Amikacin Monotherapy for Sepsis Caused by Panresistant Pseudomonas aeruginosa

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Two patients with severe sepsis due to panresistant Pseudomonas aeruginosa, deteriorating despite therapy with colistin and β-lactams, were cured with a high daily dose (25 to 50 mg/kg) of amikacin to obtain a peak/MIC ratio of at least 8 to 10 (MIC = 16 µg/ml). Concomitant use of continuous venovenous hemodiafiltration (CVVHDF) provided no deterioration in renal function after treatment. High dosage of aminoglycosides combined with CVVHDF may represent a valuable therapeutic option for infection due to multiresistant pathogens.

Pseudomonas aeruginosa is one of the leading Gram-negative pathogens associated with life-threatening nosocomial infections (7, 12). The increasing frequency of panresistant (PR) strains of P. aeruginosa poses a considerable therapeutic challenge (4, 8). Amikacin remains a therapeutic option for the treatment of Gram-negative infections (11). Optimal antibacterial activity is achieved when peak serum concentrations reach at least 8 to 10 times the MIC of the causative pathogen (6).

We describe herein two patients with severe sepsis due to PR P. aeruginosa who were successfully treated with a high daily dose of amikacin, given as monotherapy and adapted to the MIC of the isolated strain, combined with continuous venovenous hemodiafiltration (CVVHDF).

**Patient 1.** Patient 1 was a 50-year-old obese woman (body weight [BW], 100 kg; body mass index [BMI], 35) with an elective sleeve gastrectomy complicated by intraabdominal abscesses due to a gastric fistula. An endoscopic prosthesis was placed, and optimal drainage of abdominal collections was performed percutaneously. Cultures from the drainage fluid showed Candida albicans and Klebsiella pneumoniae in addition to P. aeruginosa, which was resistant to all antibiotics except amikacin and colistin. Despite treatment with meropenem (1 g every 8 h [q8h]), colistin (3 × 10⁶ IU q8h), and fluconazole (400 mg/day), severe sepsis developed and two blood cultures were positive for P. aeruginosa resistant to all β-lactams, gentamicin, tobramycin, ciprofloxacin, and fosfomycin. According to the European Committee on Antibiotic Susceptibility Testing (EUCAST) criteria (3), the organism was sensitive only to colistin (MIC = 2 µg/ml) and was intermediate to amikacin (MIC = 16 µg/ml). Metallo-β-lactamase (MBL)-mediated resistance (VIM-2) was confirmed by PCR analysis and DNA sequencing (5). Antimicrobial treatment was therefore changed to amikacin, given at a dose of 25 mg/kg (2,500 mg) in a 30-min infusion. In view of the patient’s altered renal function (serum creatinine, 2.2 mg/dl) and to avoid amikacin nephrotoxicity, CVVHDF (blood flow, 180 ml/h; dialysate, 2,500 ml/h; ultrafiltrate, 2,500 ml/h) was initiated 2 h after the start of the amikacin infusion and continued thereafter. The peak concentrations (obtained 1 h after the start of the infusion) are shown in Fig. 1. Amikacin was administered daily with the same regimen as CVVHDF, allowing trough concentrations below 5 to 10 µg/ml. Her clinical status improved after a few days, with resolution of signs of sepsis and improvement in inflammatory parameters (Fig. 2A). The patient was discharged from the intensive care unit (ICU) at the end of therapy (12 days) and went home 10 days later. Serum creatinine at hospital discharge was normal.

**Patient 2.** Patient 2 was a 66-year-old obese man (BW, 120 kg; BMI, 39) with chronic renal failure admitted to the ICU for septic shock following gastric perforation complicated by left

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FIG. 1. Peak concentrations of amikacin in patient 1 (daily dose of amikacin, 2,500 mg [black circles]) and patient 2 (daily dose of amikacin, 3,000 mg [white circles], and then 6,000 mg following day 4 [white triangles]). Dotted lines indicate amikacin levels between 108 and 160 µg/ml, corresponding to 8 to 10 times the MIC (MIC = 16 µg/ml) for the isolated Pseudomonas strains.
thoracic empyema. Thirteen days thereafter, the patient developed an episode of septic shock. Left-lung pneumonia due to VIM-2-producing *P. aeruginosa* highly resistant to all antibiotics and intermediate only to amikacin (MIC = 16 μg/ml) was diagnosed. The patient’s clinical condition worsened despite administration of cefepime and aztreonam (2 g q8h each) combined with colistin (6 × 10^6 IU every 12 h [q12h]). Treatment was changed to amikacin at 25 mg/kg (3,000 mg), and CVVHDF (blood flow, 180 ml/h; dialysate, 2,500 ml/h; ultrafiltrate, 2,500 ml/h) was also initiated. As the peak/MIC ratio was still below 8 after the first 3 days of therapy (Fig. 1) and the patient’s hemodynamic condition worsened, the dose of amikacin was increased to 50 mg/kg (6,000 mg), resulting in optimal peaks. The patient slowly improved, vasopressors could be stopped, and inflammatory parameters decreased. He was treated for 12 days and finally returned home at day 48 with no further antimicrobial treatment. Serum creatinine values at discharge were similar to those before ICU admission (Fig. 2B).

**Discussion.** We have described two cases of successful treatment of PR *Pseudomonas* sepsis with an antimicrobial strategy using high-dose amikacin monotherapy adapted to the MIC of the pathogen and combined with CVVHDH.
Aminoglycosides have been used for decades; however, monotherapy was effective only in urinary tract infections, and meta-analyses have failed to show the superiority of aminoglycoside–β-lactam combination therapy compared to β-lactams alone (9). Nevertheless, in these studies, aminoglycosides were given in multiple daily injections and no peak monitoring was performed to optimize the drug regimen. As pharmacokinetics (PKs) of antimicrobials are severely altered during sepsis, higher-than-recommended doses of aminoglycosides are usually required to reach therapeutic peak concentrations under this condition (13). Our report suggests that optimizing aminoglycoside peaks according to the MICs of the isolated pathogens may result in increased therapeutic efficacy and in the clinical curing of severe infections, even when given as monotherapy and when a PR pathogen is found.

Aminoglycosides are eliminated by the kidneys, and the potential for renal toxicity has largely limited the use of these drugs. Renal uptake of amikacin by tubular cells is a saturable mechanism when drug concentrations exceed 15 μg/ml (9). Clinical studies suggested that nephrotoxicity is more prevalent when there is preexisting renal impairment or diabetes mellitus or in the case of prolonged therapy (9). In PK studies, an area under the concentration-time curve (AUC) above 700 has been shown as one of the best parameters to predict renal dysfunction during aminoglycoside therapy (10). Simulation of the clinical effects of amikacin given once daily showed that, for a MIC of 16 μg/ml and a desired cure rate of at least 90%, the probability of renal failure was expected to be 100% (2). Both patients in our report already had renal failure, and the use of high-dose amikacin to treat pathogens with a MIC of 16 μg/ml would have resulted in drug accumulation with deleterious effects on renal recovery and in delaying following infections (1). Thus, we used CVVHDF to enhance extrarenal clearance of the drug. Continuous renal replacement therapy, which includes CVVHDF, has gained increasing relevance in clinical management of ICU patients and provides removal of solutes similar to conventional hemodialysis, without adversely affecting cardiovascular stability (14). CVVHDHDF is able to remove aminoglycoside at a rate equivalent to a creatinine clearance of 30 to 50 ml/min, the efficiency of drug removal being dependent on CVVHDHDF characteristics (surface area, hemofilter) and operating conditions (predilution, postdilution, ultrafiltration, and/or dialysate flow rates). In our patients, this strategy resulted in high peak concentrations, with increased antimicrobial efficacy, and a rapid decrease in drug levels below the threshold of toxicity, thus lowering the risk of renal dysfunction. Unfortunately, we could not perform an audio-metric test, and any potential ototoxicity of this strategy can be excluded in our patients.

In conclusion, we showed that the curing of infection due to PR P. aeruginosa could be obtained by adapting the amikacin regimen to the MIC of the pathogen. The use of CVVHDHDF could prevent the development of nephrotoxicity related to the amikacin accumulation and increase the antimicrobial activity by allowing daily drug administration. This combination strategy may be considered an effective therapeutic option in these problematic infections.

We do not have any conflicts of interest to declare related to this paper.

REFERENCES