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Effects of Difluoromethylornithine Chemoprevention on Audiometry Thresholds and Otoacoustic Emissions

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Objectives: To determine the effects of long-term, low-dose difluoromethylornithine (DFMO) on audiometric thresholds and distortion product otoacoustic emission (DPOAE) levels in humans.

Design: A prospective, randomized, placebo-controlled phase 2 clinical trial of DFMO in participants with a prior adenomatous colonic polyp.

Setting: Academic tertiary care referral center.

Participants: One hundred twenty-three volunteer subjects with colorectal polyps and normal hearing for the frequencies 250 through 2000 Hz.

Interventions: Subjects were randomized to receive placebo or oral DFMO at daily dosages between 0.075 and 0.4 g/m² of body surface area for 12 months.

Outcome Measures: Pure-tone audiometric thresholds for the frequencies 250, 500, 1000, 2000, 3000, 4000,

6000, and 8000 Hz and DPOAE levels were measured at baseline and 1, 3, 6, 9, and 12 months after starting treatment with DFMO or placebo and 3 months after cessation of treatment if there was a suggestion of possible changes at the 12-month measurement.

Results: At these low dosages, there was little evidence for shifts in auditory pure-tone thresholds, and there were no statistically significant shifts in DPOAE levels. For auditory pure-tone thresholds, there was a subtle, approximately 2- to 3-dB hearing level decrease in hearing sensitivity for the 2 higher DFMO dosages, but only at the 2 lowest frequencies, 250 and 500 Hz.

Conclusions: Administration of low-dose DFMO for 12 months did not produce hearing loss, in contrast to prior studies that used higher dosages.

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AUDIOLGIC monitoring for the purpose of prevention of hearing loss is often used for known ototoxic medications such as the aminoglycoside antibiotics and cisplatin. Such monitoring usually consists of behavioral pure-tone testing at baseline and during the treatment regimen.¹ More recently, evoked otoacoustic emissions (OAE) testing has been compared with behavioral pure-tone monitoring in hopes that OAE testing would detect sensory damage before the onset of permanent pure-tone threshold shifts.² The OAEs are sounds emanating from the cochlea that are recorded from the external ear canal.³ Intermodulation distortion product (DPOAE) levels can be recorded in OAE to 2-tone stimulation.⁴ The DPOAEs, like the other evoked OAEs, are reproducible and are vulnerable to insults that damage cochlear outer hair cells.⁵ Their usefulness in measuring ototoxicity has been sug-

gested because they are objective (ie, they do not require subjective responses from the patient), they provide information at different frequencies, and they may be measured in a few minutes.⁶

The polyamines putrescine, spermidine, and spermine are organic cations involved in the process of cell growth and differentiation.⁷ A specific inhibitor of ornithine decarboxylase and polyamine synthesis, α -difluoromethylornithine (DFMO), has been used at high dosages in cancer chemotherapy and, more recently, at lower dosages in cancer chemoprevention.^{8,9} In several studies, DFMO has been found to be ototoxic at higher dosages. For example, at dosages of 8 g/m² in continuous infusion for colon cancer chemotherapy over 28 days, Ajani et al⁸ found reversible hearing loss in some patients. Croghan et al¹⁰ assessed the ototoxic effects of DFMO administered to 58 patients treated with dosages ranging from 2 to 12 g/m² per day for metastatic mela-

SUBJECTS AND METHODS

SUBJECTS

Difluoromethylornithine or placebo was administered to 123 volunteer subjects at the University of California, Irvine (University of California, Irvine, Medical Center and Long Beach Veterans Affairs Medical Center). Subjects were randomly assigned in a double-blinded fashion to receive either daily oral placebo or 1 of 3 dosages of DFMO (0.075, 0.20, or 0.40 g/m² per day). Men and women aged 40 to 80 years (median, 65 years) who met the following criteria were included in the study: history of colon polyp removal without familial polyposis, colon resection of greater than 40 cm, history of cancer within 5 years, or other chronic medical problems. Audiologic criteria required that subjects have no worse than 20-dB hearing level (HL) thresholds for the frequencies 250, 500, 1000, and 2000 Hz. All patients signed a consent form approved by the institutional review boards of the University of California, Irvine, Medical Center or the Long Beach Veterans Affairs Medical Center.

PURE-TONE AUDIOMETRY

Bilateral pure-tone air-conduction audiograms were performed in a sound-treated booth by an audiologist at baseline and 1, 3, 6, 9, and 12 months after the onset of DFMO treatment in all study participants and 3 months after drug discontinuation in 15 patients who experienced a more than 15-dB increase in baseline threshold at any frequency. At baseline, air-conduction and bone-conduction pure-tone testing was completed for the frequencies 250, 500, 1000, 2000, 3000, 4000 Hz, and air-conduction thresholds were obtained for the frequencies 6000 and 8000 Hz. Following completion of the trial, baseline thresholds were compared with 12-month thresholds.

DISTORTION PRODUCT OTOACOUSTIC EMISSIONS

Distortion product otoacoustic emissions were measured concurrently with pure-tone threshold measurements. The DPOAE testing was carried out in a quiet room using the Otodynamic Analyzer ILO92 (Otodynamics Ltd, Hatfield, England). For tone pairs of frequencies f_1 and f_2 , each was presented through the probe at a 75-dB sound pressure level (SPL) (equilevel and $f_2/f_1 = 1.22$), with f_2 values of 1000, 1600, 2000, 3200, 4000, and 5100 Hz. Emissions of $2(f_1 - f_2)$ were measured and plotted as DP-grams (graphs of emission amplitudes in dB SPL as a function of f_2 frequency).

STATISTICAL ANALYSIS

Pure-Tone Audiometry

Pure-tone air-conduction thresholds were recorded for each ear of each study subject, and a total of 5 pure-tone audiograms were collected over the 12-month period. Although

periodic testing provided close subject monitoring, the baseline and 12-month thresholds were compared to determine the greatest effects of the dosing regimen. For each patient with incomplete data, the baseline thresholds were compared with the final threshold measurements for that patient. For most test frequencies, the hearing threshold levels at baseline and the final threshold measurements were higher for the placebo group than for the DFMO groups; thus, all statistical comparisons were based on the average change from baseline. The mean and SD for the change in HL in the last audiometric test following baseline was computed for each patient and for each ear at each of the 8 test frequencies. For each frequency, regression analysis was used with the mean change in decibels as the dependent variable and dosage group as the explanatory variable.

Paired *t* tests were applied to examine the difference in mean change between the right and left ears at the same frequency for each dosage group. At $P \leq .05$, differences were found for only 4 of 32 comparisons—at the 3000-, 4000-, and 6000-Hz frequencies for the placebo group and at the 6000-Hz frequency for the 0.2-g/m² group. A major natural loss would be presbycusis (aging), which is bilateral. Because unilateral loss is uncommon and usually traumatic, the mean change from baseline for left and right ears was computed for each subject and each frequency. An analysis of variance followed by a post hoc Dunnett test was then performed to compare the mean change from baseline for the control group with that of the 3 dosage groups. Multiple regression analysis was used, with mean change in decibels as the dependent variable and dosage group, age, sex, and race as the explanatory variables. For each frequency, the overall *F* test of significance of the model and *t* tests for slope parameters were performed.

Pure-Tone Recovery

Pure-tone threshold data were also analyzed from a subset of 14 patients who had measurements taken at baseline, at the end of drug administration at 12 months, and following recovery at 15 months. For each subject and each frequency, the mean change from baseline for the left and right ears was computed. Repeated-measures analysis of variance followed by the Dunnett test was used to compare the mean change from baseline for the control group vs that of the 3 dosage groups.

Distortion Product Otoacoustic Emissions

In the analysis of the DPOAE data, the baseline DPOAE levels in decibels SPL for each f_2 value tested were compared with the corresponding 12-month DPOAE level or the DPOAE level at final measurement. For each subject, a 3-level categorical variable was created, and the differences between the baseline and 12-month DPOAE levels were recorded as “no change,” “decrease,” or “increase.” The DPOAE values for the left and right ears were considered separately. For each ear and each f_2 value, a Fisher exact test was applied to examine the association between dosage group and change category.

noma. In this study, 75% of patients who received total doses of more than 250 g/m² developed hearing loss of more than 30 dB, across the frequency range of 500 to 8000 Hz. These studies created concern that ototoxic ef-

fects could limit the usefulness of DFMO in cancer chemoprevention.

Two studies were designed to investigate whether DFMO administered at low dosages produced hearing loss,

Table 1. Number of Patients Audiologically Tested, by Dosage Group, at Baseline and in the Final Month of Testing*

Month	No. of Patients			
	Placebo (n = 32)	DFMO Dosage, g/m ²		
		0.075 (n = 27)	0.2 (n = 25)	0.4 (n = 27)
0	32	27	25	27
1	0	1	1	1
3	1	0	1	3
6	2	1	1	2
9	0	0	1	4
12	27	21	18	14
15†	2	4	3	3

*DFMO indicates difluoromethylornithine.

†Testing at 15 months was performed for any patient who demonstrated an increase in hearing threshold of more than 15 dB at any test frequency.

while concurrently investigating the minimum dosage of DFMO required to lower polyamine content in tissues. One study, by Pasic et al,¹¹ observed an average pure-tone audiometric shift of 16.8 dB in patients taking DFMO for 6 to 12 months at the highest tested dosages (2, 3, and 5 g/m² per day).¹¹ Only 3 of 32 subjects receiving the lowest dosage (500 mg/m²) developed pure-tone shifts of more than 15 dB at 2 frequencies. Pasic et al also demonstrated that the hearing loss was reversible in all subjects, with a median recovery time of 58 days following drug cessation. In an earlier study, the present investigators used much smaller daily dosages of DFMO (0.075, 0.20, or 0.40 g/m² per day) in a year-long chemoprevention trial of 123 patients¹² and found that dosages of 0.2 and 0.4 g/m² reduced polyamine levels to 34% and 10%, respectively, of levels observed in the placebo group. Pure-tone audiometry was performed in all subjects at baseline and at 3-month intervals throughout the study. In the present article, the results of pure-tone audiometric and DPOAE testing are reported for patients in the earlier study.

RESULTS

Pure-tone audiometry was performed at baseline and in at least 1 subsequent month for 111 (90%) of 123 patients. **Table 1** shows the number of patients, by dosage group, who had pure-tone threshold measurements at baseline and the number of patients who had their final measurement made at months 1, 3, 6, 9, 12, and 15. Patients from all 4 groups dropped out for different reasons. Table 1 shows that patients were more likely to drop out of the study as the dosage increased. One patient from the 0.4-g/m² dosage group who met the toxicity criterion (>20-dB HL increase in threshold at any frequency) was dropped from the study after 9 months because of hearing loss. No other patients were removed because of hearing loss, although 4 patients from the 2 higher-dosage groups were dropped from the study because of symptoms of dizziness and imbalance that resolved following discontinuation of the drug.

Table 2. Mean Change From Baseline in Hearing Threshold*

Frequency, Hz	Change in Hearing Threshold, dB HL			
	Placebo (n = 32)	DFMO Dosage, g/m ²		
		0.075 (n = 27)	0.20 (n = 25)	0.40 (n = 27)
250	-0.08	0.74	1.70	3.24†
500	-0.16	0.56	2.90†	2.13
1000	0.86	0.46	2.10	2.13
2000	0.94	2.87	1.70	2.32
3000	-0.40	0.65	1.90	2.32
4000	1.09	2.04	2.50	2.41
6000	0.78	2.41	2.00	1.39
8000	2.66	3.06	0.60	1.11

*HL indicates hearing level; DFMO, difluoromethylornithine.

†P ≤ .05 compared with placebo.

PURE-TONE AUDIOMETRY

For each ear and each of the 8 test frequencies, regression analysis was used to examine the mean change in decibels across dosage groups. The *P* value for the trend of the regression slope parameter was computed. Those with *P* ≤ .05 had a positive slope, giving evidence for a trend toward worsening thresholds in the highest-dosage group. For the right ear, at a frequency of 250 Hz, there was an estimated hearing loss of 2.2 dB HL, on average, for each 0.1-g/m² increase in dosage (95% confidence interval [CI], 0.3-4.1 dB HL). Similarly, at 500 and 3000 Hz, the estimated average hearing losses were 1.7 dB HL (95% CI, 0.0-3.3 dB HL) and 2.7 dB HL (95% CI, 0.8-4.6 dB HL), respectively. For the left ear, the average hearing losses were 1.9 dB HL (95% CI, 0.3-3.5 dB HL) at 250 Hz and 1.4 dB HL (95% CI, 0.0-2.8 dB HL) at 500 Hz for each 0.1-g/m² increase in dosage. Although significant trends were found for low frequencies, we note that the probability of false-positive results likely increased, given that multiple significance tests were applied to data from the same dosage groups.

For each subject and each frequency, the mean change from baseline for the left and right ears was computed. Analysis-of-variance results are given in **Table 2**, with the average change from baseline for the 2 ears as the dependent variable for each frequency. Dosage levels were significant at 250 and 500 Hz (*P* = .005 and *P* = .02, respectively), but nonsignificant at other frequencies. **Figure 1** shows the mean change from baseline pure-tone threshold for the average of the left and right ears at 250 and 500 Hz as a function of dosage. Figure 1A shows that for 250 Hz, there was an average 2-dB HL worsening of threshold for each 0.1-g/m² increase in DFMO dosage (95% CI, 0.6-3.5 dB HL; *P* for trend, .01), adjusting for age, sex, and race. Figure 1B demonstrates an average 1.5-dB HL increase in threshold at 500 Hz for each 0.1-g/m² increase in DFMO dosage (95% CI, 0.2-2.8 dB HL; *P* for trend, .02), adjusting for age, sex, and race. The variability within each dosage group obscured any mean change between the treatment and placebo groups, with the exception of 250 Hz (0.4 g/m² per day different from placebo, *P* = .01) and 500 Hz (0.2 g/m² per day different from placebo, *P* = .02).

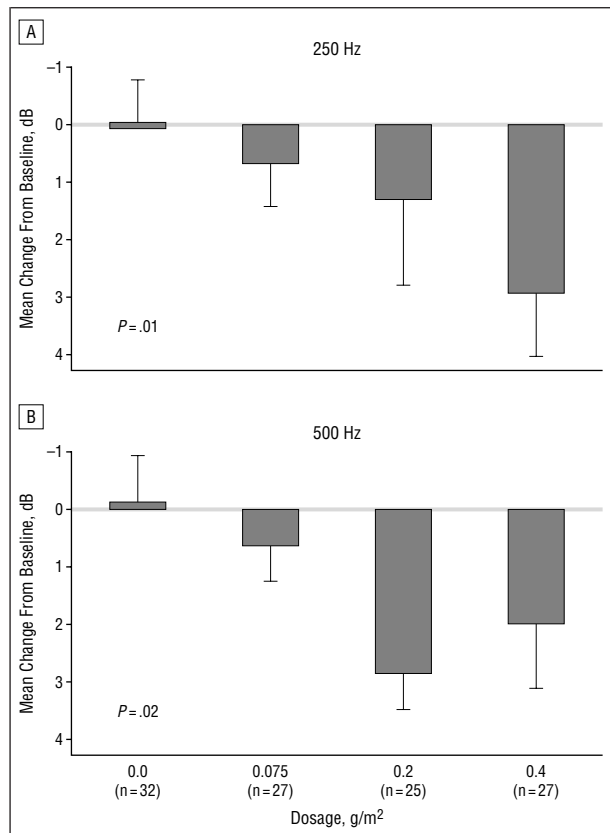


Figure 1. Mean change in pure-tone threshold from baseline for the average of left and right ears at 250 Hz (A) and 500 Hz (B) as a function of dosage. P values for trend were adjusted for age, sex, and race.

PURE-TONE THRESHOLD RECOVERY

Thresholds for the 8 pure-tone frequencies were averaged for the left and right ears for the subset of 14 patients who had pure-tone threshold measurements at baseline, at the end of drug administration (12 months), and following recovery (15 months). Of the 14 patients, 2 were from the placebo group, 4 were from the 0.075-g/m² dosage group, 3 were from the 0.2-g/m² dosage group, and 5 were from the 0.4-g/m² dosage group. The hypothesis was that hearing thresholds would return to baseline levels following cessation of DFMO treatment.

Figure 2 shows the mean hearing thresholds across time for all 4 study groups measured at 250 (A), 500 (B), 1000 (C), 2000 (D), 3000 (E), 4000 (F), 6000 (G), and 8000 (H) Hz:

- For the placebo group, follow-up mean thresholds at 5 of the 8 frequency levels (500, 1000, 3000, 6000, and 8000 Hz) were equivalent to or lower than baseline thresholds.
- For the 0.075-g/m² dosage group, follow-up mean thresholds at 4 of 8 frequencies (250, 1000, 3000, and 6000 Hz) were equivalent to or lower than baseline thresholds.
- For the 0.2-g/m² dosage group, follow-up mean thresholds at 2 of 8 frequencies (3000 and 4000 Hz) were equivalent to or lower than baseline thresholds.
- For the 0.4-g/m² dosage group, follow-up mean thresh-

olds from 2 of 8 frequency levels (6000 and 8000 Hz) were equivalent to or lower than baseline thresholds.

Overall, results from graphical analysis suggest that at the lower frequencies, recovery had not occurred by 3 months after the end of drug administration, whereas at the higher frequencies, recovery had occurred. However, paired *t* tests indicated no statistically significant differences from baseline to the 15-month follow-up at any of the 8 frequencies tested. Analysis of variance of the mean change in hearing threshold from baseline to the 15-month follow-up indicated no dosage effect at any of the 8 frequencies tested.

DISTORTION PRODUCT OTOACOUSTIC EMISSIONS

We emphasize qualitative rather than quantitative analysis for the DPOAE test results. Statistical analysis was problematic, because emissions were often absent or nondetectable above the noise floor, even at baseline. Most patients experienced a decrease in DPOAE level from baseline, had no change from baseline, or had nondetectable DPOAEs both before and after treatment. These data did not provide any evidence that DPOAE levels were significantly affected by DFMO at any dosage compared with placebo.

These observations were confirmed by analysis of corresponding baseline and 12-month DPOAE levels categorized as no change, decrease, or increase. Patients who had a pretreatment value greater than the posttreatment value or a measurable pretreatment value but a nondetectable posttreatment value were considered to have had a decrease in amplitude over time. Patients who had equal pretreatment and posttreatment values or with nondetectable DPOAEs measured both before and after treatment were considered to have had no change. Patients who had a pretreatment value less than the posttreatment value or a nondetectable posttreatment value and a measurable pretreatment value were considered to have had an increase in amplitude over time. There was no significant association between the change in amplitude and dosage for the left and right ears (Fisher exact test), with the exception of the level of the DPOAE level at 4000 Hz for the left ear (**Figure 3**) ($P=.008$), because most patients in the 0.2-g/m² dosage group had no change in DPOAE. Overall 67% (64/96) of patients experienced no change in DPOAE, compared with 18% (17/96) who experienced a decrease in DPOAE and 15% (14/96) who experienced an increase in DPOAE.

COMMENT

Overall, the results demonstrate that 1 year of chemoprevention with DFMO at the low dosage (≤ 0.4 g/m² per day) used in this study did not produce hearing loss. All of the dosages employed in this study were lower than those used in earlier DFMO treatment studies; thus, the results do not disagree with those of earlier reports. Pasic et al¹¹ measured pure-tone auditory thresholds in 66 subjects in a cancer chemoprevention trial.¹¹ The sub-

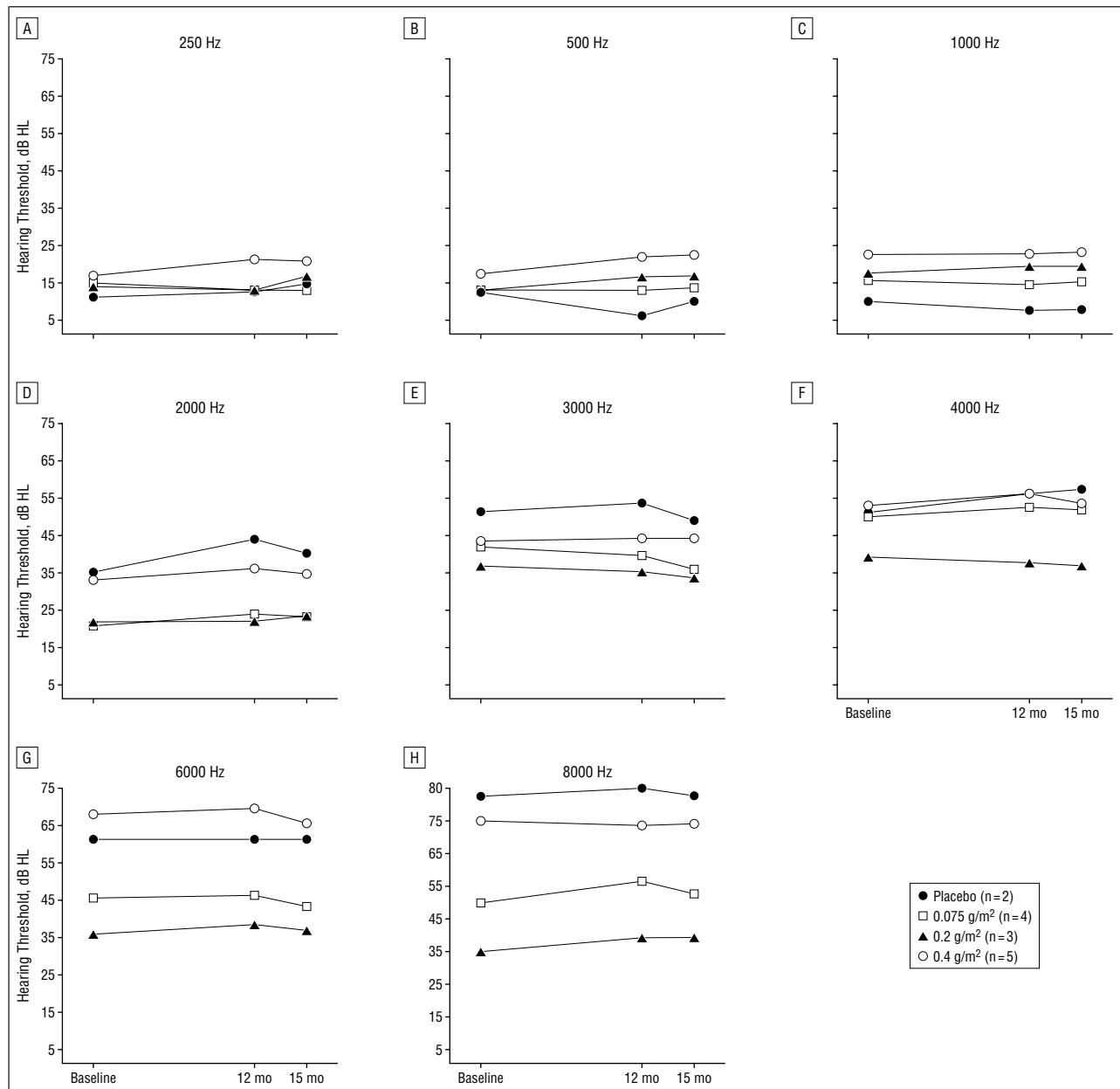


Figure 2. Mean hearing thresholds across time for all 4 study groups (placebo and difluoromethylornithine, 0.075, 0.2, and 0.4 g/m²) at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. HL indicates hearing level.

jects received placebo or DFMO at dosages between 0.5 and 3 g/m² for 6 to 12 months. The magnitude and incidence of threshold shifts correlated with the daily DFMO dosage, and the shifts occurred predominantly at low frequencies. The extent of threshold shifts was greater for higher than for lower dosages, averaging 16.8 dB at the 3 highest daily dosages. Finally, the time between DFMO treatment and the onset of hearing loss was strongly associated with increasing daily dosages, in that subjects receiving higher daily dosages demonstrated hearing loss earlier than those given lower daily dosages. Ten of the 13 subjects in the study by Pasic et al¹¹ who underwent a threshold shift of 15 dB or greater at 2 or more frequencies underwent regular pure-tone threshold measurements after DFMO therapy was stopped. All threshold shifts were reversible, and recovery occurred after a

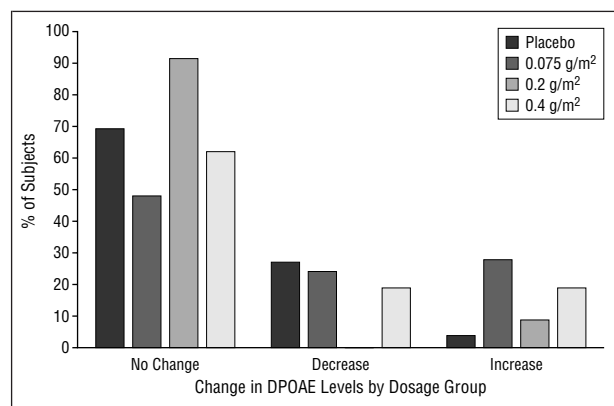


Figure 3. Mean change in DPOAE (distortion-product otoacoustic emission) levels for the left ear at 4000 Hz.

median of 58 days. Pasic et al¹¹ concluded that DFMO administration is associated with a predictable shift in auditory thresholds. In the present study, we used lower DFMO dosages than Pasic et al, and there was little evidence for shifts in auditory pure-tone thresholds. Instead, a subtle, approximately 2- to 3-dB, decrease in sensitivity occurred only at the 2 higher dosages for the 2 lowest frequencies tested. Like Pasic and colleagues, who found a lesser incidence of hearing loss with their lowest-dose regimen of 0.5 g/m², in our study, we found that 1 patient receiving the highest-dosage regimen had clinically significant hearing loss that necessitated his removal from the study. This patient's hearing returned to baseline levels after 3 months. In combination, these studies suggest that a dosage of DFMO of about 0.5 g/m² is near the threshold for audiometric change as a function of drug administration time, at least for a period of 12 months.

In an earlier study, Plinkert and Krober¹³ compared pure-tone audiometry with click-evoked OAEs in 29 patients receiving cisplatin chemotherapy. They found that amplitude loss of click-evoked OAEs was a more sensitive tool for the early detection of cochlear dysfunction than pure-tone audiometry, because amplitude loss of click-evoked OAEs was noted earlier than losses of pure-tone thresholds. The authors concluded that measurement of OAEs permitted the diagnosis of cochlear lesions induced by cisplatin before they became clinically manifest. Other researchers have investigated the role of DPOAEs in the measurement of ototoxic effects.^{14,15} However, no formal guidelines have been formulated for OAE testing in ototoxic monitoring because OAE testing is a new tool that has been incompletely studied. In the present study, which found no significant pure-tone threshold shifts with low-dose DFMO, DPOAEs were of less use for monitoring hearing changes, mainly because in this older subject population, they were frequently absent, even at baseline.

CONCLUSIONS

Many studies have been performed to investigate the ototoxic characteristics of medications such as aminoglycoside antibiotics and the chemotherapeutic agent cisplatin.¹⁶⁻¹⁸ Such studies describe the minimum dosages and minimum cumulative doses that produce ototoxic effects, the typical patterns of hearing loss, and other factors that interact with the agent in question. The American Speech, Language, and Hearing Association has published guidelines for audiologic testing of individuals receiving ototoxic drug therapy.¹ The current recommendations include baseline pure-tone air-conduction threshold testing at octave intervals from 250 to 6000 Hz. However, the monitoring schedule depends on the medication given because drugs differ in the rapidity with which therapeutic schedules produce hearing loss. The National Cancer Institute is currently creating recommendations for pure-tone audiometric monitoring in chemoprevention trials. Because chemoprevention requires long-term dosing compared with traditional cancer-treatment regimens, monitoring must be carried out over long periods. In addition, higher levels of toxic effects

are acceptable in cancer-treatment regimens than would be acceptable in chemoprevention, since the latter patients do not actually have cancer. A decrease in hearing as measured by pure-tone threshold assessment of DFMO does not seem to occur at dosages lower than 0.5 g/m². This dosage probably can be used safely in long-term chemoprevention trials, as other adverse effects did not occur more frequently in the present study compared with placebo.⁷ Since the duration of all trials reported has been 1 year, the effect on hearing in longer-term studies will need to be periodically monitored in investigative trials.

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