Calcium supplementation and ototoxicity in patients receiving cisplatin

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We have studied the effect on ototoxicity of maintaining serum calcium concentration by calcium gluconate infusion in cancer patients receiving high-dose cisplatin in a randomized study in two groups: 11 patients received calcium gluconate, 4 mg kg⁻¹ i.v. infusion during cisplatin therapy; 11 other patients without any calcium supplementation served as controls. All of them received the first course of chemotherapy, based on cisplatin, 120 mg m² with a hydration schedule. An audiogram was performed in each patient just before cisplatin and repeated after 1 day and 3 weeks. Mean total calcium concentration in control patients before and after chemotherapy was 2.2 ± 0.14 (95% confidence interval 1.9–2.5) and 2.0 ± 0.13 (95% CI 1.7–2.24) mmol l⁻¹ respectively (*P* = 0.0004) and for ionized calcium 1.22 ± 0.52 (95% CI 0.21–2.23) and 1.11 ± 0.07 (95% CI 0.97–1.25) mmol l⁻¹ respectively (*P* = 0.0005). Serum magnesium levels were maintained or increased by magnesium supplementation. Although there was no change in serum total or ionized calcium, or serum magnesium in the calcium infusion group, no differences in hearing loss between the groups were observed. High-dose cisplatin chemotherapy for cancer patients induces an acute decrease of serum total calcium and serum ionized calcium and audiometric changes. Maintenance of calcium serum levels by calcium gluconate infusion did not protect against ototoxicity in those patients.

Keywords cisplatin ototoxicity calcium

Introduction

Ototoxicity is a well-known adverse side effect of cisplatin chemotherapy, and is almost always irreversible. No clinical interventions are known to diminish this toxicity. Some authors reported as high as 81% of incidence rate [1]. It appears to be related to the loss of outer hair cells in the basal turn of the cochlea and is histologically similar to aminoglycoside-induced ototoxicity [2], which in animals is known to be related in a dose dependent manner to displacement of Ca⁺⁺ ions from the cell membrane of the sensory hair cells [3]. The provision of excess Ca⁺⁺ at the sensory hair cells surface results in protection for the hair cells during treatment with aminoglycoside antibiotics [4–6].

We examined the hypothesis that by avoiding the

acute decrease of serum calcium levels induced by cisplatin therapy we could prevent the hearing loss.

The serum concentrations of calcium and magnesium and audiometric results, were studied before and after chemotherapy in a randomized parallel-group study of patients receiving cisplatin with or without infusion of calcium during chemotherapy.

Methods

Twenty-two consecutive patients (17 males and 5 females, aged 16–73 years) were studied. All gave their informed consent and fulfilled the following eligibility criteria: (1) histologically proven cancer requiring cisplatin therapy; (2) no prior cytotoxic treatment; (3)

no administration of diuretics in the last month; (4) normal liver and kidney function, and (5) performance status of at least 2, according to the WHO classifications.

Treatment

On the day of cisplatin (120 mg m^{-2}) infusion, each patient received a hydration schedule consisting of 1500 ml of 5% dextrose in one-half normal saline fluid plus KCl 20 mmol l^{-1} and mannitol 20%, 250 ml before and repeated after cisplatin. All patients received magnesium sulphate, 6.25 mmol l^{-1} i.v. diluted in 100 ml of saline fluid over 15 min before cisplatin infusion. Duration of treatment was 4 h.

Patients were randomized to receive calcium gluconate i.v. 4 mg kg^{-1} in 100 ml of saline fluid in infusion 4 h long *vs* no further therapy as a control group.

Other non ototoxic chemotherapeutic agents were added to cisplatin depending on the primary tumour origin: bleomycin for head and neck; etoposide for lung, malignant melanoma and lymphoma; etoposide plus doxorubicin for stomach; vindesine for unknown primary cancer.

Serum analysis

A complete baseline blood exam including haemoglobin, WBC and platelet count and kidney and liver function was performed in all patients before cisplatin.

In all patients total serum calcium, (reference range: $2.1\text{--}2.6 \text{ mmol l}^{-1}$), ionized serum calcium (reference range: $1.0\text{--}1.3 \text{ mmol l}^{-1}$) and total serum magnesium concentration (reference range: $0.7\text{--}1.2 \text{ mmol l}^{-1}$) were assessed just before and at the end of chemotherapy schedule.

Audiometric studies

Three audiometric studies were performed in every patient: first, before cisplatin; second, at 24 h; and third, 3 weeks later. The audiometrist did not know the therapeutic arm to which the patients had been allocated.

Before treatment, an audiologic history was taken and the patient's ears were examined. Routine air conduction pure-tone audiometry (0.25, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 kHz) was performed under standard con-

ditions in a sound proof test box, using an Amplaid A 208 Audiometer, calibrated according to International Organization for Standardization 389. The patients were considered to have developed a significant change in hearing threshold if they showed deterioration in pure-tone air-conduction threshold of 15 dB or more at one frequency [7] or deterioration of 10 dB or more at three frequencies in one ear [1].

Statistical studies

Comparison of the means of serum concentration levels of calcium and magnesium before and after cisplatin infusion was performed using the *t*-test. Statistical analysis of audiometric changes before and after cisplatin was carry out using the nonparametric Wilcoxon test. Hearing loss was transformed as $\log(x+1)$ for the analysis of quantitative data. Differences were compared by an 'split-plot' design with MANOVA procedure of SPSS-X.PC.

Results

In the group of patients treated by calcium infusion (and magnesium infusion) there were no significant differences in the mean ($\pm$ s.d.) in serum concentration before and after cisplatin for total calcium 2.3 ± 0.13 (95% CI 2.0–2.5) and 2.2 ± 0.16 (95% CI 1.9–2.7); ionized calcium, 1.20 ± 0.1 (95% CI 1.00–1.40) and 1.28 ± 0.08 (95% CI 1.13–1.43); or total magnesium, 0.8 ± 0.16 (95% CI 0.5–1.13) and 0.88 ± 0.06 (95% CI 0.75–1.0), $P > 0.05$.

In the control group of patients who received no calcium infusion, there were significant differences in the mean ($\pm$ s.d.) in serum concentration before and after cisplatin for total calcium 2.2 ± 0.14 (95% CI 1.9–2.25) and 2.0 ± 0.13 (95% CI 1–73–2.2); ionized calcium, 1.22 ± 0.06 (95% CI 1.10–1.34) and 1.11 ± 0.07 (95% CI 0.97–1.25); and total magnesium, 0.45 ± 0.08 (95% CI 0.57–0.9) and 0.88 ± 0.08 (95% CI 0.72–1.05), $P < 0.005$.

Audiometric loss

In 20 out of 22 patients (90%) some hearing loss was observed (Table 1). Audiometry was altered in five (right ear), and six (left ear) patients of the calcium infused

Table 1 Hearing loss according to therapy

	Right ear				Left ear			
	2nd		3rd		2nd		3rd	
	4 kHz	8 kHz	4 kHz	8 kHz	4 kHz	8 kHz	4 kHz	8 kHz
Calcium infused patients	0.56 ± 1.4	0.52 ± 1.4	0.62 ± 1.5	1.02 ± 1.6	0.49 ± 1.4	0.43 ± 1.4	0.37 ± 1.6	0.91 ± 1.7
Control group	0.23 ± 1.4	1.05 ± 1.3	0.54 ± 1.5	1.41 ± 1.3	0.18 ± 1.3	0.56 ± 1.5	0.41 ± 1.5	0.89 ± 1.4

Geometric mean and standard error of differences of hearing loss.

group; and in three (right ear), and two (left ear) in the controls after 24 h of cisplatin infusion (second audiometry). After 3 weeks the third audiometry shows alterations in seven (right ear) and eight (left ear) patients in the calcium infusion group; and in eight (right ear) and eight (left ear) patients in the control group. No cumulative audiometric alteration was observed in 10 out of 22 patients. There were no statistical differences between any subset of patients in the audiometric alterations.

Quantitatively analysis showed no statistically significant differences between both groups. The means of the differences in hearing loss in the 4000 Hz and 8000 Hz range were 7.22 db and 3.18 db respectively for treated patients *vs* 2.82 db and 6.81 db respectively in non treated patients. Factorial analysis of variance only shows significant differences in favour of left ear of the controls in the aforementioned ranges ($F=252$, $P=0.033$).

Discussion

Cisplatin-induced hypomagnesaemia and hypocalcaemia are reported by several authors and seem to be due to a renal tubular injury with selective wasting [8]. Hypocalcaemia appears to develop in those with the most severe renal magnesium wasting and the greatest hypomagnesaemia [9]. Nevertheless, hypocalcaemia was observed in our patients in the group despite magnesium levels kept in the normal range by magnesium supplementation.

We observed a significant fall in serum calcium concentration after cisplatin therapy in absence of calcium supplementation. These patients had significant audiometric loss. Calcium gluconate infusion was able to maintain serum calcium concentration, but audiometric loss was similar 24 h after cisplatin infusion. Disturbances in audiograms were even worse after 3 weeks of cisplatin therapy suggesting that damage of outer hair cell of the cochlea persists after 24 h.

Calcium protection of the aminoglycoside cochlear lesion demonstrated in animals [4–6] has not been confirmed in human ototoxicity caused by cisplatin. Further studies are needed which should focus on other protective approaches such as fosfomycin [10] or on cisplatin damage over outer hair cells of the cochlea.

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