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Long-term pharmacokinetic behavior of platinum after cisplatin administration

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Abstract *Purpose*: The platinum concentration in plasma was studied in 19 patients treated by 3 or 4 successive courses of chemotherapy including cisplatin for head and neck cancers. *Methods*: Cisplatin was given i.v. daily at 25 mg/m^2 by 1-h infusions for 4 days every 3 weeks. Total and ultrafiltrable platinum were measured in plasma using an inductively coupled plasma mass spectrometry (ICPMS) technique. *Results*: A progressive accumulation of total platinum in plasma was observed with consecutive infusions. The mean ($\pm$ SD) total plasma platinum level detected at the end of cisplatin infusion was 1134 ± 234, 1407 ± 268, and 1618 ± 282 µg/l at the end of the first, second, and third courses, respectively. The minimal platinum concentration measured before the second and third courses also increased to 221 ± 59 and 309 ± 76 µg/l, respectively. The steady state was not reached before the third course. However, differences in the evolution of platinum plasma levels were found among the 19 patients. In 14 patients the pharmacokinetics of platinum was characterized by low initial levels, a progressive accumulation, and a long terminal half-life with a very late steady state. In 5 patients, the pharmacokinetic behavior of platinum was different: platinum levels were directly high, without progressive accumulation, the steady state being reached as early as the first course. Significant levels of ultrafiltrable platinum were found throughout the treatment, even during the intervals between courses with this very sensitive analytical method. A close equilibrium between ultrafiltrable and total platinum (ratio, 6%) persisted for as long as 3 weeks after cisplatin administration. *Discussion*: These results underline the importance of individual differences in platinum metabolism. The relationship between total and ultrafiltrable platinum are discussed.

Keywords Platinum · Total platinum · Long-term pharmacokinetics · Ultrafiltrable platinum · ICPMS

Introduction

Many studies have described the early pharmacokinetics, distribution, and elimination of platinum after cisplatin administration, but much less has been published about its long-term retention. According to the duration of sampling after the discontinuation of cisplatin administration, three or four successive exponential terms were necessary to characterize the platinum plasma decrease [2, 3, 14, 28]. The values comprised between 1 and 5 days for the third half-life and between 7 and 15 days for the fourth [6, 15, 28]. However, most studies have been hampered by a lack of sensitivity in the analytical technique, shortening the time scale of observation. Thus, most authors reported a fast and complete disappearance of ultrafiltrable platinum and concluded a dissociation of the pharmacokinetic behavior of ultrafiltrable versus bound platinum.

Inductively coupled plasma mass spectrometry (ICPMS) greatly increases the pharmacokinetic time scale for study because of its very high sensitivity and specificity. With this new technique we studied some aspects of platinum pharmacokinetics during successive courses of chemotherapy.

Patients

Patients

The 19 patients selected for the study had histologically proven head and neck cancers. Their mean age was 57 (range, 45–66) years. None

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of them had received chemotherapy before. All patients had normal renal function (creatinine clearance, > 65 ml min^{-1}, 1.73 m^{-2}), normal hepatic function, and no sign of ascites or pleural effusion. They were treated with a regimen combining cisplatin (CDDP) and 5-fluorouracil (5-FU) every 3 weeks; 25 mg/m^2 CDDP was given daily as a 1-h infusion in sterile normal saline solution at 3 p.m. every day for 4 days. Mannitol was added (250 ml, 10% mannitol solution) during CDDP injection. Patients were hydrated with 1 l of 5% glucose serum and 1 l of isotonic normal saline per day and were maintained on i.v. fluids for a minimum of 24 h after the last infusion of CDDP. 5-FU was given daily at 1 g/m^2 by 96-h continuous infusion. All 19 patients received at least 3 courses of the combination of CDDP + 5-FU, and 5 patients received 4 courses. Blood samples (5 ml) were collected into heparinized evacuated tubes at 8 a.m. and 8 p.m. every day during CDDP administration. All blood samples were centrifuged immediately and the plasma was stored at -20°C until analysis.

Methods of analysis

Instrumentation

The instrument used was a prototype from Nermag (Rueil-Malmaison, France) that consisted of an ICP source and a modified Nermag R 1010 C mass spectrometer. The plasma source was a Durr tuned-line type, 56-MHz, 1.2-kW source (Albertville, France) with a Jobin-Yvon Fassel-type torch, a Meinhard nebulizer and a Scott chamber. The flow of argon gas was controlled by a Brooks 5878 mass flowmeter with a plasma gas flow rate of 12 l/min and a nebulizer flow rate of 0.8 l/min. The mass spectrometer, a specially modified Nermag R 1010 C, was equipped with a two-cone interface, three independent pumping stages, a quadrupole inlet ion optic, a 350-mm quadrupole mass analyzer with a prefilter, and an analogue mode of detection with a photonic converter. The mass range was 0–300 u and the scanning speed was 2000 u/s.

The ions selected from platinum and europium, which was used as an internal standard, were measured at mass numbers of 194 and 195, respectively. The background signal, measured at 220.5, was automatically substracted from each ion signal by the data system, an IBM AT.

Samples

Total platinum in plasma was measured after a 20-fold dilution; up to 100 µl of plasma was added to 1900 µl of a diluent containing 1% HNO_3 and 25 µg/l of europium used as an internal standard. Free platinum, i.e., platinum not bound to plasma proteins, was determined in the supernatant obtained by ultracentrifugation for 3 h in a Beckman TL 100 ultracentrifuge. The supernatant was diluted 7-fold with the diluent before nebulization. Platinum atomic standard solution (1 g/l; Sigma) was diluted in an artificial plasma solution (Tritrisol, Merck) containing 3.3 g of Na/l, 0.15 g of K/l, 0.1 g of Ca/l, and 0.02 g of Mg/l and was used for calibrations. The diluted solutions were introduced into the nebulization chamber. The detection limit was calculated as the equivalent in concentration to 1 SD of the blank signal. The detection limit for platinum measured in water was 0.05 µg/l.

The recoveries were close to 100% since after the addition of 400 µg/l of plasma of healthy subjects the concentration found was 406 ± 15 µg/l ($n = 50$) and after the addition of 50 µg/l to a clear supernatant obtained from plasma of treated patients by ultracentrifugation the concentration found was 49.9 ± 2.8 µg/l ($n = 8$). The within-run and between-days reproducibility tested by the determination of Pt in two different plasma samples gave a narrow dispersion of results (mean ± SD): 679 ± 4 µg/l ($n = 8$) and 826 ± 16 µg/l ($n = 9$), respectively, corresponding to a coefficient of variation lower than 2%. Plasma samples were obtained from patients who were being treated with CDDP and 5-FU and who needed monitoring of their 5-FU plasma levels.

Results

The mean levels of total platinum measured in the plasma of the 19 patients increased significantly during the treatment, reaching the following values at the end of the first, second, third, and fourth courses: 1134 ± 284, 1407 ± 268, 1618 ± 282, and 1769 ± 320 µg/l, respectively (Fig. 1, Table 1). The values were statistically significantly different (Student's paired t-test, $P = 0.001$). The extreme values were 831 and 1709 µg/l for the first course, 1065 and 1925 µg/l for the second one, 1179 and 2122 µg/l for the third course, and 1401 and 2168 µg/ml for the fourth one.

Residual levels measured just before the beginning of the second, third, and fourth courses were 221 ± 59, 309 ± 76, and 457 ± 66 µg/l, respectively ($P = 0.001$). The extreme values were 100 and 312 µg/l for the first couse, 136 and 431 µg/l for the second one, and 382 and 541 µg/l for the third course.

The steady state of the average platinum concentration was not reached before the end of the third couse and, for two of the five patients who received four courses, it was not reached at the end of the fourth course. The global platinum half-life estimated from only 2 points, the first being at the end of the course and the second being just before the following one, was 8 days.

The analysis of the patients' results showed different pharmacokinetic behavior (Table 2). A total of 14 patients had low initial platinum levels, which significantly increased from one course to the next ($> 10\%$). Final platinum levels measured at the end of the first, second, third, and fourth courses were 1032 ± 218, 1412 ± 276, 1695 ± 287, and 1768 ± 320 µg/l respectively ($P < 0.002$). Minimal levels determined at the beginning of the second, third, and fourth courses were 206 ± 60, 334 ± 63, and 481 ± 53 µg/l, respectively ($P = 0.001$). The plasma platinum steady state was not reached by the third course. The global plasma half-life determined from two points was 7.5 days at the first couse, 9 days at the second course, and 10 days at the third course. The other 5 patients had constant final platinum levels at the end of the first, second, and third courses (1399 ± 279, 1388 ± 278, and 1435 ± 177 µg/l, respectively) as well as constant residual concentrations before the second and third courses (258 ± 38 and 243 ± 70 µg/l, respectively). The plasma platinum steady state was reached at the first course. The global plasma platinum half-life was 7.5 days.

As shown in Fig. 2, the evolution of the total platinum concentrations differed between the two groups (Table 2). Final platinum levels measured at the frist course were significantly higher for the 5 patients

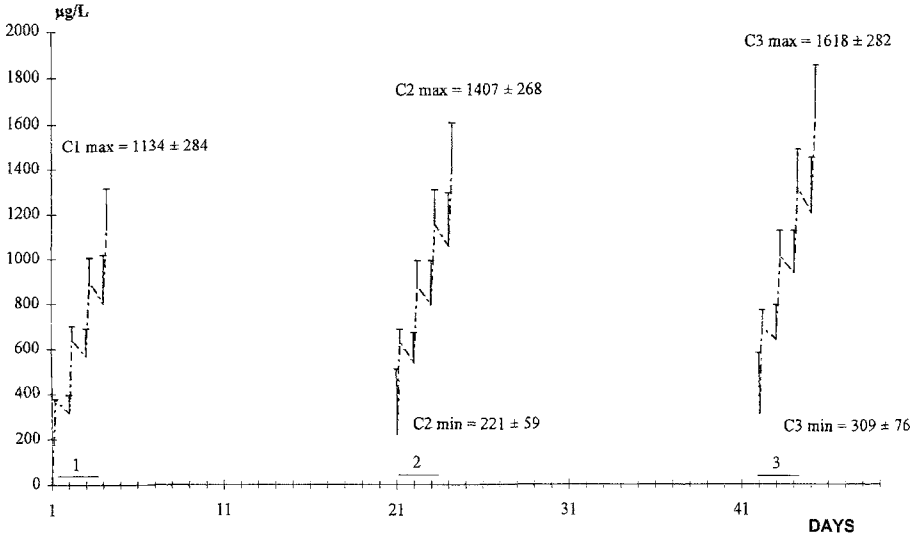

Fig. 1 Mean total platinum levels measured during 3 courses of cisplatin treatment in 19 patients. Standard errors represent only in the upper range

Table 1 Mean (± SD) plasma levels of total platinum measured in 19 patients over 3 courses of cisplatin therapy[a]. Plasma assays were performed twice a day during 3 courses. Plasma platinum levels increased statistically significantly at the second and third courses. The steady state was not reached after 3 courses for 5 patients

	Day 1		Day 2		Day 3		Day 4	
	8 a.m.	8 p.m.	8a.m.	8 p.m.	8 a.m.	8 p.m.	8 a.m.	8 p.m.
First course	0	377 ± 81	314 ± 64	635 ± 125	565 ± 107	897 ± 219	800 ± 181	1134 ± 284
Second course	221 ± 59	624 ± 136	533 ± 111	878 ± 197	793 ± 152	1152 ± 238	1054 ± 197	1407 ± 268
Third course	309 ± 76 ($P = 0.001$)	691 ± 155	635 ± 115	1000 ± 189	933 ± 170	1313 ± 247	1199 ± 228	1618 ± 282 ($P = 0.001$)
Fourth course (5 patients)	457 ± 66	851 ± 219	767 ± 218	1149 ± 243	1057 ± 217	1478 ± 226	1347 ± 194	1769 ± 277

[a]Data are expressed in µg/l

versus the other 14 patients (1399 ± 258 versus 1032 ± 218 µg/l; $P < 0.001$). In contrast, at the end of the third course the platinum levels of the 14 patients were significantly higher than those of the 5 patients (1695 ± 287 versus 1435 ± 177 µg/l, $P < 0.01$).

The ultrafiltrable platinum levels varied widely during the intervals between courses. They ranged from a minimum of 110 µg/l at the end of a course to a maximum of 5 µg/l at the end of an interval between courses. Significant levels of ultrafiltrable platinum, ranging from 5 to 25 µg/l, were detected until 18 days after cisplatin administration. The amount of ultrafiltrable platinum was always proportional to the amount of total platinum, whatever the concentration of total platinum in plasma and whatever the time of sampling (Fig. 3). The coefficient of correlation between ultrafiltrable and total platinum was 0.978 ($P < 0.001$) . The mean percentage of ultrafiltrable versus total platinum was 6%. It increased slightly with the amount of total platinum, from 3% to 7%, with a significant positive correlation ($r = 0.63$; $P < 0.01$).

Discussion

To our knowledge, this is the first study based on results obtained using ICPMS as the analytical method. The main advantage of ICPMS over other methods, particularly electrothermal atomic absorption spectrometry, is its higher sensitivity, enabling the detection of very low levels of platinum.

Taking all data into account, in agreement with some previously published reports, we found a highly significant increase in total platinum during three or even four courses [5, 7, 13]. Residual plasma platinum concentrations determined between the courses were very high, ranging from 100 to 312 µg/l after the first course, from 136 to 431 µg/l after the second course and from 382 to 541 µg/l after the third course. As the global mean platinum half-life determined from two points remained apparently constant for the whole period of treatment, it could be supposed that a decrease in the initial volume of distribution was responsible for the

Table 2 Mean (± SD) plasma levels of total platinum recorded over 3 courses of cisplatin therapy for groups I and II[a]. The profiles of the plasma platinum curves allowed us to distinguish between the 2 groups of patients. Group I had low initial concentrations, which progressively increased to become higher than those of group II, which rapidly reached the steady state. The differences were statistically significant at the beginning and the end of each course, according to Student's *t*-test

		Day 1		Day 2		Day 3		Day 4	
		8 a.m.	8 p.m.	8a.m.	8 p.m.	8 a.m.	8 p.m.	8 a.m.	8 p.m.
First course	Group I ($n = 14$)	0	361 ± 85	305 ± 71	596 ± 117	538 ± 103	896 ± 206	750 ± 170	1032 ± 218 $P < 0.001$
	Group II ($n = 5$)	0	436 ± 68	346 ± 42	780 ± 139	666 ± 95	1126 ± 189	986 ± 150	1399 ± 258
Second course	Group I	206 ± 60 $P < 0.01$	600 ± 121	508 ± 97	862 ± 201	779 ± 160	1142 ± 249	1043 ± 206	1412 ± 276
	Group II	260 ± 38	712 ± 177	626 ± 134	937 ± 207	846 ± 140	1188 ± 227	1092 ± 191	1388 ± 243
Third course	Group I	334 ± 63 $P < 0.01$	691 ± 168	643 ± 105	1000 ± 194	947 ± 169	1336 ± 268	1210 ± 245	1695 ± 287 $P < 0.01$
	Group II	269 ± 70	726 ± 130	605 ± 115	1000 ± 175	879 ± 133	1224 ± 124	1157 ± 148	1435 ± 177

[a]Data are expressed in μg/l

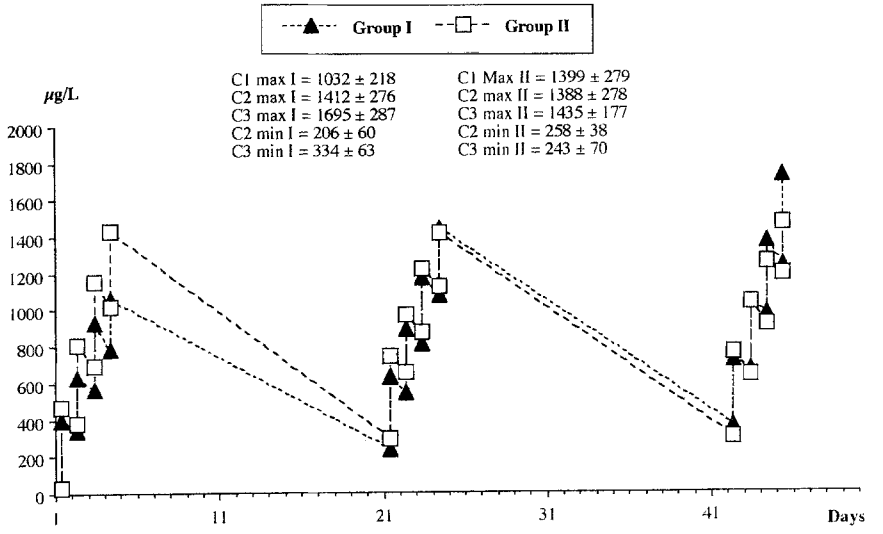

Fig. 2 Mean total platinum levels measured during 3 courses of cisplatin treatment in groups I and II. The profiles of the platinum curves differed greatly between the 2 groups of patients. In group II, plasma platinum levels reached the steady state as early as during the first course. In group I they increased continually througout the 3 treatment courses

increase in plasma platinum during the successive courses, probably because of its progressive saturation. That the plasma platinum steady state was generally not reached at the end of the third course, and sometimes, not even at the end of the fourth, suggests a very long terminal half-life, a slow storage in deep compartments, and a potential accumulation with consecutive infusions [26].

Among the 19 patients studied, the pharmacokinetic characteristics of 5 patients differed from those of the other 14. Instead of very low initial platinum levels and a progressive plasma platinum accumulation, they directly presented significantly higher platinum levels ($P < 0.001$) with constant residual plasma levels. The platinum plasma steady state was obtained as early as the end of the first course. Consequently, there was no platinum accumulation in plasma during the entire treatment period. At the end of the treatment, the final platinum levels of the 14 patients were significantly higher ($P < 0.001$). Our results are in agreement with those of Gullo et al. [15], who also reported high variations in the volume of distribution of platinum in a small group of patients but did not distinguish between two populations. These results imply different pharmacokinetic behavior of platinum. The platinum volume of distribution should be very different, and it could be suggested that it was higher in the 14 patients than in the 5 patients. The global half-life remained constant for the 5 patients (7.5 days) but increased with the 3 consecutive infusions for the 14 patients (7, 9, and 10 days). This result could involve variations in the volume of distribution or a reduced ability to clear platinum with repeated courses as reported [23]. These results could have some consequences

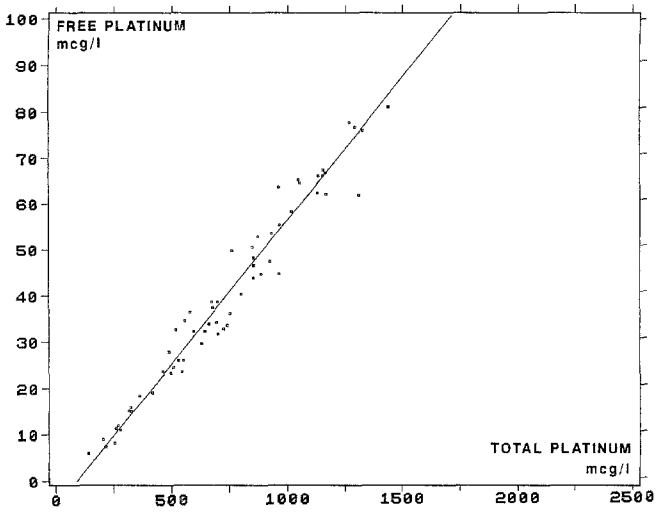

Fig. 3 Ratio of free and total platinum levels measured during 3 courses of cisplatin therapy. The highly sensitive ICPMS method enabled us to show that free and total platinum levels were strictly proportional, whatever the levels, and that free platinum persisted for the duration of the treatment period

in practice, but the treatment period was too short for the observation of chronic toxicity [7, 16, 78].

The application of ICPMS to the determination of platinum in biological samples had seldom been described [25, 26]. Previous studies showed the remarkable senstivity of ICPMS, which permitted the measurement of platinum at 0.6 μg/l [25]. Our technique allowed us to measure platinum at 0.05 μg/l and, therefore, to detect even physiological levels [1]. A previous study compared ICPMS with graphite-furnace atomic absorption spectrometry (GFAAS) [26]. The results were in good agreement for levels of > 6 μg/l; but all characteristics were better with ICPMS, especially the sensitivity. It allowed an extension of the time scale for the study of the distribution and retention of platinum.

We detected significant ultrafiltrable platinum levels at 18 days after cisplatin infusion. The range of levels was between 5 and 25 μg/l, which were always greater than physiological levels (< 0.5 μg/l) [1]. Hence, our results differ from those of previous studies, during which the disappearance of ultrafiltrable platinum species was quick and complete after 3 h [4, 11, 13, 21, 28–30].

A monoexponential and, rarely, a biphasic decline in ultrafiltrable platinum concentration has been described with a terminal half-life of about 25–200 min [21, 28, 30]. In all, 96% of the platinum was bound to plasma proteins after 24 h [22]. The irreversibility of the binding was mainly affirmed by in vitro studies based on the release of platinum from plasma preincubated with cisplatin [28]. Some authors have reported two distinct, types of pharmacokinetic behavior for the two species. In fact, they had to limit the duration of their studies to 2 or 3 h after cisplatin administration because of the lack of sensitivity of their analytical methods [16, 28–30]. However, observation of the plasma platinum curves in some articles showed that the free platinum concentration followed the bound platinum level until it disappeared because of the limit of detection. Our study showed that the concentration of ultrafiltrable platinum was proportional to the concentration of total platinum for the duration of the treatment and that the percentage increased in a narrow range of values with the amount of total platinum. These results strongly suggest a close equilibrium between ultrafiltrable and total platinum, and it may be that the link of platinum to the proteins is not irreversible as is usually reported [28]. It appears artificial to consider ultrafiltrable and total platinum separately.

ICPMS coupled with ultracentrifugation measures ultrafiltrable platinum, which consists of non-protein-bound intact drug and metabolites. Several low-molecular-weight metabolites were found with liquid chromatography, especially cysteine-, methionine- or glutathione-platinum complexes [8, 20]. ICPMS cannot distinguish unchanged cisplatin from its metabolites, but thus far no sensitive analytical technique has been capable of elucidating the chemical composition of the metabolites and of determining the extent to which cisplatin and its metabolites contribute to the antitumor activity and/or toxic side effects. Thus, ultrafiltrable platinum is usually thought to represent all species with antitumor and toxic properties. When it becomes undetectable, plasma platinum levels are thought principally to represent platinum irreversibly bound to plasma proteins, which is considered to have little therapeutic or toxic effect [8, 9]. As we could detect significant ultrafiltrable platinum levels for the duration of the treatment that were proportional to the amount of total platinum, the question arises as to whether ultrafiltrable platinum is composed exclusively of metabolites, active or inactive, or whether it might also contain free platinum with therapeutic or toxic potential. High-performance liquid chromotography coupled with ICPMS could help to answer this question and to improve our understanding of the relationship between platinum species and their antitumor activity and chronic toxicity [8, 10, 12].

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