

Single Daily Dosing of Gentamicin: Pharmacokinetic Comparison of Two Dosing Methodologies for Postpartum Endometritis

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ABSTRACT

Objective: We compared the pharmacokinetics of two methods for dosing gentamicin for the treatment of postpartum endometritis with the goal of achieving adequate peak serum concentrations (>12 mg/L) and prolonged trough levels below 2 mg/L.

Methods: Group-I subjects (n = 5) received intravenous gentamicin, 5 mg/kg per total body weight over 60 min., with a maximum dose of 500 mg. Group-II subjects (n = 17) were dosed intravenously according to the following formula: Dose = desired peak concentration (fixed at 14 mg/L) * (volume of distribution, i.e., 0.35 L/kg) * adjusted body weight (in kilograms). Serum gentamicin levels were obtained 1 hr. and 8–12 hr. after infusion of the second dose. Pharmacokinetic parameters for the subjects in each group were calculated according to standard formulas.

Results: Subjects in Group I had significantly higher doses and peak drug concentrations ($P < 0.01$), while in Group II, 76% of patients had peak levels less than desired (<12 mg/L). Both groups maintained trough levels of <2 mg/L in excess of 12 hr.

Conclusions: Changing to the adjusted body weight formula for Group I, while maintaining a dose between 4 and 5 mg/kg, would reduce excessive peak concentrations. Using a calculated volume of distribution of 0.4 L/kg in Group II would improve peak serum concentrations to the desired levels. Both dosing regimens ensure adequate aminoglycoside pharmacokinetic parameters and avoid the need for monitoring serial serum drug concentrations, provided the expected clinical response is also achieved. While the first dosing formula is simpler to calculate, the second dosing formula allows for more individualized dosing considerations. *Infect. Dis. Obstet. Gynecol.* 7:133–137, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS

endometritis; gentamicin; pharmacokinetics

Aminoglycosides in combination with ampicillin, clindamycin, or metronidazole represent a cost-effective treatment for postpartum endometritis, provided excessive serum concentration monitoring and nephrotoxicity do not occur.¹ Traditionally, peak concentrations of aminoglycosides >6.0 mg/L have been associated with efficacy, and

trough concentrations <2.0 mg/L have been associated with decreased toxicity.² Administering aminoglycosides as single, large, daily doses takes advantage of several pharmacokinetic (i.e., concentration-dependent killing activity) and pharmacodynamic (i.e., postantibiotic effect) properties.³ Nephrotoxicity is reported to occur in 5–10% of

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patients receiving aminoglycosides. Major risk factors for developing nephrotoxicity include older age, multisystem disease, preexisting renal disease (estimated by a creatinine clearance <60 mL/min), and concomitant administration of nephrotoxic drugs.⁴ Once-daily dosing has demonstrated equal efficacy and toxicity when compared with conventional dosing for many serious infections.³

Postpartum patients are often initially underdosed with aminoglycosides, presumably due to their altered physiologic state.⁵⁻⁷ Equilibrium for creatinine clearance in the postpartum state has been noted to be reestablished within 2-5 days following delivery.⁸ Administering large, single, daily doses may represent a strategy to ensure optimal peak concentrations and minimize both toxicity and the need for therapeutic drug monitoring.^{9,10}

The purpose of this study was to compare the pharmacokinetics of two methods of single, daily dosing of aminoglycosides for the treatment of postpartum endometritis. Goals included 1) achieving adequate peak serum concentration (12-14 mg/L) and 2) prolonged period of serum concentration below 2 mg/L. The data presented are those derived from two independently run obstetric services within a single health care system as a part of a clinical trial to establish optimal dosing regimens.

SUBJECTS AND METHODS

This study was, by design, observational only. Patients in Group I being treated for a clinical diagnosis of postpartum endometritis were prescribed gentamicin and received a dose of 5 mg/kg per total body weight once daily (maximum dose = 500 mg). Patients in Group II were dosed according to the following formula: dose = desired peak concentration (fixed at 14 mg/L) * (volume of distribution, 0.35L/kg) * adjusted body weight (ABW, in kilograms).¹¹ Exclusion criteria included renal dysfunction (creatinine clearance < 50 mL/min), history of ototoxicity or nephrotoxicity due to aminoglycosides, and age <16 years. All doses were infused over 60 min.

All patients were monitored daily by the respective hospital pharmacy pharmacokinetic services. Blood samples for drug concentrations were drawn by venipuncture after the second dose. Peak concentration was drawn 1 hr following end of infusion, and a midpoint concentration was drawn 8-12

TABLE I. Patient characteristics^a

Characteristic	Group I (n = 5)	Group II (n = 17)
Race: black/white	4/1	13/4
Age (y)	18.8 (1.9)	23.3 (3.6)
Range	17-22	18-33
Total body weight (kg)	80.0 (17.7)	88.2 (19.7)
Range	56-100	42-118
Ideal body weight	57.1 (7.1)	52.4 (5.3)
Adjusted body weight	69.3 (3.1)	68.8 (8.1)
Height (in)	65.0 (3.2)	63.2 (2.4)

^aResults given as mean (standard deviation). There were no statistically significant differences between the two groups.

hr following end of infusion. Trough concentration was calculated using a one-compartment equation and data from the two levels.

Statistical analysis for characteristics of the patient population and pharmacokinetic parameters of the two gentamicin dosing regimens were performed using the unpaired Student *t* test (*P* < 0.05).

RESULTS

Five patients were studied using weight-based calculations, and 17 were studied using standard pharmacokinetic equations. Table 1 presents patient characteristics for the two groups. No statistical differences between the groups were found. Table 2 compares the pharmacokinetic parameters for the two groups. Peak and trough values were extrapolated using the two measured concentrations. Both total dose and calculated peak concentrations were statistically higher for Group I. Figures 1 and 2 graphically represent individual patient data. For Group I, all patients had peak serum concentrations >12 mg/L; however, 40% had peaks over 20 mg/L. For Group II, 76% of patients had peak concentrations less than desired (< 12 mg/L). All patients in both groups were below 2.0 mg/L for ≥12 hr. Table 3 compares baseline renal function for patients in both groups. Nearly all patients were discharged before follow-up creatinine levels were obtained. No clinically apparent ototoxicity was observed. Although clinical efficacy was not a planned objective of this study, all patients demonstrated appropriate resolution of their clinical infections in a timely fashion.

DISCUSSION

This observational study demonstrates two methods of single-daily dosing of aminoglycosides in

TABLE 2. Pharmacokinetic comparisons of Group I and Group II^a

Parameter	Group I (n = 5)	Group II (n = 17)
Dose (mg)*	404 (97.4)	325 (53.2)
Range	280–500	210–400
Peak ^b (mg/L)**	20.54 (4.12)	12.28 (3.21)
Trough ^b (mg/L)	0.056 (0.037)	0.050 (0.066)
K _a (h ⁻¹)	0.25 (0.01)	0.28 (0.07)
Clearance (mL/min)	112.55 (35.79)	130.20 (49.02)
Half-life (hr)	2.62 (0.33)	2.60 (0.70)
VD ^c (L)	26.72 (8.28)	27.80 (6.97)
VD (L/kg)	0.39 (0.10)	0.43 (0.10)

^aResults given as mean (standard deviation).

^bExtrapolated values.

^cVD, volume of distribution.

**P* < 0.05.

***P* < 0.01.

postpartum patients with endometritis. These data are consistent with Del Priore et al.⁹ and Mitra et al.,¹² who demonstrated the efficacy of this dosing regimen compared with traditional thrice-daily administration. Additionally, our data compare two different methodologies for calculating the gentamicin dose and point out potential areas for improvement.

The weight-based method achieved adequate peak concentrations, although 40% of our study patients had peaks in excess of 20 mg/L. In the Del Priore et al.⁹ study, in which the same 5-mg/kg calculation was used, the investigators reported peak concentrations (16.6 mg/L) similar to those in our study, but did not indicate the number of subjects with peak levels >20 mg/L.

The formula-based method resulted in 76% of patients reaching peak concentrations below our target of 12 mg/L. Of note, all of these patients would have been considered successes in the Del Priore et al.⁹ study, since the target peak concentration in that study was >5 mg/L. Although the general literature acknowledges that the lower peak concentration is acceptable for gentamicin dosing, higher values provide an increased likelihood of organism susceptibility. Also of interest is the fact that we used the well accepted volume of distribution of 0.35 L/kg in our formula-based calculation,⁹ whereas the actual calculated mean value for the group was 0.43 L/kg.

Garrelts¹³ compared formula-based and weight-based once-daily aminoglycoside dosing through a Bayesian software program using data from a variety of patients, excluding pregnant and postpartum

women. Patients included 100 adults who were treated with aminoglycosides for pneumonia, sepsis, skin and soft tissue infections, endocarditis, intraabdominal infection, and urinary tract infection. Computer simulation demonstrated that weight-based calculations for once-daily aminoglycosides would not reliably produce clinically acceptable serum concentrations or target values. Patients most likely not to achieve target values included the young and the elderly and patients with creatinine clearances below 60 mL/min or above 119 mL/min. The author recommended individualized regimens based upon evaluating the peak-to-minimum inhibitory concentration ratio, time above minimum inhibitory concentration, and patient response.

Using Group I's pharmacokinetic data, we performed a limited simulation to estimate peak aminoglycoside concentrations by varying patient weights (ideal body weight and ABW) and drug doses. These results are displayed in Table 4 and suggest either 4 mg/kg (based on total body weight) or 5 mg/kg (based on ABW) would result in acceptable peak concentrations.

In summary, if a weight-based formula is the basis for calculating the gentamicin dose, using either 4 mg/kg or 5 mg/kg per ABW would achieve appropriate peak concentrations while avoiding excessive values for both patients near ideal body weight and obese patients. Empirically, we would suggest using a formula-based calculation for patients requiring more than 500 mg daily dosing, based on the weight-based method. When using the formula-based method approach, a volume of distribution of 0.4 L/kg to calculate the original dose would increase the peak concentration to desired levels and maintain troughs below 2 mg/L. In a subsequent group of 10 patients at our institution dosed according to the formula calculation using 0.4L/kg, all had peaks between 12 and 20 mg/L and troughs <2 mg/L. Pharmacokinetic parameters (drug clearance, half-life, and volume of distribution) were all similar to our original study population, and eight of the 10 were above 30% of ideal body weight.

Both the weight-based and formula-based dosing regimens ensure adequate aminoglycoside pharmacokinetic parameters and obviate the need for monitoring serum drug concentrations. Of course, this is provided that the expected clinical outcomes are also achieved. While the weight-

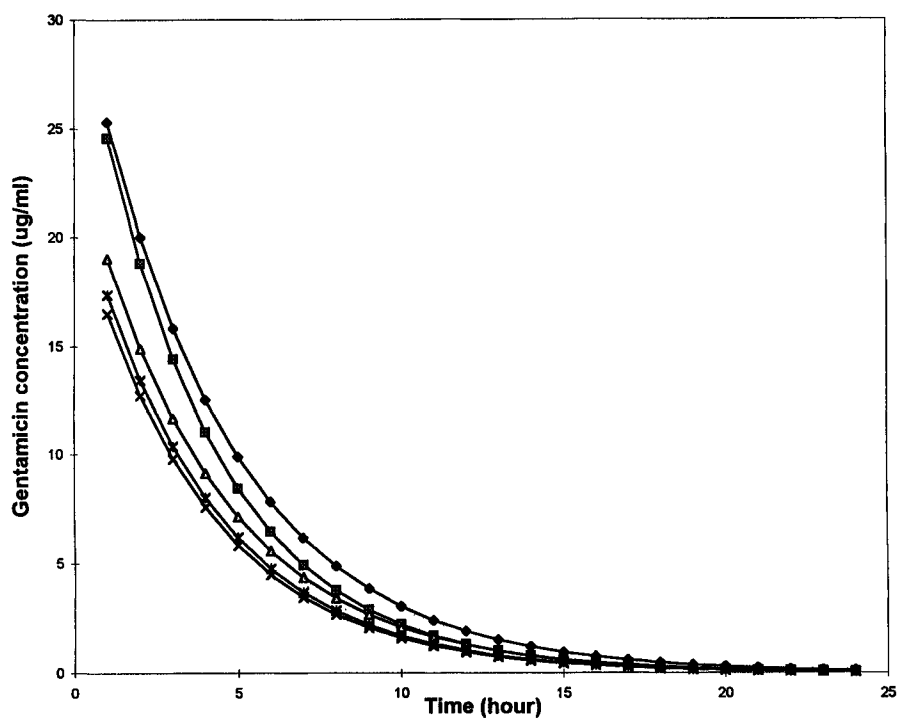


Fig. 1. Gentamicin time-concentration curve in Group-I patients.

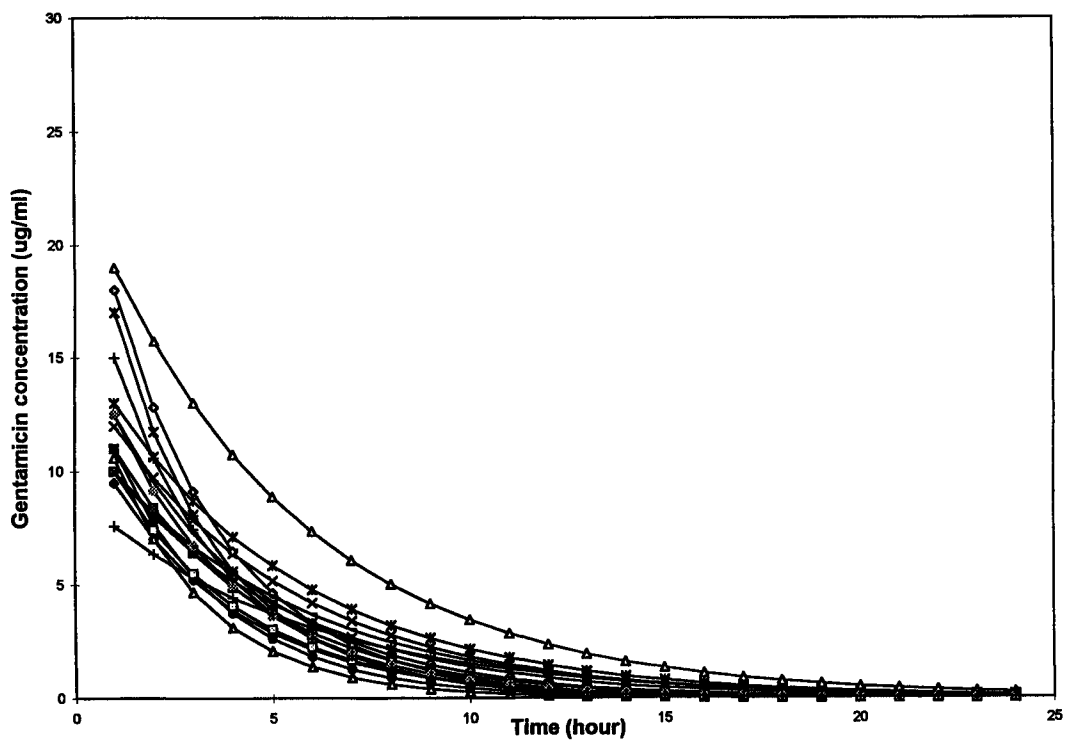


Fig. 2. Gentamicin time-concentration curve in Group-II patients.

TABLE 3. Baseline renal function^a

Parameters	Group I (n = 5)	Group II (n = 17)
Creatinine (mg/dL)	0.85 (0.10)	0.75 (0.15)
Range	0.8–1.0	0.6–1.1
Creatinine clearance (mL/min)	94.7 (5.82)	99.21 (20.88)
Range	81.30–100.5	64.67–120.63

^aResults given as mean (standard deviation).

TABLE 4. Simulated peak concentrations based on Group-I patient data^a

Dose	Patients @ IBW	Patients > 30% IBW
5 mg/kg TBW	16–17 µg/mL	19+ µg/mL
5 mg/kg ABW	16–17 µg/mL	16–17 µg/mL
4 mg/kg TBW	12–13 µg/mL	16+ µg/mL
4 mg/kg ABW	12–13 µg/mL	12–13 µg/mL

^aTBW, total body weight; IBW, ideal body weight; ABW, adjusted body weight.

based method is simpler to calculate, the formula-based method allows for more individualized dosing considerations.

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