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Clinical Report

The Incidence of Ototoxicity in Patients Using Iron Chelators

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OBJECTIVE: In this study, we aimed to detect the incidences of ototoxicity in patients with hemoglobinopathies taking deferoxamine (DFO), deferiprone, and deferasirox using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale to obtain more objective data.

MATERIALS and METHODS: Fifty-five transfusion-dependent patients were evaluated in this study. The NCI CTCAE scale was used to assess ototoxicity levels. The average ferritin and hemoglobin levels, the type of iron chelator, and the duration of therapy of all the patients were recorded.

RESULTS: Ototoxicity was observed in 15 patients (31.9 %), all of whom were taking DFO. The median age was 19.5 (6–43) in patients without ototoxicity and 29 (16–50) in those with ototoxicity; this difference was statistically significant ($p<0.05$). The median ferritin and pre-tx Hb levels were 1391 ng/mL and 9.06 mg/dL, respectively, in patients with ototoxicity and 986.7 ng/mL and 9.24 mg/dL, respectively, in those without ototoxicity; these differences were not significant ($p>0.05$). Ototoxicity was not observed in the eight patients who used only deferasirox and deferiprone.

CONCLUSION: The ototoxicity incidence with DFO at doses below 50 mg/kg/day was 27.3%. Deferiprone and deferasirox were not associated with ototoxic effects in patients taking these drugs.

KEYWORDS: Deferoxamine, deferiprone, deferasirox, hemoglobinopathies, ototoxicity.

INTRODUCTION

Transfusion and iron chelation are essential to treat hemoglobinopathies, including thalassemias, the most common inherited hemoglobinopathies worldwide. Deferoxamine (DFO; Desferal 500 mg; Novartis, Stein, Switzerland) was the first and, until recently, the preferred iron-chelating drug [1, 2]. However, there have been several reports of DFO ototoxicity [1–6], especially with long-term use and at higher doses. In recent years, deferiprone (Ferriprox 500 mg; Ontario, Canada) and deferasirox (Exjade 500 mg; Novartis, Stein, Switzerland) have largely replaced DFO due to their ease of use, as they can be taken orally. However, there have been insufficient studies regarding their ototoxicity risks. As high iron load can also damage hearing, proper interpretation of the ototoxicity risk of these drugs is crucial. However, when the literature is assessed, no standardized method is found to assess DFO-related ototoxicity, which may give rise to differing results. According to the product monograph of deferasirox, high frequency hearing loss has been observed in <1% of treated patients. However, no other reports of hearing loss in patients taking deferasirox or on the ototoxicity of deferiprone are available. No acoustic symptoms have been reported for patients receiving deferiprone therapy [7].

In this study, we aimed to identify the frequency of ototoxicity associated with the iron-chelating agents deferiprone, deferasirox, and DFO in transfusion-dependent patients. Ototoxicity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale, and correlations of ototoxicity with duration of therapy, ferritin, and pre-transfusion (pre-tx) Hb levels were assessed.

MATERIALS and METHODS

Patients

This cross-sectional study included 55 transfusion-dependent patients who were referred to our Thalassemia Center between 2013 and 2015. The study protocol was approved by Ethics Committee of Muğla Sıtkı Koçman University, Medical School.

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Verbal informed consent was obtained from patients and the parents of the patients who participated in this study. Patients with active or recent histories of ear disturbance, previous ear surgery, exposure to acoustic trauma, family history of hereditary hearing loss, mental disturbance, age less than 6 years, or exposure to other known ototoxic medications were excluded from the study, which sought to assess ototoxicity as a result of iron-chelating treatment.

To achieve hemoglobin levels above 9–9.5 g/dL, transfusions were performed every 2–4 weeks. Ferritin levels were checked quarterly, and iron-chelating agents were started when ferritin levels were 1,000 ng/mL or above at the age of 2 years. DFO (Desferal 500 mg; Novartis, Stein, Switzerland) was administered at 30–50 mg/kg/day subcutaneously, deferiprone (Ferriprox 500 mg; Ontario, Canada) was administered at 75–100 mg/kg/day orally, and deferasirox (Exjade 500 mg; Novartis, Stein, Switzerland) was administered at 20–40 mg/kg/day orally.

Mean serum ferritin and pre-iron chelation hemoglobin levels over the last year were recorded. For each chelating agent, we classified the duration of drug use as 0–5, 5–10, and 10 or more years.

All patients were examined by otoscopy, and an acoustic immittance meter was used to verify the normal condition of the middle ear. No patient discontinued treatment with iron-chelating agents due to otological problems. Conventional audiometric evaluations were performed with an AC 40 audiometry device. Pure-tone audiometric thresholds were determined between 0.25 and 8 kHz (0.25, 0.5, 1, 2, 4, 6, and 8 kHz). To determine ototoxicity, the NCI CTCAE ototoxicity grades (listed below) were used.

Grade 1: Threshold shift or loss of 15–25 dB relative to the baseline, averaged at two or more contiguous frequencies in at least one ear.

Grade 2: Threshold shift or loss of 26–90 dB, averaged at two contiguous test frequencies in at least one ear.

Grade 3: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., >20 dB bilateral HL in speech frequencies, >30 dB unilateral HL), and requiring additional speech/language-related services (for adults, >25–90 dB, averaged at three contiguous test frequencies in at least one ear).

Grade 4: Indication for cochlear implant and requiring additional speech/language-related services (for adults, profound bilateral hearing loss >90 dB HL).

Statistical Analysis

The data were analyzed using IBM® SPSS® Statistics 20 (IBM Corp.; Los Angeles, California, USA). The Kolmogorov-Smirnov test was used to test the normality of data distribution. Parametric tests (independent samples test) were used when the distribution of the data was normal, and the values are presented as mean ± standard deviation. The Mann-Whitney U test was used for non-normally distributed values, and the values are presented as medians (min-max). The values of categorically independent groups were compared using the χ^2 test. P values <0.05 were considered to indicate statistical significance.

RESULTS

In total, 55 patients met the inclusion criteria, including 50 patients with thalassemia major and one patient each with S-beta, thalassemia intermedia, sideroblastic anemia, and dyserythropoetic anemia. The study population included 27 (49.1%) females and 28 (50.9%) males, ranging in age from 6 to 50 years (mean age: 23±8.9 years). Both acoustic immitance (Type A tympanogram) tests and acoustic-reflex thresholds for ipsilateral and contralateral ears were normal in all patients. Distribution of the use of each type of iron-chelating agent, diagnosis, duration of chelating agent use, and frequency of ototoxicity are presented in Table 1. Ototoxicity according to NCI CTCAE criteria was observed in 15 (31.9 %) patients, all of whom were taking DFO. We detected grade 1 ototoxicity in six patients, grade 2 ototoxicity in nine patients, unilateral ototoxicity in nine patients, and bilateral ototoxicity in six patients. The hearing loss affected only high frequencies, from 4,000 to 8,000 Hz. Pure tone average values were below 20 dB in all patients. No patient had hearing loss combined with vertigo complaints. Two patients had tinnitus; however, only one of these had ototoxicity.

The patients were separated into two groups: those with ototoxicity and those without ototoxicity. The median age was 19.5 (6–43) in patients without ototoxicity and 29 (16–50) in those with ototoxicity; this difference was statistically significant (p<0.05). The median ferritin and pre-tx Hb levels were 1391 ng/mL and 9.06 mg/dL, respectively, in patients with ototoxicity, and 986.7 ng/mL and 9.24 mg/dL, respectively, in those without; these differences were not significant (p>0.05). The Hb and ferritin values are presented in Table 2. The pe-

Table 1. Duration of iron-chelating agent use and ototoxicity frequency

		Deferiprone					Deferasirox				
	DDU	PNU/ ototoxicity event	1–5 years/ ototoxicity event	5–10 years/ ototoxicity event	More than 10 years/ ototoxicity event	Total	PNU/ ototoxicity event	1–5 years/ ototoxicity event	5–10 years/ ototoxicity event	More than 10 years/ ototoxicity event	Total
DFO	PNU	3/0	5/0	0	0	8/0	1/0	3/0	4/0	0	8/0
	1–5 years	0	16/2	3/1	3/2	22/5	0	4/2	17/2	0	21/4
	5–10 years	1/0	1/0	8/1	1	11/2	0	3/1	8/0	0	11/1
	More than 10 years	0	1/0	4/3	9/6	14/9	1/1	9/5	4/3	0	14/9
Total		4/0	23/2	15/5	13/8		2/1	19/8	33/5	0	

PNU: Number of patients who have never used the drug; DDU: duration of drug use; DFO: deferoxamine

Table 2. Ferritin and Hb values in the ototoxicity and non-ototoxicity groups (Values presented as median, maximum, and minimum due to non-normal distribution)

	Ototoxicity observed group	No ototoxicity observed group	
	n=15	n= 40	p
Hb (mg/dL)	9.06 (8-9.58)	9.24 (7.52-9.8)	0.098
Ferritin (ng/mL)	1391 (257-4529.7)	986.7 (333.8-6315)	0.705

Table 3. Demographic and laboratory findings of patients using only deferiprone or deferasirox

Age	Disease	Gender	Ferritin level	Hb Level	Use of deferiprone duration	Use of deferasirox duration
16	Thalassemia major	Male	2871.7	9.01	1-5 years	5-10 years
14	Thalassemia major	Female	625.2	9.06	1-5 year	5-10 year
20	S-Beta thalassemia	Female	489	7.52	1-5 year	Didn't use
12	Thalassemia major	Male	625.5	9.3	1-5 year	5-10 year
14	Thalassemia major	Female	2324	9.4	1-5 year	5-10 year
6	Thalassemia major	Male	720	9.2	Didn't use	1-5 year
9	Thalassemia major	Male	1107.4	9.1	Didn't use	1-5 year
6	Thalassemia major	Female	2153	9.2	Didn't use	1-5 year

riod of DFO use was significantly longer among patients with ototoxicity (p<0.05). Ototoxicity was not observed in the eight patients who had never used DFO. Data on these patients are given in Table 3. No patient required cessation of therapy.

DISCUSSION

DFO has been used for many years to prevent transfusion-related iron overload in thalassemia patients [8, 9]. DFO may cause growth retardation, sensorineural ototoxicity, ocular toxicity, and bone deformities [3, 10–12]. Although the exact mechanism has not been explained, ototoxicity in thalassemia patients has been attributed to DFO [3, 6]; this may occur through direct toxic effects on the cochlea and reduction of trace elements such as Zn, Cu, and Mn [9, 11].

The reported incidence of DFO-related ototoxicity varies from 3.8%–57% [3, 5, 6, 13]. DFO-related ototoxicity was observed in 31.9% of patients given the drug in our study. Similar to previous studies, sensorineural hearing loss was seen at higher frequencies, especially 4,000 Hz and above [6, 9, 10]. Olivieri et al. [10] reported that patients with sensorineural hearing loss were younger and had lower ferritin levels than those who did not experience ototoxicity. Karimi et al. [6] found no correlation between the duration of DFO therapy or serum ferritin levels and ototoxicity; serum ferritin levels were only slightly higher in patients with hearing loss (2015±1437 ng/mL vs. 1815±1140 ng/mL). Ambrosetti et al. [12] reported that there was no correlation between ototoxicity and age or ferritin level. Similarly, Shamsian et al. [1] reported no relationship between ferritin level, duration of DFO therapy, or dosage (48.9±9.6 mg/kg/day) of DFO therapy with hearing loss; also, Styles and Vichinsky [14] found no significant difference between ototoxicity and non-ototoxicity groups with respect to age, DFO dose, length of chelation, or ferritin level. In contrast, Porter et al. [9] concluded that DFO ototoxicity was related to high dosage and low ferritin levels, and in a large series (283 cases) analyzed by Faramarzi et al. [4] the incidence of ototoxicity, occurring only in those taking doses greater than 50 mg/kg/day, was 3.5%. Similarly, Chao et al. [11] showed that patients who experienced hearing loss while undergoing DFO treatment (35.1%) had lower serum ferritin levels and duration of DFO use; however, pre-tx Hb levels did not correlate with hearing loss. Also, no direct relationship was established between hearing loss and transfusion-dependent hemoglobinopathies.

Ototoxicity was seen at an older age in our study and, consistent with previous studies, there was no relationship of ferritin or pre-tx Hb level between the ototoxicity and non-ototoxicity groups (p=0.705) [1, 4, 6]. Ototoxicity was, however, significantly associated with duration of DFO use (Pearson Chi-Square test, p<0.05). We believe that ototoxicity is not related to age. None of the age groups in our study intersect with the presbycusis age group. Age influences the duration of DFO usage. Elderly patients have greater exposure to cumulative DFO doses because DFO was the only iron-chelating agent available earlier in their lives. However, the majority of young patients were treated with oral iron chelators rather than DFO. Therefore, we believe that ototoxicity is associated with exposure to higher cumulative doses of DFO. In both patient groups, ferritin levels were similar and were below 2000 ng/mL. This indicates that the iron overload control was similar and effective in both groups.

The doses of DFO in this study ranged from 30–50 mg/kg/d. Although the "safe" dosage of DFO is accepted to be below 50 mg/kg/d [3, 12], we observed a high rate of DFO-related ototoxicity (31.9%). Thus, we believe that no dose of DFO should be considered totally safe.

Deferiprone and deferasirox are oral iron chelators. Although the deferasirox prospectus states that the ototoxicity incidence is 1%, no clinical reports have examined deferiprone- or deferasirox-related ototoxicity. In this study, ototoxicity was not observed in the eight patients taking chelators other than DFO. Thus, deferiprone and deferasirox treatments may not be associated with ototoxicity; however, to confirm this, a larger series with long term follow up is required.

The reported ototoxicity incidence with DFO varies widely, which may result from different definitions of hearing loss. In some previous studies, the minimum sensorineural hearing loss to conclude ototoxic effects of DFO was 15 dB and above at any audiometry frequency, while in others, it was 20 dB and above [1, 6]. However, ototoxicity evaluation scales will give more accurate results in the assessment of drug ototoxicity. The most reliable scales for this purpose are American Speech-Language-Hearing Association (ASHA, 1994), NCI CTCAE (used here) and Brock's Hearing Loss Grades [15]. The NCI CTCAE scale grades ototoxicity (Grade 1–4) by calculations using conventional audiometric data (0.25 and 8 kHz). Therefore, we prefer the NCI CTCAE scale to the ASHA scale. To our knowledge, this is the first reported study using the NCI CTCAE scale to show that iron-chelating agents induce ototoxicity. This scale should be implemented in the audiological evaluation of patients receiving chelating treatment to obtain objective and reliable results.

In the present study, the ototoxicity incidence with DFO at doses below 50 mg/kg/day was 31.9%, suggesting that the risk of ototoxicity

is present at all doses. Hearing impairment was concentrated between 4000 and 8000 Hz. Ototoxicity was related to duration of DFO use but not to serum ferritin or Hb levels. Deferiprone and deferasirox were not associated with ototoxic effects in the few patients taking these drugs. In conclusion, patients receiving iron chelators should be closely monitored for auditory side effects. Routine audiometry is still recommended for early detection in patients receiving any iron-chelating treatment because sensorineural hearing loss may develop and may result in long-term morbidity.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Muğla Sıtkı Koçman University Medical Faculty.

Informed Consent: Verbal informed consent was obtained from patients and the parents of the patients who participated in this study.

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