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Lack of Ciprofloxacin Ototoxicity after Repeated Ototopical Application

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The possible side effects of ototopically applied ciprofloxacin on inner ear function were investigated. The hearing function of pigmented guinea pigs was evaluated by daily frequency-specific evoked response audiometry after repeated application of the drug to both ears. Ciprofloxacin appeared to have no statistically significant effect on the hearing thresholds of the experimental animals.

The ototopical use of antimicrobial agents is part of the commonly recommended treatment for chronic suppurative otitis media (6). Many antibiotics, however, appear to penetrate through the round window membrane (4) and exert a toxic effect on inner ear function (3, 5). Since ciprofloxacin is specific for the aerobic bacteriological spectrum found in chronic suppurative otitis media (7), it can be used in the topical treatment of this condition. We conducted an ototoxicity study of ototopically applied ciprofloxacin.

(Part of this study was presented at the Conference on the Eustachian Tube and Middle Ear Diseases, Geneva, Switzerland, 26 to 29 October 1989.)

For five consecutive days, both male and female pigmented guinea pigs received, under general anesthesia, daily bilateral ototopical applications of a test drug through a transbullar approach. A piece of Gelfoam was used to keep the drug in close and permanent contact with the round window membrane. Gelfoam was soaked in a 2-mg/ml ciprofloxacin solution and applied in 11 animals. Seven animals received neomycin (5 mg of neomycin sulfate powder with an activity of 681 μg/mg was absorbed with saline on Gelfoam) as a positive control, and a group of 12 animals receiving a single topical saline application served as negative controls. Hearing thresholds were measured before treatment, at each day of the treatment period, and 24 h after the last application. The cochlear function of each animal was monitored by evoked response audiometry. Acoustic broad-band clicks (80 μs) were generated by an evoked response audiometry MK III stimulator (Amplaid) and were filtered by a set of digital filters with slopes of 90 dB per octave (multichannel programmable filter instrument model 9016; Frequency Devices Inc.) to a narrow-band noise with a band width of one-third of an octave centered at 1, 2, 4, 8, 16, and 32 kHz. An amplifier (model M-505; Onkyo) and a speaker (model SB-F4F; Technics) were used. The guinea pigs were put in front of the speaker at a distance of 50 cm. The response signal was averaged over 200 cycles. The resulting curves were only interpreted as to hearing threshold, defined as the minimal sound level that could yield a reproducible peak III and/or peak V. Individual test-retest threshold differences of 10 normal animals with this methodology never exceeded 5 dB at any frequency. Hearing thresholds are expressed as normal hearing level (dB NHL), i.e., compared with the median thresholds of a group of 35 normal guinea pigs, determined as above. Statistical analysis was performed on the raw hearing threshold data at each frequency separately. Paired values, comparing the shift of threshold between 2 days, were analyzed by the Wilcoxon matched pairs signed rank test. Zero values were neglected. A Mann-Whitney U-test was used to compare intergroup differences. All distributions were considered one-tailed. Cutoff values were set at a 5% level of significance.

For clear visualization of the evoked response audiometry results, frequency-specific hearing thresholds were pooled per day and are represented in Fig. 1. The evolution of the hearing thresholds of the seven guinea pigs receiving neomycin is shown in Fig. 1A. Before treatment (day 1), the distribution of the sample was normal (median, +2 dB NHL; spread, 3 dB). A progressive hearing loss was found during therapy, while the spread of the sample drastically increased (day 6: median, −60 dB NHL; spread, 49 dB). At all frequencies, the hearing losses between days 1 and 6 were significant. The losses were already significant at all frequencies after 1 day of application (Table 1). The evolution of the hearing thresholds of the 11 guinea pigs receiving ciprofloxacin is shown in Fig. 1B. Before treatment (day 1), the sample had a normal distribution (median, 0 dB NHL; spread, 7 dB). No obvious losses in hearing threshold could be seen in the 6-day period, while the spread remained normal (day 6: median, −4 dB NHL; spread, 11 dB). No significant losses could be seen between days 1 and 6 for 1, 2, 4, and 8 kHz. For 16 and 32 kHz, however, the ability to hear dropped significantly ($P < 0.01$), although the median losses were small, i.e., a 7.5-dB loss at 16 kHz and a 16-dB loss at 32 kHz. These losses can be entirely attributed to day 1 of drug application, on which 5- and 15-dB losses were seen at 16 and 32 kHz, respectively. At 1 and 2 kHz, a small but significant hearing loss was also seen at day 2. This loss was not consistent and therefore was not significantly present at day 6 (Table 1). The evolution of the hearing thresholds of the 12 guinea pigs receiving saline is shown in Fig. 1C. Otitis media was found in several animals in the saline group at day 3. For this reason, the group was no longer monitored. Before treatment (day 1), the sample had a normal distribution (median, 0 dB NHL; spread, 7 dB). The overall tendency between days 1 and 2 is comparable to the tendency of the animals in the ciprofloxacin group, with a very slight hearing loss, while the spread of the distribution

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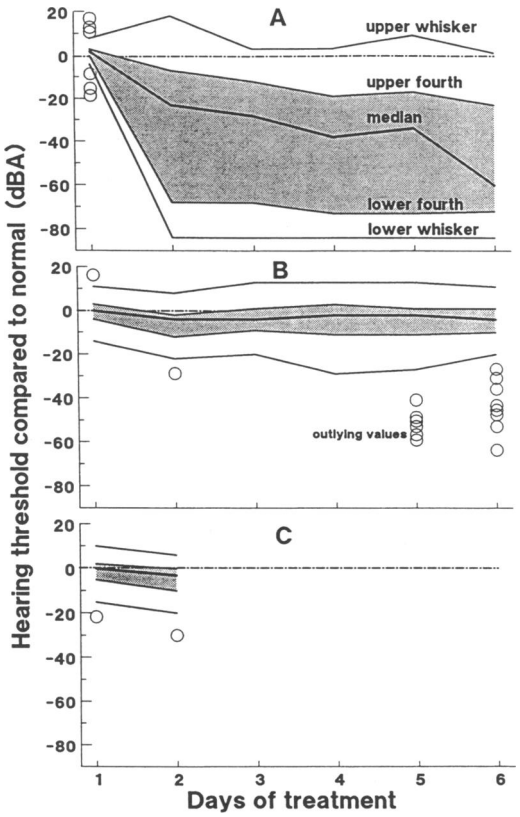

FIG. 1. Evolution of the hearing thresholds in the different groups, expressed as the five box plot parameters (central position is represented by the median, dispersion by the interval of the fourths, extremes by the whiskers) of the pooled hearing thresholds at all frequencies. (A) Neomycin group, showing a progressive hearing loss and an increasing spread of the sample. (B) Ciprofloxacin group, showing no hearing loss. The outlying values at days 5 and 6 come from one animal that presented technical problems at day 4. Its data were not excluded from statistical analysis. (C) Saline group, which was only observed for 2 days.

TABLE 1. Differences in the median hearing thresholds (decibels) between days 1 and 2, days 2 and 6, and days 1 and 6 of the neomycin (N), ciprofloxacin (C), and saline (S) groups

Frequency (Hz)	Day	N (n = 7)[a]	C (n = 11)[a]	S (n = 12)[a]	N − S[b]	C − S[b]
1,000	1–2	−20*	−5*	−1	−20*	−5*
	2–6	−19	+2.5			
	1–6	−39*	−2.5			
2,000	1–2	−26*	−7*	−5*	−25*	−5
	2–6	−20	0			
	1–6	−46*	−7			
4,000	1–2	−15*	0	0	−10*	−5
	2–6	−40	−7			
	1–6	−55*	−7			
8,000	1–2	−5*	−3	+0.5	−8*	0
	2–6	−40	+5.5			
	1–6	−45*	+2.5			
16,000	1–2	−25*	−5*	−3*	−17.5*	−2.5
	2–6	−30*	−2.5			
	1–6	−55*	−7.5*			
32,000	1–2	−50*	−15*	−15*	−35*	0
	2–6	(−10)	−1			
	1–6	−60*	−16*			

[a] An asterisk (*) indicates statistically significant losses ($P < 0.05$) after Wilcoxon testing. Values are in parentheses if too few data were available to perform statistics.

[b] Differences in the median hearing losses between neomycin and saline groups (N − S) or between ciprofloxacin and saline groups (C − S) between days 1 and 2 were analyzed by the Mann-Whitney U-test. An asterisk (*) indicates that these values (blank subtracted) are statistically significant ($P < 0.05$).

remained small. At 1, 4, and 8 kHz, no statistically significant hearing losses were seen. On the other hand, significant hearing losses of 5, 3, and 15 dB occurred at 2, 16, and 32 kHz, respectively (Table 1). Comparing the hearing losses at 2, 16, and 32 kHz between days 1 and 2, the Mann-Whitney U-test could not reveal a difference between the saline group and the ciprofloxacin group. The differences at all frequencies were significant in the neomycin group compared with the saline group (Table 1).

Detection of high-frequency hearing loss is considered to be an early indication of ototoxicity of systemically administered drugs (1). This is even more true for ototoxicity of ototopical preparations (3). Intratympanically applied molecules can diffuse through the round window membrane and exert their toxic effect primarily to the basal coil of the cochlea (4). The dose of neomycin that was applied ototopically in this study was probably too high to induce a selective high-frequency hearing loss. Indeed, Harada et al. (2) demonstrated morphological changes in the guinea pig cochlea as early as 4 h after topical application of neomycin in the round window niche.

Topical application of 2 mg of ciprofloxacin per ml on the round window membrane for 5 days did not yield any significant hearing loss at 1, 2, 4, or 8 kHz. At 16 and 32 kHz, however, a significant loss was found. The losses were small and were present after the first application. No further deterioration occurred afterward, which is an argument against the losses being the result of a toxic effect of the drug. The saline group, acting as negative controls for the first 2 days in the study, showed the same hearing losses at 16 and 32 kHz, both statistically significant. We therefore assume that these hearing losses are merely the result of the technique as such. The significant losses at 2 kHz that were only seen at day 2 in both groups are probably also related to the technique of application.

We concluded that no statistically significant hearing loss, monitored as described above, can be demonstrated after repeated topical application of ciprofloxacin on the guinea pig round window.

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