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Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

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Ertapenem plus doripenem or meropenem were given in three patients suffering from pandrug-resistant, KPC-2-positive *Klebsiella pneumoniae* bacteremia (2 patients) and urinary tract infection (1 patient), respectively. All responded successfully, without relapse at follow-up. The results obtained should probably be attributed to ertapenem's increased affinity for the carbapenemases hindering doripenem/meropenem degradation in the environment of the microorganism.

The worldwide spread of enterobacteriaceae producing carbapenemases, particularly carbapenemase-producing *Klebsiella pneumoniae* (CPKP) isolates, is of great concern (1, 2). In Greece, CPKP is becoming endemic in intensive care units (ICUs), causing a crude mortality in bacteremic patients of 34.5%, mainly attributed to the limited choice of effective antimicrobials (3). Polymyxins, tigecycline, and fosfomycin are the only compounds available against extensively drug-resistant (XDR) strains of CPKP, i.e., strains defined as nonsusceptible to at least one agent in all but two or fewer antimicrobial categories (4, 5, 6, 7). Unfortunately, because of its expanding use, the emergence of resistance to colistin has already been reported (8), whereas clinical experience with fosfomycin is limited (7). In a compassionate attempt to solve the therapeutic problem, the Bulik and Nicolau approach, based on the simultaneous administration of two carbapenems, was successfully attempted in three Greek patients (9). To our knowledge, there are no previously reported cases in humans in which a double-carbapenem regimen has been administered.

Case 1. A 54-year-old man, after an accidental fall that caused spinal cord injury, was admitted to an orthopedic hospital in Athens. He was subjected to posterior spinal fusion plus lumbar laminectomy. The cauda equina injury caused urine retention, and a permanent indwelling bladder catheter was necessary. During his hospitalization, he spiked high fevers (≥39°C), and a pandrug-resistant (PDR) CPKP strain, i.e., a strain defined as nonsusceptible to all agents in all antimicrobial categories, was isolated from both blood and urine cultures at $>10^5$ CFU/ml (5). The patient was transferred to Hygeia Hospital, where blood cultures from a central venous catheter (CVC), blood, and urine were positive for the same KPC-2-producing *Klebsiella* strain shown by PCR and in pulsed-field gel electrophoresis (PFGE). A combination of colistin (3 MU every 8 h), doripenem (2 g every 8 h), gentamicin (340 mg once daily), and fosfomycin (6 g every 6 h) was given without any clinical or bacteriological response. Since the time to positivity was >2 h for comparing the CVC blood culture to the peripheral, the CVC was removed, and the patient remained afebrile after 24 h. Cultures of the tip of the CVC revealed the same *K. pneumoniae* strain. The patient was transferred to a rehabilitation center with subsequent negative blood cultures but constantly positive urine cultures with the same CPKP strain. Six weeks after his discharge, he was readmitted to Hygeia Hospital because of high fever (>39°C) and was found to be septic, with normal lung X-rays and positive blood and urine cultures in which a PDR-CPKP strain, identical with the previous ones as proved by PFGE, was isolated, the susceptibilities of which are shown in Table 1. The diagnosis of acute bacteremic pyelonephritis complicating preexisting bacteriuria was made. He was given 1 g ertapenem every 24 h plus 2 g doripenem every 8 h (1 h after ertapenem administration) in 4-h infusions. The patient became afebrile on the 4th day of therapy, with negative blood and urine cultures after 48 h of treatment. Therapy continued for 20 days, and the patient was followed up for 10 months without evidence of relapse.

Case 2. A 42-year-old woman was admitted to the ICU of Hygeia Hospital in November 2012 because of subarachnoid hemorrhage due to a ruptured aneurysm. Endovascular occlusion of the aneurysm was successfully performed, and subsequently, an indwelling bladder catheter was applied. While the patient was asymptomatic a week after surgery, a PDR, KPC-2-producing *K. pneumoniae* strain was isolated in urine cultures at 10^5 CFU/ml (Table 1). Because of urine catheter obstruction, the catheter was urgently replaced. Eighteen hours thereafter, the patient became febrile (39.3°C) and septic. In blood cultures, a CPKP strain identical with the urine isolate was revealed by PFGE. A 14-day course of 1 g ertapenem every 24 h, followed 1 h later by 1 g meropenem every 8 h (reduced dose because of creatinine clearance equal to 30 ml/h) in 3-h infusions, was administered. After the 3rd day of therapy, the patient became afebrile, with sterile blood and urine cultures during therapy and after a 3-week follow-up.

Case 3. A 44-year-old woman was admitted in March 2012 to the ICU of Hygeia Hospital because of a car accident. The patient suffered from fractures of the pelvis plus spinal cord injury that consequently led to retroperitoneal hematoma complicated with abscesses and cauda equina syndrome. Subsequently, the patient underwent many surgical debridements and orthopedic reconstructions and a permanent indwelling bladder catheter was

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TABLE 1 Antimicrobial susceptibility patterns of *Klebsiella pneumoniae* KPC-2-positive isolates

Antimicrobial	MIC[a] (mg/liter) for isolates from:		
	Blood and urine specimens from patient:		Urine specimen from patient 3
	1	2	
Amikacin	>64	>64	>64
Aztreonam	>64	>64	>64
Cefepime	>64	>64	>64
Chloramphenicol	>64	>64	>64
Ciprofloxacin	>4	>4	>4
Colistin	>16	>16	>16
Doripenem	>8	>8	>8
Ertapenem	>8	>8	>8
Fosfomycin	>256	>1024	128
Gentamicin	>16 (>256)	>16 (>256)	>16 (>256)
Imipenem	>16	>16	>16
Meropenem	>16 (>32)	>16 (>32)	>16 (>32)
Netilmicin	>32	>32	32
Nitrofurantoin	>512	>512	>512
Piperacillin-tazobactam	>128	>128	>128
Tigecycline	>8 (12)	>8 (12)	4 (4)
Tobramycin	>16	>16	>16
Trimethoprim-sulfamethoxazole	>320	>320	>320

[a] All susceptibility tests were performed using the Vitek 2 automated system (bioMerieux, Marcy L' Etoile, France). Susceptibility testing for meropenem, gentamicin, and tigecycline was also performed with the Etest (bioMerieux, Marcy L' Etoile, France), and the results are shown in parentheses.

placed. After 5 months of hospitalization in the ICU, the patient was transferred to a medical ward. Intermittent catheterization was decided, but the patient had bacteriuria with a PDR, KPC-2-producing *K. pneumoniae* strain (Table 1) at 10^5 CFU/ml. Thus, efforts to sterilize the urine were considered necessary before the initiation of self-catheterizations to avoid any septic episodes. One gram ertapenem was given every 24 h, followed after 1 h by 2 g meropenem every 8 h in 3-h infusions. Two days later, the urine culture was sterile, and the patient was discharged on intermittent catheterization after a total of 10 days of therapy. After a follow-up of 6 months, the patient remained asymptomatic, with sterile urine.

In the PDR era, the Bulik and Nicolau proposal based on the administration of double carbapenems for CPKP infections seems to be a revolutionary approach (9). The investigators combined ertapenem, the carbapenem with the least *in vitro* activity against KPC-positive *K. pneumoniae*, whose activity is attributed to its increased affinity for carbapenemases, with doripenem, considered the most potent carbapenem in regard to enzyme stability. In their *in vitro* chemostat model and in an immunocompetent murine thigh infection model, they used a KPC-3-producing *K. pneumoniae* isolate with MICs of 64 mg/liter and 4 mg/liter to ertapenem and doripenem, respectively, applying a human simulated dosage regimen. Doripenem and ertapenem either alone or in combination achieved a fast, >3-log decrease in bacterial inoculum within 6 h. Whereas rapid regrowth to control levels was observed in monotherapy regimens, the combination maintained the bacterial reduction for 16 h. In the *in vivo* model, the use of the combination also achieved a statistically significant reduction in bacterial density compared to that obtained with doripenem alone. The enhanced benefit of the combination was attributed to enzyme consumption by ertapenem, permitting the presence of higher concentration of doripenem in the environment of the microorganism instead of the copious amounts of KPC that would be freely available to degrade doripenem, as happened initially when the first patient was given only one carbapenem.

The three patients described in the present report were exceptional, since no antibiotic that was active *in vitro* was available. For at least two of them, who were septic and bacteremic, with high MICs of the isolated CPKP strains to all available carbapenems (>32 mg/liter), the administration of ertapenem plus doripenem or meropenem was a life-saving combination, without any relapse at the follow-up. In the 2nd and 3rd patients, instead of doripenem, which was no longer permitted to be given at a high dose (13), 2 g meropenem in 3-h infusions was given based on previous evidence of optimization of the pharmacokinetics/pharmacodynamics of meropenem by prolonged infusion (10).

An alternative explanation for the greater *in vivo* killing by the combination was offered recently, based on the initial reduction in inoculum density by ertapenem acting as a suicide substrate and thereby permitting doripenem to express its successful activity against an already reduced, manageable inoculum (11). In order to support their view, the authors performed further experiments in human simulated dosing regimens of ertapenem at 1 g every 24 h administered to immunocompetent mice infected with one of three different CPKP isolates with doripenem MIC values of 8, 32, and >64 mg/liter. The results were supportive of their theory without excluding the possibility that some reduction in the bacterial inoculum by ertapenem contributed to the enhanced efficacy of the combination (12).

The encouraging sustained clinical results obtained in our patients, without any adverse effect or toxicity, deserve further elucidation regarding the mechanism of the synergism obtained, whereas additional clinical experience is required in CPKP infections, particularly whenever a PDR profile coexists, as in the reported three cases.

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