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Letters to the Editor

Activity of Temocillin against KPC-Producing *Klebsiella pneumoniae* and *Escherichia coli*▽

Temocillin, a 6-α-methoxy derivative of ticarcillin, is currently approved for treatment of infections due to members of the *Enterobacteriaceae* in Belgium and the United Kingdom. It is stable against hydrolysis by most β-lactamases, including extended-spectrum β-lactamases (ESBLs) and AmpC-type β-lactamases, with studies reporting MICs at which 90% of bacteria are inhibited (MIC_{90}s) between 16 and 32 μg/ml (3, 4, 8). Temocillin is thus drawing attention as a potential alternative to carbapenems in treatment of infections caused by the *Enterobactericeae* producing these broad-spectrum β-lactamases.

Carbapenem-resistant *Klebsiella pneumoniae* producing KPC-type β-lactamase has emerged in recent years and caused hospital outbreaks of serious infections in the United States and other parts of the world (7). Furthermore, KPC-type β-lactamase is increasingly identified in other species of the *Enterobacteriaceae* as well, including *Escherichia coli*. One concerning recent phenomenon is the occurrence of urinary tract infections due to KPC-producing organisms at nursing homes (10). Currently, the limited treatment options for infections due to KPC-producing organisms include colistin and tigecycline. Concern over nephrotoxicity due to colistin limits its use outside closely monitored settings, whereas tigecycline does not achieve a therapeutic concentration in urine (2). Furthermore, emergence of resistance to these agents has recently been recorded for the *Enterobacteriaceae* (5, 6).

The present study was conducted to evaluate the in vitro activities of temocillin against clinical isolates of *K. pneumoniae* and *E. coli* producing KPC-type β-lactamase. A total of 33 KPC-producing clinical isolates (30 *K. pneumoniae* isolates and 3 *E. coli* isolates) were used. KPC production was confirmed by an ertapenem resistance phenotype, a positive modified Hodge test, and positive PCR for the KPC structural gene. The isolates were collected from hospitals in three states in the United States. The MIC of temocillin was determined by the standard agar dilution method (1). Temocillin was provided by Eumedica (Brussels, Belgium). In addition, MICs of temocillin against an *E. coli* isogenic clone producing KPC-3 were tested to determine the direct effect of KPC production on the temocillin MIC. *E. coli* ATCC 25922 was used as the control strain.

Table 1 summarizes the results. For *K. pneumoniae*, the MICs ranged between 16 μg/ml and 64 μg/ml (MIC at which 50% of bacteria were inhibited = 32 μg/ml; MIC_{90} = 32 μg/ml). The *E. coli* clinical isolates had MICs between 8 and 16 μg/ml. *E. coli* DH10B both with and without the cloning vector pBCSK− (Stratagene, La Jolla, CA) encoding bla_{KPC-3} had an MIC of 8 μg/ml. An inoculum effect was not observed at 10^5 CFU, whereas a mild inoculum effect averaging within a twofold MIC difference was seen with *K. pneumoniae* when 10^6 CFU was inoculated (Table 1). This result was in line with those of a previous study documenting a modest inoculum effect of temocillin for non-KPC-producing isolates (9). The frequencies of mutants of representative clinical isolates that grew at their MICs and at 2× MICs were calculated to be approximately 1×10^{-10} and 0 for *K. pneumoniae* and 3×10^{-10} and 1×10^{-10} for *E. coli*, respectively.

Currently, the British Society for Antimicrobial Chemotherapy (BSAC) is the only organization that defines temocillin MIC breakpoints for the *Enterobacteriaceae*. The BSAC defines temocillin susceptibilities at ≤8 and ≤32 μg/ml in systemic and urinary tract infections, respectively (http://www.bsac.org.uk/). One gram of temocillin is known to achieve a peak serum concentration of approximately 160 μg/ml, with serum binding of 85% and a half-life of 4 to 5 h (9). The urinary concentration after a 500-mg dose is approximately 500 μg/ml (9). These pharmacokinetic properties of temocillin make it a potential alternative treatment option for mild to moderate urinary tract infections caused by KPC-producing members of the *Enterobacteriaceae*.

TABLE 1. Susceptibilities of KPC-producing *K. pneumoniae* and *E. coli* isolates to temocillin

Inoculum (CFU)	Species (n[a])	No. of isolates inhibited at temocillin MIC (μg/ml) of:								
		1	2	4	8[b]	16	32[c]	64	128	256
1×10^4	*K. pneumoniae* (30)					12	15	3		
	E. coli (3)				1	2				
1×10^5	*K. pneumoniae* (30)					12	15	3		
	E. coli (3)				1	2				
1×10^6	*K. pneumoniae* (30)				1	3	15	10	1	
	E. coli (3)				1	1	1			

[a] n, no. of isolates.
[b] BSAC breakpoint for systemic infections.
[c] BSAC breakpoint for urinary tract infections.

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