Gentamicin Administration in Dialysis Patients

Grit, Geeske F; Toren-Wielema, Marlous L; Colin, Pieter J; Touw, Daan J

Published in:
Therapeutic Drug Monitoring

DOI:
10.1097/FTD.0000000000001058

Publication date:
2023

Therapeutic Drug Monitoring Publish Ahead of Print
DOI: 10.1097/FTD.0000000000001058

Gentamicin Administration in Dialysis Patients: Before or After Hemodialysis?

Geeske F Grit, BSc[1]; Marlous L Toren-Wielema, MSc[1]; Pieter J. Colin, PhD[2]; Daan J Touw, PhD[1]

[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands;

[2]Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Correspondence: Daan J Touw, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, P.O. Box 30.001 (internal postcode AP50), 9700 RB Groningen, the Netherlands, Phone: +31 - 50 361 4071 Fax: +31 - 50 361 4087 (e-mail: d.j.touw@umcg.nl).

Conflicts of Interest and Source of Funding: The authors declare no conflicts of interest. No funding sources were used for this study.

Acknowledgments:

The authors would like to thank Dr. Robert AG Huis in 't Veld for his valuable comments on the manuscript.

Abstract

Background: Gentamicin is used to treat severe infections and has a small therapeutic window. This study aimed to optimize the dosing strategy of gentamicin in intermittently hemodialyzed patients by simulating concentration/time profiles during pre- and post-dialysis dosing, based on a published pharmacokinetic model.

Methods: Pharmacokinetic simulations were performed with virtual patients, including septic patients, who were treated with gentamicin and received weekly hemodialysis with an interval of 48h-48h-72h. The following dosing regimens were simulated: for non-septic patients, 5 mg/kg gentamicin was given 1h/2h before dialysis, or a starting dose of 2.5 mg/kg and a maintenance dose of 1.5 mg/kg immediately after dialysis; for septic patients, 6 mg/kg gentamicin was given 1h/2h before dialysis, or a starting dose of 3 mg/kg and a maintenance dose of 1.8 mg/kg immediately after dialysis. The mean C_{max}, AUC_{24h}, and target attainment (TA) of pharmacodynamic targets were calculated and compared. The following targets were adopted from literature: C_{max} >8 mg/L and <20 mg/L and AUC_{24h} >70 mg·h/L and <120 mg·h/L.

Results: In non-septic patients, postdialysis dosing resulted in a TA of 35% for C_{max} >8 mg/L, 100% for <20 mg/L and AUC_{24h} >70 mg·h/L, and 45% for <120 mg·h/L. Dosing 2h prior to dialysis resulted in a TA of 100% for C_{max}> 8 mg/L, 40% for <20 mg/L, 65% for AUC_{24h} >70 mg·h/L, and 77% for <120 mg·h/L. Simulations of septic patients resulted in comparable outcomes with higher TAs for C_{max} <20 mg/L (96%), AUC_{24h} >70 mg·h/L (90%), and <120 mg·h/L (53%) for dosing 1h prior to dialysis.

Conclusions: Postdialysis dosing resulted in a low TA of C_{max} >8 mg/L; however, predialysis dosing ensured a high TA of C_{max} >8 mg/L and acceptable TA of C_{max} <20 mg/L, AUC_{24h} >70 mg·h/L, and <120 mg·h/L, which could increase the efficacy of gentamicin. Therefore, clinicians should consider predialysis dosing of gentamicin in patients undergoing intermittent

hemodialysis.

Keywords: aminoglycosides; gentamicin; hemodialysis; kidney failure; pharmacokinetics

Introduction

Patients with renal failure require renal replacement therapy; one option is to undergo intermittent dialysis. However, infections are a major cause of mortality in those who undergo hemodialysis.[1] Gentamicin is an aminoglycoside that plays an important role in the treatment of severe infections caused by aerobic gram-negative bacteria.[2] It is a concentration-dependent antibiotic, such that increasing its concentration results in more rapid bacterial killing.[3] The minimal inhibitory concentration (MIC) refers to the minimal concentration of an antibiotic that prevents the growth of microorganisms. The maximum concentration (C_{max})/MIC and area under the curve (AUC)/MIC are important pharmacokinetic/pharmacodynamic (PK/PD) indices that reveal the efficacy of aminoglycosides.[3-6]

Side effects of aminoglycosides include nephrotoxicity, ototoxicity, and vestibulotoxicity.[2, 7, 8] The uptake of aminoglycosides in the kidney and inner ear is saturable at relatively low concentrations.[2, 7, 9]

Current recommendations for patients who undergo intermittent hemodialysis include the administration of approximately 1–1.7 mg/kg of gentamicin after each hemodialysis session (postdialysis dosing).[2, 10, 11] However, several reports suggest that predialysis dosing (off-label) is more favorable than postdialysis dosing.[7, 8, 12-14] Nevertheless, there are no existing studies that have directly compared the efficacy of pre- and post-dialysis dosing of aminoglycosides.

Thus, this simulation study aimed to determine the optimal dosing regimen of gentamicin and whether the predialysis dosing of aminoglycosides is preferable to postdialysis dosing. This study included hemodialyzed patients who underwent a 4-hour session of high-flow dialysis thrice weekly. Since the volume of distribution (Vd) of septic patients is higher,[2] a distinction was made between patients with and without sepsis.

Materials and Methods

PHARMACOKINETIC SIMULATIONS

To determine the optimal gentamicin dosage regimen, pharmacokinetic simulations were performed for non-septic and septic patients using the following programs: Rcpp, tidyverse, magrittr, lubridate, RxODE, shiny, thematic, and mvtnorm for R (version 4.0.5; see text, Supplemental Digital Content 1, http://links.lww.com/TDM/A632, which elaborates R code). Concentration-time graphs were generated for 1000 simulated subjects for each dosing regimen. The one-compartment pharmacokinetic model from Jelliffe *et al.* was used.[15] For the simulations, an average hemodialysis patient without sepsis had the following gentamicin characteristics: weight = 70 kg; height = 175 cm; creatinine clearance (CL) = 2 mL/min/1.73 m^2; $CL_{non\text{-}dialysis}$ = 0.2462 L/h; Vd = 17.50 L; $t_{1/2}$ = 49.28h.[15] In contrast, an average hemodialysis patient with sepsis had the following gentamicin characteristics: weight = 70 kg; height = 175 cm; creatinine clearance = 2 mL/min/1.73 m^2; $CL_{non\text{-}dialysis}$ = 0.4787 L/h; Vd = 35.00 L; $t_{1/2}$ = 50.68h.[15] Since Vd is known to increase in cases of sepsis,[16] we used the worst-case scenario by doubling the Vd to 0.5 L/kg. The $CL_{dialysis}$ rate of gentamicin was set at 150 mL/min. This value is based on the plasma flow of the dialyzer, since the gentamicin clearance is almost identical to the plasma flow, as the serum protein binding of gentamicin is almost zero.[17, 18] This is in line with the findings of Vossen *et al.*[19] who recently studied the clearance of gentamicin from different dialyzers. A variance of 25% for $CL_{non\text{-}dialysis}$, $CL_{dialysis}$,

and Vd was used.[15] In addition, several scenarios were simulated to provide a complete picture of target attainment in different patients/models. Simulations of septic patients were also performed using the model PK parameters of Franck *et al*.,[20] who performed a similar study. Moreover, individual variants were simulated: $CL_{dialysis}$, which is the variation within membranes,[19] measuring 90 ml/min and 188 ml/min and obese patients weighing 90, 110, and 130 kg.

Different dosing regimens were simulated, including 1h and 2h predialysis dosing and dosing immediately after dialysis. The 1h and 2h predialysis dosing regimens were chosen because adaptive resistance starts within 1–2 hours after aminoglycoside administration and this interval has been frequently used in other studies.[5, 7, 12-14] The dosing regimens for non-septic patients and septic patients were as follows:

Non-septic patients:

1: 5 mg/kg 1h prior to dialysis

2: 5 mg/kg 2h prior to dialysis

3: Starting dose of 2.5 mg/kg, maintenance dose of 1.5 mg/kg postdialysis

Septic patients:

4: 6 mg/kg 1h prior to dialysis

5: 6 mg/kg 2h prior to dialysis

6: Starting dose of 3 mg/kg, maintenance dose of 1.8 mg/kg postdialysis

Gentamicin was administered with an infusion time of 30 minutes. A dialysis interval of 48h-48h-72h was used, with each dialysis session lasting for 4 hours.

The mean AUC_{24h} (mg·h/L), mean C_{max} (mg/L), and target attainment of the PD targets after each administration were calculated. The mean of the first four doses was used to calculate the mean AUC_{24h}, C_{max}, and target attainment. Additionally, the predicted concentration-time graphs were plotted.

PHARMACODYNAMIC TARGETS

The following PD targets were used for efficacy: C_{max}/MIC >8 and AUC_{24h}/MIC >70.[6, 21, 22] To avoid nephrotoxicity, AUC_{24h} must be below 120 mg·h/L.[23-25] The desired C_{max} value is <20 mg/L because this is the maximum concentration that is regarded as safe.[2, 26] Therefore, this value was also targeted (target attainment).

An MIC of 1 mg/L was used for analyzing target attainment since this was used in most studies.[5, 6] In addition, the target attainment for an MIC of 2 mg/L has also been simulated, since this is the epidemiological cut-off value (ECOFF) for *Enterobacterales* and *Staphylococci*.[27]

Results

The simulation results are presented in **Table 1** and **Figure 1**. Predialysis dosing of non-septic patients (regimens 1 and 2) achieved the PD targets C_{max} >8 mg/L and AUC_{24h} <120 mg·h/L in 100% and ±80% of simulated patients, but C_{max} <20 mg/L and AUC_{24h} >70 mg·h/L target attainment was low (±42% and ±60%, respectively). This is due to the low AUC_{24h} relative to C_{max} and inter-individual variability. Dosing 1h before hemodialysis had a slightly lower AUC than dosing 2h before hemodialysis (regimen 1 vs. 2). Postdialysis dosing (regimen 3) achieved target attainment of C_{max} <20 mg/L and AUC_{24h} >70 mg·h/L in 100% of simulated patients but demonstrated low target attainment of C_{max} >8 mg/L and AUC_{24h} <120 mg·h/L (35% and 45%, respectively). This is due to the high AUC_{24h} relative to C_{max} compared to the predialysis dosing.

Predialysis dosing in septic patients achieved a target attainment of C_{max} >8 mg/L in ±99%, C_{max} <20 mg/L in ±97%, and AUC_{24h} >70 mg·h/L in ±91%, but only ±52% achieved AUC_{24h} <120 mg·h/L (regimens 4 and 5). In septic patients with predialysis dosing, a higher

AUC relative to C_{max} was achieved than that in non-septic patients, which resulted in higher target attainment. Postdialysis dosing (regimen 6) achieved a PD target of C_{max} <20 mg/L, AUC_{24h} >70 mg·h/L, and AUC_{24h} <120 mg·h/L (100%, 93%, and 91%, respectively); however, only 3% achieved C_{max} >8 mg/L.

The results of target attainments of simulations with the PK parameters of Franck *et al*.[20] are provided in **Supplemental Digital Content 2**http://links.lww.com/TDM/A632; the results of patients with a $CL_{dialysis}$ of 90 ml/min and 188 ml/min in **Supplemental Digital Content 3**http://links.lww.com/TDM/A632; target attainments of patients weighing 90 kg, 110 kg, and 130 kg are shown in **Supplemental Digital Content 4**http://links.lww.com/TDM/A632**,** and target attainments for MIC = 2 mg/L are included in **Supplemental Digital Content 5**http://links.lww.com/TDM/A632**.**

Discussion

This study provides a complete picture of the target attainment of predialysis versus postdialysis dosing in patients undergoing intermittent hemodialysis, since different scenarios have been simulated, including non-septic vs. septic patients and variations in weight, $CL_{dialysis}$, MIC, and model PK parameters. A good insight into the optimal efficacy and low risk of toxicity was provided by choosing PD targets for both C_{max} and AUC_{24h}.

PHARMACODYNAMIC TARGETS

C_{max}/MIC >8 and AUC_{24h}/MIC >70 were chosen as PD targets for efficacy based on several studies that measured the relationship between the PK/PD indices of aminoglycosides and clinical response. Zelenitsky *et al.* concluded that a ≥90% chance of clinical cure was associated with C_{max}/MIC >8 and AUC_{24h}/MIC >70.[6] Kashuba *et al.* concluded that a ≥90% probability of temperature resolution on day 7 was associated with C_{max}/MIC >10 and AUC_{0-}

$_{24h}$/MIC >150.[4] Moore *et al.* measured a significantly higher C_{max}/MIC (6.6 vs 4.6) in patients with clinical response vs no response.[21] Keller *et al.* found a significantly higher C_{max} in patients receiving hemodialysis who survived compared with patients who expired (8.2 vs 5.9 mg/L).[22] Zhuang *et al.* found that C_{max}/MIC and AUC_{24h}/MIC were significantly related to bacterial response in patients who received hemodialysis.[5] C_{max}/MIC >8 could prevent the development of resistance and, therefore, bacterial regrowth.[7] C_{max}/MIC is probably a better PD target than AUC_{24h}/MIC, as Zelenitsky *et al.* concluded that only C_{max}/MIC was an independent variable related to clinical cure.[6] Moreover, once-daily dosing results in slightly better clinical outcomes than multiple daily dosing of the same dose, arguing that an adequate C_{max} is more important than AUC.[28, 29] Therefore, C_{max}/MIC should be considered the major PD target for efficacy.

An AUC_{24h} <120 mg·h/L was chosen as the PD target for safety, as several pharmacokinetic studies adopted this target to prevent toxicity.[12, 14] However, this AUC was only based on standard dosing in patients with normal renal function.[23, 24] Therefore, there is uncertainty regarding which AUC results in an increased risk of nephrotoxicity. Nevertheless, it is plausible that nephrotoxicity is related to a large AUC and not high peak levels.[25] C_{max} <20 mg/L was chosen as the desired value because this is the currently accepted safe upper threshold.[2, 26]

PHARMACOKINETIC SIMULATIONS

In our simulations, the $CL_{dialysis}$ (150mL/min) was higher than that in other studies (80–134 mL/min)[13, 14, 30, 31] because these studies were published between 2006 and 2013; currently, higher dialyzer blood flows are used (200–400 ml/min).[19, 32] Therefore, our simulations better reflect the modern dialysis technique which favors a high blood flow

through the dialyzer. In our study, an average blood flow of 250 ml/min was calculated for plasma flow using a hematocrit of 0.4.

A recent study by Franck *et al.*,[20] where popPK values were derived from patients on dialysis, is in line with our study; however, in their study, only C_{max}/MIC >8 and C_{min} <1 mg/L targets were provided, whereas our study also targeted AUC_{24h} values for efficacy and toxicity. This provides a better insight since the AUC_{24h} is a better predictor of the risk for toxicity than C_{min}<1 mg/L. Moreover, our study provides a more complete insight into the effect of individual variance on target attainment.

DOSING REGIMEN IN NON-SEPTIC PATIENTS

Administering gentamicin before dialysis could increase efficacy and decrease toxicity based on more favorable drug levels than postdialysis dosing. Postdialysis dosing results in a very high AUC_{24h} relative to C_{max}. Therefore, efficacious postdialysis treatment with C_{max}/MIC >8 would have an increased risk of toxicity compared with predialysis dosing.

Nevertheless, caution should be exercised for predialysis dosing. Predialysis dosing resulted in a low mean AUC_{24h} (regimens 1 and 2) because most of the gentamicin concentration is eliminated by dialysis. Simulations show that dosing 2h prior is more favorable than 1h before hemodialysis to obtain a higher AUC_{24h}. Moreover, it is not known if gentamicin is still effective when low drug levels persist for a long period (between 1–2 mg/L for 42h or 66h between dialysis). A higher dose could be administered to achieve a higher AUC_{24h}; however, strict therapeutic drug monitoring is required because C_{max} and AUC_{24h} could be far above the target values. Dosing longer than 2h before dialysis to increase the AUC_{24h} is not advisable, because adaptive resistance can occur within 1–2h after dosing.[7]

Teigen *et al.* and Dang and Duffull also concluded that predialysis dosing results in better target attainment than postdialysis dosing.[12, 14] However, Zhuang *et al.* concluded that

postdialysis dosing results in the same bacterial response as predialysis dosing based on a PK/PD model and advised postdialysis dosing with gentamicin.[5]

Clinicians should be aware of the variations in target attainment due to individual variations. Nevertheless, target attainment for predialysis dosing is more favorable in all scenarios than for postdialysis dosing. A higher $CL_{dialysis}$ resulted in significantly lower values for AUC_{24h} and *vice versa*. Furthermore, similar target attainment was found in obese patients (≥90 kg) compared to that in patients with a healthy weight (70 kg). However, AUC_{24h} is higher in obese patients; therefore, TDM is recommended. Patients infected with microorganisms displaying an MIC of 2 mg/L would require an AUC_{24h} of 140 mg·h/L for effective treatment, which is higher than the maximum of 120 mg·h/L established as the PD target for safety. Therefore, the benefits of gentamicin treatment should be weighed against the potentially higher risk of toxicity.

DOSING REGIMEN IN SEPTIC PATIENTS

Septic patients receiving predialysis dosing had a higher AUC_{24h} relative to C_{max} than non-septic patients. This is a result of the lower extraction of gentamicin by the dialyzer due to a higher volume of distribution. Thus, dosing 1h before dialysis is considered the optimal dosing regimen (regimen 4).

LIMITATIONS

The selected PD targets were primarily based on patients with normal renal function. Therefore, it cannot be concluded with certainty that these PD targets are valid in patients with renal dysfunction. Furthermore, gentamicin is normally used in combination with other antibacterial drugs such as beta-lactams; however, the influence of the combination therapy on PD targets was not considered because published PD studies are based on gentamicin

monotherapy. However, we hypothesize that an optimized gentamicin dosing scheme will result in optimized combination therapy.

Dosing 1–2 hours before dialysis is logistically inconvenient for patients who are not hospitalized especially since hemodialysis is already a time-consuming treatment. Therefore, whether the benefit of predialysis dosing is worth the extended time in the hospital should be discussed with the patient so that an informed decision can be made.

Another limitation is that several other dialysis modalities were not discussed in this study (*e.g.*, sustained low-efficiency (daily) dialysis, peritoneal dialysis, and continuous renal replacement therapy).

Conclusions

Currently, gentamicin is recommended for intermittent hemodialysis. Based on our simulations, we conclude that the target attainment for the PK/PD indices of predialysis dosing is preferred compared to that of postdialysis dosing. However, caution is needed because there is some uncertainty about the PD targets used, and there are no clinical studies to prove the benefit of predialysis dosing. Clinicians should consider predialysis dosing of gentamicin in combination with strict monitoring of gentamicin levels and adherence to targets to attain the desired PK/PD index. It is recommended to keep updating the pharmacokinetic profile of gentamicin in hemodialysis patients, as clearance by dialysis is improving with advances in dialysis technology.

Further research must be conducted to conclude with certainty the benefits of predialysis dosing in patients undergoing intermittent hemodialysis. The ideal design would be a randomized, double-blind study that compares pre- and post-dialysis dosing of aminoglycosides with clinical endpoints. Due to the limited number of patients treated with gentamicin, this randomized, double-blind study would require a multicenter approach. An

international organization (*e.g.* the International Association of Therapeutic Drug Monitoring and Clinical Toxicology) could play a coordinating role.

References

1. Gupta V, Yassin MH. Infection and hemodialysis access: an updated review. *Infect Disord Drug Targets*. 2013;13(3):196-205.

2. TDM-monografie. Gentamicine. 2018. https://tdm-monografie.org/monografie/gentamicine Accessed June, 2020.

3. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26(1):1-12.

4. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob Agents Chemother*. 1999;43(3):623-629.

5. Zhuang L, He Y, Xia H, Liu Y, Sy SK, Derendorf H. Gentamicin dosing strategy in patients with end-stage renal disease receiving haemodialysis: evaluation using a semi-mechanistic pharmacokinetic/pharmacodynamic model. *J Antimicrob Chemother*. 2016;71(4):1012-1021.

6. 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;52(4):668-674.

7. Eschenauer GA, Lam SW, Mueller BA. Dose Timing of aminoglycosides in hemodialysis patients: A pharmacology view. *Semin Dial*. 2016;29(3):204-213.

8. O'Shea S, Duffull S, Johnson DW. Aminoglycosides in hemodialysis patients: is the current practice of post dialysis dosing appropriate? *Semin Dial*. 2009;22(3):225-230.

9. Verpooten GA, Giuliano RA, Verbist L, Eestermans G, De Broe ME. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. *Clin Pharmacol Ther.* 1989;45(1):22-27.

10. Gentamicin 40mg/ml Injection. Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/6531/smpc#CLINICAL_PRECAUTIONS Published 2021. Accessed November 5, 2021.

11. Gentamicin Injection, USP. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/062366s033lbl.pdf. Published 2013. Accessed November 5, 2021.

12. Dang L, Duffull S. Development of a semimechanistic model to describe the pharmacokinetics of gentamicin in patients receiving hemodialysis. *J Clin Pharmacol.* 2006;46(6):662-673.

13. Veinstein A, Venisse N, Badin J, Pinsard M, Robert R, Dupuis A. Gentamicin in hemodialyzed critical care patients: early dialysis after administration of a high dose should be considered. *Antimicrob Agents Chemother.* 2013;57(2):977-982.

14. Teigen MM, Duffull S, Dang L, Johnson DW. Dosing of gentamicin in patients with end-stage renal disease receiving hemodialysis. *J Clin Pharmacol.* 2006;46(11):1259-1267.

15. Jelliffe RW, Iglesias T, Hurst AK, Foo KA, Rodriguez J. Individualising gentamicin dosage regimens. A comparative review of selected models, data fitting methods and monitoring strategies. *Clin Pharmacokinet.* 1991;21(6):461-478.

16. Triginer C, Izquierdo I, Fernández R, et al. Gentamicin volume of distribution in critically ill septic patients. *Intensive Care Med.* 1990;16(5):303-306.

17. Gordon RC, Regamey C, Kirby WM. Serum protein binding of the aminoglycoside antibiotics. *Antimicrob Agents Chemother.* 1972;2(3):214-216.

18. Rosenkranz H, Scheer M, Scholtan W. Binding of aminoglycoside antibiotics to human serum proteins. III. Effect of experimental conditions. *Infection.* 1978;6(2):57-64.

19. Vossen MG, Pferschy S, Milacek C, et al. In vivo / in vitro Correlation of Pharmacokinetics of Gentamicin, Vancomycin, Teicoplanin and Doripenem in a Bovine Blood Hemodialysis Model. *Front Pharmacol.* 2021;12:702455.

20. Franck B, Monchaud C, Saint-Marcoux F, et al. Population pharmacokinetics of gentamicin in haemodialysis patients: modelling, simulations and recommendations. *Eur J Clin Pharmacol.* 2020;76(7):947-955.

21. 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;155(1):93-99.

22. Keller F, Borner K, Schwarz A, Offermann G, Lode H. Therapeutic aminoglycoside monitoring in renal failure patients. *Ther Drug Monit.* 1987;9(2):148-153.

23. Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. *Br J Clin Pharmacol.* 1995;39(6):605-609.

24. Barclay ML, Duffull SB, Begg EJ, Buttimore RC. Experience of once-daily aminoglycoside dosing using a target area under the concentration-time curve. *Aust N Z J Med.* 1995;25(3):230-235.

25. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother.* 1999;43(7):1549-1555.

26. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother.* 1995;39(3):650-655.

27. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 11.0, 2021. http://www.eucast.org. Accessed November , 2021.

28. Prins JM, Büller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. *Lancet.* 1993;341(8841):335-339.

29. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother.* 1996;37(4):645-663.

30. 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;3(2):355-361.

31. Decker BS, Mohamed AN, Chambers M, Kraus MA, Moe SM, Sowinski KM. Gentamicin pharmacokinetics and pharmacodynamics during short-daily hemodialysis. *Am J Nephrol.* 2012;36(2):144-150.

32. Said N, Lau WJ, Ho YC, Lim SK, Zainol Abidin MN, Ismail AF. A review of commercial developments and recent laboratory research of dialyzers and membranes for hemodialysis application. *Membranes (Basel).* 2021;11(10):767.

Table 1 Simulated mean maximal concentrations (C_{max}), area under the curve over 24 h (AUC_{24h}), and target attainment of the pharmacodynamic targets for the different dosing regimens of both non-septic and septic patients (n = 1,000 subjects).

					TARGET ATTAINMENT				
Regimen	**Time**	**Dose**	**Mean C_{max} (mg/L)**	**Mean AUC_{24h} (mg·h/L)**	**C_{max}> 8 mg/L**	**C_{max}<20 mg/L**	**AUC_{24h}> 70 mg·h/L**	**AUC_{24h}<120 mg·h/L**	**All**
1	1 h prior	5 mg/kg	21	80	100%	44%	57%	80%	18%
2	2 h prior	5 mg/kg	21	87	100%	40%	65%	77%	18%
3	post	start 2.5 mg/kg, then 1.5 mg/kg	7	129	35%	100%	100%	45%	4%
SEPTIC PATIENTS:									
4	1 h prior	6 mg/kg	14	126	99%	96%	90%	53%	39%
5	2 h prior	6 mg/kg	14	129	98%	97%	91%	51%	39%
6	post	start 3 mg/kg, then 1.8 mg/kg	5	94	3%	100%	93%	91%	1%

Figure Legend

Figure 1 Predicted gentamicin concentration-time curves of different dosing regimens of non-septic (regimens 1–3) and septic patients (regimens 4–6) based on the simulations (n = 1,000 subjects). Black area: dialysis session of 4 h; arrow: gentamicin administration; grey: 90% prediction interval; black line: median concentration.

List of Supplemental Digital Content

Supplemental Digital Content 1.docx

Supplemental Digital Content 2.docx

Supplemental Digital Content 3.docx

Supplemental Digital Content 4.docx

Supplemental Digital Content 5.docx