

all these reasons, the presence of PMQR in reptiles should be seen as a public health concern.

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Transparency declarations

None to declare.

Supplementary data

Table S1 and Figure S1 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

References

- 1 Strahilevitz J, Jacoby GA, Hooper DC *et al.* Plasmid-mediated quinolone resistance: a multifaceted threat. *Clin Microbiol Rev* 2009; **22**: 664–9.
- 2 Veldman K, Cavaco LM, Mevius D *et al.* International collaborative study on the prevalence of plasmid mediated quinolone resistance (PMQR) in *Salmonella* and *E. coli* isolated from humans and animals in Europe. In: *Abstracts of the Second ASM Conference on Antimicrobial Resistance in Zoonotic Bacteria and Foodborne Pathogens in Animals, Humans and the Environment, Toronto, 2010*. Abstract 87A, p. 13. American Society for Microbiology, Washington, DC, USA.
- 3 García-Fernández A, Fortini D, Veldman K *et al.* Characterization of plasmids harbouring *qnrS1*, *qnrB2* and *qnrB19* genes in *Salmonella*. *J Antimicrob Chemother* 2009; **63**: 274–81.
- 4 Hammerl JA, Beutlich J, Hertwig S *et al.* pSGI15, a small ColE-like *qnrB19* plasmid of a *Salmonella enterica* serovar Typhimurium strain carrying *Salmonella* genomic island 1 (SGI1). *J Antimicrob Chemother* 2010; **65**: 173–5.
- 5 Carattoli A. Resistance plasmid families in Enterobacteriaceae. *Antimicrob Agents Chemother* 2009; **53**: 2227–38.
- 6 Jones C, Stanley J. *Salmonella* plasmids of the pre-antibiotic era. *J Gen Microbiol* 1992; **138**: 189–97.
- 7 Ahmed AM, Motoi Y, Sato M *et al.* Zoo animals as reservoirs of Gram-negative bacteria harboring integrons and antimicrobial resistance genes. *Appl Environ Microbiol* 2007; **73**: 6686–90.
- 8 Jones TF, Ingram LA, Cieslak PR *et al.* Salmonellosis outcomes differ substantially by serotype. *J Infect Dis* 2008; **198**: 109–14.

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Long-term stability of temocillin in elastomeric pumps for outpatient antibiotic therapy in cystic fibrosis patients

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Sir,
Outpatient antibiotic therapy (OPAT) is often proposed to cystic fibrosis (CF) patients in order to reduce the risk of cross-infection and the duration of hospital stay.¹ However, the long-term stability of the drug in the home-supplied device needs to be assessed under conditions mimicking their projected use before any large-scale implementation of OPAT. This is particularly critical for β -lactam antibiotics, as these are notoriously unstable in aqueous solutions; however, there are quite large variations among them.² We previously reported that temocillin, a 6- α -methoxy-carboxypenicillin with exceptional stability in the presence of most β -lactamases, including extended-spectrum β -lactamases,³ is very stable even when kept at 37°C for several hours in concentrated solutions, as required for use in continuous infusion.⁴ While being useless for infections caused by *Pseudomonas aeruginosa* or *Acinetobacter* spp., temocillin shows good *in vitro* activity against *Burkholderia cepacia* complex (Bcc),⁵ a difficult-to-treat opportunistic organism that often affects vulnerable individuals such as CF patients.⁶ Since most Bcc isolates are resistant to many, if not all, other antibacterial agents commonly used in CF patients, temocillin could be potentially useful, and even life-saving, in severe pulmonary exacerbations.

We have assessed the stability of temocillin in two frequently used elastomeric devices, namely: (i) the Easypump® 100-0.5 (I-Flow Corp., Lake Forest, CA, USA; also called Home-pump Eclipse® in some other countries); and (ii) the Inter-mate® SV200 (Baxter Healthcare Corp., Deerfield, IL, USA), taking care to mimic the actual projected use of these devices for OPAT in CF patients. Thus, 30 pumps from each brand were loaded at room temperature with concentrated temocillin

Table 1. Temocillin stability in elastomeric devices

Storage conditions	Pump	Initial temocillin concentration (g/L)	Temocillin remaining (% of initial concentration)				
			0 week	1 week	2 weeks	3 weeks	4 weeks
4°C	Easypump®	10	100±1.6	98.7±1.1	98.5±0.8	96.2±0.9	95.5±0.6
		20	100±1.0	99.4±0.7	98.3±0.3	96.2±0.6	95.5±0.3
	Intermate®	10	100±1.0	99.6±0.4	97.1±0.7	94.5±0.8	94.8±0.5
		20	100±3.1	97.7±0.3	95.0±0.2	93.1±0.1	94.1±0.4
4°C+24 h at room temperature	Easypump®	10	96.4±1.7 ^C	98.1±0.8	97.1±1.2	94.9±0.2	91.1±0.7
		20 ^A	98.5±1.2 ^{C,D}	98.5±0.6 ^D	96.3±0.4	94.8±0.3 ^D	91.0±0.7
	Intermate®	10 ^B	97.1±1.8	97.8±0.4	98.6±0.5	95.1±0.9	91.5±1.6*
		20 ^{A,B}	96.2±0.5 ^D	95.6±1.7 ^D	96.3±0.3	92.6±1.0 ^D	92.0±1.1

All values are means ± SD ($n=3$); only relevant pairwise comparisons (between brand at the same concentrations and storage conditions, among a brand between concentrations, and between storage conditions) were made by two-way ANOVA taking all values in a row. The capital letters A or B indicate rows between which the difference was significant ($P < 0.05$). The Bonferroni post-test was then used to analyse the corresponding pairs in each column, and pairs with significant differences ($P < 0.05$) are marked by the capital letters C or D.

*One replicate below the 90% threshold.

solutions (10 or 20 g/L, prepared by dissolving the standard powder doses of 1 or 2 g in 100 mL of water for injection) at room temperature (preparation time ~10 min), and then cooled and maintained at 4°C in a standard home refrigerator for up to 4 weeks. Every week, three new pumps of each concentration were sampled for testing of stability under storage, and then brought to and maintained at room temperature for an additional 24 h (as would be the case if used to treat a patient), and resampled. Temocillin was assayed by a previously validated HPLC method.⁴ Data were analysed by two-way ANOVA (time, concentration and interaction parameters were all statistically significant at $P < 0.001$) and linear regression. Each relevant data pair was analysed independently by two-way ANOVA followed by Bonferroni post-tests. A limit of stability of 90% was taken, as in our previous studies.^{2,4}

The results are presented in Table 1. At 4°C, temocillin proved >90% stable for ≥4 weeks. No significant differences were observed between the pumps or the two concentrations tested. Likewise, temocillin remained on average >90% stable for ≥24 h at room temperature after being removed from the refrigerator. Only a minimally faster degradation was seen for the 20 g/L compared with the 10 g/L concentration when using the Intermate® pump, but these differences did not cause the 90% threshold to be reached (except for one replicate after 4 weeks at 4°C and 24 h at room temperature, but for the 10 g/L concentration only).

In conclusion, temocillin was shown to remain stable in elastomeric devices commonly used for OPAT when stored (up to 4 weeks) and handled as for home-based therapy. By application of a principle of precaution, we would, however, recommend to users: (i) not to store the pumps for >3 weeks at 4°C; (ii) to install a temperature-monitoring device in the refrigerator where the pumps are stored; and (iii) to strictly limit the storage to 24 h once out of the refrigerator. OPAT with temocillin performed under these conditions may be both helpful and safe for CF patients when *Bcc* infection is suspected or proven.

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References

- Gilchrist FJ, Lenney W. A review of the home intravenous antibiotic service available to children with cystic fibrosis. *Arch Dis Child* 2009; **94**: 647.
- Viaene E, Chanteux H, Servais H *et al.* Comparative stability studies of antipseudomonal β-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). *Antimicrob Agents Chemother* 2002; **46**: 2327–32.
- Livermore DM, Tulkens PM. Temocillin revived. *J Antimicrob Chemother* 2009; **63**: 243–5.
- 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.
- 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.
- Mahenthalingam E, Baldwin A, Dowson CG. *Burkholderia cepacia* complex bacteria: opportunistic pathogens with important natural biology. *J Appl Microbiol* 2008; **104**: 1539–51.