*Case Report*

# Fatal Overdosage with Cisplatin

C. Charlier[1,*], P. Kintz[2], N. Dubois[1], and G. Plomteux[1]

[1]*Laboratory of Clinical Toxicology, University Hospital, Liege, Belgium and* [2]*Institut de Médecine Légale, Faculté de Médecine de Strasbourg, 11 rue Humann, 67000 Strasbourg, France*

## Abstract

**This paper presents a case of fatal overdosage due to an accidental massive administration (750 mg instead of 170 mg) of cisplatin, an anticancer agent, to a 63-year-old patient suffering from lymphoma. Platinum was measured in various postmortem samples by means of inductively coupled plasma mass spectrometry. Heart and peripheral blood concentrations of platinum were 1515 and 1253 µg/L, respectively. Concentrations in urine and bile were 1038 and 501 µg/L, respectively. Renal dialysis was started immediately after the end of cisplatin perfusion, when the mistake was noticed, but the patient deceased at day 16, presenting renal and hepatic insufficiency, ototoxicity, and pancytopenia.**

## Introduction

Cisplatin (Figure 1) is a widely used anticancer agent (Platinol®) administered in combination chemotherapy against a variety of tumors: colorectal cancer, uterine cancer, small-cell lung carcinoma, or recurrent lymphoma (1). Nausea, vomiting, and diarrhea are the most common nonhematologic toxic properties of the drug. Neutropenia, lymphocytopenia, and thrombocytopenia are observed in 15–30% of the treated subjects. Nephrotoxicity and ototoxicity seem clearly related to plasma concentration of platinum 12 or 24 h after the end of the perfusion (2), even if pharmacokinetic data depends on the way cisplatin is administered (3) and on the renal function of the patient. After cisplatin infusion, platinum accumulates in different organs, and peak platinum levels (reached after 90–150 min) decline in a triphasic manner in all blood compartments ($T_{½}$ α: 13 min, $T_{½}$ β: 43 min, and $T_{½}$ δ: 7776 min) (2,4). The clearance and volume of distribution for all platinum species are significantly related to body surface area of the patient (5). Usual doses are 60–140 mg/m², with intravenous constant infusion for 90 min for 3–5 consecutive days every 3 weeks (5,6), but the optimal administration schedule of cisplatin is still controversial (1). Cisplatin can be pharmacokinetically monitored by measurement of parent compound in blood (therapeutic range 1000–5000 µg/L) (7) or by platinum determination in whole blood, plasma, or plasma ultrafiltrate. Platinum concentrations in whole blood are highly related to administration schedule and body surface area but should not be higher than 5000 µg/L because toxicity can occur even at therapeutic level (2,7). Free platinum can be detected in blood at low levels for up to three months after last administration, and platinum quantitation before a new administration is recommended to avoid a cumulative toxicity (2). If platinum quantitation is not available, hematological formula has to be controlled. Moreover, the residual nephrotoxicity after the last cisplatin treatment can be appreciated by serum creatinine and creatinine clearance determinations (8).

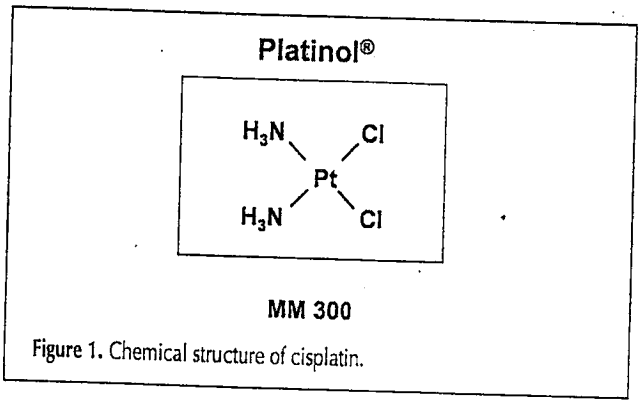


Figure 1. Chemical structure of cisplatin.

## Case History

This paper presents a case of fatality due to the accidental administration of 750 mg cisplatin instead of 170 mg to a 63-year-old male treated for a recurrent lymphoma. The patient was hospitalized for the third course of cisplatin therapy when the error occurred. Immediately after perfusion, the mistake was noticed and the patient was transferred in the nephrology department for dialysis. After a first extra-renal dialysis cycle, the patient was admitted to the intensive care unit for repeated renal dialysis. At admission, his Glasgow score was 15, and hemodynamic parameters were normal. *N*-Acetylcystein was administered as adjuvant therapy. On day 2, serum creatinine was increased and patient complained of ototoxicity. On day 3, severe alteration of visual field was noticed, and the patient be-

* Author to whom correspondence should be addressed: Dr. Corinne Charlier, Laboratoire de Toxicologie Clinique, Tour II, 5ème étage, CHU du Sart-Tilman, B-4000 Liège, Belgique. E-mail: C.CHARLIER@chu.ulg.ac.be.

came completely deaf and finally blind at day 6. Hepatic cytolysis was moderate, but a severe hematotoxicity appeared at day 5 with thrombopenia (< 20,000/µL) and neutropenia (< 2000/µL). Due to anemia, globule transfusion and erythropoïetin administration were started at day 5. Despite repeated plasmapheresis, the patient developed septicemia at day 8. Antiobiotherapy was immediately started and was successful. An important polypnea appeared and the patient was intubated at day 10. Coma occurred at day 11, and only sedative treatments were continued. The patient deceased at day 16. Autopsy findings were unremarkable. Cardiac and femoral blood, urine, and bile were sampled for toxicological investigations.

## Toxicological Analysis

Antemortem determinations of cisplatin in blood were carried out by high-performance liquid chromatography (HPLC) (9) and are presented in Table I. After perfusion and just before renal dialysis, the cisplatin concentration exceeded the highest therapeutic level by approximately 2 times. Autopsy samples were analyzed for general unknown using head-space gas chromatography (GC), GC–mass spectrometry (MS), and liquid chromatography–diode array detection (LC–DAD), with a special focus for alcohol, benzodiazepines, carboxyhemoglobinemia, and opiates. Alcohol was undetectable in both blood and urine, and carboxyhemoglobinemia was strictly normal. Midazolam was identified in postmortem blood by LC–DAD and quantitated at 563 ng/mL, which is higher than the therapeutic concentration but compatible with emergency doses. Morphine was detectable in blood (free morphine: 288 ng/mL) and in urine (total morphine: 351 ng/mL). Despite higher than therapeutic concentrations, these levels are in agreement with the palliative treatment started at day 11. Platinum was quantitated in autopsy samples by inductively coupled plasma-MS (ICP-MS) on an Agilent 7500a (Palo Alto, CA) apparatus. The ICP conditions are listed in Table II. Sample preparation consisted of 20-fold dilution of 500 µL whole blood with nitric acid (0.5%), *n*-butanol (0.2%), and triton (0.1%) in ultrapure water. Rhodium was used as internal standard (Sigma R8134, Bornem, Belgium). All reagents were of analytical grade. The five-point standard curve of calibration showed a good linearity ($r = 0.9994$) over the concentration range tested (10–5000 µg/L). The limit of quantitation (10 times the background noise at *m/z* 195) was 10 µg/L. Within-run accuracy and precision, measured at 1000 µg/L (10 replicates), were 8.9 ± 1.6% and 6.5 ± 2.3%, respectively.

**Table I. Antemortem Blood Concentrations of Cisplatin from Day 1 to Day 10**

| | Cisplatin Concentration (µg/L) |
|---|---|
| Day 1 at the end of perfusion | 8570 |
| Day 1 just before renal dialysis | 7470 |
| Day 5 | 3130 |
| Day 10 | 1500 |

**Table II. ICP Instrumental Parameters**

| | |
|---|---|
| RF generator power | 1.38 kW |
| Plasma gas flow rate (argon) | 1.17 L/min |
| Observation height (above load coil) | 8.2 mm |
| Observation time | 11.1 s (0.5 s/point) |
| Pt *m/z* | 195 |
| Rh *m/z* | 103 |

## Results and Discussion

Usually, platinum concentrations in plasma have to be monitored after cisplatin therapy, before a new drug administration, in order to prevent nephrotoxicity and accumulation of platinum in tissues. It has been previously reported that plasma platinum concentration decreased to below the detection limit three months after the final dose (10), which is correlated with the cumulative toxicity of the drug. ICP-MS technique was validated to quantitate platinum in various samples and provides a good sensitivity and an excellent specificity together with the ease of sample preparation.

To our knowledge, this case report represents the first accidental fatal outcome by cisplatin poisoning ever published. Results are presented in Table III. The platinum concentrations reported here are in agreement with the case history, and analytical results only confirm the clinical conclusions. Nephrotoxicity of cisplatin is known to be associated with platinum concentration in blood 12 or 24 h after the end of the perfusion (2,11). Even if the reported platinum concentrations are included in the therapeutic range, it is clear that these values are postmortem results and that two weeks had occurred since the last cisplatin perfusion. Antemortem cisplatin measurements found in this case were associated with acute drug poisoning, and clinical events observed in this case are clearly related to the massive administration of cisplatin. Ototoxicity and visual alterations both occurred during the first 48 h. Renal insufficiency, with elevation of serum creatinine, was observed in the same time and was not corrected by renal dialysis. Hematotoxicity appeared later, concerning all the blood cells. Only hepatic necrosis was moderate; this is in agreement with the reported observation (3) that intravenous administration of cisplatin did not result in high accumulations of platinum in the liver. Quantitation of platinum in the liver of the patient after death should have been interesting to confirm this hypothesis.

**Table III. Platinum Concentration in Autopsy Samples**

| | Platinum Concentration (µg/L) |
|---|---|
| Heart blood | 1515 |
| Peripheral blood | 1253 |
| Urine | 1038 |
| Bile | 501 |

The postmortem findings and case history are consistent with the death of this man due to cisplatin toxicity. Renal failure occurred despite repeated renal dialysis, and hematotoxicity was severe. Plasmapheresis appeared to be without clinical benefit, despite other existing reports concerning accidental cisplatin overdose corrected by plasmapheresis (12,13), followed by intranenous hydration and sometimes kidney transplant (13). The poor efficacy of therapeutic means can be related to the poor condition of the patient; it is possible that the cancer disease of the patient also played a role in his death. Moreover, granulocyte-macrophage colony stimulating factors were used to ameliorate myelosuppression in other massive cisplatin overdoses (12,13) but were not in the present reported case. Finally, the fact that the patient was treated with cisplatin for more than one year may have contributed to accumulation of platinum in tissues, with a significant release of the drug in blood caused by cellular necrosis at the time of overdose. This can explain the poor apparent efficacy of renal dialysis and plasmapheresis.

The medical cause of death was attributed to acute cisplatin toxicity, and the manner of death was accidental.

## Acknowledgment

We acknowledge C. Rivière for technical assistance.

## References

1. K. Ikeda, M. Terashima, H. Kawamura, I. Takiyama, K. Koeda, A. Takagane, N. Sato, K. Ishida, T. Iwaya, C. Maesawa, H. Yoshinari, and K. Saito. Pharmacokinetics of cisplatin in combined cisplatin and 5-fluorouracil therapy: a comparative study of three different schedules of cisplatin administration. *Jpn. J. Clin. Oncol.* **28:** 168–175 (1998).
2. T. Gougnard, C. Charlier, and G. Plomteux. Surveillance thérapeutique des traitements anticancéreux. *Immunoanal. Biol. Spec.* **15:** 258–261 (2000).
3. T. Minami, Y. Tohno, S. Tohno, M. Utsumi, M. Yamada, K. Hashii, I. Tateyama, E. Kadota, and Y. Okazaki. Tissue platinum after clinical treatment with cisplatin or carboplatin in tumor-bearing patients. *Biol. Trace Elem. Research* **58:** 77–83 (1997).
4. J. Morrison, P. White, S. McDougall, J. Firth, S. Woolfrey, M. Graham, and D. Greenslade. Validation of a highly sensitive ICP-MS method for the determination of platinum in biofluids: application to clinical pharmacokinetic studies with oxaliplatin. *J. Pharm. Biomed. Anal.* **24:** 1–10 (2000).
5. K. Hanada, K. Nishijima, H. Ogata, S. Atagi, and M. Kawahara. Population pharmacokinetic analysis of cisplatin and its metabolites in cancer patients: possible misinterpretation of covariates for pharmacokinetic parameters calculated from the concentrations of unchanged cisplatin, ultrafiltered platinum and total platinum. *Jap. J. Clin. Oncol.* **31:** 179–184 (2001).
6. E. Fokkema, H. Groen, J. Bauer, D. Uges, C. Weil, and I. Smith. Phase II study of oral platinum drug JM21 6 at first-line treatment in patients with small-cell lung cancer. *J. Clin. Oncol.* **17:** 3822–3827 (1999).
7. R.J. Flanagan. Guidelines for the interpretation of analytical toxicology results and unit of measurement conversion factors. *Ann. Clin. Biochem.* **35:** 261–367 (1998).
8. D. Stewart, C. Dulberg, N. Mikhael, M. Redmond, V. Montpetit, and R. Goel. Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods. *Cancer Chem. Pharmacol.* **40:** 293–308 (1997).
9. C. Riley, L. Sternson, and A. Repta. High-performance liquid chromatography of cisplatin. *J. Pharm. Sci.* **72:** 351–355 (1983).
10. K. Hirai, O. Ishiko, T. Sumi, Y. Kanaoka, and S. Ogita. Kinetics of platinum in hemodialysis patients receiving repeated doses of cisplatin. *Oncol. Reports* **7:** 1243–1245 (2000).
11. M. English, S. Lowis, B. Peng, A. Boddy, D. Newell, L. Price, and A. Pearson. Pharmacokinetically guided dosing of carboplatin and etoposide during peritoneal dialysis and hemodialysis. *Br. J. Cancer* **73:** 776–780 (1996).
12. H.K. Jung, J. Lee, and S.N. Lee. A case of massive cisplatin overdose managed by plasmapheresis. *Korean J. Int. Med.* **10:** 150–154 (1995).
13. G. Chu, R. Mantin, Y.M. Shen, G. Baskett, and H. Sussman. Massive cisplatin overdose by accidental substitution for carboplatin. Toxicity and management. *Cancer* **72:** 3707–3714 (1993).

Manuscript received November 13, 2002;
revision received February 20, 2003.