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Short communication

Carboplatin is ototoxic

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Summary. For assessment of the ototoxic potential of carboplatin [*cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II); CBDCA], pure-tone audiograms were evaluated in 27 patients receiving a total of 119 doses of carboplatin in the range of 300–400 mg/m^2. Pure-tone audiometry (PTA) was done immediately prior to and 4 weeks after the administration of 80 doses (67%). Defining carboplatin ototoxicity as an increase of ≥ 30 dB in auditory thresholds that was unexplainable by other causes, we identified 5 examples (19%). Hearing loss tended to be cumulative with increasing dose and was always maximal at 8,000 Hz. Two patients had an increase in auditory thresholds at 1,000 Hz, but this only amounted to 10 dB in each case. Patients developing ototoxicity tended to be older. Sex, the pre-treatment creatinine clearance, the pre-treatment audiogram, the number of doses, and the cumulative dose did not emerge as being reliable predictors of subsequent ototoxicity. We conclude that although carboplatin is ototoxic, clinically significant deafness does not occur with conventional dosing and routine audiometric monitoring is therefore unnecessary. However, we suggest that caution should be exercised when carboplatin is given either at higher doses or for longer periods when there is concomitant use of other potentially ototoxic agents or when there is significant pre-existing auditory impairment.

Introduction

Cisplatin [*cis*-diamminedichloroplatinum(II)] possesses substantial activity against a range of human neoplasms. Unfortunately, its full potential is often limited by considerable gastrointestinal, renal, and neurologic toxicity. Carboplatin [*cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II); CBDCA; JM8] is one of a number of cisplatin analogues developed in an attempt to circumvent the dose-limiting toxicity of the parent compound while retaining its clinical activity [1]. The principal toxicity of carboplatin is myelosuppression, especially thrombocytopenia. Renal toxicity is not a major problem, and neurotoxicity is minimal [2]. Initial reports suggesting the complete ab-

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Table 1. Characteristics of patients receiving carboplatin

Age (years)	Sex	Minimal Pre-treatment creatinine clearance (ml/s)	Auditory threshold at 8,000 Hz[a]:		Cumulative carboplatin Dose (mg)
			Pre-treatment	Post-treatment	
62	F	1.2	15	60[b]	3,600
54	F	1.0	35	70[b]	1,350
71	F	1.4	20	55[b]	2,500
41	M	2.6	40	70[b]	3,250
59	M	1.8	40	70[b]	3,750
33	F	1.7	0	0	1,870
43	F	1.6	20	20	1,200
26	M	1.8	40	65	1,200
72	F	1.4	60	55	2,700
68	F	1.2	80	100	3,000
48	M	1.2	15	10	3,000
20	F	2.1	10	15	3,600
40	F	1.9	75	65	2,250
45	M	1.6	20	15	1,300
51	F	1.6	20	20	2,250
67	F	1.5	10	10	600
49	F	2.0	20	15	3,600
57	F	1.0	80	75	825
46	F	1.4	20	20	3,600
54	F	1.7	70	60	3,600
37	F	1.0	15	15	2,250
48	F	1.4	15	10	3,600
54	F	2.4	10	15	1,200
43	F	1.3	15	10	3,600
48	F	1.6	15	20	1,350
46	F	1.4	30	40	2,400
65	F	0.8	45	50	560

[a] Data from the right ear only are shown. Values obtained from the left ear were not significantly different.

[b] Carboplatin ototoxicity was defind as an increase of ≥ 30 dB in auditory thresholds that was unexplainable by other causes

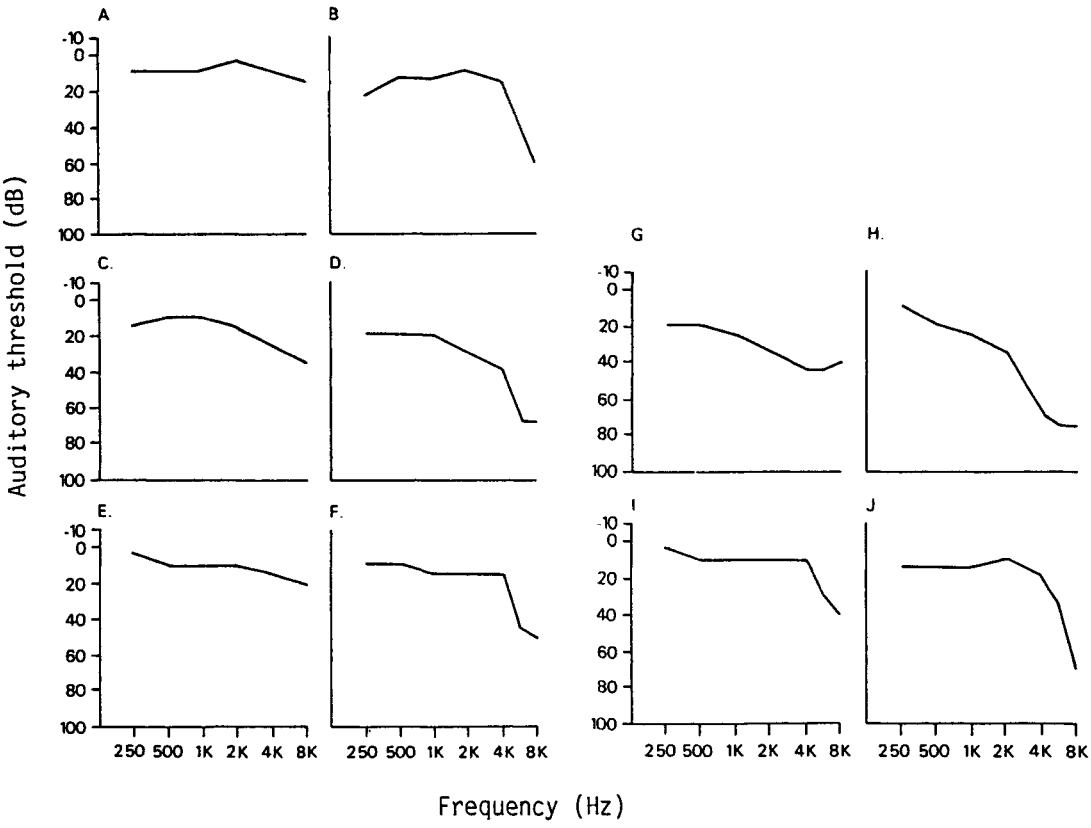

Fig. 1 A–J. Audiograms of patients developing carboplatin ototoxicity, defined as an increase of ≥30 dB in auditory thresholds that was unexplainable by other causes. **A** Patient 1, pre-treatment. **B** Patient 1, post-treatment. **C** Patient 2, pre-treatment. **D** Patient 2, post-treatment. **E** Patient 3, pre-treatment. **F** Patient 3, post-treatment. **G** Patient 4, pre-treatment. **H** Patient 4, post-treatment. **I** Patient 5, pre-treatment. **J** Patient 5, post-treatment. Note that the audiogram from the right ear only is shown; in each case, similar results were obtained from the left ear. *K* = 1,000 Hz

sence of ototoxicity [1] have prompted us to follow closely in a prospective fashion the pure-tone audiometry (PTA) of patients receiving carboplatin.

Patients and methods

Patients. From March 1986 until March 1988, all patients receiving carboplatin at this institution were enrolled in this prospective study. Of the 37 patients so treated, 10 were excluded from subsequent analysis: 7 because early death meant that only one dose of carboplatin was given and follow-up audiometry was not carried out, and 3 because of incomplete audiological data. The characteristics of the remaining 27 evaluable patients are summarised in Table 1.

Carboplatin administration. Before each dose of carboplatin, patients underwent a full physical examination, with measurement of creatinine clearance, routine blood chemistries, and haematological profile. Carboplatin was given intravenously at a dose of 300–400 mg/m^2 over 1 h. No special supplemental hydration was given.

Audiological assessment. PTA was conducted by a clinical audiologist prior to each dose. In a sound-treated test booth, stimuli generated by an interacoustic AC3 clinical audiometer were delivered via TDH-39 earphones mounted in MX-41 rubber cushions. Stimuli were calibrated to the 1969 standards of the American National Standards Institute. Audiometric testing was conducted at 250, 500, 1,000, 2,000, 4,,000, 6.000, and 8,000 Hz in 5-dB steps. When a hearing deficit was detected, bilateral acoustic reflex testing, impedance tympanography, and bone masked conduction as well as clinical assessment were used to exclude a conductive cause.

Results

The 27 evaluable patients received 119 doses of carboplatin, of which 80 doses (67%) were both immediately preceded and followed 4 weeks later by audiometry. The median number of carboplatin doses given was 5, with a range of 1–6. Prior to the commencement of carboplatin dosing 16 patients had auditory thresholds of <25 dB across the range of 250–8,000 Hz, 2 patients had at least one threshold in the range of 25–34 dB, and 9 had at least one threshold of >35 dB.

Defining carboplatin ototoxicity as an increase of ≥30 dB in auditory thresholds that was unexplainable by other causes, we identified 5 examples (19%; 95% confidence interval, 4%–33%). Significantly, the maximal increase in thresholds consistently occurred at 8,000 Hz, and in only 2 patients was this associated with a deterioration of 10 dB, at the 1,000-Hz level. Similarly, none of the remaining 22 patients sustained an increase in auditory thresholds at the 1,000-Hz level. The audiograms of the five patients developing carboplatin ototoxicity are shown in Fig. 1.

Univariate analysis revealed that patients developing hearing loss were more likely to be older (P <0.05) than those who did not. There was no statistically significant difference between patients who did and those who did not develop ototoxicity with respect to the following parameters: sex (chi-square test, P >0.05), pre-treatment creat-

inine clearance, pre-treatment auditory threshold at 1,000 and 8,000 Hz, number of doses, or total cumulative dose of carboplatin (two-tailed t-test, $P > 0.05$).

Discussion

Carboplatin is one of a number of cisplatin analogues developed in an attempt to circumvent the dose-limiting toxicity of the parent compound while retaining its clinical activity [1]. The ototoxic potential of cisplatin was very quickly appreciated after it entered clinical trial [4]. Clinical high-tone hearing loss occurs in approximately 20% of patients, whereas a further 74% develop audiologically detectable but subclinical hearing loss [2]. Hearing loss can occur unpredictably, although it tends to be worse with increasing age, dose, and frequency of treatment [8]. The mechanisms of ototoxicity remains obscure, but studies in both guinea pigs and man have demonstrated degeneration of outer hair cells in the basal turns of the cochlea, similar to the degenerative pattern documented with aminoglycoside antibiotics [11].

The ototoxic potential of carboplatin is less clearly defined. The initial report by Calvert et al. [1] revealed no change in the audiograms of 13 patients, and similar results have been recorded in subsequent phase II and phase III trials that have specifically included audiometric assessment [5, 9, 12, 15].

In contrast to studies that did not reveal ototoxicity, Canetta et al. [2] who summarised the results of 23 phase II and phase III trials involving 710 patients, noted clinical ototoxicity manifesting principally as tinnitus in 8 patients (1%). When audiometry was carried out, subclinical deafness was found in 6 of 41 patients (15%). Other phase II studies incorporating audiometry that have demonstrated ototoxicity include those of Curt et al. [3], Leyvraz et al. [10] and Dones et al. [4], with incidences of 1 in 38, 3 in 38, and 3 in 58 patients, respectively; however, none of these studies listed audiologic data or provided criteria defining carboplatin ototoxicitiy.

An increase in auditory threshold of as little as 10 dB has been used as evidence of cisplatin ototoxicity [14]. Although the test-retest reproducibility of high-tone audiometry is well established [6], with maximal differences of approximately 4 dB [7], a change of 10 dB is unlikely to be associated with clinically significant hearing loss [13]. For this reason, we deliberately took the much higher figure of a 30 dB change as representing evidence of significant ototoxicity. Despite this higher value, we detected ototoxicity in 5 of 27 patients (19%), a greater proportion than has been hitherto described. However, this hearing loss was only recorded at higher frequencies that are unlikely to impair speech discrimination, and no patient suffered significant hearing loss at the more important lower frequencies [13] of 1,000–4,000 Hz, although two patients (numbers 3 and 5) complained of tinnitus. In patient 1, hearing loss occurred in an idiosyncratic fashion (after the first cycle), although it more often occurred in a cumulative pattern with increasing dose (patients 2–5). Patients developing ototoxicity tended to be older, but no pre-treatment patient parameters emerged as being reliable predictors of subsequent hearing loss.

We conclude that a significant proportion (approximately 20%) of patients develop high-tone hearing loss, generally in a cumulative fashion, after the administration of carboplatin at conventional doses (300–400 mg/m^2 for 5 or 6 courses), but that clinically important deafness does not occur and routine audiometric monitoring is therefore unnecessary.

However, we do suggest that caution should be exercised when carboplatin is given either at higher doses or for longer periods when there is concomitant use of other potentially ototoxic agents or when there is significant pre-existing auditory impairment.

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