Amikacin monotherapy for pan-resistant *Pseudomonas aeruginosa* sepsis

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Abstract

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

Keywords: sepsis, amikacin, *Pseudomonas aeruginosa*, multi-drug resistance
Pseudomonas aeruginosa is one of the leading Gram-negative pathogens associated with life-threatening nosocomial infections (7, 12). The increasing frequency of pan-drug resistant (PDR) 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 8-10 times the minimal inhibitory concentration (MIC) of the causative pathogen (6).

We herein described two patients with severe sepsis due to PDR 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 veno-venous hemodiafiltration (CVVHDF).

Patient 1

A 50-year old obese woman (body weight, BW = 100 kg; body mass index, BMI = 35) complicated an elective sleeve gastrectomy by intra-abdominal 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, Klebsiella pneumoniae, and P. aeruginosa, which was resistant to all antibiotics except amikacin and colistin. Despite treatment with meropenem (1g q8h), colistin (3x10^6 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 EUCAST criteria (3), the organism was only sensitive to colistin (MIC=2 μg/mL) and intermediate to amikacin (MIC=16 μg/mL). Metallo-β-lactamase (MBL)-mediated resistance (VIM-2) was confirmed by PCR and DNA sequencing (5).
Antimicrobial treatment was therefore changed to amikacin, given at a dose of 25 mg/kg (2500 mg) in a 30-minute 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 2500 mL/h; ultrafiltrate 2500 mL/h) was initiated 2 hours after the start of the amikacin infusion and continued thereafter. The peak concentrations (obtained 1h after the start of the infusion) are shown in Figure 1. Amikacin was administrated daily with the same regimen as CVVHDF allowed trough concentrations below 5-10µg/ml. Her clinical status improved after few days with resolution of signs of sepsis and improvement in inflammatory parameters (Figure 2A). The patient was discharged from the ICU at the end of therapy (12 days) and went home 10 days later. Serum creatinine at hospital discharge was normal.

**Patient 2**

A 66-year old obese (BW = 120; BMI = 39) man with chronic renal failure was admitted to the ICU for septic shock following gastric perforation complicated by left thoracic empyema. Thirteen days thereafter, the patient developed an episode of septic shock. Left pneumonia due to VIM-2 producing *P. aeruginosa*, highly resistant to all antibiotics and only intermediate to amikacin (MIC= 16µg/mL) was diagnosed. The patient’s clinical condition worsened despite administration of cefepime and aztreonam (2g q8h each) combined with colistin (6*10^6 IU q12h). Treatment was changed to amikacin 25 mg/kg (3000 mg) and 4

CVVHDF (blood flow 180 mL/h; dialysate 2500 mL/h; ultrafiltrate 2500 mL/h) was also initiated. As the peak/MIC ratio was still below 8 after the first 3 days of therapy (Figure 1) and the patient’s hemodynamic condition worsened, the dose of amikacin was increased to 50 mg/kg (6000 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 returns home at day 48 with no further antimicrobial treatment. Serum creatinine values at discharge were similar to those before ICU admission (Figure 2B).

Discussion

We described two cases of successful treatment of PDR-\textit{Pseudomonas} sepsis with an antimicrobial strategy using high-dose amikacin monotherapy, adapted to the MIC of the pathogen and combined with CVVDHF.

Aminoglycosides have been used for decades, however, monotherapy was effective only in urinary tract infections, and meta-analyses have failed to show superiority of aminoglycoside/\textbeta-lactam combination therapy when compared to \textbeta-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 antimicrobials PKs are severely altered during sepsis, higher than recommended aminoglycosides doses are usually required to reach therapeutic peak concentrations in this condition (13). Our report suggests that optimizing aminoglycoside peaks according to the MIC of the isolated pathogens may result in increased therapeutic efficacy and in clinical cure of severe infections, even when given as monotherapy and when a PDR-pathogen is found.

Aminoglycosides are eliminated by the kidneys and the potential 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 $\mu$g/mL (9). Clinical studies suggested that nephrotoxicity is more prevalent when there is pre-existing renal impairment, diabetes mellitus or in case of prolonged therapy (9). In PK studies, an area under the curve (AUC) above 700 has been shown as one the best parameter to predict renal dysfunction during aminoglycoside therapy (10). Simulation on 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 injections (1). Thus, we used CVVHDF to enhance extra-renal 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). CVVDHF is able to remove aminoglycoside at a rate equivalent to a creatinine clearance of 30-50 mL/min, the efficiency of drug removal being dependent from CVVDHF 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 and audiometric test and any potential ototoxicity of this strategy can be excluded in our patients.

In conclusion, we showed that cure of infection due to PDR *P. aeruginosa* could be obtained by adapting the amikacin regimen to the MIC of the pathogen. The use of CVVDHF 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 as an effective therapeutic option in these problematic infections.

**Conflicts of interest.**

The authors do not have any conflicts to declare related to this manuscript.


Figures Legends.

**Figure 1.** Peak concentrations of amikacin in patient 1 (daily dose of amikacin 2500mg – black circles) and patient 2 (daily dose of 3000mg – white circles; then 6000mg since day 4 – white triangles). Dotted lines: amikacin levels between 108 and 160 µg/mL, corresponding to 8-10 times the minimal inhibitory concentration (MIC = 16 µg/mL) for the isolated *Pseudomonas* strains.

**Figure 2.** Evolution of C-reactive protein (CRP) and creatinine levels during the ICU stay in patient 1 (A) and patient 2 (B). CVVHDF = continuous veno-venous hemodiafiltration.