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# Ototoxicity of *cis*-Diamminedichloroplatinum (II): Influence of Dose, Schedule and Mode of Administration

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**Abstract**—*During and after 233 cycles of* cis*-diamminedichloroplatinum (II) (CDDP), 197 serial audiograms were obtained in 48 patients and compared with baseline audiograms. Use was made of three dose schedules (20 mg/m², 25–50 mg/m² and 70–120 mg/m²), two regimens (single-day or daily for 5 days) and three modes of administration (rapid infusion, 2- or 3-hr infusion, 24-hr infusion). Clinical hearing loss occurred in 12.5% and tinnitus in 25% of all patients. The incidence of audiographic changes (65% overall, 81% bilaterally) increased with increasing cumulative CDDP dose independent of treatment schedule. The incidence was correlated with the daily dose (P = 0.0037) and changes were more severe after single high doses. No difference was found between the single low dose and the daily for 5 days regimen. Rapid infusion of a single high dose was more ototoxic than a 24-hr infusion of the same dose (P = 0.0015). It is concluded that, compared with the single high-dose regimen, the daily low dose for 5 days is preferable in cases where the patient might be cured by a regimen including CDDP.*

## INTRODUCTION

*cis*-DIAMMINEDICHLOROPLATINUM II (CDDP) is one of the most effective anti-neoplastic agents. Since this drug is being used in chemotherapeutic regimens with curative potential, it is important to be aware of its long-term side effects. In 1971 hearing loss was first reported in a patient receiving CDDP in a dose of 4 mg/kg [1]. Few prospective studies on CDDP ototoxicity in relation to dose and treatment schedules have been done in man. In a randomized phase II study performed to compare five daily injections of 20 mg/m² of CDDP with a single high dose of 120 g/m² with mannitol-induced diuresis, the latter dose was the more toxic to both the kidney and the inner ear [2]. Recently, it has been suggested that audiometric abnormalities are correlated with the mode of CDDP administration, the highest incidence being associated with bolus injection [3]. Serial audiography indicated that CDDP ototoxicity is dose-related [3–6].

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In the present study hearing acuity was assessed by serial audiography prior to each successive cycle of treatment with CDDP given according to three protocols differing as to dose or schedule. The results show correlation between daily dose and the occurrence of ototoxicity as well as an influence of infusion duration.

## MATERIALS AND METHODS

### *Patients*

Forty-eight patients with advanced cancer received CDDP as a single drug or in combination with other anti-neoplastic agents. The diagnosis included head and neck cancer (10 patients), ovarian cancer (10), testicular teratoma (9), cancer of the uterine cervix (7), lung cancer (4) and other types (8).

CDDP was administered every 3–6 weeks in several ways: (1) a single low dose (SLD) of 25–50 mg/m² (16 patients); (2) a single high dose (SHD) of 70–120 mg/m² (14 patients); or (3) a daily dose for 5 days (LD5) of 20 mg/m²/day (15 patients); also, 3 patients received varying doses. The doses were given by rapid infusion (4–15 min), 2- or 3-hr infusion or 24-hr infusion.

In the SLD group 3 patients received CDDP by rapid infusion, 10 by a 2- or 3-hr infusion and 3 by a 24-hr infusion. In the SHD group 5 patients were given the drug by rapid infusion, 3 by a 3-hr infusion and 6 by a 24-hr infusion. All patients in the LD5 group received a 3-hr infusion.

Median ages in the SLD, SHD, and LD5 groups were 48 yr (range: 39–73 yr), 61.5 yr (30–80 yr) and 37 yr (18–61 yr) respectively. Fifteen patients received CDDP as a single agent and 33 patients were given combination regimens including such agents as vincristine, vinblastine, vindesine, bleomycin, mitomycin C, adriamycin, cyclophosphamide, hexamethylmelamine, methotrexate and 5-fluorouracil, none of which is known to be ototoxic in doses currently used in human antitumour therapy.

Serum creatinine was below 120 μmol/l (upper limit of normal) in all but one patient, who belonged to the SLD group (145 μmol/l). Creatinine clearance was below 80 ml/min in 3 or 4 patients in each group (52–79 ml/min).

Before each treatment course a detailed history was taken on the occurrence of tinnitus and/or hearing loss, and baseline (pure tone) audiography was performed. Audiography was done prior to each treatment course and more than two weeks after the end of treatment. All tests were carried out in a sound booth with a Peeters Clinical Audiometer, type AP-6. Stimuli were delivered via TDH-39 ear phones mounted in audiocups. All stimuli were calibrated to American National Standard Institute 1969 standards. Air-conduction thresholds were obtained separately for each ear at 250, 500, 1000, 2000, 4000 and 8000 Hz. Starting with 30 db at 1000 Hz, pulsed pure tones were presented at decrements of 10 db or increments of 5 db. In all, 197 serial audiograms were completed during or after 233 cycles of CDDP. In patients showing threshold drops bone conduction was also tested. In addition, a total of 126 examinations of speech-reception thresholds and discrimination scores was tested in 31 patients. After discontinuation of treatment, follow-up audiography was done in 11 patients.

Because of the occasional differences between the baseline audiograms of the left and right ears, the patients' ears were divided into three groups i.e. with (a) normal hearing function, (b) moderate pre-existing hearing loss (PHL) and (c) severe PHL. Normal hearing was defined as an average threshold decrease within the 250–8000 Hz range of less than 15 db, moderate pre-existing hearing loss as an average decrease of 15–30 db and a severe hearing loss as an average decrease of 30 db or more [7].

Patients were considered to have significant hearing loss if serial audiography showed a drop of 15 db or more in pure-tone threshold in one ear or a drop of 10 db or more in both ears at one or more frequencies [4]. For the detection of correlations with other types of toxicity, renal function was evaluated weekly on the basis of the serum creatinine concentration and/or creatinine clearance, neurotoxicity on the basis of a detailed history and clinical neurological examination, and myelotoxicity from blood-cell counts.

## RESULTS

Clinical hearing loss occurred in 6 of the 48 patients (12.5%), all belonging to a group of 25 patients with moderate PHL (Table 1). Three of the 48 patients had pre-existing tinnitus as well as moderate PHL and all three showed audiographic changes during treatment. Audiographic changes occurred in 31 patients (65%), 25 of them bilaterally (81%) and 6 unilaterally. In 13 patients the audiographic changes were the only manifestation of toxicity (27%). Such changes were observed in 11 of the 12 patients who developed tinnitus during treatment. Audiographic changes were transient in 3 patients, and only 28 patients had persisting change at the end of the treatment.

*Table 1. Incidence of ototoxicity in patients with normal hearing function or pre-existing hearing loss (PHL)*

| Toxicity | Normal hearing | PHL Moderate | PHL Severe | Overall |
|---|---|---|---|---|
| Clinical hearing loss | 0/16 | 6/25 | 0/7 | 6/48 |
| Tinnitus | 5/16 | 7/25 | 0/7 | 12/48 |
| Audiographic changes | 11/16 | 17/25 | 3/7 | 31/48 |

Table 2 shows the distribution of hearing loss over the frequencies studied in these 28 patients. Hearing loss occurred predominantly in the higher frequency range. The 3 patients with transient abnormalities showed 10–25 db decrements, one at 250 Hz and two at 4000 Hz. The largest threshold drops were observed at 8000 Hz. The seven patients with the most severe hearing loss (50–70 db) were all in the SHD group (cumulative dose of CDDP 215–590 mg/m$^2$).

*Table 2. Distribution of hearing loss over six frequencies in 28 patients (52 ears) showing toxicity*

| | 250 Hz | 500 Hz | 1000 Hz | 2000 Hz | 4000 Hz | 8000 Hz |
|---|---|---|---|---|---|---|
| No. of patients | 4 | 3 | 2 | 8 | 13 | 27 |
| No. of ears | 7 | 4 | 4 | 14 | 24 | 50 |

The incidence of ototoxicity increased with each additional treatment cycle (Table 3). Six

*Table 3. Incidence of ototoxicity after each of the first four cycles of CDDP*

| Cycle No. | Evaluable patients | Unilateral toxicity | Bilateral toxicity | Overall toxicity | (%) |
|---|---|---|---|---|---|
| 1 | 41 | 4 | 8 | 12 | (29) |
| 2 | 32 | 2 | 9 | 11 | (34) |
| 3 | 24 | 3 | 7 | 10 | (42) |
| 4 | 20 | 5 | 8 | 13 | (65) |

patients given 8 cycles with a median cumulative dose of CDDP of 625 mg/m$^2$ (range: 440–800 mg/m$^2$) all developed audiographic changes. There was no difference between the incidence of ototoxicity in patients receiving single-agent chemotherapy and those on combination chemotherapy within either the SLD or the SHD group. In the SLD group 1 out of 5 on single-agent chemotherapy and 2 out of 11 on combination chemotherapy showed ototoxicity, and in the SHD group this was the case for 6 out of 8 patients receiving CDDP alone and 5 out of 6 on combination chemotherapy.

Of the 31 patients in whom speech discrimination was studied during CDDP therapy, 22 showed significant hearing loss at audiometric evaluation for pure tones, and in 6 of these the discrimination score dropped 7–34%; of the remaining 9 patients, 8 showed no changes in either the pure-tone threshold or the discrimination score and the other showed a 15% drop in the score for one ear.

For evaluation of the influence of dose and treatment schedule, the development of ototoxicity in the three groups was analysed up to the moment these schedules changed. These groups differed as to median cumulative dose and median age of the patients (Table 4). Figure 1 shows the relation between the development of audiographic changes and the cumulative dose for the SLD, SHD and LD5 treatment groups. The graph was constructed using the method of Kaplan-Meier. With the overall log rank test a statistically significant difference was found between the three groups ($P = 0.0037$). A multiple comparison analysis indicated that the SHD regimen induced ototoxicity at a lower dose than the other two

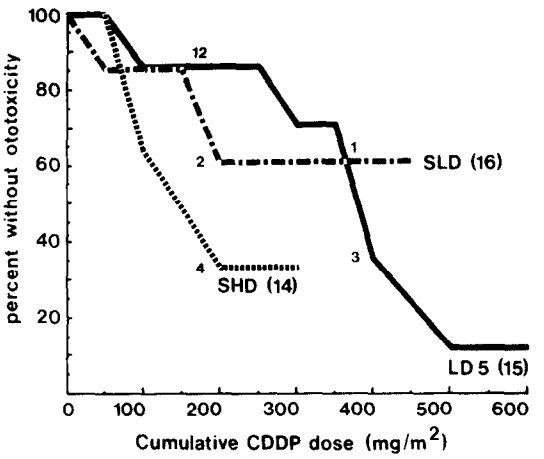


*Fig. 1. Incidence of audiographic changes in relation to cumulative CDDP dose in patients treated with single low doses (SLD), single high doses (SHD), or a daily low dose for 5 days regimen (LD5).*

regimens did (SHD vs SLD: $P = 0.046$, age corrected; SHD vs LD5: $P = 0.034$, age corrected). No difference was found between SLD and LD5 ($P = 0.56$). Not only the incidence of ototoxicity but also the severity of the lesion differed between SHD and LD5. To evaluate this, threshold drops at 8000 Hz were analysed at the end of the treatment period in patients showing toxicity. Notwithstanding the higher median cumulative CDDP dose in the LD5 patients showing toxicity compared with those in the SHD group (400 mg/m$^2$ vs 335 mg/m$^2$ respectively), the threshold decrements (measured in the more severely affected ear) were significantly smaller in the LD5 group ($P < 0.05$, Wilcoxon test). Within groups the increase in threshold drop showed no correlation with the age of the patients.

Within groups of patients receiving a comparable dose of CDDP per treatment course (SHD and LD5 groups, $\geqslant$100 mg/m$^2$) the incidence of ototoxicity was highest for rapid infusion. A multiple comparison analysis showed that rapid infusion was significantly more toxic than the 24-hr infusion ($P = 0.0015$, log rank test).

Because of the great difference between the numbers of toxic and non-toxic patients in both the SHD and the SLD groups, it was to be expected that no influence of age on the

*Table 4. Age, cumulative dose, and ototoxicity, according to treatment group*

| Treatment group* | No. of patients | Median age | Median cumulative dose (mg/m$^2$) | Clinical hearing loss | Tinnitus | Audiographic changes |
|---|---|---|---|---|---|---|
| SLD | 16 | 48 | 137 | 0 | 0 | 3 |
| SHD | 14 | 61.5 | 285 | 3 | 5 | 11 |
| LD5 | 15 | 37 | 400 | 2 | 4 | 9 |
| Total | 45 | | | 5 | 9 | 23 |

*SLD = single low dose; SHD = single high dose; LD5 = daily low dose for 5 days.

occurrence of audiographic changes could be detected within these groups. In the LD5 group, however, numbers of toxic and non-toxic patients were more equal and analysis showed that age does have an influence on the development of ototoxicity ($P = 0.041$, log rank test).

No significant influence of pre-existing hearing loss was found ($P = 0.29$, log rank test). Patients with other types of toxicity showed an increased incidence of ototoxicity (Table 5). Follow-up audiography was performed in 11 patients after termination of treatment. In two patients, one of whom received 500 mg/m$^2$ and the other 515 mg/m$^2$ CDDP and neither of whom showed toxicity at the end of therapy, hearing function was normal up to 8 and 12 months after termination. Of the other 9 patients who showed audiographic changes during treatment 4 had unchanged audiograms during post-treatment periods of 4–15 months. Three patients showed a slight deterioration during post-treatment periods of 4–9 months. Although threshold drops were limited to 15 db or less, they occurred in the speech range (2000–4000 Hz). The remaining two patients showed improvement after cessation of treatment.

*Table 5. Numbers of patients with ototoxicity among patients with (+) or without (–) other types of toxicity**

| Type of toxicity | + | – | *P*-value‡ |
|---|---|---|---|
| Nephrotoxicity† | 22/29 | 6/18 | 0.011 |
| Neurotoxicity | 7/9 | 2/6 | — |
| Neutropenia (WBC) | 8/9 | 3/6 | — |
| Thrombocytopenia | 5/5 | 6/10 | — |

*For comparison with the occurrence of neurotoxicity and myelosuppression, only patients given CDDP as a single agent were evaluated.

†Expressed as reduction of creatinine clearance amounting to >25%. In one patient pre-treatment clearance was unknown.

‡$\chi^2$ test.

## DISCUSSION

The results of the present prospective study including various schedules and doses of CDDP indicate that ototoxicity is a serious side effect of this drug in man and has a higher incidence and a higher degree of toxicity in patients given single high doses. Furthermore, single high doses administered by rapid infusion were the most toxic to the inner ear, which is in agreement with the results reported by Reddel *et al.* [3].

In six previous phase II studies on high dose CDDP (100–120 mg/m$^2$) the overall incidence of clinical hearing loss in 109 patients was 5.5%, whereas that of tinnitus varied widely [8–13]. In four of these studies serial audiography was performed [8, 10, 11, 13]. The overall incidence of audiometric abnormalities was 58.7% (range: 14.3–90%). At a dose of 100 mg/m$^2$, Reddel *et al.* found pure-tone hearing loss in 12 out of 21 patients [3].

In phase II studies on low or moderate doses of CDDP (20–75 mg/m$^2$) the overall incidence of clinical hearing loss in 179 patients was 4.5% and that of tinnitus 2.8% [14–20]. At these lower doses audiometric changes were seen in 14 out of 65 patients (21.5%). In two recent studies the incidence of audiometric abnormalities at these lower doses was 27 and 64% respectively [3, 6], but this divergence is explained by the difference in the duration of treatment (and therefore in cumulative dose). The incidence of audiometric changes in our study, i.e. 79% for patients receiving SHD and 19% for SLD, is in agreement with these earlier findings. In other phase II studies with a daily low dose for 5 days, where 10–20 mg/m$^2$/day was given, no clinical hearing loss was observed and tinnitus or serial audiographic changes occurred in 5–11% [21, 22].

In the present study the incidence of ototoxicity increased with increasing (cumulative ) exposure in both the SHD and the LD5 groups. The median cumulative doses at which audiographic changes occurred in the SHD and LD5 groups were 110 and 400 mg/m$^2$ respectively. In the SLD group only three patients developed toxicity.

CDDP administration is often accompanied by a hydration scheme and use of the potentially ototoxic agent furosemide to reduce the nephrotoxic effect of the drug. In the present study patients in the SLD and SHD groups received the same dose of furosemide, whereas those in the LD5 group were given the diuretic more frequently. Our data indicate that a contribution by furosemide to the development of ototoxicity is unlikely when this drug is used in low doses. Potentiation of the nephrotoxic effect of CDDP by aminoglycosides has been reported, but not in connection with the cochlear damage caused by these drugs. In the present study none of the patients received aminoglycosides.

Although a greater susceptibility to ototoxicity has been reported in patients with pre-existing hearing loss [5, 6, 8], our results do not confirm these findings. Nonetheless, ototoxicity in patients with PHL does result in clinical hearing loss at lower cumulative doses than in patients with normal hearing. All our six patients with clinical hearing loss had PHL in one or both ears. Although the ototoxicity appeared to be partially reversible, the audiograms of the majority of the patients did not improve after termination of treatment.

The audiographic abnormalities we observed were, like those described by other investigators

[4–6, 8], mainly bilateral and predominantly in the 4000 and 8000 Hz ranges, which is higher than the speech range of 500–4000 Hz. At increasing cumulative dose of CDDP lower frequencies also tend to be affected and this may result in clinical hearing loss. Speech-discrimination scores showed no consistent change with CDDP dose. Other significant signs of toxicity (renal, bone marrow, neurologic) appeared to be associated with an increased incidence of ototoxicity.

The pathogenesis of CDDP ototoxicity is unknown, but several hypotheses have been offered [4, 23]. Comparisons have been made with the toxicity caused by aminoglycosides and furosemide. The former have been shown to accumulate selectively in the perilymph and endolymph of the inner ear, possibly causing damage to the cochlear secretory and reabsorptive tissue [24, 25]. No attempt has yet been made to detect the presence of CDDP in the endolymph or perilymph of the inner ear. It has been suggested that a common mechanism underlies both CDDP and furosemide toxicity, namely inhibition of ATPase in both the kidney and the inner ear [23]. It remains unclear whether or not CDDP causes primary neural degeneration in addition to the changes seen in the neuro-epithelium. This has been observed after administration of certain ototoxic antibiotics [26].

The value of the present study is that it shows that regimens including CDDP are toxic to the inner ear in a significant number of patients. In clinical practice it is therefore advisable to perform baseline audiography prior to the initiation of CDDP treatment, and follow-up audiography is recommended before each course of therapy in patients with pre-existing hearing loss as well as patients receiving single high doses. It does not seem necessary to perform sequential audiography in patients with normal hearing function and given low doses. A second audiogram will suffice after a cumulative dose of 200 mg/m$^2$ CDDP unless the patient complains of tinnitus or clinical hearing loss at an earlier stage. A threshold drop below 4000 Hz is a warning for clinically significant hearing loss and the risk/benefit ratio of continued CDDP treatment will then have to be carefully assessed.

Unless a distinct therapeutic benefit is demonstrably certain, administration by rapid infusion should be avoided when single high-dose treatment is given. Furthermore, because there is little or no evidence that a single high dose of CDDP has a greater anti-tumour effect than the daily low dose for 5 days regimen does, the LD5 regimen seems to deserve perference for cases in which a regimen including CDDP might lead to cure.

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