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Correlation between free platinum AUC and total platinum measurement 24 h after i.v. bolus injection of cisplatin in humans

C. Fournier, P. Vennin, and B. Hecquet

Laboratoire de Pharmacodynamie Clinique, Centre Oscar Lambret, B.P. 307 F-59020 Lille Cedex, France

Summary. The plasma kinetics of platinum after i.v. bolus administration of cisplatin was determined for 17 patients with advanced cancer. Statistical analysis of individual values revealed a high correlation between the area under the plasma concentration-time curve (AUC) of free platinum (unbound to proteins) and the concentration of platinum bound to plasma proteins 24 h after drug administration (C_{p24}). A similar correlation was found between the peak plasma values of ultrafiltrable platinum (C_{p0}) and C_{p24}. When studied in the same patient, increases in free platinum AUC and C_{p0} were also found to result in increased C_{p24}. It is suggested that a single measurement of plasma platinum concentration 24 h after i.v. infusion of cisplatin could be a simple method either of detecting patients with extreme values of AUC and C_{p0} or of studying the evolution of these parameters during multiple courses of treatment, although it cannot be used to give precise values for AUC and C_{p0}.

Introduction

The toxicity of cisplatin seems to be related to some extent to the circulating non-protein-bound fraction [1, 3, 4, 11], and on account of the interindividual variability in drug distribution this could justify pharmacokinetic monitoring of the free drug, particularly when high doses are administered or when the drug is given repetitively (in several courses).

But determination of the clinical pharmacokinetics of free platinum involves limitations. Since cisplatin is rapidly bound to plasma proteins, blood samples must be centrifuged immediately they are taken and then ultrafiltered to separate protein-bound platinum from ultrafiltrable platinum. Accuracy of blood sampling times is also an important factor and requires continuous surveillance, at least during the first 2 h after the end of the infusion. These requirements may then act as barriers precluding the routine use of pharmacokinetic monitoring. Therefore, the current study was designed in order to look for an easily measurable parameter which might reflect the pharmacokinetics of ultrafiltrable platinum and avoid expensive and time-consuming standard methods of determining the pharmacokinetics.

Offprint requests to: B. Hecquet

Methods

Cisplatin administration. Cisplatin was given i.v. as a 30-min infusion in normal saline solution to 17 patients with advanced cancer of the uterine cervix, 15 receiving 100 mg/m^2 and 2 (patients 10 and 11) 50 mg/m^2. All patients had normal renal function and were hydrated with normal saline solution i.v. 4 h before cisplatin infusion (21) and 6 h after cisplatin infusion (21). Mannitol was added (250 ml 10% mannitol solution) 30 min before and 30 min after cisplatin injection. Cisplatin was also injected via the hypogastric arteries in 9 of these patients according to the same protocol.

Blood samples were drawn into heparinized tubes at 5, 10, 30, 60, 90, 120, 150 and 180 min after the end of the infusion for 10 patients. Accurate adjustment between experimental values and a first-order pharmacokinetic model allowed a reduction of the number of sampling times for the 7 other patients. After centrifugation at +4°C, plasma samples were ultrafiltered through Amicon Centriflo CF50A cones (molecular weight cut-off = 50000 daltons) to separate ultrafiltrable platinum and protein-bound platinum. Blood samples were also drawn 24 h after the end of the infusion for total platinum determination.

Platinum analysis. Plasma and ultrafiltrates were digested in nitric acid (1 h at 100°C). After evaporation of the acid, platinum was measured by flameless atomic absorption spectrophotometry (FAAS) according to the methods previously described [6, 8].

Pharmacokinetic analysis. Curves of ultrafiltrable platinum versus time were analysed using the iterative CFT4A computer program [9]. Standard pharmacokinetic equations were used to calculate t½, AUC and C_{p0}.

Statistical analysis. Correlations between pharmacokinetic parameters were checked by using the Spearman rank correlation coefficient (R) and the linear correlation coefficient (r) with regression analysis.

Results

The disappearance of ultrafiltrable platinum from plasma after the end of the i.v. infusion in all 17 patients was well described by a mono-exponential model, and the pharmacokinetic parameters obtained are shown in Table 1.

Table 1. Pharmacokinetic parameters after i.v. administration

Patient	AUC (mg · h l^{-1})	C_{p0} (mg · l^{-1})	C_{p24} (mg · l^{-1})
1	3.98	4.67	2.61
2	3.59	2.87	1.09
3	2.94	2.95	0.99
4	4.06	4.83	2.34
5	4.09	4.04	2.22
6	3.61	3.74	1.8
7	6.84	6.45	2.52
8	1.75	2.61	1.3
9	4.17	3.67	2.37
10	0.75	0.97	0.6
11	0.67	0.94	0.62
12	2.69	2.84	2.54
13	1.8	1.91	1.45
14	3.38	4.34	2.3
15	5.14	5.66	3.1
16	4.39	4.04	2.2
17	3.72	3.56	1.51

Mean values were t½ = 39.1 ± 6.3 min, AUC = 3.3 ± 1.5 mg h l^{-1}, and C_{p0} = 3.5 ± 1.4 mg l^{-1} for platinum in the ultrafiltrate. These results are in good agreement with those previously published by other authors [1, 5, 7, 12]. Total platinum (C_{p24}) was measured in the plasma 24 h after the end of the infusion (Table 1). The mean value for plasma platinum level after 24 h was 1.85 ± 0.75 mg l^{-1}. No correlation was found between t½ and C_{p24}.

In contrast, analysis of the relation between AUC of ultrafiltrable platinum and C_{p24} revealed a highly significant Spearman correlation coefficient (R = 0.70, P<0.01). Despite the scatter of experimental points (Fig. 1), this result was confirmed by linear correlation coefficient calculation (r = 0.76, P<0.001) and the equation derived from the correlation was:

$$AUC = a \cdot C_{p24} + b \; (a = 1.56 \pm 0.35, b = 0.49 \pm 0.7).$$

Similar correlations were found between C_{po} and C_{p24}: Spearman coefficient R = 0.77, P<0.001; linear correlation coefficient r = 0.84, P<0.01; equation derived from correlation (Fig. 2):

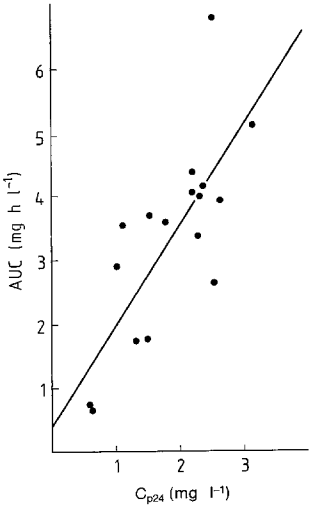

Fig. 1. Correlation between AUC of free platinum and total plasma platinum level 24 h after cisplatin administration (C_{p24})

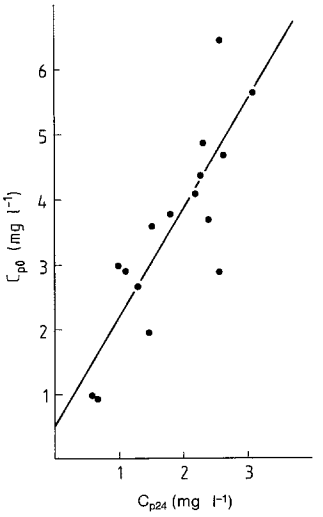

Fig. 2. Correlation between plasma peak of free platinum (C_{p0}) and total platinum level 24 h after cisplatin administration (C_{p24})

$$C_{p0} = a \cdot C_{p24} + b \; (a = 1.66 \pm 0.28, b = 0.45 \pm 0.56).$$

The modification of AUC, C_{p0} and C_{p24} as a function of a change of the route of administration was examined in 9 patients. For each patient we substracted the values obtained for each parameter after i.a. administration from those obtained after i.v. administration (ΔAUC, ΔC_{p0}, ΔC_{p24} in Table 2). For 8 patients variations in AUC and C_{p0} resulted in a variation of C_{p24} in the same direction. Nevertheless, no significant correlation was found between ΔAUC, ΔC_{p0} and ΔC_{p24} values. In 1 patient an increase in AUC or C_{p0} was observed with a decrease in C_{p24}. But it should be noted that in this case C_{p24} was so low that the accuracy of the measurement was in doubt.

Discussion

As free platinum is practically undetectable even a few hours after cisplatin infusion, it can be accepted that the total platinum measured in plasma 24 h after the end of the infusion refers to bound platinum only. Since the AUC for free platinum can provide an estimate of the plasma protein exposure to cisplatin, a correlation can be expected between the AUC and bound platinum, as suggested elsewhere [2, 10]. In a study in 17 patients, a positive and highly significant correlation was found between the total plasma platinum level (evaluated 24 h after i.v. administration) and the AUC for free platinum. A similar correlation

Table 2. Variation of the pharmacokinetic parameters with route of administration (i.a. then i.v.)

Patient	ΔAUC (mg · h l^{-1})	ΔC_{p0} (mg · l^{-1})	ΔC_{p24} (mg · l^{-1})
1	+1.249	+2.104	+0.722
2	+0.688	+0.333	−0.078
3	+1.327	+0.577	+0.273
4	+0.966	+0.785	+0.91
5	+1.294	+1.496	+1.3
6	+0.483	+0.125	+0.649
7	+0.234	+2.303	+0.195
8	+0.059	+0.273	+0.11
9	+1.195	+0.636	+1.371

was observed between C_{p24} and C_{p0}. Closer examination of the results shows that the correlations were qualitative and not quantitative. Precise values of AUC or C_{p0} could not be predicted from the C_{p24} values because of the extensive standard deviation of the regression curve coefficients (Figs. 1, 2). These results were confirmed by studying AUC or C_{p0} variations in the same patient. In most cases an increase in C_{p24} indicated an increase in AUC and C_{p0}, with no linear relation between the measured values.

On the basis of these observations we propose that platinum plasma measurement 24 h after cisplatin administration should be a rapid method of either detecting patients with extreme values for free platinum AUC and C_{p0} or evaluating the evolution of these values during multiple course treatment, although clearly it cannot be used to predict a precise value for AUC or C_{p0} in an individual patient.

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