Pharmacokinetics of amikacin in African gray parrots

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SUMMARY

Amikacin sulfate was administered to African gray parrots at 3 dosages (5, 10, and 20 mg/kg) via 2 routes (IV and IM). The elimination half-time was approximately 1 hour (range, 0.9 to 1.34 hour). The apparent bioavailability of IM administered drug was 61 to 106% and was not dose-related.

Amikacin, an aminoglycoside antibiotic, is primarily indicated for the treatment of infections caused by gentamicin-resistant gram-negative bacteria.[1] Gram-negative organisms are the most common cause of bacterial infections in psittacine birds.[2-5] *Escherichia coli, Salmonella* spp, *Enterobacter* spp, *Klebsiella* spp, *Pseudomonas* spp, *Proteus* spp, *Citrobacter* spp, *Serratia* spp, and *Pasteurella* spp are considered the most important pathogens in this group.[2,4,5] Amikacin has been used for the treatment of gram-negative infections in birds,[6] and dosages ranging from 15 to 40 mg/kg, SID or q 12 h, given IV or IM, have been recommended.[6-8] There is no information available regarding the pharmacokinetics of amikacin after systemic administration to psittacine birds.

The purposes of the study presented here were to determine the pharmacokinetics of amikacin in African gray parrots (*Psittacus erithacus*) after single IV or IM administration and to compare amikacin serum concentrations with the minimal inhibitory concentration (MIC) of amikacin required to control growth of pathogenic bacteria and thus provide guidelines for treatment of African gray parrots.

Materials and Methods

Animals—Thirty-four healthy, wild-caught, imported, adult African gray parrots, weighing 418 to 559 g, were kept in cages and given free access to food[a] and water. The parrots, whose sex was not determined, were routinely treated for coccidiosis and quarantined. They had not been given medication for at least 2 weeks before their use and there was at least 1 week between antibiotic administrations.

Experimental design—Single injections of amikacin sulfate (50 mg/ml)[b] were administered to birds via 2 routes (IV and IM) at 3 dosages (5, 10, and 20 mg/kg of body weight) for a total of 6 experiments. Since the blood volume of the birds was not sufficient to allow samples from each bird at all collection times, the birds were allotted to 5 groups of 6 birds for each IV administration experiment. Blood samples from each group were obtained at 2 of the following 10 times: 0, 5, 15, 30, and 45 minutes and 1, 2, 4, 8, and 24 hours. For each experiment with IM administration, samples were obtained from 4 groups of 6 birds at 2 of the following times: 0, 15, and 45 minutes and 1, 2, 4, 8, and 24 hours. Intramuscular administrations were into the cranial part of the breast muscle. Intravenous administrations were into the jugular vein. Blood (0.7 ml) was collected from the jugular vein with a syringe and placed in a microserum separation tube.[c] Blood samples were allowed to clot and then centrifuged (2,700 × g) to separate serum from cells. Samples were frozen (−20 C) until assayed.

Drug analysis—Serum amikacin concentrations were determined by agar gel diffusion,[9] using *Bacillus subtilis*[d] as the test organism. For standards, reference standard amikacin[b] was diluted (0.5 to 40 µg/ml) in serum from untreated African gray parrots and assayed simultaneously in triplicate with samples on each assay plate. Serum samples with concentrations > 40 µg/ml were diluted in the serum from untreated birds. Samples with < 0.5 µg/ml of amikacin were set to zero for determination of mean serum concentrations at each sampling time.

Data analysis—Mean serum concentrations were calculated for each sample time from each experiment. The serum amikacin concentration-vs-time relationship was modeled with the following equation for experiments with IV administration of amikacin:

$$C_a = C_1 \cdot e^{-\lambda_1 \cdot t} + C_2 \cdot e^{-\lambda_2 \cdot t}$$

where C_a was the mean serum amikacin concentration, e was the base of the Napierian logarithms, t was the time from administration of amikacin, and C_1, C_2, λ_1, and λ_2 were the fitting variables determined by nonlinear regression, using a computer program that minimized the sum of squared deviations.[10] The elimination rate constant was equated with λ_2. The area under the serum concentration-vs-time curve (AUC) and the area under the moment curve (AUMC) were calculated, using the following equations:

$$AUC_{IV} = C_1/\lambda_1 + C_2/\lambda_2$$

$$AUMC_{IV} = C_1/\lambda_1/\lambda_1 + C_2/\lambda_2/\lambda_2$$

For experiments with IM administration of amikacin, the serum concentration-vs-time relationship was modeled with the following equation:

$$C_a = C_1 \cdot [e^{-\lambda_1 \cdot t} - e^{-\lambda_2 \cdot t}]$$

The elimination rate was equated with λ_1. The AUC and AUMC values were calculated, using the following equations:

$$AUC_{IM} = C_1/\lambda_1 - C_1/\lambda_2$$

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[a] Mixed seed diet supplemented with cooked, dry corn and fresh fruits.

[b] Bristol-Myers Co, Evansville, Ind.

[c] Microtainer, Becton, Dickinson & Co, Rutherford, NJ.

[d] Difco Laboratories Inc, Detroit, Mich.

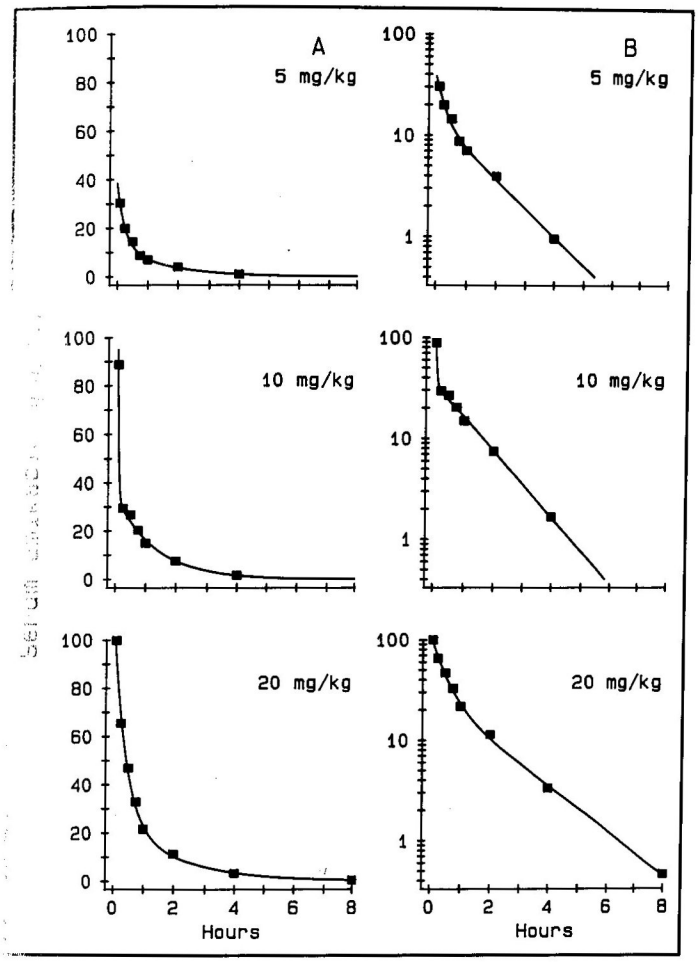

Fig 1—Linear (A) and semilogarithmic (B) plot of mean serum amikacin concentrations after intravenous administration at dosages of 5, 10, and 20 mg/kg body weight to African gray parrots. Line represents mathematical model of mean values.

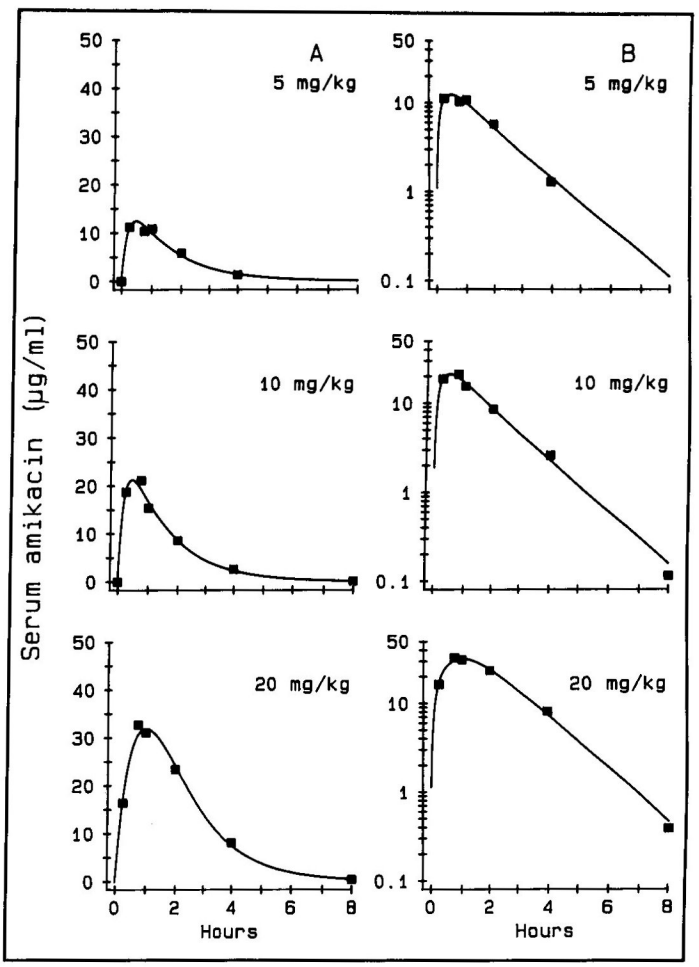

Fig 2—Linear (A) and semilogarithmic (B) plot of mean serum amikacin concentrations after intramuscular administration at dosages of 5, 10, and 20 mg/kg body weight to African gray parrots. Line represents mathematical model of mean values.

$$AUMC_{IM} = C_1/\lambda_1/\lambda_1 - C_1/\lambda_2/\lambda_2$$

For all experiments, clearance was calculated as the dose divided by the AUC. Elimination half-time ($t_{1/2}$) was calculated as the natural logarithm of 2 divided by the elimination rate constant. Volume of distribution based on AUC ($V_{d(area)}$) was calculated as the clearance divided by the elimination rate constant. Volume of distribution at steady state ($V_{d(ss)}$) was calculated from the following equation:

$$V_{d(ss)} = AUMC/AUC^2$$

Bioavailability of amikacin administered IM was calculated as the ratio of the AUC_{IM} to the AUC_{IV} of the same dosage.

Peak and trough steady-state concentrations of gentamicin (that would be obtained after multiple doses) were estimated by Curry's method, in which the accumulation of drug is calculated as the peak concentration divided by the difference between the peak concentration and the trough concentration for a single dose.[11] Mean peak and trough data for the parrots was used in the estimation.

Results

Each standard curve for each bioassay plate ranged from 0.5 to 40 µg/ml. Correlation coefficients for those standard curves were > 0.99. Sample values greater than the range of standards were determined by dilution prior to assay. Sample values less than the range of standards were recorded as zero; thus, some mean values were less than the range.

Mean serum amikacin concentrations declined rapidly after IV administration; mean serum amikacin concentrations peaked betwen 0.25 and 1 hour after IM administration (Fig 1 and 2; Table 1). More than 99% of the amikacin was eliminated by 8 hours after administration; accumulation was not observed at any dosage or either route of administration. Pharmacokinetic values for IV and IM administered amikacin were determined; the elimination $t_{1/2}$ was approximately 1 hour for all route and dosage combinations (Table 2).

Discussion

The elimination $t_{1/2}$ of amikacin was not related to the dosage, and the $t_{1/2}$ for IV administration was not different from that for IM administration. Amikacin was rapidly absorbed after IM administration; serum concentrations peaked by 45 minutes (Table 1). The low bioavailability for amikacin administered IM at the rate of 10 mg/kg may have been attributable to the high concentration of amikacin in the serum obtained 5 minutes after administration in the IV administered amikacin study at that same dosage. The high value increases the AUC_{IV}, thus lowering the ratio of AUC_{IM}/AUC_{IV}.

TABLE 1—Mean (± SEM) serum amikacin concentrations (μg/ml) after IV and IM administration of amikacin to African gray parrots

Sample time	Intravenous			Intramuscular		
	5 mg/kg	10 mg/kg	20 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
0 h	0 ±0	0 ±0	0 ±0	0 ±0	0 ±0	0 ±0
0.083 h (5 min)	30.4 ± 1.38	88.8 ± 4.96	99.8 ± 8.28	...	...	...
0.25 h (15 min)	19.9 ± 0.61	29.5 ± 0.94	65.5 ± 2.77	11.2 ± 0.38	18.8 ± 1.96	16.4 ± 4.99
0.5 h (30 min)	14.4 ± 0.51	26.7 ± 1.26	46.9 ± 1.96	...	...	...
0.75 h (45 min)	8.7 ± 0.67	20.2 ± 1.48	32.9 ± 2.81	10.3 ± 0.62	21.1 ± 1.77	32.7 ± 1.23
1 h	7.0 ± 0.28	14.9 ± 0.81	21.6 ± 1.36	10.8 ± 0.63	15.4 ± 1.30	31.0 ± 1.41
2 h	3.9 ± 0.41	7.5 ± 0.53	11.4 ± 1.89	5.8 ± 0.82	8.6 ± 0.46	23.4 ± 1.48
4 h	0.96 ± 0.201	1.67 ± 0.262	3.3 ± 1.14	1.29 ± 0.35	2.6 ± 0.78	8.1 ± 0.51
8 h	0 ± 0	0 ± 0	0.46 ± 0.128	0 ± 0	0.11 ± 0.114	0.39 ± 0.184
24 h	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0

TABLE 2—Pharmacokinetic values for IV and IM administered amikacin in African gray parrots

	Intravenous			Intramuscular		
	5 mg/kg	10 mg/kg	20 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
Elimination rate constant (h)	0.65	0.77	0.52	0.64	0.67	0.72
Elimination half-time (h)	1.06	0.90	1.34	1.08	1.04	0.97
$V_{d(area)}$ (ml/kg)	289	184	444	298	348	303
$V_{d(ss)}$ (ml/kg)	233	122	308	335	392	467
Clearance (ml/h/kg)	188	142	229	191	232	217
Bioavailability (%)	...	...	...	98	61	106

$V_{d(area)}$ is volume of distribution based on area under serum concentration-vs-time curve. $V_{d(ss)}$ is volume of distribution at steady state.

Elimination $t_{1/2}$ values for amikacin have been reported for horses (1.1 hour to 3 hours),[12-14] cats (0.85 to 2 hours),[15,16] human beings (2.0 to 2.3 hours),[17-19] and gopher snakes (71.0 to 75.4 hours).[20] Thus, amikacin $t_{1/2}$ in African gray parrots is similar to that reported for other vertebrates.

Ranges of MIC values for amikacin for bacteria isolated from avian patients at the University of Florida Veterinary Teaching Hospital were: *Escherichia coli* (30 isolates), ≤ 1 to 8 μg/ml; *Klebsiella pneumoniae* and *Enterobacter cloacae* (8 isolates each), ≤ 1 to 4 μg/ml; *Enterobacter agglomerans* (2 isolates), ≤ 1 to 2 μg/ml; *Staphylococcus* spp (6 isolates), ≤ 1 to 16 μg/ml; *Acinetobacter calcoaceticus* (5 isolates), ≤ 2 to 8 μg/ml; *Proteus mirabilis* (4 isolates), ≤ 1 to 8 μg/ml; *Pseudomonas aeruginosa* (3 isolates), 4 to 8 μg/ml; *Citrobacter freundii* (3 isolates), ≤ 1 to 2 μg/ml; *Bacillus* spp (2 isolates), ≤ 1 μg/ml; *Providencia rettgeri* (1 isolate), 2 μg/ml; *Salmonella* sp (1 isolate), 4 μg/ml; and *Corynebacterium* sp (1 isolate), ≤ 1 μg/ml.[e] The highest MIC value for the gram-negative organisms was 8 μg/ml. All dosages and routes in our study yielded serum concentrations greater than this value.

[e] Purich B, University of Florida, Veterinary Medical Teaching Hospital: Personal communication, 1987.

On the basis of these limited data, the primary indication for the use of amikacin in African gray parrots would be for the treatment of infections caused by gram-negative bacteria. We recommend a dosage of 10 to 20 mg/kg, given IV or IM, every 8 to 12 hours, depending on the MIC of the organism. Inasmuch as nearly all the amikacin was eliminated in 8 hours, no accumulation is anticipated with multiple administration at 8- or 12-hour intervals. Peak and trough concentrations should be similar to the values found after a single administration.

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