

Pharmacokinetics and clinical evaluations of gentamicin-induced nephrotoxicity in puppies

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ABSTRACT

Background: The study was aimed at investigating the effect of dosing intervals on gentamicin nephrotoxicity in puppies.

Methods: Local puppies were assigned to Groups A and B (n=6) and administered gentamicin intramuscularly once (6 mg/kg) or twice (3 mg/kg) daily, respectively, for 5 consecutive days. Biochemical parameters such as urine protein, creatinine, γ -glutamyl transferase, as well as serum creatinine (SCR) and urea nitrogen were determined spectrophotometrically using specific kits before and after treatment. Peak and trough serum concentrations of gentamicin were determined by immunoassay on 1st and 5th day treatment. Thereafter, elimination rate constants and corresponding half-lives were calculated.

Results: No significant increase in SCR concentrations in both groups was observed, but values on day 7 were slightly above normal. Conversely, there was a significant increase above normal in serum urea nitrogen on days 4 and 7 in Group A, whereas this was observed only on day 7 in Group B. Even though all other biochemical parameters assayed for were within normal, an increasing trend was noticed as the length of treatment days increased in both groups. In both groups, peak serum concentrations of gentamicin did not differ significantly. There was a 4- and 16-fold significant increase in trough levels after the last treatment in Groups A and B, respectively. Although peak and trough concentrations increased with increasing length of treatment, all the values were well below 10 μ g/ml and 2 μ g/ml, respectively, as required.

Conclusion: These suggest the risk of nephrotoxicity following treatment with gentamicin beyond 5 consecutive days irrespective of the dosing interval in puppies.

Keywords: Gentamicin, Nephrotoxicity, Dosing interval, Puppies

INTRODUCTION

Antibiotics have long been, and remain, a major cause of drug-related renal toxicity. Most cases of acute renal failure are related to acute tubular necrosis, for which aminoglycosides have been reported to be one of the leading causes.¹ Gentamicin is an aminoglycoside with a proven efficacy against many aerobic Gram-negative organisms in both human and animals.² It remains the aminoglycoside of choice in hospitals and areas that have minimal background of resistance because of its efficacy and low cost.³ However, drawbacks to the widespread use of gentamicin have included the perceived need for frequent administrations, its adverse effect and the requirement of therapeutic monitoring.

Nephrotoxicity and ototoxicity are the most frequently reported adverse effects associated with aminoglycoside therapy.⁴ The risk of nephrotoxicity due to aminoglycosides is dependent on the specific aminoglycoside used as well as peak (C_{max}) and trough (C_{min}) serum concentrations attained.⁵⁻⁸ Other risk factors include total dose administered, length of therapy, age, dehydration, concurrent liver disease, and co-administration with other potentially nephrotoxic drugs.^{9,10} Nevertheless, in an attempt to design a dosage regimen for gentamicin to reduce toxic effects, one has to in addition maximize therapeutic efficacy.

In veterinary practice, therapeutic failures and deaths of animal patients are more often attributed to the presented

clinical condition. Scarcely, a thought is given to the effect of the drug which could be influenced by the dosage regimen adopted among other factors. The study was aimed at investigating the effect of dosing intervals on gentamicin nephrotoxicity in puppies.

METHODS

Animals

A total of 12 healthy mongrel puppies of mixed sex were used. Puppies enrolled were between 2 and 3 months of age weighing 3.5-5 kg body weight. They were allowed to acclimatize for 2 weeks, during which they were fed standard diet twice a day, while potable water was provided *ad libitum*.

Experimental design

Animals were individually weighed daily for the calculation of daily gentamicin dosages. A parallel design was adopted where puppies were randomly assigned to Groups A and B with six puppies each (n=6). Before treatment, blood samples were obtained from each animal via cephalic vein into a plain 5 ml sample bottle. The blood samples were allowed to clot, centrifuged at 5000 rpm for 5 mins and the serum obtained with a micropipette and analyzed same day for serum creatinine (SCR) and urea nitrogen concentrations as baseline values. Similarly, urine sample was collected from each puppy by cystocentesis for urinalysis and to determine urine creatinine (uCr), total protein, and γ -glutamyl transferase (GGT).

Drug administration and sampling

Animals in Group A were administered gentamicin sulfate (Gentalek[®], Slovenia) by intramuscular route at a dose of 6 mg/kg once daily (24 hourly) for 5 consecutive days. Thereafter, blood samples were obtained at 1.5 and 23.5 hrs after the 1st, 3rd, and 5th treatments for peak and trough serum gentamicin concentrations. Puppies in Group B were treated twice daily (12 hourly) at a dose rate of 3 mg/kg body weight. Thereafter, a blood sample was obtained from each puppy at 1.5 and 23.5 hrs after the 2nd, 6th, 10th treatments for peak and trough serum gentamicin concentrations. All blood samples were collected into plain sample bottles, thereafter centrifuged at 5000 rpm for 5 mins to obtain the serum which were stored under -20°C till gentamicin assay. The serum samples obtained 23.5 hrs after the 3rd and 6th treatments from puppies in Groups A and B, respectively, were additionally analyzed for SCR and urea nitrogen. Similarly, urine was obtained 23.5 hrs after the 3rd and 6th doses from puppies in Groups A and B, respectively, for urinalysis, protein, creatinine, and GGT assay. Finally, blood and urine samples were taken from all the experimental animals on day 7 post first treatments for serum and urine analyses. This period was chosen based on the fact that more

overt signs of nephrotoxicity are detected about 7-10 days post initiation of treatment.¹¹

Assay of clinical biochemical markers

Urine specific gravity (USpgr) was determined with the aid of a total solid refractometer (Reichert Vet 360 TS meter, USA). Serum and uCr, serum urea nitrogen (SUN), urine total protein, and GGT were determined spectrophotometrically using their respective commercial kits (Randox Laboratories Ltd., UK).

Gentamicin assay

Gentamicin enzyme-linked immunosorbent assay kit (Green Spring, China) was employed in accordance with the manufacturer's recommendation. A linear plot was obtained when the absorption percentages of the standard solutions of gentamicin provided (0.1, 0.3, 0.9, 2.7, and 8.1 $\mu\text{g}/\text{ml}$) and their respective logarithmic value were plotted with a correlation coefficient of -0.997 .

Pharmacokinetic analysis

The elimination rate constants (β) were calculated as $\beta = (\ln C_{\max} - \ln C_{\min}) / \Delta t$.^{12,13} Where C_{\max} and C_{\min} are peak and trough serum concentrations, respectively, while Δt is the time between measurements of C_{\max} and C_{\min} . The plasma half-lives of elimination ($t_{1/2\beta}$) were obtained from $t_{1/2\beta} = 0.693 / \beta$, where β is the average of the values obtained on days 1, 3, and 5 for each group.¹⁴

Statistical analysis

One-way analysis of variance was conducted on all the values using IBM[®] SPSS statistics, version 20. The means were compared using Tukey *Post-hoc* test at $p < 0.05$ for statistical significant difference.

RESULTS

Table 1 shows some biochemical markers of nephrotoxicity after a once (6 mg/kg \times 5/7) or twice (3 mg/kg \times 5/7) daily dose regimen of gentamicin by intramuscular route.

There was no significant ($p > 0.05$) increase from the baseline value of SCR levels on days 4 and 7 in Group A, however, the increase from day 4 to 7 was significant ($p < 0.05$). Similarly, no significant effect was observed in puppies in Group A. There was a significant increase from the baseline values of SUN on days 4 and 7 in Group A whereas in Group B the increment was significant only on day 7. Urine creatinine (uCr) levels in both treatments increased significantly from the pre-treatment value in all the groups. In all the treatments, urine GGT levels decreased significantly from the baseline values on day 4, which

subsequently increased significantly on day 7 from the values observed on the 4th day. Urine protein (UP) levels were not significantly affected by any of the treatments, although an increasing trend was noticed in Group B. There was no significant effect of the two dosing intervals on UP/uCr, USpgr and urine pH values. The GGT/uCr ratio in both treatments was affected following 3 days treatments where a significant decrease was observed.

Mean peak and trough serum gentamicin concentrations (C_{max} and T_{min} respectively) for each sampling point with their corresponding mean elimination rate constants (β) and half-lives ($t_{1/2\beta}$) are presented in Table 2.

In Groups A and B, peak serum concentrations of gentamicin (C_{max}) did not differ significantly ($p < 0.05$) on days 1, 3, and 5. Although there was a marginal increase as the length of treatments increased, all the values were $< 10.0 \mu\text{g/ml}$. Trough serum concentrations (C_{min}) were not detected at 23.5 hrs following the first treatments in both groups. There was a 4 and 16 folds significant ($p < 0.05$) increase in C_{min} levels after the 5th day treatments in Groups A and B, respectively, when compared with corresponding values observed on the

2nd day of treatment. However, all the C_{min} levels observed were $< 2.0 \mu\text{g/ml}$. There was no significance difference within and between groups when the groups mean values of elimination rate constant (β) and elimination half-life ($t_{1/2\beta}$) were subjected to a multiple comparison.

DISCUSSION

A classical diagnosis of acute kidney disease involves measurement of surrogate markers of reduction in the glomerular filtration rate (GFR), which are a rise above normal in SCR and urea nitrogen.^{15,16} This study shows no significant (statistical and clinical) change in both SCR and urea concentrations 24 hrs after the 3rd day of treatment with gentamicin irrespective of the dosing interval used. Conversely, serum concentrations of creatinine increased above the normal upper limit of 1.7 mg/dl 7 days after the 5th day of treatments of the subjects on once (6 mg/kg) or twice (3 mg/kg) daily intramuscular injection.¹⁷ Likewise, SUN concentrations increased significantly from the baseline values to above the normal upper limit of 28 mg/dl reported for dogs in Groups A and B after the 5th day of treatments.¹⁷

Table 1: Some biochemical indicators of gentamicin-induced nephrotoxicity in puppies on once or twice daily intramuscular treatment (n=6).

Parameter (unit)	A (6 mg/kg 24 hourly)			B (3 mg/kg 12 hourly)		
	Day 0	Day 4	Day 7	Day 0	Day 4	Day 7
SCR (mg/dl)	1.6±0.12	1.5±0.06 ^a	1.9±0.21 ^a	1.7±0.09	1.5±0.12	1.8±0.07
SUN (mg/dl)	24.7±1.20 ^a	18.0±1.16 ^a	37.3±1.86 ^a	17.0±2.65 ^c	19.0±2.00 ^d	33.7±2.33 ^{c,d}
UGGT (U/L)	4.17±0.20 ^a	1.57±0.19 ^{a,b}	4.10±0.38 ^b	4.30±0.23 ^c	1.57±0.42 ^{c,d}	3.18±0.44 ^d
UP (mg/dl)	2.17±0.20	1.83±0.09	2.23±0.30	1.57±0.31	2.03±0.38	2.73±0.68
uCr (mg/dl)	30.0±4.36 ^a	35.7±1.76 ^b	49.7±1.76 ^{a,b}	34.3±3.38 ^c	44.3±1.76	47.3±2.33 ^c
UP/uCr	0.08±0.01	0.12±0.00	0.043±0.01	0.05±0.02	0.05±0.02	0.06±0.01
UGGT/uCr	0.15±0.02 ^a	0.05±0.00 ^a	0.08±0.01	0.13±0.02 ^c	0.04±0.01 ^c	0.08±0.01
USpgr	1.017±0.01	1.015±0.00	1.014±0.00	1.014±0.00	1.020±0.00	1.020±0.00
UpH	6.5±0.289	6.8±0.60	6.9±0.31	7.8±0.17	7.1±0.46	7.3±0.24

Data presented as mean±SEM (n=6); same superscript indicate statistically significant difference with each other at $p < 0.05$ for each analyte. GGT: γ -glutamyl transferase, UP: Urine protein, uCr: Urine creatinine, SCR: Serum creatinine, SUN: Serum urea nitrogen, UGGT: Urine γ -glutamyl transferase, USpgr: Urine specific gravity, UpH: Urine pH, SEM: Standard error mean

Table 2: Pharmacokinetic indicators of gentamicin-induced nephrotoxicity in puppies on once or twice daily intramuscular treatment (n=6).

Surrogate marker (unit)	A (6 mg/kg 24 hourly)			B (3 mg/kg 12 hourly)		
	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5
C_{max} ($\mu\text{g/ml}$)	6.31±0.59	6.39±0.48	7.59±0.99	5.91±0.31	6.88±0.93	8.51±1.50
5 days mean C_{max}	-	-	6.41	-	-	7.10
C_{min} ($\mu\text{g/ml}$)	ND	0.02±0.00	0.08±0.43*	ND	0.06±0.09	0.98±0.36*
5 days mean C_{min}	-	-	0.05	-	-	0.52
β (h^{-1})	0.29±0.03	0.21±0.02	0.29±0.05	0.27±0.02	0.27±0.04	0.27±0.07
$t_{1/2\beta}$ (h)	2.47±0.27	3.38±0.38	2.47±0.35	2.91±0.31	2.73±0.41	2.96±0.74

Data is presented as mean±SEM (n=6), *Significant difference between each other at $p < 0.05$, ND: Not detected; Reference average MIC=0.5 $\mu\text{g/ml}$, SEM: Standard error mean, MIC: Minimum inhibitory concentration

These findings suggest that a 3 days consecutive treatment of puppies with gentamicin by intramuscular route either by once (6 mg/kg) or twice (3 mg/kg) daily dose interval will not have a significant clinical effect on the GFR. On the contrary, there is a risk of nephrotoxicity when the duration of treatment is extended beyond 5 days irrespective of the dosing interval. This is because of the increase in SCR and urea nitrogen levels as the length of treatment was increased. For this reason, there is a need to institute daily monitoring of renal function and trough concentration of gentamicin when extension beyond 5 days is inevitable.

The ratio of UP/uCr is useful for quantifying urinary protein loss from renal origin.¹⁸ Values <0.5, 0.5-1.0, and >1.0 in dogs are considered normal, questionable, and abnormal, respectively.^{17,19} Simultaneous UP/uCr determinations with single sample in this study show that none of the dosing intervals used has any clinical significant effect on the glomerular integrity and subsequent GFR. This is due to the fact that the mean UP/uCr ratio obtained in all the groups at every point of assay were well within the normal limit of <0.5 reported for dogs.

Enzymes large enough to be restricted from the glomerular filtrate, but having high activity in the renal tubular epithelial cells have been measured in the urine as an indicator of tubular damage.¹⁷ One of the enzymes specific for early proximal tubular injury in gentamicin-induced nephrotoxicity is GGT.^{20,21} In various studies in dogs with gentamicin-induced nephrotoxicity, 24 hrs urinary GGT and spot uCr sample ratio were found to be more sensitive and reliable methods of detecting tubular damage, particularly in the early phase, before other serum and urine findings were altered.^{22,23} This ratio measures urinary GGT loss from renal tubular epithelial cells. In dogs, urine GGT/uCr ratio has been reported to increase thrice above baseline value before azotemia and other abnormalities occur.²⁴ Even though mean GGT/uCr ratio 24 hrs following the 3rd day of treatment for all dosing intervals used in this study differed significantly from their respective pre-dose ratios, the values were well below the normal higher limit of 0.39 ± 0.18 .²² This, therefore, suggests that there is no clinically significant effect of the two dosing regimens on the epithelial cells of the proximal tubule. No significant effect was noticed after the 5th day treatment in both groups. Above all, the mean values of GGT/uCr ratio before and after treatments in all the puppies were well below the reported normal value earlier mentioned.

Nephrotoxicity of aminoglycosides is concentration dependent which is observed in 5-10% of patients receiving these drugs.²⁴ Large serum peak and trough concentrations of gentamicin have been associated with increased incidence of nephrotoxicity and ototoxicity in human and animals. Persistence of aminoglycosides in plasma, and thus, urine is likely to predispose the tubular cells to toxicity, and the risk may be reduced by allowing plasma drug concentrations to be <2 µg/ml before the next dose.²⁵ From this study, none of the treatments was observed with a trough serum

concentration up to 2 µg/ml. Nonetheless, since there was a general trend of increment in the trough concentrations as the duration of treatment increased in all the groups, it is reminiscent that the longer the duration of treatment with gentamicin, the higher the values of trough concentration and the more the likelihood of nephrotoxicity irrespective of the dosing interval adopted.

A higher increase in trough serum concentration of gentamicin observed in puppies on twice daily treatment (16-fold increment) in comparison with those on a once daily dose (4-fold increment) is in agreement with an earlier observation that patients receiving gentamicin once daily require a longer duration of therapy before the onset of nephrotoxicity than patients on multiple daily dosing.²⁶

Equally important as the consideration regarding toxicity is that dosage regimens should be designed to optimize therapeutic efficacy. Studies have shown increased efficacy and prevention of emergence of resistant bacteria subpopulation with increased peak concentration of gentamicin and consequently increasing the ratio of the peak concentration to the minimum inhibitory concentration.²⁷ In Gram-negative sepsis, patient survival is associated with early peak drug levels, with a large percentage of deaths occurring early in the course of therapy; consequently achievement of high concentrations of drug as early as possible is essential.⁵ This study shows that average peak serum concentrations of gentamicin during the 5 days of treatments were 6.41 µg/ml and 7.10 µg/ml for Groups A and B respectively. These values are similar to 7.19 µg/ml reported in cats following 3 mg/kg, 8 hourly intravenous dose.²⁸ However, for a therapeutic efficacy to be achieved, the peak concentration must be 8-10 fold the minimum inhibitory concentration (MIC) of most sensitive bacterial organisms causing the disease.^{29,30} Based on this study, therapeutic efficacy will only be achieved if the MIC of gentamicin against the incriminating bacterial organism is ≤ 0.8 µg/ml (6.41/8) and 0.9 µg/ml (7.10/8) in puppies on once daily (6 mg/kg) and twice daily, (3 mg/kg) intramuscular dose regimens, respectively.

The use of peak and trough concentrations is a simple and rapid method for predicting half-lives, but is limited by inaccuracy of a slope derived from only two points.³¹ The mean values of the half-lives and the corresponding rates of elimination for the experimental animals did not differ significantly suggesting that the dosing intervals used have a negligible effect on these pharmacokinetic parameters of gentamicin in puppies. The mean half-life of gentamicin in this study was 2.82 hrs which is higher than 1.84 and 1.78 hrs obtained from rich sampling pharmacokinetic studies.^{32,33} Nonetheless, the two-point kinetic analysis provides an estimate of half-life that can be utilized in clinical pharmacokinetics.

There is a general risk of nephrotoxicity associated with gentamicin intramuscular therapy beyond 5 consecutive

days irrespective of the dosing interval. Although the risk is slightly more when on twice-daily dosing interval as compared with once daily dosing interval. For this reason, there is a need to monitor daily the renal function and trough concentration of gentamicin when this extension is inevitable.

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