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Pharmacokinetics of Gentamicin in Blood Plasma of Quail, Pheasants, and Cranes

Randy S. Custer, BS; Mitchell Bush, DVM; James W. Carpenter, MS, DVM

SUMMARY

Rate of appearance, peak concentration, and the biological half-life of gentamicin in the plasma of quail (*Coturnix coturnix*), pheasants (*Phasianus colchicus*), and cranes (*Grus canadensis tabida*) were studied. Gentamicin was given IM in doses of 5, 10, and 20 mg/kg of body weight. Peak plasma concentrations occurred earliest in the quail, latest in the cranes. The peak concentrations varied directly with the administered doses in all species. The biological half-life of gentamicin was 42 ± 12 minutes in the quail, 75 ± 15 minutes in the pheasants, and 165 ± 37 minutes in the cranes.

On the basis of the present data, dosage regimens for gentamicin of 5 mg/kg every 8 hours in pheasants and cranes, and 10 mg/kg every 6 hours in quail, would be expected to give constant plasma concentrations greater than 4.0 μg/ml.

Gentamicin is an aminoglycoside antibiotic active against a large number of pathogenic microorganisms, including members of the genus *Pseudomonas*, the Enterobacteriaceae and other gram-negative organisms, and most strains of *Staphylococcus aureus*. At both the National Zoological Park and the Patuxent Wildlife Research Center, gentamicin is used to treat bacterial infections in birds and to prevent infection in newly hatched chicks or incubating eggs.

An important clinical concern with the use of gentamicin is the narrow range between plasma concentrations thought to be therapeutically effective and those associated with an increased risk of nephro- or ototoxicity. Peak plasma concentrations of at least 4 μg/ml are reported necessary to effectively combat serious gram-negative infections in mammals,[1] whereas toxicosis is risked if peak concentrations surpass 12 to 15 μg/ml[2,3] or trough concentrations (ie, the lowest plasma concentrations reached by a given dose before any subsequent drug administration) exceed 2 μg/ml.[4,5] The recommended treatment schedule for gentamicin in persons is 1 to 1.7 mg/kg every 8 hours. The drug is rapidly absorbed following IM administration, with peak plasma concentrations of 3.5 to 5 μg/ml occurring in the first hour.[5]

Recent studies indicate that the pharmacokinetics of gentamicin in some animals are dissimilar from those observed in persons. In turtles[6] and snakes,[7] the biological half-life T½ of gentamicin was 32 and 82 hours, respectively, compared with a T½ in persons of only 2 to 3 hours.[8,9] The longer values in the reptiles were attributed, in large part, to their lower metabolic rates.

Gentamicin dosages extrapolated from recommended dosages for mammals can be nephrotoxic to reptiles. Visceral gout, thought to be caused by gentamicin-related kidney damage, has been reported in boid snakes.[10] Our own studies with snakes indicated excessive accumulation of the drug following daily 5 mg/kg injections; trough concentrations exceeded 20 μg/ml after 3 days of therapy.[7]

Such results became the basis for studies to determine the effects of the relatively higher metabolic rates of avian species, when compared with mammals, on the pharmacokinetics of gentamicin. In preliminary studies with pigeons, the T½ of gentamicin was 52 minutes after IM injection, and about 33 minutes after IV administration. This rapid clearance of gentamicin could be clinically significant, particularly if a bird is given the antibiotic at mammalian dosages and treatment schedules. Such regimens in birds may not provide effective plasma concentrations for adequate periods between injections.

Three avian species of distinctly different body weights were studied to determine the T½ of gentamicin after IM injection. Following these studies, various treatment regimens were evaluated in one of the species.

Materials and Methods

Japanese quail (*Coturnix coturnix*) and ring-necked pheasants (*Phasianus colchicus*) were obtained from commercial sources as eggs and as chicks, respectively, and raised at the National Zoological Park. The quail were housed, as unsexed pairs, in wire mesh battery cages. The pheasants were kept in fenced enclosures measuring approximately 1 × 3 × 3 m with concrete floors. Two-year-old greater sandhill cranes (*Grus canadensis tabida*) were maintained at the Patuxent Wildlife Research Center in individual pens of approximately 2 × 6 m. The pens and cages were cleaned each day. All species were fed appropriate avian diets and water was available ad libitum. All birds were in good health at the beginning of the experiments.

Nine quail weighing 180 to 250 g, 15 pheasants weighing 0.9 to 1.5 kg, and 10 cranes weighing 3.6 to 5.3 kg were used during the T½ study. Each species was divided into three groups. One group from each species was given 5 mg/kg of body weight of gentamicin sulfate[a] by IM injection, and the remaining two groups were

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[a] Gentocin, Schering Corp, Bloomfield, NJ.

TABLE 1—Gentamicin Plasma Concentrations Following Single IM Injections to Quail, Pheasants, and Cranes

Species and dose (mg/kg)	No. of birds	Time following administration: Minutes 15	30	45	60	Hours 2	3	6	T½ (minutes)
QUAIL									
5.0	3	13.0 ± 3.2	ND	9.4 ± 3.5	8.6 ± 1.2	3.1* ± 2.7	...	...	40 ± 4
10.0	3	14.7 ± 3.5	ND	9.4 ± 1.3	6.2 ± 2.6	8.3* ± 3.1	...	...	38 ± 10
20.0	3	32.5 ± 12.8	ND	21.8 ± 6.7	18.1 ± 2.3	11.6* ± 5.2	5.4 ± 2.4	...	48 ± 20
PHEASANTS									
5.0	5	15.4 ± 6.2	16.5 ± 3.4	12.5 ± 4.3	12.7 ± 3.0	8.5 ± 2.5	4.9 ± 2.4	...	68 ± 20
10.0	7	27.9 ± 11.7	29.8 ± 12.4	35.3 ± 11.4	23.3 ± 9.1	13.5 ± 5.3	11.2 ± 3.7	2.2 ± 1.7	72 ± 8
20.0	3	45.6 ± 26.9	81.0 ± 10.4	63.0 ± 21.1	42.0 ± 25.3	28.9 ± 15.4	15.8 ± 5.6	6.9 ± 5.9	94 ± 22
CRANES									
5.0	8	16.8† ± 8.4	15.3 ± 3.6	ND	15.4 ± 1.9	12.4 ± 2.0	10.7 ± 2.8	3.1 ± 0.6	158 ± 39
10.0	1	29.2	32.7	ND	37.5	31.0	24.4	ND	200
20.0	1	49.0	48.7	ND	70.6	47.3	43.3	ND	180

* Concentrations at 90 minutes; † mean of two birds.
Values are expressed as mean ± SD in μg/ml; ND = concentrations were not determined; ... = concentrations were not detectable (< 2 μg/ml).

given 10 mg/kg and 20 mg/kg, respectively. The gentamicin was administered into the pectoral muscle mass, using microliter syringes[b] for volumes up to 0.1 ml and tuberculin syringes for larger volumes.

Heparinized blood samples for gentamicin analysis were collected at selected intervals beginning 15 to 30 minutes after injection and continuing for up to 6 hours. The samples were collected from nonanesthetized birds by percutaneous puncture of the cutaneous ulnar, medial pedal, or jugular veins. The samples were then centrifuged, and the plasma was removed and frozen until assayed.

Eight pheasants were allotted to three groups and were given IM injections of 5, 10 or 20 mg/kg every 6 hours over periods of 2 to 14 days. Blood samples were collected each day, immediately before scheduled injections, and were assayed for gentamicin.

The microbiological, agar-well diffusion method used to assay the plasma samples for gentamicin has been described in detail.[7] The susceptible organism used was a multiple antibiotic-resistant, gentamicin-sensitive strain of *Staphylococcus epidermidis*.[c] Gentamicin concentration standards of 2 to 32 μg/ml were prepared for each of the three species with pooled plasma collected before the studies. The concentration standards provided a straight-line calibration plot for values between 2 and 32 μg/ml for which unknown plasma concentrations could be determined. If plasma concentrations exceeded 32 μg/ml, the samples were diluted to a concentration which could be determined using the calibration plot; however, the procedure could not accurately determine concentrations of less than 2 μg/ml.

Plasma concentrations were plotted against time on semi-logarithmic coordinates and the T½ was determined from the slope of the linear, least-squares regression line. Statistical analysis of T½ values between dosage groups, both intra- and interspecifically, was performed using Student's *t* test. For the purpose of statistical analysis, those concentrations which were not detectable (less than 2 μg/ml) were arbitrarily assigned values of 1 μg/ml.

Results

The plasma concentrations of gentamicin after IM administration in three dosages to quail, pheasants and cranes are shown (Table 1). Gentamicin values resulting from the administration of identical doses to individual birds varied widely within a species. Consequently, it was difficult to determine statistically significant differences among the plasma concentrations produced by nonidentical doses. The rates of appearance and clearance of gentamicin for the plasma of pheasants after they were given IM injections of 5, 10, and 20 mg/kg are illustrated (Fig 1). In all three species, the higher dosages produced higher peaks and longer periods of detectable plasma concentrations after injection. The peak gentamicin concentrations of the three species following the administration of 5 mg of gentamicin/kg were similar (Fig 2). As time progressed, however, plasma concentrations differed markedly between species. At 3 hours, gentamicin values in the quail were not detectable, while those of the pheasants and the cranes were approximately 5 and 10 μg/ml, respectively.

Significant differences ($P < 0.01$) were not found between the T½ values of different dosage groups within individual species (Table 1). Consequently, the T½ values of the three

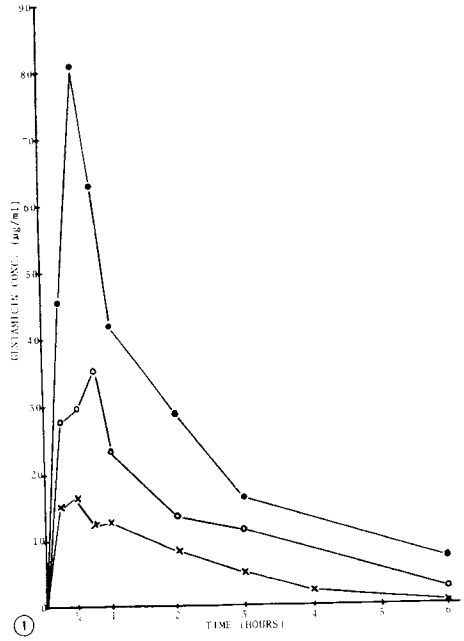

Fig 1—Plasma gentamicin concentrations at selected times following the IM administration ot 5.0 mg/kg (X——X), 10.0 mg/kg (○——○), and 20.0 mg/kg (●——●) to ring-necked pheasants.

[b] Hamilton Co, Reno, Nev.
[c] Clinical isolate, agar dilution laboratory, The Johns Hopkins Hospital, Baltimore, Md.

dosage groups were combined to obtain a mean T½ for each species. The mean T½ of 42.0 ± 12.1 minutes for quail was significantly shorter than the mean T½ of 75.1 ± 15.1 minutes for pheasants, and both were significantly shorter than the mean of 164.6 ± 37.0 minutes for cranes.

Different treatment regimens affected the plasma concentrations of gentamicin in eight pheasants (Fig 3). In the four birds given 5 mg/kg every 6 hours for 14 days, plasma trough concentrations exceeded 2 μg/ml only once, when a mean value of 2.2 μg/ml was measured. Three birds were given 10 mg/kg every 6 hours for only 2 days, because trough concentrations of 12.2 μg/ml were measured. Finally, one bird was given 20 mg/kg every 6 hours for 5 days, after which trough concentrations equaled 51.0 μg/ml.

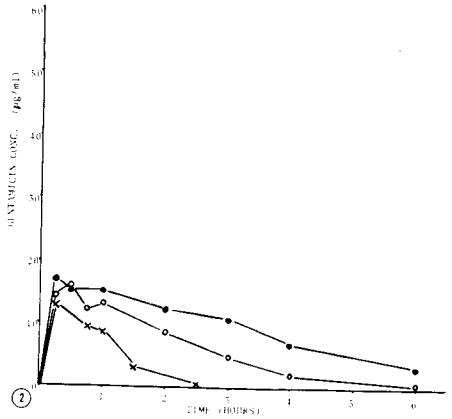

Fig 2—Plasma gentamicin concentrations at selected times following the IM administration of 5.0 mg/kg to Japanese quail (X——X), ring-necked pheasants (○——○), and greater sandhill cranes (●——●).

Discussion

The T½ of gentamicin in persons and in dogs after IM administration is approximately 2 to 3 hours.[8,9,11] In turtles after IM injection and in snakes following subcutaneous administration, the T½ of gentamicin has been reported at about 32 and 82 hours, respectively.[6,7] In the present report, following IM injection, the mean T½ of gentamicin was found to be 42.0 ± 12.1 minutes for quail, 75.1 ± 15.1 minutes for pheasants, and 164.6 ± 37.0 minutes for cranes.

In view of the birds' higher metabolic rates, the short T½ values of the quail and pheasants are not surprising, although the T½ found for the cranes is closer to those values reported for mammals.[8,9,11]

The rapid clearance of gentamicin from the plasma of some birds is especially important if they are undergoing clinical treatment based upon recommendations for mammals. The administration of 1.0 to 1.7 mg/kg every 8 hours, the mammalian dosage, to quail or pheasants would probably not provide effective plasma concentrations due to their shorter T½. For example, a 5 mg/kg dosage administered to quail, pheasants, and cranes provided plasma concentrations greater than 4 μg/ml for only 1.5, 3.5, and 5.0 hours, respectively. The administration of a dosage equal to approximately one-third of 5 mg could not be expected to provide better results.

During the varied regimen studies, the administration of 5 mg/kg every 6 hours to pheasants provided plasma concentrations of greater than 4 μg/ml for up to 3.5 hours after injection. At about 4 to 4.5 hours after injection, concentrations dropped below 2 μg/ml. The administration of 10 and 20 mg/kg every 6 hours resulted in potentially toxic plasma concentrations in the pheasants studied.

A singular observation during these studies was the positive correlation between the body weights of the birds and their gentamicin T½ value. Between species, this correlation is evident; the smallest birds (quail) had the shortest T½ while the largest birds (cranes) had the longest T½ values. The pheasants' body weight and T½ data were between the other two species. The most likely explanation for this observation may be the higher metabolic rates usually found in smaller species. The correlation between body weight and T½ was not evident within the individual species.

On the basis of the present data, the administration of 5 mg/kg every 8 hours to pheasants and cranes will provide prolonged plasma gentamicin concentrations greater than 4 μg/ml. These dosages will also produce potentially toxic plasma concentrations for about 1 hour following injection. The administration of 5 mg/kg at 8-hour intervals, however, will allow plasma concentrations to fall to innocuous concentrations between injections and will limit the number of times the bird must be handled.

The administration of 10 mg/kg every 6 hours to quail, a daily dosage of 2 to 3 times that given to pheasants and cranes, will provide similar plasma concentrations of gentamicin. Such an increase is necessary due to the relatively shorter T½ for gentamicin in quail.

The extrapolation of these dosage regimens to clinically ill birds should be done with care. Of primary consideration is the possibility that gentamicin concentrations of 4 μg/ml may not be effective against avian pathogens. The dosage regimens given are only guides used to illustrate the types

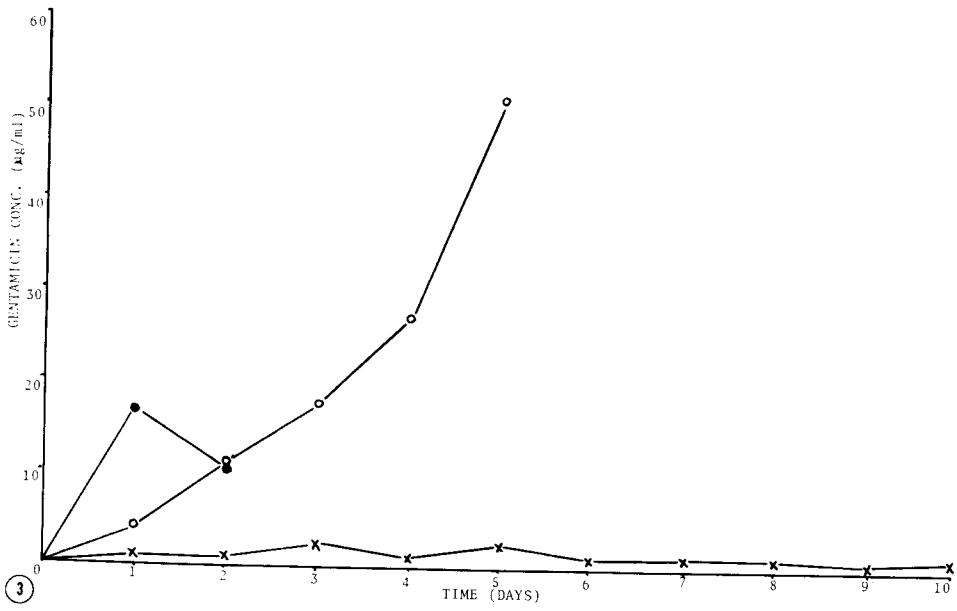

Fig 3—Mean plasma trough concentrations of gentamicin during the administration of 5.0 mg/kg (X——X), 10.0 mg/kg (○——○), and 20.0 mg/kg (●——●) every 6 hours to ring-necked pheasants.

of administration schedules necessary to attain constant plasma gentamicin concentrations in three avian species, gentamicin concentrations comparable with those accepted as therapeutically beneficial in mammals.

It should also be emphasized that these regimens are based upon data collected from normal, healthy birds. A bacterial infection is often not the only abnormality in a clinically ill bird. Other problems such as dehydration, anorexia, or disruption of body temperature-regulating mechanisms may alter the pharmacokinetics of gentamicin.

In these and other studies,[12-14] a marked variation in plasma concentrations was noted in individuals of the same species following the administration of identical doses. Such variations in plasma concentrations from individual to individual, the large variations in the gentamicin T½ from species to species, and the narrow difference between toxic and therapeutic gentamicin concentrations combine to make further study necessary before gentamicin can be used safely and effectively in clinical situations.

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