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Hearing Loss after Intratympanic Gentamicin Therapy for Unilateral Ménière's Disease

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Objective: This study set out to evaluate the hearing changes that occur during intratympanic gentamicin therapy and to correlate them with the long-term effects of the treatment on the control of vertigo and on hearing.
Study Design: This was a prospective study.
Setting: Tertiary medical center.
Patients: The 71 patients included in the study had been diagnosed with unilateral Ménière's Disease as defined within the 1995 American Academy of Otolaryngology–Head and Neck Surgery guidelines, and had been refractory to medical treatment for at least 1 year.
Intervention: Intratympanic injections of gentamicin at a concentration of 27 mg/ml were performed at weekly intervals until indications of vestibular hypofunction appeared in the treated ear. If there was a recurrence of the episodes of vertigo, an additional course of injections was performed.
Main Outcome Measure: The 1995 American Academy of Otolaryngology–Head and Neck Surgery criteria for reporting the treatment outcome for Ménière's Disease were used. During the period of gentamicin instillation, weekly audiograms were obtained. The results of the treatment were expressed in terms of control of vertigo and hearing level.
Results: Vertigo was controlled by gentamicin instillation in 83.1% of the 71 patients. Two years after the treatment, hearing loss as a result of the gentamicin injections was observed in only 11 (15.5%) patients. The recurrence of spells of vertigo after having initially achieved complete control was noted in 17 (23.9%) patients. Hearing loss at the end of the treatment occurred in 32.4% of the patients, but it was transitory so that 3 months after ending the treatment it was 12.7% and after 2 years it was 15.5%. Those patients in whom no change in their level of hearing occurred during the treatment needed another course of injections and presented poorer overall control of vertigo.
Conclusions: Ending weekly intratympanic injections when clinical signs of vestibular deafferentation appear results in the control of vertigo in the majority of patients. The hearing changes detected during the treatment are transitory and are the only clinical sign that predicts the response to gentamicin instillation. **Key Words:** Deafness—Gentamicin—Hearing loss—Ménière's Disease—Ototoxicity—Vertigo.
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Ménière's Disease (MD) is an inner-ear disorder characterized by sudden attacks of vertigo associated with tinnitus and pressure in the affected ear. Fluctuating hearing loss is another characteristic of this condition, which usually leads to a permanent hearing deficit resulting in a moderate to severe disability.

A wide variety of conservative approaches have become established as initial treatment of MD. These medical therapies include a low-salt diet and administration of diuretics, steroids, calcium channel blockers, vasodilators, and other agents, and are useful in regulating the symptoms in 50 to 70% of patients (1). For medically intractable MD, various surgical techniques have been developed. They have been criticized because of their poor results with respect to the long-term control of vertigo, the definite hearing damage that can be provoked, and the morbidity associated with the procedure. Recently, the use of aminoglycosides to destroy the vestibular remnants in the inner ear has been recommended in an attempt to minimize complications and risks involved in other procedures.

The use of systemic streptomycin to treat patients with vertigo was first reported by Fowler (2) in 1948. To avoid the systemic effects of such treatment, Schuknecht (3) developed a technique to deliver streptomycin transtympanically and described the complete control of vertigo in eight patients, although five of the eight subjects experienced complete hearing loss. Intratympanic gentamicin instillation to treat MD was subsequently described by Lange (4) and, since then, several authors have developed different protocols and treatment schedules to treat partial or total damage of the labyrinth. Despite the great heterogeneity that exists, the degree of control of vertigo reported is quite similar across all the

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techniques (81–95%), but the incidence of reported hearing loss as a result of the gentamicin therapy varies greatly (0–38%) (5). Surprisingly, there is no relationship between the control of vertigo and the total dose, dosing scheme, or method of administration (6). Various factors may be responsible for the inability to define a clear dose-response relationship and these may include exposure time and concentration of the gentamicin, anatomic differences in the round window, and individual sensitivity to aminoglycosides (7).

We chose to use a titration protocol in which the appearance of certain vestibular signs and symptoms define the end of the treatment. This protocol has been shown to be efficient and offers a low risk of hearing damage (8). The aim of this study was 1) to determine the degree of hearing loss provoked by gentamicin during the treatment and the clinical implications of this effect and 2) to establish the relevance of permanent hearing loss as a result of the treatment.

PATIENTS AND METHODS

Patients

Patients with definite MD according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines were included in this study (9). Control of these patients' vertigo had not been achieved with medical treatment (acetazolamide, betahistine, trimetazidine) in conjunction with a low-salt diet. The patients were followed up for a period of at least 1 year before being considered to be refractory to medical therapy. Subsequently, they were informed of the gentamicin treatment and surgical alternatives. Those that underwent intratympanic gentamicin treatment signed an informed consent, and 71 of them were followed up by means of regular controls for 2 years.

Methods

Pretreatment evaluation

Patients underwent a complete neurotologic examination, audiography, caloric testing, and rotatory chair testing before beginning this protocol. In addition, the patients were asked whether they had suffered spells of vertigo, tinnitus, or Tumarkin attacks. A functional level score was determined for each patient according to the six-point scale proposed by the AAO-HNS. Furthermore, two self-report measures for the functional impairment were used for each patient, the Dizziness Handicap Inventory and the UCLA Dizziness Questionnaire (10).

Treatment protocol

Gentamicin sulfate (40 mg/ml) was buffered with sodium bicarbonate to pH 6.4 to reach a final concentration of 26.7 mg/ml. Gentamicin injections were performed in an office setting using the microscope. Once the round window was located, the buffered gentamicin was injected through a 27-gauge needle to fill the middle ear. The patient remained in the Trendelenburg position for 30 minutes.

Patients returned for weekly follow-up examinations during the course of the treatment protocol. Audiography and bedside tests were performed during each follow-up examination. Three bedside tests were performed to detect any sign of unilateral vestibular hypofunction: 1) observation for spontaneous nystagmus, 2) head-shaking test, and 3) head-thrust test. The treatment was considered to be finished when any of the three beside tests was positive after the weekly injection. In the case of any of the three bedside tests being positive before beginning the treatment, the injections were administered until a test that had been negative became positive. When the pure-tone average (PTA) increased 10 dB or the speech discrimination score (SDS) fell by more than 15% between tests, the patient was informed about the risks of continuing the treatment.

Posttreatment evaluation

Patients were monitored 3 months after the completion of the therapy and were then seen at 12-month intervals. All patients were monitored for at least 2 years. Audiometric, caloric, and rotatory tests were performed in each follow-up in addition to the neurotologic examination.

In the case of recurrence of the vertigo episodes, a second course of treatment was performed. To distinguish between the recurrence of the vertigo spells and the lack of control of MD during the first course, recurrence of the disease was defined as the occurrence of two definitive episodes of vertigo, lasting 20 minutes or longer, with a deterioration of hearing and tinnitus at least 3 months after the ending of the first course of treatment. Two groups of patients were created according to the incidence of recurrence: Group I (no recurrence) and Group II (dizzy spells returned).

Audiometry and vestibular testing

Pure-tone air and bone-conduction thresholds were defined in a sound isolation chamber (IAC Mini 250) with a clinical computer audiometer (Model AC5, Interacoustics, Assens, Denmark). For air conduction, frequencies between 250 and 8,000 Hz were studied at octave intervals, whereas frequencies between 250 and 4,000 Hz were assessed for bone conduction. The PTA for air conduction was considered as the mean threshold at 500, 1,000, 2,000 and 3,000 Hz. Speech audiometry was performed in the same chamber and with the same audiometer using conventional lists to obtain the SDS.

To present the results of all the patients during the treatment, the PTA will be shown as the mean before treatment (basal), 1 week after the first dose, the second dose, and so on until the fifth dose. The follow-up results 3 months, 1 year, and 2 years after ending the treatment are also shown as the mean PTA for all the subjects.

Vestibular responses were obtained using conventional bithermal caloric testing (30.5° and 43.5°C) and 10-second ice-water caloric tests when indicated. A video-based system was used (Ulmer VNG, version 1.4, SYNAPSIS, Marseille, France) for the acquisition and analysis of the eye response. Maximum velocity of the slow-phase components of nystagmus evoked by each ear were analyzed for unilateral weakness and directional preponderance as determined by Jongkees' formula.

Statistical analysis

When studying the PTA, a repeated-measures analysis of variance was performed with subsequent application of the Dunnett test. When studying the caloric results, a Friedman test was applied with a Wilcoxon test after the Bonferroni adjustment. Finally, when comparisons were made between the groups with and without recurrences, Student's *t* test was applied as a parametric test and Kruskal-Wallis as a nonparametric test.

RESULTS

Of the 71 patients included, 36 were men and 35 were women, with a mean age of 53.6 years (95% confidence interval [CI], 50.75–56.37 years). Fifty-four (76.1%) patients needed only one course of injections to control their vertigo (Group I), and their mean number of injections was 3.1 (95% CI, 2.8–3.6). The remaining 17 patients (23.9%) required another course of treatment because they suffered a recurrence of their vertigo, with a mean of 12.6 months after the end of the first course of treatment (Group II) and with a mean number of injections during the first course of 2.5 (95% CI, 1.9–3.1).

In accordance with the AAO-HNS index, control of vertigo is shown in Table 1 for the patients that received one course of injection treatment and for those that received two. After others' methodology (8,11,12) and, because all the patients in this study were followed up 2 years after ending the treatment, we have considered all the subjects together (Group I and Group II) to assess control of vertigo. As such, complete control of vertigo (Class A) was obtained in 49 (69.0%) patients and substantial control (Class B) in 10 (14.1%). Nine patients (12.7%) were submitted to a transmastoid labyrinthectomy (Class F) because of the lack of control of vertigo. There was one patient for each remaining category (Classes C, D, and E).

Caloric responses were obtained in every patient before administering the gentamicin. It was considered normal in 29 (40.9%) patients; unilateral weakness was identified in 36 (50.7%) patients and no response to ice water was detected in 6 (8.4%) patients. Caloric tests after 2 years of the completion of therapy were obtained in 68 patients. Normal function was found in 3 (4.22%) patients, unilateral weakness was found in 32 patients (45.1%), and no response to ice water was found in 28 patients (39.4%).

The number of patients at each audiometric stage at the onset of treatment, and 3 months and 2 years onward, are shown in Figure 1. Following the AAO-HNS guidelines, the patients were grouped in stages according to their hearing level. There was 1 patient at Stage 1, 5 patients at Stage 2, 35 patients at Stage 3, and 30 patients at Stage 4. The mean PTA for the patients at each of the stages is shown in Figure 2: before treatment, 3 months, 1 year, and 2 years after the end of the treatment.

Although no statistically significant differences were observed for the mean baseline, the follow-up data of the individual subjects after 3 months, 1 year, and 2 years were analyzed to determine whether there had been a clinically significant change in hearing status. A change in hearing was defined on the basis of the recommendations of the Committee on Hearing and Equilibrium. Taking these considerations into account, hearing loss occurred in 23 patients at the end of treatment (32.4%), in 9 when hearing assessment was performed 3 months after ending the treatment (12.7%), and in 11 patients 2 years afterward (15.5%).

TABLE 1. *Control of vertigo for group I and group II patients*

	Group I		Group II	
Class	No.	%	No.	%
A	39	55	10	59
B	7	10	3	18
C	0	0	1	6
D	1	1.5	0	0
E	1	1.5	0	0
F	23	32	3	17

The PTA values before treatment (taken from the poorest audiogram within 6 months of the beginning of the protocol) was 67.25 dB (95% CI, 62.65–71.84 dB). The SDS for the same period was 68.57% (95% CI, 62.70–74.41%). The PTA values obtained during the treatment and after 3 months, 1 year, and 2 years of follow-up are shown in Table 2. Significant differences were found in the PTA values obtained during the treatment (1 day–5 days) when compared with the basal pretreatment PTA level ($p < 0.05$). In contrast, no statistical differences were found between the pretreatment levels and the PTA levels after the treatment (3 months, 1 year, and 2 years; $p > 0.05$). In summary, a slight decrease in the hearing levels was observed in each weekly audiogram obtained after every corresponding gentamicin injection, but the PTA recovered to basal levels within 3 months of the completion of the therapy and remained stable for at least 2 years. The evolution of the PTA before, during, and after gentamicin therapy is represented in Figure 3. When all the frequencies studied were considered individually, a slight increase in PTA was observed at each one, but reverted to the pretreatment basal level frequency (except at 6 kHz) within 3 months after the end of the treatment (Fig. 4).

This tendency was observed in Group I patients (no recurrence of their symptoms) and was equivalent to that previously observed in the global population. In contrast, the evolution of the PTA in Group II patients (those in whom symptoms of vertigo recurred and who subsequently needed another course of injections) was remarkable in that no statistically significant differences were found between the PTA levels determined after each gentamicin injection and the pretreatment basal levels (Table 3). Therefore, no changes were detected in hearing levels during the gentamicin therapy in those patients. The evolution of the PTA over time for both groups is shown in Figure 5.

To see whether we could detect any difference between Group I and Group II patients that might explain the differences in the control of vertigo and the audiometric results, we analyzed the distribution of the indications that defined the completion of therapy. All the patients in Groups I and II responded to the first course of treatment by producing a positive result in a test that had previously been negative. No differences were observed in the distribution of the positive or negative signs with respect to the tests performed in each group ($\chi^2 > 0.05$). Likewise, no differences were found in the number

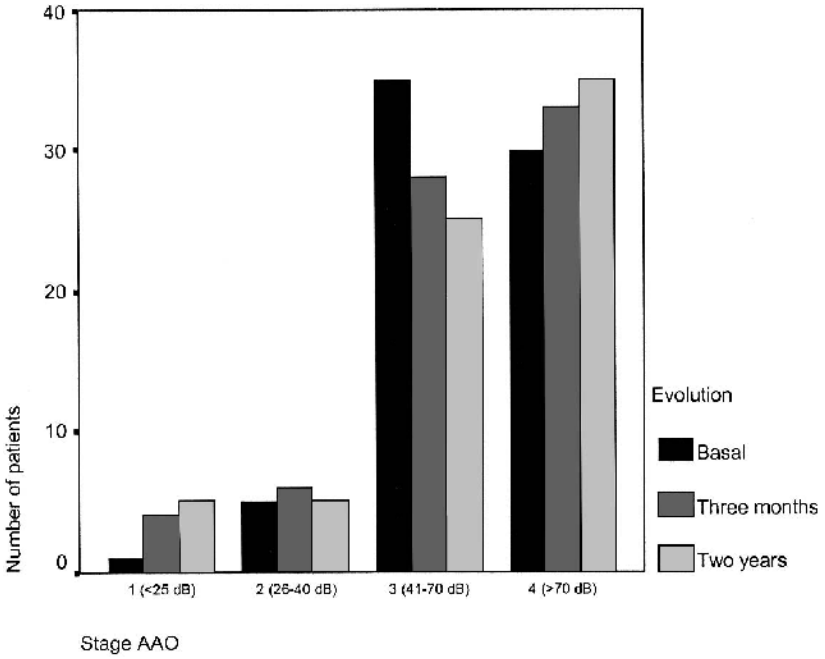

FIG. 1. Number of patients at each audiometric stage before and after treatment (3 months and 2 years).

of injections received during the first course of treatment of either group ($p > 0.05$). Furthermore, no differences were detected between the caloric responses obtained in caloric tests performed 3 months after the treatment had ended ($p > 0.05$). Finally, when the incidence of long-term hearing loss was analyzed 2 years after the completion of the treatment, no significant differences were found with the incidence of hearing loss observed in Group I (14.8%) and in Group II (16.1%).

DISCUSSION

The loss of hearing after treatment with intratympanic gentamicin is an important issue, given the well-known ototoxic effects of this drug. In this sense, the guidelines set up by the AAO-HNS have helped to compare the results generated using different modalities of treatment. According to these guidelines, hearing deterioration is defined as an increase in PTA of 10 dB or a 15% deterioration of word recognition when compared with the pretreatment values. Two years after ending the treatment, loss of hearing was still detected in 11 of our patients (15.5%), less than that reported by Minor (8), whose procedure we have followed up. In this earlier study, Minor reported a 32% incidence of hearing deterioration in a population of 31 patients with a mean follow-up time of 15 months. The follow-up of eight patients was less than 3 months, which we think may contribute to this discrepancy (see below). Similarly, Hirsch and Kamerer (13) reported a 31% loss of hearing after a weekly/biweekly protocol, although the number of injections administered was similar to that of our protocol. In another procedure of weekly injections that limited the number of administrations to four, a 17% incidence of hearing loss was observed between 12 and 24 months after the end of the treatment. However, it was not established whether patients with hearing loss in the 12- to 24-month interval were those that suffered hearing deficiencies 6 months after the end of the treatment, raising the question of the natural progression of the disease, given its well-known fluctuations (14). Other authors have also reported hearing loss in the 11 to 22% range (15–17).

From the initiation of the protocol, we were aware that the possibility of profound hearing loss could be expected in 3% of the patients, and that those that had been previously operated on and that were now being treated with intratympanic gentamicin (three subjects in this study) were at particular risk (8). However, in our study,

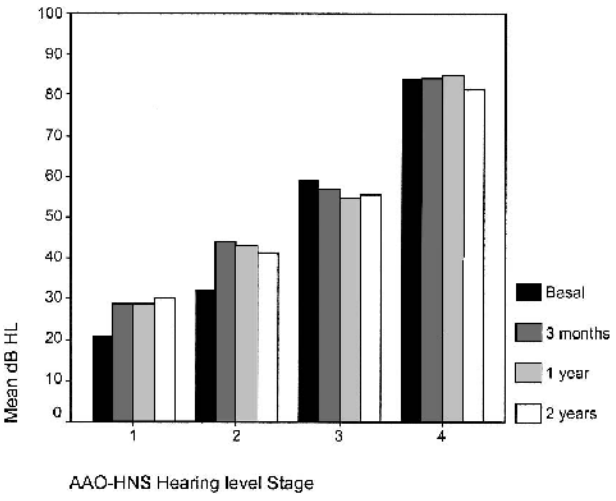

FIG. 2. Mean PTA obtained before and after the treatment by stage according to hearing level (AAO-HNS).

TABLE 2. *Pure-tone average levels obtained before (basal), during (1D–5D), and after the treatment (3 mo, 1 yr, and 2 yr)*

	Basal	1D	2D	3D	4D	5D	3 mo	1 yr	2 yr
N	71	71	62	43	31	12	71	58	71
PTA (dB)	67.25	74.85	75.34	78.19	75.88	80.41	66.67	66.58	68.37
CI									
Lower limit	62.65	69.90	69.87	71.99	68.56	68.10	61.33	60.34	62.32
Upper limit	71.84	79.93	80.81	84.39	83.21	92.74	72.01	72.82	74.42
SD	19.40	22.82	21.53	20.14	19.96	19.39	16.25	23.72	25.55

N, number of patients tested; CI, 95% confidence interval; SD, standard deviation; Basal, pretreatment PTA; D, PTA determined 1 wk after the corresponding number of doses; PTA, pure-tone average.

none of the patients developed such a problem. It should be noted that this risk increases if the concentration of the antibiotic is increased or the doses are not sufficiently spaced in time. As such, when 40 mg/ml of gentamicin is administered on a daily basis over four injections, a 10% incidence of deafness is observed (17). Otherwise, if the instillation procedure is sufficiently well spaced, the use of gentamicin 40 mg/ml is not associated with an increase in hearing loss (18).

When considering the degree of hearing loss before treatment, we observed that the patients' behavior depended on the stage in which they were classified. In the first follow-up visit, deterioration of hearing is more prominent in those patients in Stages 1 and 2, whereas those with the poorest hearing (i.e., at Stages 3 and 4) do not show significant differences. On the whole, the long-term variations in hearing of 3 to 5 dB after 2 years are of little relevance. In an earlier study, similar findings were demonstrated for hearing deterioration at 8 kHz. Patients with a pretreatment threshold above that of the median of the population were at risk for developing a hearing impediment at that particular frequency after gentamicin treatment. However, this finding was not corroborated when PTA or SDS was analyzed (13).

The study of PTA behavior over time adds relevant information to previously reported data. As expected, hearing loss after the first administration is provoked because of the ototoxic effect of the drug. This effect is slight, but the difference is significant, and ensuing injections cause a further moderate increase, probably in a dose-dependent fashion and without significantly affecting the treatment evaluation. In the follow-up, the mean PTA reverts to close to the basal pretreatment levels 3 months after treatment, and 1 and 2 years later, only small irrelevant changes in PTA can be seen. This probably explains the difference in audiometric results between our patients and those reported by Minor mentioned above. As the PTA is calculated as a function of the response at 0.5, 1, 2, and 3 kHz, the pattern followed up in these particular frequencies is similar to the one just described. However, complete recovery is not observed in the response at 6 kHz, and there is a small but significant deterioration at this frequency after treatment. The trend found at the 8-kHz threshold was toward a change in early hearing loss (15), but when the mean thresholds for 1 kHz and 4 kHz ware analyzed separately, as in the study by Murofushi et al. (11), no differences were found in terms of the number of subjects that showed deterioration in hearing after gentamicin treatment.

During treatment, hearing deterioration well exceeded the 10-dB hearing loss limit considered as significant in the AAO-HNS guidelines in 23 patients (32.4%). A detailed analysis of the data reveals that this occurred in

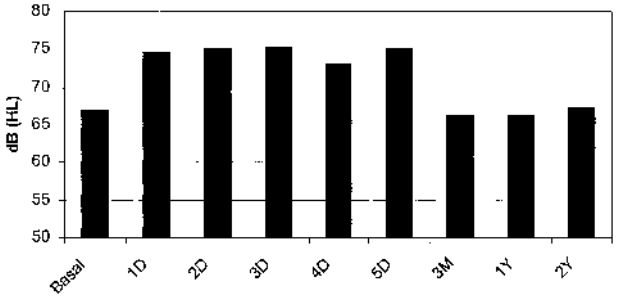

FIG. 3. Mean PTA obtained before (basal), during (1 day–5 days), and after the treatment (3 months, 1 year, and 2 years).

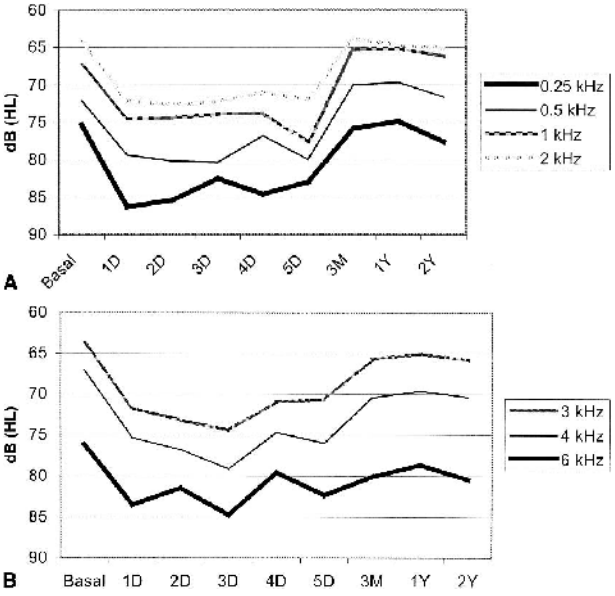

FIG. 4. (*A*) PTA for the 0.25-, 0.5-, 1-, and 2-kHz frequencies represented as function of the length of treatment and the follow-up period. (*B*) PTA for 3-, 4-, and 6-kHz frequencies represented as function of the time of treatment and follow-up period.

TABLE 3. *Pure-tone average levels obtained before beginning the treatment (basal), during the treatment (1D–5D), and during the follow-up period (3 months, 1 year and 2 years) for group I and group II patients.*

	Group I			Group II		
	No.	Mean	SD	No.	Mean	SD
Basal	54	68.62	20.29	17	62.82	15.28
1D	54	76.75	21.50	17	67.43	17.86
2D	47	77.42	23.31	15	68.82	12.78
3D	32	81.01	21.19	11	69.68	13.96
4D	21	79.58	19.92	10	68.18	17.68
5D	8	88.01	20.51	4	68.25	10.40
3 mo	54	66.94	23.91	17	65.85	17.26
1 yr	46	67.32	24.82	12	63.75	19.64
2 yr	54	68.90	25.40	17	65.27	26.64

SD, standard deviation; D, PTA determined 1 week after the corresponding number of doses.

nine subjects that did not show signs of vestibular hypofunction. Of these, seven rejected any kind of surgical intervention for their disease and decided to proceed with the treatment whatever hearing results might be expected, and two decided to stop the treatment. In 14 patients, the symptoms and signs of vestibular damage were concurrent with those of hearing deterioration. However, these subjects' pretreatment hearing level recovered, as seen in the first follow-up audiometry performed 3 months later. In light of our findings, at this point, the 10-dB hearing loss difference in PTA stipulated in the AAO-HNS guidelines as clinically significant should be reconsidered because of the degree of recovery documented here.

The absence of hearing loss during treatment was a common finding in patients that presented new dizzy spells after the initial control of vertigo. This recurrence of vertigo occurred during the 2-year follow-up period and after a mean vertigo-free period of 12.6 months. When considered in conjunction with the fact that the treatment was stopped in these patients on the basis of definitive symptoms and signs of unilateral vestibular damage, we can exclude any possible placebo effect. It is possible that these patients express differences in their susceptibility to the ototoxic damage displayed by the cochlear and vestibular hair cells related to the higher endolymphatic potential in the former and/or specific

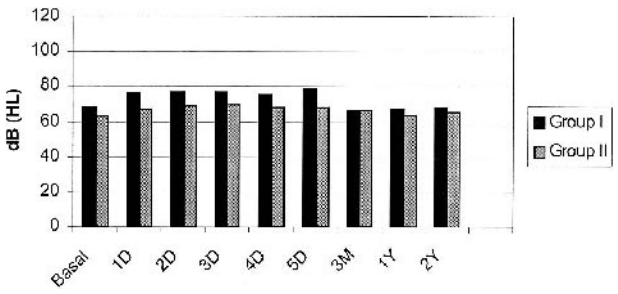

FIG. 5. PTA levels obtained at each time point in Groups I and II.

characteristics of the cell membrane that impede the attachment of the drug and the initiation of the cascade that leads to cell death (19). It must also be taken into consideration that patients may enter into a spontaneous remission phase.

To our knowledge, there are no other published protocols showing this gentamicin-induced transient cochleotoxic damage. The reason may lie in the methodology and the assessment of the hearing function during the treatment. Whatever the cause, it is tentatively suggested that these findings may represent a prognostic factor for the clinical outcome of the treatment. The absence of significant hearing loss at the end of intratympanic gentamicin treatment is associated with a recurrence of the vestibular symptoms. As such, these patients should be advised of this problem. However, a longer follow-up period, the assessment of more patients, and prospective studies of other groups will be needed to define the feasibility of implementing this protocol and to confirm the prognosis factor that the transitory cochleotoxic effect may represent.

CONCLUSION

Long-term hearing loss as a result of intratympanic gentamicin treatment in patients with unilateral disabling Ménière's disease was found to be 15.5%. The patients most at risk for developing hearing loss were those with better hearing (PTA < 40 dB). There was a trend toward a recovery of threshold values from the audiometric test performed when the treatment ended to the last audiometric test performed 2 years later. However, this was not the case with respect to threshold values at the 6-kHz frequency. The absence of hearing loss during treatment may be a prognostic factor indicating that the control of vertigo will be insufficient or that a spontaneous transitory or gentamicin-evoked remission will occur.

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