (bioMérieux, Marcy l'Étoile, France) was 6 mg/L. Temocillin treatment was initiated with a loading dose of 25 mg over 30 min followed by continuous infusion of 70 mg (10 mg/kg) per day for 10 days. Clinical improvement was noticed after 24 h of treatment and the fever resolved. During the remaining 8 days, symptoms regressed then completely disappeared. Finally, haemoculture and urine culture performed after 3 and 5 days of treatment, respectively, were negative. Since no specific dosage of temocillin was recommended in preterm infants and especially with severe renal failure, temocillin concentrations were ascertained in urine and plasma samples. Determination of temocillin concentration was performed by UPLC coupled with a photodiode array detector (Thermo Fisher Scientific, Illkirch-Graffenstaden, France) with a limit of quantification of 1.0 mg/L. Free temocillin concentrations were estimated from the percentage of protein binding described for temocillin.[2] The evolution of serum creatinine concentration and urine and plasma temocillin concentrations is shown in Figure 1. Temocillin total concentration in plasma ranged from 47.0 to 61.8 mg/L, corresponding to free concentration of 7.0 and 9.2 mg/L, after 6 and 10 days of treatment, respectively. In urine, temocillin concentration increased from 21.6 to 35.5 mg/L between the first and the sixth day of treatment. Temocillin concentrations measured in plasma and urine were above the determined MIC of 6 mg/L. Finally, temocillin was successfully stopped at the end of the whole 10 day period of treatment and no adverse effects occurred. The other medications included sodium polystyrene sulfonate for

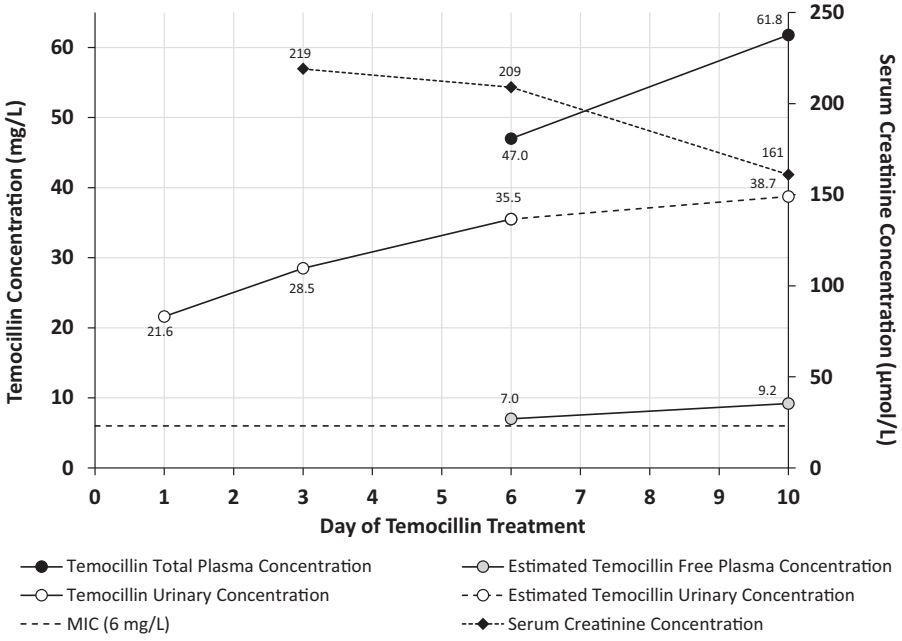

Figure 1. Evolution of serum creatinine concentration and temocillin concentration in plasma and urine during the whole 10 day period of temocillin treatment.

hyperkalaemia, esomeprazole, sodium alginate, sodium bicarbonate and calcium carbonate for gastro-oesophageal reflux disease, modular feed (dextrin/maltose, complete amino acid mix), vitamin D, folic acid and L-carnitine supplementations, sodium feredetate and erythropoietin. One month later, no recurrence was observed and the patient was authorized for the first time to leave our hospital.

Discussion

The recommended dosage of temocillin is 4–6 g per day and 25–50 mg/kg/24 h for adults or children with normal renal function, respectively. Even though the uncertainty over effectiveness relative to these doses is mentioned in the summary of product characteristics of temocillin, De Jongh *et al.*[7] showed by Monte Carlo simulation that a dose of 2 g of temocillin given every 12 h to adult intensive care patients allowed a $\%fT_{>MIC}$ of above 40% for MICs of 8 and 16 mg/L for the 95% percentile and the median value of the population, respectively. Similar results were observed in the study of Laterre *et al.*,[8] performed in critically ill adult patients using a daily dose of 6 g of temocillin. A daily dose of 6 g by intermittent administration (2 g every 8 h) or by continuous infusion (bolus of 2 g followed by perfusion of 6 g/24 h) allowed free temocillin serum concentrations above 16 mg/L. In adult patients with impaired renal function, Boelaert *et al.*[13] showed a significant positive linear relationship ($r = 0.945$; $P < 0.001$) between temocillin clearance and creatinine clearance and a 3.7-fold increase of the AUC value in patients with severe renal dysfunction. Based on these findings, temocillin dosing adjustment was proposed to be reduced by 0.6-, 0.3- and 0.1-fold for a creatinine clearance of 60, 30 and 10 mL/min/1.73 m^2, respectively. Similar results were found in the pharmacokinetics study of Leroy *et al.*[14] who exhibited a linear relationship between temocillin elimination rate constant and GFR ($r = 0.771$; $P < 0.001$) and between temocillin elimination half-life and serum creatinine ($r = 0.621$; $P < 0.01$). Half-lives increased from 5 to 30 h in patients with severe renal impairment. For dosage adjustment, Leroy *et al.*[14] proposed to maintain the same dose as in normal patients but to increase the dosing interval by a 1- to 2-fold, 2-fold and 3- to 4-fold factor for a GFR of >30 ml/min/1.73 m^2, 10–30 mL/min/1.73 m^2 and <10 mL/min/1.73 m^2, respectively. Wright *et al.*[15] reported a similar suggestion. In terms of dosing interval, Boelaert *et al.*[13] proposed an increase of this parameter by a 1.7-, 3.3- and 10-fold factor for a creatinine clearance of 60, 30 and 10 mL/min/1.73 m^2, respectively. If temocillin dosage in adult patients and its adjustment in renal-impaired patients can be supported by studies, the same challenge in our preterm infant was hazardous since data in children were very limited.[10,11] Interestingly, Verboven *et al.*[11] reported the clinical efficacy and safety of temocillin IV (25 mg/kg twice a day) in 22 children aged between 3 months and 13 years (mean 5.8 years) treated for acute pyelonephritis. As we observed, clinical improvement was noticed after 24–36 h in children infected by temocillin-susceptible pathogens. Based on the data available for an adult population, the French guidelines on β-lactam therapy optimization[16] and the creatinine clearance of our preterm infant (14 mL/min/m^2), we decided to administer temocillin by continuous infusion after a loading dose of 3.5 mg/kg followed by a maintenance dose of 10 mg/kg daily. The maintenance dose corresponded to a dose 5-fold lower than the usual paediatric recommended dose of 50 mg/kg daily described in the temocillin summary of product characteristics for infections due to ESBL-producing Enterobacteriaceae. The loading dose was empirical and was equal to one-third of the maintenance dose. Furthermore, as suggested by Wright *et al.*,[15] we decided to monitor plasma and urinary concentrations of temocillin even if we did not manage to check temocillin concentration every day. In urine, the temocillin concentration increased from 21.6 to 35.5 mg/L between the first and the sixth day of treatment. Since the three measured urinary concentrations fitted a logarithmic model [$c_u = 7.6234\ln(t) + 21.1885$; $r^2 = 0.9821$, where c_u is temocillin urine concentration and t is time], it was possible to estimate the concentration of 38.7 mg/L in urine at the end of the treatment. The rate of temocillin accumulation in urine found in our patient was in line with that found by Boelaert *et al.*[13] in adult patients with severe renal insufficiency [$c_u = 7.2941\ln(t) + 16.9025$; $r^2 = 0.9967$], contrary to patients with normal renal function [$c_u = 14.6557\ln(t) + 55.5111$; $r^2 = 0.9800$]. Finally, we can postulate that $100\%fT_{>MIC}$ was achieved in urine since temocillin elimination in urine is predominant (52% to 92%),[9] in the unchanged form, for 80% of a dose and delayed in patients with renal impairment.[13] This assertion may remain valid even if minor extrarenal routes of elimination (biliary excretion and degradation to a penicillanic acid derivative),[14] which become more important in the case of renal dysfunction, are considered.[13]

In plasma, temocillin concentration was 47.0 and 61.8 mg/L after 6 and 10 days of treatment, respectively. Considering that the percentage of protein binding of temocillin is reported to be around 80%–85%,[2] the free concentration of temocillin was estimated to be at 7.0 and 9.2 mg/L after 6 and 10 days of treatment, respectively. Albumin and protein levels were 35.6 g/L (normal range: 35.0–52.0 g/L) and 70 g/L (normal range: 66–83 g/L), respectively. Since the determined MIC was 6 mg/L, we can suggest that free plasma concentrations of temocillin were at least above MIC during the last 4 days of the 10 day treatment, corresponding to a $\%fT_{>MIC}$ minimally equal to 40% over the whole period of treatment. If we postulate that the half-life of temocillin is equal to 30 h, as described in adult patients with severe renal impairment, the plasma concentration observed at Day 6 could be considered the steady-state concentration. Unfortunately, temocillin plasma concentration was not determined during the previous days. Nevertheless, we can estimate that temocillin free concentration was above the MIC value since temocillin was administered by continuous infusion after a loading dose.[16] If protein binding of temocillin is described to be dose-dependent, ranging from 63% to 85% after an IV dose of 2 g and 500 mg, respectively,[2] its distribution was reported to be unaffected by renal dysfunction with a half-life of distribution around 20 min.[13] Finally, the absence of measured concentration within the first hours of the treatment also impeded evaluation of the effect of the loading dose.

Conclusions

The present report showed the safety and efficacy of temocillin treatment by continuous infusion using a loading dose of 3.5 mg/kg followed by a 10 mg/kg daily maintenance dose in a preterm infant with end-stage renal disease suffering from bacteraemic urinary tract infection due to a susceptible ESBL-producing ECC. Determination of MIC and therapeutic drug monitoring in

plasma and urine were two very useful tools in the management of this infection. Since major studies on temocillin pharmacokinetics have only been conducted in adults, optimal dosing regimens of temocillin in children and infants are still not well defined and further clinical studies based on the results of the present work should be conducted.

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Transparency declarations

None to declare.

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