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

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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 *mycobacteriae* [1], [2]. They are derived from either streptmoycetae 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 amoniglycosides 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 little elevation (alcalic 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 O_2 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.

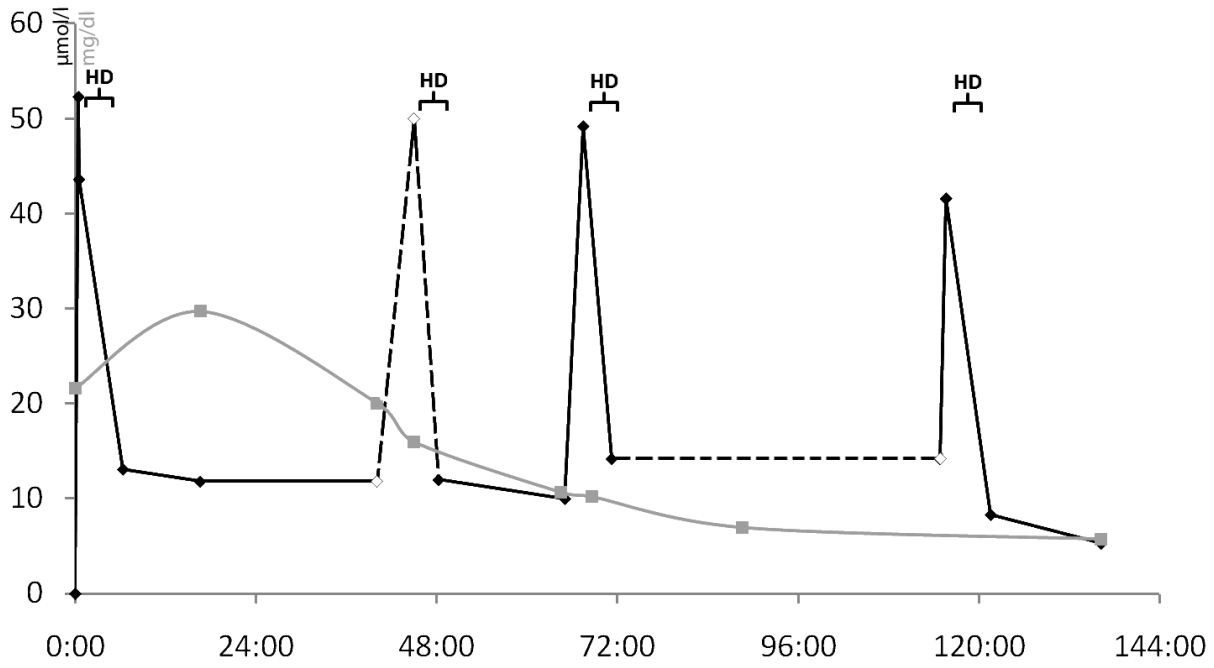

Figure 1: Multiple-dose pharmacokinetics of amikacin during hemodialysis. black: amikacin concentration in µmol/l, grey: CRP in mg/dl, white knobs with black lining: extrapolated values, dashed lines: lines in connection with an extrapolated value.

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 AUC_{0-136} 1167 mg/L.h, the AUC for the first dosing interval as $AUC_{0-16.19}$ 170 mg/L.h (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

1. Brewer NS. Antimicrobial agents – Part II. The aminoglycosides: streptomycin, kanamycin, gentamicin, tobramycin, amikacin, neomycin. Mayo Clin Proc. 1977 Nov;52(11):675-9.
2. Pien FD, Ho PW. Antimicrobial spectrum, pharmacology, adverse effects, and therapeutic use of amikacin sulfate. Am J Hosp Pharm. 1981 Jul;38(7):981-9.

3. Schatz A, Bugie E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. 1944. Clin Orthop Relat Res. 2005 Aug;(437):3-6. DOI: 10.1097/01.blo.0000175887.98112.fe
4. Jones D, Metzger HJ, Schatz A, Waksman SA. Control of gram-negative bacteria in experimental animals by streptomycin. Science. 1944 Aug;100(2588):103-5. DOI: 10.1126/science.100.2588.103
5. Herrell WE, Nichols DR. The clinical use of streptomycin. Proc Staff Meet Mayo Clin. 1945;20:449-62.
6. Reimann HA, Price AH, Elias WF. Streptomycin for certain systemic infections and its effect on the urinary and fecal flora. Arch Intern Med (Chic). 1945 Nov-Dec;76:269-77. DOI: 10.1001/archinte.1945.00210350015003
7. Kuharcik CM, Craig AC. New trends in aminoglycoside dosing. ANNA J. 1994 Dec;21(7):447-8, 468.
8. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis. 2007 Sep;45(6):753-60. DOI: 10.1086/520991
9. Drusano GL, Louie A. Optimization of aminoglycoside therapy. Antimicrob Agents Chemother. 2011 Jun;55(6):2528-31. DOI: 10.1128/AAC.01314-10
10. Craig WA, Redington J, Ebert SC. Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. J Antimicrob Chemother. 1991 May;27 Suppl C:29-40. DOI: 10.1093/jac/27.suppl_C.29
11. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr,. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother. 1999 Mar;43(3):623-9.
12. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE. Treatment and outcome of Pseudomonas aeruginosa bacteraemia: an antibiotic pharmacodynamic analysis. J Antimicrob Chemother. 2003 Oct;52(4):668-74. DOI: 10.1093/jac/dkg403
13. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987 Jan;155(1):93-9. DOI: 10.1093/infdis/155.1.93
14. Pagkalis S, Mantadakis E, Mavros MN, Ammari C, Falagas ME. Pharmacological considerations for the proper clinical use of aminoglycosides. Drugs. 2011 Dec;71(17):2277-94. DOI: 10.2165/11597020-000000000-00000
15. Toxicity of Streptomycin. Br Med J. 1957;1(5033):1466-7. DOI: 10.1136/bmj.1.5033.1466
16. Xie J, Talaska AE, Schacht J. New developments in aminoglycoside therapy and ototoxicity. Hear Res. 2011 Nov;281(1-2):28-37. DOI: 10.1016/j.heares.2011.05.008
17. Hinshaw HC, Feldman WH. Streptomycin in treatment of clinical tuberculosis: a preliminary report. Proc Mayo Clinic. 1945;20:313–8.
18. Brazil OV, Corrado AP. The curariform action of streptomycin. J Pharmacol Exp Ther. 1957 Aug;120(4):452-9.
19. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy. 2009 May;29(5):562-77. DOI: 10.1592/phco.29.5.562
20. Bennett WM, Aronoff GR, Morrison G, Golper TA, Pulliam J, Wolfson M, Singer I. Drug prescribing in renal failure: dosing guidelines for adults. Am J Kidney Dis. 1983 Nov;3(3):155-93.
21. Keller F, Wagner K, Borner K, Kemmerich B, Lode H, Offermann G, Distler A. Aminoglycoside dosage in hemodialysis patients. J Clin Pharmacol. 1986 Nov-Dec;26(8):690-5. DOI: 10.1002/j.1552-4604.1986.tb02974.x
22. O'Shea S, Duffull S, Johnson DW. Aminoglycosides in hemodialysis patients: is the current practice of post dialysis dosing appropriate? Semin Dial. 2009 May-Jun;22(3):225-30. DOI: 10.1111/j.1525-139X.2008.00554.x
23. Matsuo H, Hayashi J, Ono K, Andoh K, Andoh Y, Sano Y, Saruki K, Tanaka J, Yamashita M, Nakamura K, Kubo K. Administration of aminoglycosides to hemodialysis patients immediately before dialysis: a new dosing modality. Antimicrob Agents Chemother. 1997 Dec;41(12):2597-601.
24. Roberts JA, Field J, Visser A, Whitbread R, Tallot M, Lipman J, Kirkpatrick CM. Using population pharmacokinetics to determine gentamicin dosing during extended daily diafiltration in critically ill patients with acute kidney injury. Antimicrob Agents Chemother. 2010 Sep;54(9):3635-40. DOI: 10.1128/AAC.00222-10
25. Dang L, Duffull S. Development of a semimechanistic model to describe the pharmacokinetics of gentamicin in patients receiving hemodialysis. J Clin Pharmacol. 2006 Jun;46(6):662-73. DOI: 10.1177/0091270006286902
26. Teigen MM, Duffull S, Dang L, Johnson DW. Dosing of gentamicin in patients with end-stage renal disease receiving hemodialysis. J Clin Pharmacol. 2006 Nov;46(11):1259-67. DOI: 10.1177/0091270006292987
27. Kamel Mohamed OH, Wahba IM, Watnick S, Earle SB, Bennett WM, Ayres JW, Munar MY. Administration of tobramycin in the beginning of the hemodialysis session: a novel intradialytic dosing regimen. Clin J Am Soc Nephrol. 2007 Jul;2(4):694-9. DOI: 10.2215/CJN.01600407
28. Sowinski KM, Magner SJ, Lucksiri A, Scott MK, Hamburger RJ, Mueller BA. Influence of hemodialysis on gentamicin pharmacokinetics, removal during hemodialysis, and recommended dosing. Clin J Am Soc Nephrol. 2008 Mar;3(2):355-61. DOI: 10.2215/CJN.02920707
29. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. Ann Pharmacother. 2006 Jan;40(1):9-14. DOI: 10.1345/aph.1G064
30. Agarwal R, Cronin RE. Heterogeneity in gentamicin clearance between high-efficiency hemodialyzers. Am J Kidney Dis. 1994 Jan;23(1):47-51.
31. Kunzendorf U, Keller F, Walz G, Haller H, Offermann G, Borner K, Lode H. Multivariate analysis of aminoglycoside levels in hemodialysis patients. Chemotherapy. 1989;35(1):1-6. DOI: 10.1159/000238628
32. Vossen MG, Thalhammer F. Effects of renal replacement therapy on antimicrobial therapy. Curr Clin Pharmacol. 2013 Feb;8(1):39-45. DOI: 10.2174/1574884711308010006
33. Bourguignon L, Goutelle S, Gérard C, Guillermet A, Burdin de Saint Martin J, Maire P, Ducher M. Pharmacocinétique de l'amikacine chez l'adulte: une hétérogénéité qui remet en cause le calcul de la dose basé sur le poids [Amikacin pharmacokinetics in adults: a variability that question the dose calculation based on weight]. Therapie. 2009 Jan-Feb;64(1):47-53. DOI: 10.2515/therapie/2009009

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