Pre-dialytic administration of aminoglycosides – case report and review of literature

Abstract

Objectives: Aminoglycoside (AG) antimicrobial agents are potent therapeutics against a wide variety of gram positive and negative bacteria including *Pseudomonas aeruginosa*. Until now AGs are usually administered post-hemodialysis (HD) in patients receiving chronic HD. This regimen has been doubted with increasing knowledge of their PK/PD characteristics. Due to the concentration dependent mechanism of these drugs, high peak and low trough levels seem desirable, leading to the conclusion that a pre-dialytic administration would probably yield increased killing and reduced toxicity. This has already been proposed by O’Shea et al. Unfortunately until now there is little clinical data to support this claim. This report aims to provide an overview of the available literature as well as clinical expertise to the discussion.

Methods: We present a case of a 55-year-old double lung transplant patient with chronic renal failure and recurring episodes of sepsis. The patient had received multiple antimicrobial agents without a significant reduction in inflammation parameters (CRP, WBC) or a marked improvement of her general status. Due to the lacking effect of piperacillin/tazobactam as well as carbapenems in this patient, she received 7.1 mg amikacin per kg bodyweight two hours previous to dialysis. To ensure patient safety as well as treatment efficacy amikacin peak as well as trough levels were assessed by the treating physicians.

Results: The reported peak concentration was 53.3 µmol/l after the first administration, and 43.6 µmol/l 30 minutes post-infusion. During the subsequent HD the amikacin serum concentration dropped to 13.1 µmol/l. In the following days HD was performed daily with a trough-level adapted dose of amikacin two hours pre-HD, each time resulting in high peak and low trough levels. During this treatment the CRP level dropped from 30 mg/dl to 5.73 mg/dl within six days, and the patient recovered clinically within the first 24 hours. No difference between pre-treatment and post-treatment audiograms was observed.

Discussion: Predialytic administration of AGs is a compelling regimen from a pharmacokinetic point of view. In the presented case very high peak and low trough concentrations were reached, showing that the previously proposed regimen is easily employable in daily patient care. The often expressed concern this treatment might lead to treatment failures may be countered with the good clinical result in our patient. We feel that a comparative trial is warranted and might provide better insight into the matter.

Keywords: aminoglycosides, dialysis, pharmacokinetics, pharmacodynamics

Introduction and review of literature

Aminoglycoside antimicrobial agents are potent therapeutics, active against a wide variety of gram positive and negative bacteria including *Pseudomonas aeruginosa* as well as *mycobacteria* [1], [2]. They are derived from either streptomycetae or micromonospora. The first agent of this class, streptomycin, was first described in 1944 and has been in clinical use since 1945 [3], [4], [5], [6]. Although, as in other antimicrobial agents, resistance is increasing, aminoglycosides pose a powerful measure of last resort in some cases. Patients infected with bacteria expressing resistance to most modern therapeutics, but with low MICs for aminoglycosides due to the generally reduced application of those drugs will show good response to aminoglycoside therapy. Initial dosing regimens for aminoglycosides proposed a twice or thrice daily dosing of aminoglycosides, which was
adapted to a once daily administration to reduce toxicity once a better understanding of aminoglycoside pharmacokinetics and pharmacodynamics was reached [7], [8], [9]. It is important to notice that the bactericidal activity of aminoglycosides seems to be dependent on the AUC above the MIC (AUC:MIC) [10], [11]. However, it should be mentioned that there is also data to support the claim that aminoglycoside activity is only dependent on the maximum concentration (peak:MIC) [12], [13]. Recently a target peak serum concentration of eight to tenfold of the MIC, combined with a AUC$_{0-24}$ of 100 mg.h/L has been hypothesized as optimal reference for maximized efficacy when administering aminoglycosides [14]. At the same time the significant toxicity to vestibular and cochlear cells, tubular cells of the kidney as well as the ability to provoke a neuromuscular block seems to be related to the complete AUC [8], [15], [16], [17], [18]. As a result there is a broad therapeutic window for pathogens with low MICs, while treatment of less susceptible organisms may result in a reduced success rate or increased toxicity [8], [11].

Due to the excellent dialysability of aminoglycosides they are usually administered post-hemodialysis in patients receiving chronic hemodialysis (HD) to allow for prolonged aminoglycoside exposure of the pathogen [19], [20], [21]. This regimen has been doubted with increasing knowledge of the PK/PD characteristics of aminoglycosides [20]. Due to the concentration/AUC:MIC dependent mechanism of these drugs an increased control over the pharmacokinetics with resulting high peak and low trough levels seem desirable, leading to the conclusion that a pre-dialytic administration would probably yield increased killing and reduced toxicity. This has already been proposed by Matsuo et al. as well as O’Shea et al. [22], [23]. Unfortunately until now there is little clinical data to support this claim. However, Roberts et al. have successfully performed Monte-Carlo simulations for pre-dialytic aminoglycoside administration in extended daily diafiltration [24]. This data is being backed by a model developed by Dang and Dufull [25], [26]. Kamel Mohammed et al. described administration of standard doses of tobramycin at the beginning of haemodialysis resulting in similar peak plasma levels as in post-hemodialytic administration, but a 8.5 times reduced AUC [27]. This might not only lead to reduced toxicity but as well to a reduced efficacy. However, by increasing the pre-dialytic administered dose to allow for a peak concentration eight- to tenfold above the MIC efficacy might be greatly increased [28]. For extended daily diafiltration a gentamycin administration about 30 minutes to one hour prior to commencement of diafiltration was deemed the most effective regimen in Monte Carlo simulations performed by Roberts et al. [24].

Significant inter-individual serum concentration variability when administering a specific dose of aminoglycosides demands measurement of peak and trough level in hemodialysis patients to ensure efficacy and low toxicity of the regimen [14], [29], [30], [31].

Concluding the above mentioned, most of the recently published manuscripts have suggested a beneficial effect of pre-dialytic dosing regiments when administering aminoglycosides. However, to our knowledge there have been no trials or even reports of cases where a pre-dialytic regimen has been employed in a patient up to this point.

**Case report**

We present a case of a 54-year-old female double lung transplant patient (bodyweight 70 kg, height 158 cm) with end stage renal disease (Creatinin 4.90 mg/dl (normal value 0.5–0.9 mg/dl) receiving 4 hours hemodialysis thrice a week) and recurring episodes of clinically diagnosed sepsis without a clear focus. The first hemodialysis session was performed two months prior to admission, double-lung transplantation was performed five years previous to the described septic episode. The CRP showed constantly elevated levels with a baseline of 6 to 7 mg/dl (normal value $<$0.5 mg/dl) and recurring peaks of up to 30 mg/dl. White blood cell counts showed only slight elevation with 13,200 leucocytes/liter. Other laboratory values showed only slight elevation (alkalic phosphatase 136 U/l (35–105 U/l), ASAT 37 U/l (<35 U/l), ALAT 36 U/l (<35 U/l), gamma-GT 136 U/l (<40 U/l)). She was dialyzed via a perm-cath, which was exchanged without any improvement of the pathology. Multiple blood cultures, Septifast® and in-house broad spectrum bacterial and fungal PCR remained without evidence of a microbiologic pathogen. There was no serological or molecular-biological evidence for a viral infection or reactivation. A chest X-ray was performed on admission, which revealed a suspect area in the right lower lobe, which however was interpreted as reduced ventilation by the radiologist. She had received multiple antimicrobial agents without a significant reduction in inflammation parameters (CRP, WBC) or a marked improvement of her general status. On admission she showed a slightly elevated heart rate of 87/min. She had been in need of oxygen insufflations for several years but did show eupnoea under 2l O₂ insufflation on admission. Due to the lacking effect of piperacillin/tazobactam as well as carbapenems, she received a near standard post-hemodialysis dose of 7.1 mg amikacin per kg bodyweight [32] (bodyweight 70 kg, administered dose 500 mg), two hours previous to dialysis when she experienced another septic episode with CRP levels of 22 mg/dl and a rising tendency. Peak and trough levels were assessed to ensure high enough drug plasma levels as well as low trough levels considering the very variable pharmacokinetic profile of aminoglycosides as well as the employed regimen [33]. In the following hemodialysis over four hours using a Nipro NI-210E® dialyzer was employed. Figure 1 shows the amikacin serum concentration together with the development of the CRP. The Patient received four predialytic aminoglycoside treatments – each followed by a four hour dialysis session – over the course of five days.
Due to the non-controlled environment serum concentration at three timepoints could not be assessed. Missing data were extrapolated in a very conservative way from surrounding timepoints. Precisely there was missing data for the second hemodialysis session (timepoints 40:06 h and 44:59 h missing), the corresponding serum concentrations were extrapolated from the data of the third hemodialysis session, as well as a missing pre-HD baseline datapoint for the fourth hemodialysis (114:50 h) which was extrapolated from the post-HD baseline of the third hemodialysis session.

The dose administered previous to the first HD session resulted in a high peak concentration of 53.3 µmol/l directly after administration, and a reduced level of 43.6 µmol/l 30 minutes post-infusion. During the hemodialysis session the amikacin serum concentration dropped to 13.1 µmol/l. In the following days hemodialysis was performed daily with a trough-level adapted dose of 400 mg amikacin for the second and third, and 350 mg (equaling a dose of 5 mg/kg) for the fourth dialysis. Each time high peak and low trough levels were reached, with a lowest trough level of 8.3 µmol/l following the fourth hemodialysis.

The AUC for the complete dosing interval was calculated as $\text{AUC}_{0-136} = 1167 \, \text{mg/Lh}$, the AUC for the first dosing interval as $\text{AUC}_{0-16.19} = 170 \, \text{mg/Lh}$ (AUCs were calculated using Thermo Scientific Kinetica® 5.0)

During the treatment the patient showed a swift clinical recovery with decline of fever and ague within 24 hours and the CRP level dropped from 30 mg/dl to 5.73 mg/dl within six days.

No difference between pre-treatment and post-treatment audiograms was observed.

About four weeks after the initial treatment a multi resistant, but amikacin sensitive 
Pseudomonas aeruginosa strain could be isolated from a broncho alveolar lavage. Shortly after this the patient suffered a further septic shock and again received a pre-HD amikacin regimen. She recovered swiftly.

**Conclusion**

Pre-dialytic administration of aminoglycosides allows for high peak and low trough concentrations. When administering high doses around 5 to 7.5 mg/kg of amikacin, a sufficient AUC combined with low trough levels may be expected. However, therapeutic drug monitoring of peak and trough levels should be employed in all cases. The presented literature and case report illustrate the necessity for further clinical research into this subject.

**Notes**

**Competing interests**

The authors declare that they have no competing interests.

**References**


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