Short Communication

Irreversible Ototoxicity Associated with Difluoromethylornithine

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Abstract

Difluoromethylornithine (DFMO) is a potent, irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in the synthesis of polyamines that promote cellular proliferation. DFMO has been tested as a potential cancer therapeutic and chemopreventive agent in clinical trials. Reversible hearing loss is a recognized toxicity of DFMO that usually occurs at doses above 2 g/m^2/d, and generally when the cumulative dose exceeds 250 g/m^2. In a recently completed Barrett's esophagus chemoprevention trial, a participant receiving DFMO and, thus, trial participants should be made aware of this small but important risk.

Introduction

Difluoromethylornithine (DFMO) is a potent, irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in the synthesis of polyamines involved in cellular proliferation. DFMO is approved by the Food and Drug Administration for the treatment of meningoencephalitis associated with *Trypanosoma brucei var. gambiense* (African sleeping sickness). DFMO has been shown to have antineoplastic activity in vitro and has been studied as a cancer therapeutic and chemopreventive agent (1). Reversible hearing loss is a recognized toxicity of DFMO (2-5), but there have been no previous reports of permanent threshold shifts. We now report a case of irreversible hearing loss presumably due to DFMO in a clinical trial participant receiving DFMO and, thus, trial participants should be made aware of this small but important risk.

Case Report

The participant is a 57-year-old man with a history of asthma, hypertension, coronary artery disease, and Barrett's esophagus who was enrolled in a Barrett's esophagus chemoprevention trial in February 2000. This double blind trial randomized individuals to receive 0.5 g/m^2/d DFMO or placebo. After written informed consent was obtained, the participant was randomized to DFMO (actual dose: 900 mg daily). Concomitant medications included 40 mg lisinopril daily since 1994; 50 mg metoprolol twice daily since 1994; 30 mg lansoprazole twice daily since 1999; and albuterol and ipratropium bromide inhalers since 1993. He previously worked as a building contractor and had a smoking history of greater than 20 years duration. Physical exam was unremarkable and baseline audiologic evaluation revealed a mild bilateral sensorineural hearing loss at 3,000 Hz (30 dB HL; Fig. 1). Eleven weeks after initiation of DFMO, follow-up audiologic evaluation showed a 20-dB decrease in hearing at 4,000 to 6,000 Hz in the left ear after taking 0.5 g/m^2/d DFMO for approximately 13 weeks (cumulative dose of 45 g/m^2). The threshold shifts persisted 7 months after DFMO was discontinued. There was no obvious impact on the participant's clinical hearing, but these findings were consistent with irreversible hearing loss. This is the first case reported of irreversible ototoxicity in a clinical trial participant receiving DFMO and, thus, trial participants should be made aware of this small but important risk.
of repeat audiologic testing 29 weeks after discontinuation of DFMO were consistent with permanent hearing loss (Fig. 1).

It was the impression of the investigators that the participant was compliant with the study drug. The participant denied excessive noise or other known ototoxic exposures during the study period. Thus, it was felt that the irreversible hearing loss was caused by DFMO. Although the hearing loss had no apparent impact on his activities of daily living, this was an unexpected serious adverse event. Due to the previously unreported irreversible nature of the hearing loss, the event was appropriately reported to all regulatory and monitoring authorities.

Discussion

Temporary hearing loss is a known toxicity of DFMO that most often occurs with daily doses above 2 g/m² and generally when the cumulative dose exceeds 250 g/m² (3-8). Before this case, there have been no reports of irreversible hearing loss due to DFMO, regardless of dose (9-17).

Numerous treatment and chemoprevention trials have reported reversible hearing loss due to DFMO (3-6, 8), but few clinical studies have been designed to examine this relationship (7, 8, 18). Doyle et al. (18) performed rigorous follow-up of 123 participants in a DFMO chemoprevention trial (17) (doses of 0.075 g/m²/d to 0.4 g/m²/d with pure tone audiometry (250 to 2,000 Hz) and distortion product otoacoustic emissions (DPOAEs). Statistically significant mean threshold shifts of 2 to 3 dB occurred in the two highest dosage groups at 250 and 500 Hz. However, none of the 20 participants with suspected clinically significant threshold shifts (≥15 dB at one-octave interval) was noted to have irreversible hearing loss (reported in ref. 17). Other investigators have reported hearing loss associated with DFMO that was allegedly reversible, but complete recovery in all participants was not always documented (7, 8).

In 1991, Croghan et al. (7) reported ototoxicity in patients given DFMO at doses ranging from 2 to 12 g/m²/d for metastatic melanoma. Fifty-eight patients developed pure tone threshold shifts while on study, but recovery of hearing was not fully assessable due to insufficient follow-up audiograms. Pasic et al. (8) reported audiometric results on subjects taking DFMO at daily doses between 0.5 and 3 g/m² for 6 to 12 months on phase I and II trials. Fifteen of 66 subjects developed threshold shifts > 15 dB at two-octave intervals. All subjects who underwent serial audiologic testing had reversal of threshold shifts regardless of DFMO dose; however, only 10 of 15 subjects were tested.

Serial monitoring for toxicities is extremely important in chemoprevention trials, because safety data are a critical part of any drug profile. Shotland et al. (19) published recommendations for audiometric testing in cancer prevention trials similar to the protocol used in this Barrett’s esophagus trial. They advocate audiometric monitoring using a pre-determined schedule to detect and address ototoxicity that may arise during investigational testing. The audiometric testing in this trial included pure tone audiometry (250 to 8,000 Hz octave frequencies and 3,000 to 6,000 Hz one-half octave frequencies) done in a sound suite. Evaluations were done after week 8 following the first dose, at week 26, and at week 52 (study completion). This monitoring was more rigorous than most previous studies and allowed for the detection and follow-up of asymptomatic individuals. Thus, it is possible that irreversible hearing loss is a side effect of DFMO that has simply been under-recognized due to less rigorous monitoring.

The mechanism of hearing loss due to DFMO is unknown, but it is believed to be related to polyamine depletion in the cochlea. Polyamines and ornithine decarboxylase have been detected in the cochleas of experimental animals (20, 21) and their inhibition by DFMO has resulted in cochlear dysfunction (22). Polyamines are important in the functioning of voltage-dependent ion channels, which are essential for the maintenance of the electrolytic concentration and positive polarization of the endolymph (21, 23). Theoretically, disruption of this endocochlear potential by DFMO can lead to varying degrees of ototoxicity, including irreversible hearing loss.

Hearing loss due to DFMO might also occur when the stereocilia of hair cells are disrupted, damaged, or lost. Interestingly, DFMO seems to affect low- as well as high-frequency hearing with preferential loss of inner hair cells (20, 24, 25). Other ototoxic agents, for example, aminoglycosides and cisplatin, result primarily in high-frequency hearing loss due to outer hair cell damage (26). Permanent hearing loss has resulted from inner and/or outer hair cell loss and has been associated with excessive noise exposure (27), higher doses of ototoxic drugs (26), and concomitant exposures to both (28). For
individuals taking DFMO, age, gender, renal function, and previous hearing loss have not been consistently correlated with subsequent ototoxicity (3, 7, 8) Thus, it is unclear why the participant developed permanent hearing loss given the lack of excessive noise exposure and relatively limited drug exposure (daily dose of 0.5 g/m²/d and cumulative dose of approximately 45 g/m²).

The incidence of irreversible hearing loss due to DFMO exposure may be underestimated given the inadequacies of previous monitoring techniques and protocols. Participants in clinical trials using DFMO should be informed of the risk of irreversible hearing loss, and should be monitored closely for early detection of ototoxicity (19).

References
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