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SHORT COMMUNICATION

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# Long-term platinum excretion in patients treated with cisplatin

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**Abstract** The purpose of this study was to determine long-term renal platinum excretion after chemotherapy with cisplatin. We examined urinary platinum concentrations in 23 men at 150–3022 days after anticancer treatment for testicular neoplasm. Spot urine samples were analyzed by voltammetry. This new, subtle method with a detection limit of 2 pg platinum allows determination of even the natural background level. Urinary platinum concentrations in our patients ranged between 0.74 and 77.24 μg/g creatinine, depending on the total delivered dose and follow-up period. Regression analysis of the data showed two phases of long-term renal platinum excretion, one occurring at between 150 and 900 days of follow-up and the other with an onset at 900 days after cisplatin administration ($r_1^2 = 0.82$, $r_2^2 = 0.88$). Two biological half-lives of 160 and 720 days were calculated. Our results show that urinary platinum concentrations determined at 8 years after cisplatin therapy are 40 times higher than the background level (up to 0.02 μg/g creatinine). Our findings on the long-term pharmacokinetics of this anticancer agent may facilitate further studies on sites of platinum storage in the human body as well as clinical studies on the late adverse effects of cisplatin.

**Key words** Cisplatin · Pharmacokinetics · Urinary platinum

## Introduction

Environmental and occupational aspects of platinum are under growing consideration. In medical treatment the platinum-containing compound *cis*-dichlorodiammineplatinum(II) (cisplatin) is a widely used chemotherapeutic agent against various neoplasms (e.g., lung, bladder, and gastric cancers). Clinical trials have shown its particular effectiveness in testicular cancer [1, 2] occurring mainly in patients aged 25–30 years. Primarily due to the use of cisplatin, the mortality of testicular cancer has been reduced considerabely [3]. Most young patients can now be cured and seem to have a normal life expectancy. However, the follow-up of the first patients treated with cisplatin is too short for verification of such a prognosis. Acute adverse drug reactions arising after cisplatin administration, such as nausea, vomiting, and nephro- and neurotoxicity, are well known [4–6]. Long-term effects concerning neuro- or nephrotoxicity as well as secondary malignancies have been the subject of clinical research since the follow-up of the first groups of patients treated with cisplatin reached several years [7–11]. In this context it seems worth mentioning that the International Agency for Research on Cancer (IARC) recently classified cisplatin as a potentially carcinogenic agent [12]. Considering their young age and excellent prognosis, patients suffering from testicular cancer are prone to develop long-term side effects after therapy.

For purposes of risk assessment, exact knowledge about cisplatin's long-term pharmacokinetics is fundamental. Hitherto, the limits of the analytic methods have not allowed the observation of renal excretion of platinum for longer than several weeks. Therefore, only two phases of platinum clearance were known: a first half-life of 18–37 h and a second one of 44–190 h. Now a considerably more sensitive analytic method using voltammetry is available. Even background concentrations of platinum in human urine can be detected by this method [13]. Our intention was to determine the urinary platinum concentration of patients with testicular cancer at 6 months to 8 years after treatment with cisplatin.

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## Patients and methods

### Patients and sample collection

We examined 23 patients attending the regular after-cure clinic who had been treated with chemotherapeutic regimens for cancer of the testis at 150–3022 days before the investigation. All patients participating in the study gave informed consent. Their age ranged from 23 to 45 years (median, 33 years). Among the drugs used for anticancer treatment, apart from cisplatin, were bleomycin, vinblastin, etoposide, ifosfamide, and vincristine. Daily doses of cisplatin had been 20 mg/kg in 17 cases, 25 and 36 mg/kg in 1 case each, and 50 mg/kg in 2 cases. The total dose of cisplatin at the end of the therapy ranged between 180 and 2253 mg as individually adapted according to body surface area, risk classification, and adverse drug effects. Two patients had been treated a second time for relapse (patients 8 and 12) at 5 and 3 years after primary therapy, respectively. In these cases the follow-up period was calculated beginning at the last day of their second therapy, the total dose reflecting the sum of the primary and the secondary treatment. At the time of the investigation, all patients were either in complete remission or showed no evidence of disease. Renal function, screened by measurement of serum creatinine, as well as blood urea nitrogen (BUN) and serum electrolyte values were normal in all patients. One blood sample and single-spot urine specimen were collected from each patient.

### Platinum determination

In quartz vessels, 0.2 ml urine, 5 ml ultrapure water, 100 µl sulfuric acid (96% Merck Suprapur) and 300 µl hydrogen peroxide (30%, Merck Suprapur) were irradiated for 2 h in a 705 UV Digestor (Metrohm). After photolysis the total amount was poured into a voltammetric vessel to which 1 ml of supporting electrolyte (72 mmol sulfuric acid, 0.67 mmol formaldehyde, and 0.3 mmol hydrazine sulfate in a 100-ml flask) was added. The determination of platinum concentrations was performed by a voltammetric method [13]. The detection limit of this method is 2 pg platinum. The recovery rates of spiked urine samples (10 pg) were in the range of 93%–104%. Variation coefficients of replicates were typically in the range of 5%–10%.

### Statistical analysis

Correlation and regression analysis were performed using the SPSS statistical package; the determination of half-lives is described in detail below.

## Results

Urinary platinum levels detected in all 23 patients are given in Table 1. In a previous study we had found a strong dependence of platinum excretion on urinary creatinine concentration [13]. Therefore, platinum concentrations were expressed on the basis of creatinine values. The absolute Pt values ranged between 0.74 and 77.24 µg/g creatinine. Depending on the risk classification, body surface area, and complications arising during therapy, the total doses of cisplatin differed in the study group (Table 1).

Taking this into consideration, we related the current platinum excretion to the total cisplatin dose in milligrams. Assuming first-order kinetics of renal excretion, we transformed these data by natural logarithm. In Fig. 1 the log of urinary platinum concentration is plotted against the time

**Table 1** Patients' data and urinary platinum results

| Patient | | Total dose of cisplatin (mg) | Days since administration | Urinary platinum (µg/g creatinine) |
|---|---|---|---|---|
| Number | Age (years) | | | |
| 1 | 43 | 800 | 150 | 77.24 |
| 2 | 26 | 525 | 306 | 30.49 |
| 3 | 33 | 350 | 376 | 5.65 |
| 4 | 24 | 580 | 621 | 11.63 |
| 5 | 37 | 830 | 625 | 11.06 |
| 6 | 23 | 900 | 642 | 10.70 |
| 7 | 40 | 850 | 698 | 7.46 |
| 8 | 38 | 1070[a] | 710 | 5.12 |
| 9 | 31 | 800 | 752 | 5.31 |
| 10 | 28 | 920 | 921 | 12.62 |
| 11 | 31 | 600 | 978 | 5.94 |
| 12 | 33 | 2253[b] | 1077 | 16.18 |
| 13 | 33 | 220 | 1194 | 1.67 |
| 14 | 33 | 180 | 1351 | 0.90 |
| 15 | 26 | 1200 | 1929 | 3.49 |
| 16 | 26 | 800 | 1971 | 1.93 |
| 17 | 37 | 1070 | 2063 | 4.18 |
| 18 | 34 | 1290 | 2392 | 2.47 |
| 19 | 28 | 1080 | 2488 | 2.10 |
| 20 | 39 | 390 | 2747 | 0.74 |
| 21 | 45 | 826 | 2760 | 1.77 |
| 22 | 33 | 1735 | 2816 | 1.73 |
| 23 | 34 | 875 | 3022 | 1.50 |

[a] 470 mg in 1987
[b] 1635 mg in 1988

since the last cisplatin treatment. There appear to be two phases of excretion, one phase lasting for 900 days and a second, much slower phase. Statistical analysis reflected excellent fitting of the data obtained by single-spot urine samples with $r_1^2 = 0.85$ and $r_2^2 = 0.88$, respectively ($P < 0.0001$).

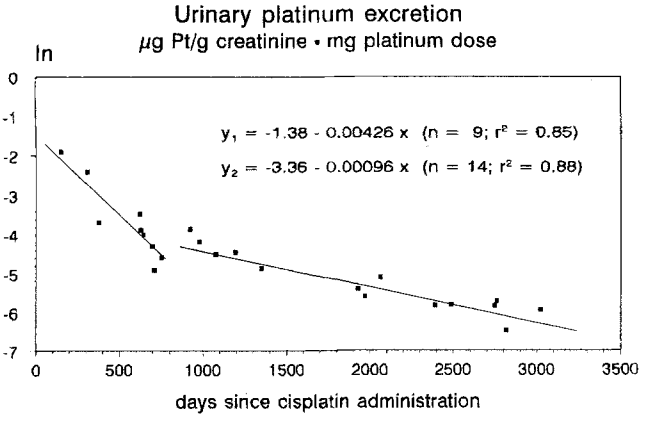
Regression analysis and the basic equations of decay

$$P/P_0 = a_1 \times \exp(-k_1 t) + a_2 \times \exp(-k_2 t) \text{ and} \quad (1)$$

$$K = \ln 2/T_{0.5} \quad (2)$$

allowed the calculation of half-lives. In an approximation, we neglected the first term in Eq. 1 for $t > 900$ days and the second term for $t < 900$ days. This approach results in Eq. 3:

**Fig. 1** Logarithmic plot of time-dependent platinum excretion



$$P/Po = 0.25 \exp(-\ln 2 \cdot t/160) + 0.035 \exp(-\ln 2 \times t/720). \quad (3)$$

Thus, the two long-term biological half-lives of 160 and 720 days represent a platinum pool of nearly 30%, which is in agreement with the observation that most of the delivered cisplatin dose is excreted in the first few days.

On the basis of a biological half-life of 720 days, we calculated the current urinary platinum concentration of individual patients from 18 months after therapy onward as follows:

$$Pt_c = Pt_{dose} \times e^{-(3.36 + 0.00096 \times t)}, \quad (4)$$

where $Pt_c$ is the current platinum (excretion expressed in micrograms per gram of creatinine), $Pt_{dose}$ is the total amount of Pt applied (expressed in milligrams), and $t$ represents the number of days since the last administration.

From a delivered dose of 800 mg cisplatin (500 mg platinum), approximately 1000 µg is left in the "long-term excretion pool" after 3000 days (Eq. 3). This explains a daily urinary excretion of 1 µg after 8 years.

## Discussion

An appropriate technique for the determination of urinary platinum that is sensitive enough for measurement of natural background concentrations has been available for only a few years [14, 15]. Background values have been found to range from 1 to 20 ng Pt/l urine [13–16]. Other investigators [15] report 20–920 ng Pt/l for people living in Sydney, which seems to be a rather high upper limit. Men occupationally exposed to platinum dust (e.g., manufacture of catalytic converters) show urinary levels of up to 2900 ng Pt/l. As compared with these data, the absolute platinum levels determined in the present study appear rather high, even at 8 years after therapy. Occupational exposure to platinum leads to a constant inhalative platinum intake, whereas therapeutic intravenous application causes high blood levels over a short, defined period. Although these two situations are not comparable from a toxicological point of view, it is interesting that the platinum burden of patients treated with cisplatin exceeds that of occupationally exposed persons, even at several years after therapy.

To date, a two-phase kinetic pattern of biological excretion for cisplatin has been postulated. A first half-life of 14–18 [17] or 18–37 min [18] and a second one of 15–190 [11] and 44–190 h [18] have been estimated. Some authors obtained results inconsistent with these and expected a third, longer biological half-life [19, 20]. Our findings confirm this assumption; however, we postulate at least a four-phase kinetic pattern. Between 31% and 85% of the cisplatin dose is excreted during the first 51 days via the two fast phases [20]. Due to this large biological variability, exact calculation of the long-term pool is not possible. Analysis of our data showed that a remaining level of platinum amounting to less than 5% of the total dose would explain our longest half-life of 720 days.

The question as to whether platinum is stored in specific compartments (e.g., the kidney or muscle) or is circulating remains unresolved. Due to the high detection limits, data from former pharmacokinetics studies allowed solely speculation about the involvement of a multicompartment model [21]. The analytical procedure for determination of platinum in biological materials presented herein will facilitate further pharmacokinetics studies on the compartments of platinum storage in the human body. These, again, are fundamental for the generation of hypotheses on possible sites of long-term platinum toxicity. This includes the possibility of secondary malignancy, as cisplatin has been classified as a potentially carcinogenic agent by the IARC [12]. Additional knowledge on possible locations of late adverse effects of cisplatin therapy is essential for the problem-oriented observation of patients after treatment with cisplatin. Considering their young age and good prognosis with regard to their primary disease, especially patients with germ-cell tumors may benefit from a more elaborate after-cure.

Clinical investigations aiming at a correlation of platinum excretion with manifestation of long-term cisplatin toxicity such as restrained renal function or neurologic symptoms are now also expedited. As statistical analysis shows, intra- and interindividual variability of urinary platinum concentrations in single-spot urine samples is very small. The close correlation of urinary platinum concentration with the interval since the last cisplatin treatment allows estimation of the individual renal platinum excretion over time. Furthermore, our data confirm the assumed dependence of platinum excretion on urinary creatinine concentration, in agreement with a former study [13]. This finding reveals another advantage with regard to the practical use of this method in research and clinical routine because single-spot urine samples can be used instead of 24-h samples.

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