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Comparative Ototoxicity of Amikacin and Gentamicin in Cats

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The ototoxic potentials of two aminoglycoside antibiotics, amikacin and gentamicin, were compared in cats, using several otoxicity assessment techniques. Daily subcutaneous doses of 90 and 45 mg of amikacin per kg and 18 and 9 mg of gentamicin per kg (approximately six and three times the daily human dose) were administered to cats for extended periods of time until cochlear or vestibular dysfunction developed. Renal tissue damage and serum and perilymph antibiotic concentrations were also monitored. Amikacin selectively produced an impairment of cochlear function after an approximate cumulative dose of 3,600 mg/kg obtained after 41 days at 90 mg/kg per day or 78 days at 45 mg/kg per day, as determined by electrophysiological assessment. Gentamicin caused an impairment of vestibular function after an approximate cumulative dose of 700 mg/kg obtained after 42 days at 18 mg/kg per day or 68 days at 9 mg/kg per day, as determined by ataxia and impaired righting reflex. Gentamicin also moderately reduced electrophysiological cochlear responses and appeared to cause histological renal tissue change more frequently than did amikacin.

Aminoglycoside antibiotics are potentially ototoxic, and this untoward effect may be manifested primarily as cochlear or vestibular dysfunction (1). Results of an earlier study in cats revealed amikacin, a new aminoglycosode (13), to be toxic to the cochlear at doses not affecting vestibular function (14). In contrast, gentamicin has been reported to cause primarily vestibular dysfunction at doses that may also be cochleotoxic (7-9, 11). In the present study cats were treated with amikacin or gentamicin daily for extended periods of time until definitive signs of ototoxicity developed. Multiples of approximately three and six times the recommended daily human clinical doses of amikacin (15 mg/kg per day) and gentamicin (3 mg/kg per day) (12) were used to compare the ototoxic liabilities of these antibiotics with respect to time and cumulative dose.

MATERIALS AND METHODS

Male and female adult mongrel cats obtained from local suppliers were selected to receive amikacin (Amikin, amikacin sulfate, Bristol Laboratories) as a 25% aqueous solution at 90 and 45 mg/kg once a day 7 days per week by subcutaneous injection. The cats, weighing between 2.1 and 4.2 kg when started on the study, were immunized against feline panleukopenia and feline rhinotracheitis and conditioned for at least 4 weeks prior to use. Complete blood counts as well as blood urea nitrogen (BUN) determinations and complete urinalyses were performed prior to the start of dosing, and the cats were divided into groups of five according to body weight and sex. BUN determinations were repeated on the last treatment day.

Similar tests were made in groups of five cats that received gentamicin (Garamycin injectable, gentamicin sulfate, Schering Corp.) as a 4% aqueous solution at doses of 18 or 9 mg/kg per day or sterile water at 0.45 ml/kg per day as a negative control.

Both antibiotics were administered as the sulfate salts, and doses are expressed in terms of the free base.

Prior to testing, all cats exhibited normal gait and normal righting reflex, indicating normal vestibular function, and demonstrated a Preyer-like pinna reflex (15), suggesting the normal ability to detect sound. After the initiation of drug treatment, changes in general health or behavior were recorded daily, food intakes were estimated each day, and body weights were determined twice a week. At 5 to 6 h after each daily dosing all cats were observed for evidence of ataxia, impaired righting reflex, and auditory deficit. Ataxia was evaluated while allowing the cat to walk about the room and was scored as follows: 0—no ataxia, normal gait; 1—slight ataxia, faltering gait on change of direction; 2—moderate ataxia, incoordination evident while walking; and 3—marked ataxia, equilibrium markedly affected, barely able to stand. Righting impairment was examined by the drop fall righting reflex (from approximately 1 m onto a rubber pad) and was scored on the basis of the number of abnormal falls from the inverted position in three drops. Auditory deficit was evaluated by observing for the Preyer pinna orienting reflex response to various sound stimuli, including a whistle, a vocal call, or a hand clap and

was scored as a good, a questionable, or no detectable response.

The end point of ototoxicity was considered either the nearly complete loss of vestibular function as indicated primarily by marked ataxia (grade 3) or the nearly complete loss of hearing as indicated by lack of the Preyer pinna reflex response and later confirmed by electrophysiological determinations. When these behavioral indications of end-point ototoxicity were detected, termination procedures were initiated after a final dose. A blood sample was collected at 2 h after the last injection, clinical observations were confirmed, and the cat was terminated 1 day later for electrophysiological determinations.

Once a week the duration of postrotatory nystagmus (PRN) was determined in all cats. For this test the stimulus was provided by the sudden stop of motion after a constant lateral clockwise rotation of 1 rps for 40 s in a box designed to hold a cat horizontally in a fixed position. A stopwatch was started when the table stopped, and the number of saccades and the end of nystagmus was recorded by two independent observers. PRN determinations were repeated immediately prior to termination.

At 24 to 28 h after the last treatment, each cat was anesthetized with sodium pentobarbital (30 mg/kg intraperitoneally), and electrophysiological function was determined for both ears. Control cats were evaluated in a similar fashion.

By using modified head-holder equipment that did not obstruct either ear, each cat was positioned in a sterotaxic apparatus. The ventrolateral aspect of the tympanic bulla was opened to place a ball-tipped, silver wire electrode (active) on the round window (RW) membrane. A second input electrode was clipped to muscle tissue at the incision site, and one indifferent electrode was placed in rear leg muscle. The two active electrodes provided input to the differential amplifier of a Tektronix storage oscilloscope (model 7613 or 7313). Care was taken to prevent the accumulation of fluid near the RW.

The background noise environment was about 50 dB (1 dB = 0.0002 dyne/cm^2) as measured with a sound level meter (General Radio type 1565-A).

Two types of sound stimuli were presented to the ear from a 2,000-Ω headset speaker (Radio Shack catalog 33-180) placed directly over the pinna opening. A connecting tube was not placed into the external auditory canal. In the first test mode, a predetermined series of brief sound bursts was generated by a switch-controlled audio oscillator (Hewlett Packard model 200 AB). The frequencies used were approximately 810, 2,500, and 6,000 Hz. The oscillator output to the speaker was monitored by a digital volt meter (Data Precision type 2440) and adjusted to produce 10-dB-step sound levels from 80 to about 120 dB. At intervals, sound intensities at the speaker face were checked by substituting a sound level meter for the animal preparation. For each sound stimulus to a control or treated cat, the observed alternating current cochlear microphonic (CM) response detected at the RW membrane was measured from the oscilloscope display in terms of microvolts from peak to peak.

In the second test mode, nerve action potentials (NAP), the negative N_1 deflections, were detected at the RW after the induction by a speaker click generated from a Grass S8 stimulator. The stimulus was a 10-s train of pulses, 150 V, 0.1 ms duration, synchronized to the oscilloscope trigger sweep with a 0.1-ms delay. The superimposed responses were photographed from the oscilloscope screen for subsequent measurements in terms of microvolts of response from sweep base line to maximum deflection.

Electrophysiological assessments were not performed on ears with obvious otitis media. Past experience (14) has indicated that inflammation and associated detritus in the middle ear and on the RW will reduce the CM and NAP responses to test stimuli.

The CM data were reduced to identify the level of maximal response for each cat. Only the maximal alternating current CM amplitude measurements at 810 and 2,500 Hz were averaged for both ears. A separate average for both ears was determined for the NAP deflection response from each cat. Mean values between cats in each treatment group were used to represent results of the experiment.

Blood samples were obtained from all treated cats 2 h after the administration of the dose on the first and last treatment days and at the termination after electrophysiological determinations 24 to 28 h after the last dose. Perilymph samples (approximately 10 μl) were collected in a micropipette from the RW of both ears after the electrophysiological determinations were completed and were expanded with pH 6 phosphate buffer to a workable volume (0.1 ml). The serum and perilymph samples were assayed for drug concentration by the cup-plate assay method, using *Bacillus subtilis* ATCC 6633 as the test organism and the respective antibiotic as a standard.

Immediately after the electrophysiological assessment, the cats were sacrificed and examined for gross pathological lesions. Kidneys were submitted for histopathological assessment of renal toxicity and scored as follows: 0—none; 1—slight; 2—moderate; 3—marked; and 4—pronounced.

RESULTS

Impaired behavioral reaction to sound was difficult to identify. The initial group of cats receiving amikacin at 90 mg/kg per day was terminated for suspected hearing impairment after 63.4 treatment days or a 5,706-mg/kg cumulative dose. However, when tested for CM and NAP reactions to sound, none of the ears of these cats responded. This left in question the minimum number of daily doses required to produce the end point of a perceptible but small response to sound. After this initial test with amikacin, an improved procedure for the detection of hearing deficit was employed using sounds previously recorded on a model TC-90A Sony tape cassette recorder, and treatment with amikacin was started in a second group (group 1A) of cats at 90 mg/kg per day. These

animals were paired with five negative control cats receiving sterile water (group 6). The dosing periods for amikacin and gentamicin that were required to produce nearly complete cochlear or vestibular dysfunction in the test cats (groups 1A to 4) are summarized in Table 1.

All cats treated with amikacin were terminated for behavioral indications of hearing impairment, and electrophysiological responses were used to establish the duration of dosing required to produce end-point ototoxicity. The examination of individual data revealed that three high-dose cats (group 1A, no. 228, 229, and 232) reacted rather uniformly (31 to 47 doses), and there were measurable electrical responses in these animals, whereas no evidence of electrical activity was found in a fourth cat (no. 230). A fifth cat (no. 231), terminated with suspected hearing impairment after receiving amikacin at 90 mg/kg per day for 23 days, evidenced bilateral otitis media, a condition reported to significantly increase the ototoxicity of some aminoglycosides (3–5). A similar analysis of individual cats receiving the lower dose of amikacin (45 mg/kg per day) identified electrical responses in cats 217, 218, and 221, which were dosed for 76 to 80 days, but none in cats 219 and 220, which were dosed for 125 or 128 days. Consequently, data from four cats (no. 230 and 231, high dose; and no. 219 and 220, low dose) were excluded from cochlear toxicity evaluations. Inclusion or exclusion of data from these cats showing aberrations affected significance levels very little.

The high dose of amikacin (90 mg/kg per day, group 1A) induced behavioral indications of ototoxicity in three cats after an average of 38.7 daily doses, and they showed end-point cochlear toxicity at the termination after an average of 40.7 dosing days. The mean cumulative dose of

TABLE 1. *Clinical assessment of ototoxicity in cats given daily subcutaneous doses of amikacin or gentamicin*

Drug	Group no.	Daily dose (mg of base/kg/day)	Cat no. and sex	Treatment day showing: Development of impaired pinna reflex response to sound	Treatment day showing: Development of marked ataxia or impaired righting response	No. of doses administered	Total dose at end-point ototoxicity (mg of base/kg)
Amikacin	1A	90	228 ♂	47	None	48	4,320
			229 ♂	38	None	38	3,510
			(230 ♀)[a]	(36)	None	(37)	(3,330)
			(231 ♀)[b]	(23)	None	(23)	(2,070)
			232 ♀	31	None	35	3,150
Mean ± SE[c] (n = 3)				38.7 ± 4.6	None	40.7 ± 3.8	3,660 ± 346
	2	45	217 ♂	76	None	76	3,420
			218 ♂	78	None	79	3,555
			(219 ♂)[a]	(123)	None	(125)	(5,625)
			(220 ♀)[a]	(126)	None	(128)	(5,760)
			221 ♀	79	None	80	3,600
Mean ± SE (n = 3)				77.8 ± 0.9	None	78.3 ± 1.2	3,525 ± 54
Gentamicin	3	18	197 ♂	None	41	42	738
			198 ♂	None	29	30	522
			199 ♂	None	36	37	648
			200 ♀	None	60	60	1,080
			201 ♀	None	42	43	756
Mean ± SE (n = 5)				None	41.6 ± 5.1	42.4 ± 5.0	749 ± 93
	4	9	(202 ♂)[d]	None	(168)	(168)	(1,512)
			203 ♂	None	92	93	828
			204 ♂	None	80	80	720
			205 ♀	None	39	41	351
			206 ♀	None	60	62	540
Mean ± SE (n = 4)				None	67.8 ± 11.6	69.0 ± 11.3	610 ± 105
Water control	5	0.45 ml/kg	222–226 (n = 5)	None	None	168.6 ± 0.2	
	6	0.45 ml/kg	233–237[b] (n = 4)	None	None	36.3 ± 5.2	

[a] No electrophysiological response; data not included.
[b] Bilateral otitis media; data not included (group 6 = cat no. 237).
[c] SE, Standard error.
[d] End-point ototoxicity not reached; data not included.

amikacin received by these animals was 3,660 mg/kg. The low dose of amikacin (45 mg/kg per day, group 2) required a longer average dosing period of 77.8 days to produce similar behavioral effects in three cats, and these animals exhibited end-point ototoxicity at the termination after receiving 78.3 daily doses. A statistical evaluation (10) demonstrated that the average cumulative dose of amikacin at 45 mg/kg per day (3525 mg/kg) was not different from that of the high-dose level.

None of the cats treated with amikacin showed behavioral signs of vestibular dysfunction at the termination.

In contrast, cats given gentamicin were terminated for signs of vestibular dysfunction, as indicated by marked ataxia and impaired righting reflex. The high dose (18 mg/kg per day) induced these signs after an average of 41.6 treatment days, although there was a rather wide variability (29 to 60 days) in the number of doses required to produce end-point ototoxicity in all five cats. The low dose of gentamicin (9 mg/kg per day) induced similar signs in four cats after an average of 67.8 treatment days. One other animal (no. 202) receiving this aminoglycoside at 9 mg/kg per day evidenced only intermittent ataxia after 168 days when the study was arbitrarily terminated and was not included in the evaluations. Cumulative doses of gentamicin analogous to the amikacin end point or total doses were 749 mg/kg at the high dose and 610 mg/kg at the low dose. A statistical evaluation (10) revealed that these total gentamicin doses were similar.

Terminal evaluations of cochlear function are presented in Table 2. Amikacin at both dose levels (90 and 45 mg/kg per day) produced significant and almost complete abolition of CM and NAP responses. When compared with control cats, the average CM and NAP responses for amikacin ranged from 1 to 4% and 4 to 8% at the high (group 1A) and low (group 2) doses, respectively.

Gentamicin at 18 and 9 mg/kg per day also produced significant reductions in cochlear responses although they were not detected clinically. The average level of cochlear responses after gentamicin ranged from 31 to 46% of levels determined in the control cats (Table 2). These observations indicate that gentamicin also has a liability to produce cochlear damage in cats, although its primary clinical ototoxic effect was on vestibular function.

During the course of the experiment, markedly reduced PRN values became evident in some gentamicin-treated cats, but this parameter did not reliably predict end-point vestibular ototoxicity when the test was performed at 7-day intervals. Repeat assessments at the termination revealed that PRN values had declined in all cats, including the controls (Table 3). However, only the animals receiving gentamicin at 18 or 9 mg/kg per day exhibited a markedly reduced duration of nystagmus and numbers of saccades when compared with the control and amikacin groups. A borderline reduction in the number of saccades but not the duration of nystagmus was detected in the group 1 amikacin cats (90 mg/kg per day) only at a termination after 63.4 doses, well beyond the dose time (40.7 doses, group 1A) to produce cochlear impairment, indicating a very low potential for vestibular effects with amikacin.

Appetite suppression also became evident in some cats receiving gentamicin. In contrast, the doses of amikacin were well tolerated for the duration of treatment, and no behavioral changes other than apparent hearing impairment were evident in these animals.

Table 4 shows that amikacin and gentamicin produced serum levels that were dose related, and practically no accumulation was evident with either antibiotic at the dose levels em-

TABLE 2. *Electrophysiological assessment of cochlear toxicity in cats given daily subcutaneous doses of amikacin or gentamicin*

Drug	Group no.	No. of cats	Daily dose (mg of base/kg)	Group mean of avg response/cat ± SE[a]				Avg % dysfunction
				Maximum peak-to-peak CM amplitude (μV)	% Control	(NAP) N_1 action potential deflection (μV)	% Control	
Amikacin	1A	3	90	31 ± 4[b]	1	90 ± 46[b]	4	98
	2	3	45	88 ± 44[b]	4	183 ± 94[b]	8	94
Gentamicin	3	5	18	738 ± 294[c]	35	920 ± 354[c]	41	62
	4	4	9	958 ± 294[c]	46	710 ± 245[c]	31	62
Water control	5, 6	9	0.45 ml/kg	2,097 ± 278		2,261 ± 381		

[a] SE, Standard error.
[b] $P < 0.01$ versus control (one-tailed Mann-Whitney U test).
[c] $P < 0.05$ versus control (one-tailed Mann-Whitney U test).

ployed, except where renal damage appeared substantial. Additionally, the antibiotic in serum declined to very low levels within 24 h after the last treatment in animals without indications of severe kidney damage.

The levels of antibiotic in perilymph were often below the sensitivity of the assay, although measurable amounts were identified in some cats. This was particularly true in cats showing substantial increases in BUN and histological renal change.

Evidence of nephrotoxicity is presented in Table 4. Two of five cats receiving amikacin at 90 mg/kg per day and one of five cats at the lower dose of 45 mg/kg per day exhibited moderate to marked renal histopathological changes. The kidneys of the other three animals at the high-dose level and four of five cats receiving the antibiotic at 45 mg/kg exhibited slight to moderate renal alterations.

Gentamicin at 18 and 9 mg/kg per day produced moderate to marked renal tissue alterations in four of five and two of five cats, respectively. Another cat (no. 205) at 9 mg/kg per day was apparently quite sensitive to the nephrotoxic effects of this aminoglycoside and exhibited severe microscopic renal lesions. Kidneys of the remaining cats, one of five at the high dose and two of five at the low dose, exhibited slight to moderate renal histopathological changes.

The kidneys of two of ten control cats also exhibited moderate to marked renal tissue alterations, and six other control cats had slight to moderate changes, making the interpretation of aminoglycoside nephrotoxic effect uncertain. The kidneys of the remaining two control animals were normal.

Within limits of the numbers of animals used, a statistical evaluation (10) revealed that the incidence of histological nephrotoxicity in gentamicin-treated animals was significantly greater than that in the control cats, whereas the incidence in animals receiving amikacin was not different from controls. Since these aminoglycosides are both potentially nephrotoxic as well as ototoxic, cats with renal toxicity were not excluded from the evaluation.

BUN levels were monitored as indirect evidence of nephrotoxicity, but a correlation between this parameter and renal histopathology did not always exist (Table 4).

DISCUSSION

It has been established that the ototoxic liability of amikacin in laboratory cats is cochlear (14). In contrast, the clinical liability of gentamicin is considered to be primarily vestibular, although cochlear toxicity has also been observed in humans (2, 7) and in animals (6, 9). Consequently, the end points of ototoxicity selected for this comparative study were hearing impairment for amikacin and ataxia for gentamicin.

Cats were chosen for this experiment because both cochlear and vestibular dysfunctions can be detected clinically in this species, permitting an evaluation of primary and secondary ototoxic potentials in the same animal. Serum and perilymph antibiotic levels can also be monitored, and nephrotoxicity can be assessed in each individual animal. The detection and progression of cochlear toxicity was difficult to monitor by behavioral changes, as demonstrated in the first group of cats receiving amikacin at 90 mg/kg per day. When clinical observations indicated a loss of behavioral reactions to sound, the cats commonly demonstrated very low or absent electrophysiological responses at the termination. The neurophysiological determinations (CM and NAP) defined the response of each animal to sound very well and were used to establish the number of doses required to reach the chosen end point. The PRN measurements taken at the termination correlated well with clinical observations of marked ataxia and impaired righting reflex and also supported the liability of gentamicin to produce

TABLE 3. *PRN determinations in cats given daily subcutaneous doses of amikacin or gentamicin*

Drug	Group no.	No. of cats	Daily dose (mg of base/kg)	Group mean of avg response/cat ± SE[a]			
				Duration of nystagmus		No. of saccades	
				Predose	Termination	Predose	Termination
Amikacin	1	5	90	21.2 ± 1.0	15.6 ± 1.3	65.1 ± 2.8	34.0 ± 3.2[b]
	2	5	45	19.7 ± 0.5	15.1 ± 1.1	56.0 ± 2.0	30.5 ± 1.6
Gentamicin	3	5	18	17.8 ± 0.9	2.7 ± 0.3[c]	55.7 ± 3.0	2.0 ± 1.0[c]
	4	5	9	18.8 ± 0.7	3.3 ± 0.6[c]	56.6 ± 2.6	3.5 ± 1.3[c]
Water control	5	5	0.45 ml/kg	20.7 ± 0.9	14.5 ± 1.2	65.9 ± 3.2	31.9 ± 2.9

[a] SE, Standard error.

[b] $P = 0.05$ versus control at comparable time period (one-tailed Mann-Whitney U test).

[c] $P < 0.01$ versus control at comparable time period (one-tailed Mann-Whitney U test).

TABLE 4. *Nephrotoxicity evaluations and antibiotic concentrations in serum and perilymph of cats given daily subcutaneous doses of amikacin or gentamicin*

	Daily dose (mg of base/kg)	Cat no. and sex	Nephrotoxicity			Antibiotic concn				
			BUN (mg/100 ml)		Microscopic renal changes[a]	Serum (μg/ml)			Perilymph (μg/ml)	
			Predose	Last day		Day 1	Last day	Termination	Right ear	Left ear
Amikacin	90	228 ♂	18	19	1-2	135	150	0.5	—[b]	—[b]
		229 ♂	18	19	1	180	150	0.3	6.0	5.0
		230 ♀	22	18	0-1	180	185	1.0	7.0	10.7
		231 ♀	24	20	2-3	135	130	0.3	—[b]	—[b]
		232 ♀	29	59	2-3	170	300	11.0	32.9	25.0
Mean			22	27	1.6	160	183	2.6	15.3	13.6
	45	217 ♂	20	20	1	62	61	—[c]	—[c]	2.0
		218 ♂	19	16	0-1	78	68	—[c]	—[c]	—[c]
		219 ♂	27	21	1-2	71	120	0.3	5.5	7.0
		220 ♀	15	25	2-3	60	70	—[c]	1.0	—[c]
		221 ♀	22	25	1-2	84	48	—[c]	—[c]	—[c]
Mean			20	20	1.4	71	73			
Gentamicin	18	197 ♂	18	22	2-3	46	33	0.6	—[c]	—[c]
		198 ♂	23	40	2-3	44	53	2.3	—[b]	—[b]
		199 ♂	27	28	2-3	40	54	1.3	—[c]	—[c]
		200 ♀	27	27	1-2	34	35	0.3	2.0	2.0
		201 ♀	23	20	2-3	45	34	0.4	—[c]	—[c]
Mean			24	27	2.3	42	42	1.0		
	9	202 ♂	21	25	2-3	16	24	0.2	—[c]	—[c]
		203 ♂	23	31	2-3	—[c]	26	0.6	—[c]	—[c]
		204 ♂	22	25	1	22	13	—[c]	—[c]	—[c]
		205 ♀	16	351	4	18	100	78.0	41.0	37.5
		206 ♀	19	19	1-2	25	18	—[c]	1.4	—[c]
Mean			20	90	2.3	20	36			
Control (sterile water)	0.45 mg/kg	222 ♂	20	28	2-3					
		223 ♂	21	27	1-2					
		224 ♂	30	34	1					
		225 ♀	22	27	0					
		226 ♀	25	23	0-1					
		233 ♂	20	24	1-2					
		234 ♂	28	21	0					
		235 ♀	29	21	2-3					
		236 ♀	28	24	1					
		237 ♀	24	18	1					
Mean			25	25	1.2					

[a] Microscopic renal change: 0, none; 1, slight; 2, moderate; 3, marked; 4, pronounced.
[b] No sample obtained.
[c] Below assay sensitivity.

vestibular impairment in all cats tested.

The cochleotoxic liability of amikacin was confirmed in this study, and none of the cats receiving this aminoglycoside exhibited behavioral changes indicative of vestibular dysfunction. In contrast, gentamicin produced ataxia, confirming the vestibular liability of this antibiotic. However, the CM and NAP determinations revealed that in some cats gentamicin also significantly reduced the cochlear responses. These observations with gentamicin in cats generally agree with the clinical ototoxic side effects in humans (7).

Table 1 shows that similar time periods (dosing days) were required to produce definitive ototoxicity when both drugs were administered at a dose ratio of 5 to 1. The relationship appeared at both dosage levels. An examination of the total or cumulative dose also demonstrated a similar ratio. The cumulative quantities of amikacin were 3,660 mg/kg for the 90-mg/kg dose for 40.7 days or 3,525 mg/kg for the 45-mg/kg dose for 78.3 days, respectively, as determined by an electrophysiological assessment of cochlear function. The analogous cumulative quantities of gentamicin were 749 and 610 mg/

kg for the 18-mg/kg dose for 41.6 days or 9-mg/kg dose for 67.8 days, respectively, as determined by ataxia or impairment of the righting reflex (Table 1), and these doses appear similar to the vestibulotoxic doses administered by Waitz et al. (16).

Nephrotoxicity was evident for both aminoglycosides, but the presence of renal tissue alterations in control cats made the interpretation of aminoglycoside nephrotoxic effect uncertain. A statistical evaluation (10) revealed that the incidence of histological renal changes in amikacin cats was similar to controls, whereas the frequency of such changes in gentamicin cats was significantly greater. There appeared to be a separation between renal damage and ototoxicity since not all cats terminated with marked ototoxicity demonstrated significant renal damage histologically. However, the possibility of enhanced ototoxicity in the presence of elevated serum levels associated with kidney damage should be considered. Two cats severely affected by the ototoxic manifestations of the antibiotics (no. 232, 90 mg of amikacin per kg per day, and no. 205, 9 mg of gentamicin per kg per day) also evidenced marked renal changes and elevated serum and perilymph antibiotic levels.

In summary, this safety evaluation in laboratory cats demonstrated that amikacin was selectively toxic to the cochlea at five times the dose of gentamicin that produced both vestibular and cochlear toxicities.

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