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Renal handling of carboplatin*

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Summary. The mechanism for renal handling of carboplatin was studied in 17 ovarian cancer patients treated with a combination of carboplatin and cyclophosphamide. Carboplatin and [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA) renal clearances were measured simultaneously during short intervals of from 45 to 120 min. A total of 131 clearance intervals were analyzed during 35 chemotherapy courses. The carboplatin/[^{51}Cr]-EDTA clearance ratio (R) served as an indicator of the net tubular reabsorption (R<1) or secretion (R>1). The R value was calculated for each sampling interval. No significant difference was found between interpatient and intertreatment variation. The intertreatment variation as tested against the variation in the short intervals by an *F*-test was highly significant. We calculated the average R value for each treatment and consequently based our results on a total of 35 observations. The mean R value was 0.77 (*t*-test for R = 1; $P < 0.001$). We conclude that the renal elimination of carboplatin takes place by glomerular filtration followed by tubular reabsorption.

Introduction

The increasing clinical use of carboplatin as an alternative to cisplatin makes studies of carboplatin pharmacokinetics important for the safe administration of the drug. A high correlation has been demonstrated between the total plasma clearance of carboplatin and the glomerular filtration rate (GFR) as measured by [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA) clearance [3, 9]. Thus far, all studies have indicated that the plasma clearance of carboplatin exceeds the GFR, suggesting either nonrenal elimination or renal tubular secretion of carboplatin [3, 8, 9].

In humans, the renal elimination of carboplatin is generally believed to take place by glomerular filtration, whereas the elimination of cisplatin apparently involves a certain element of tubular secretion. Jacobs et al. [10] studied the relationship in man between the clearance of creatinine and that of cisplatin measured as free Pt at 4-h intervals. The results showed that the renal clearance of free Pt exceeded the GFR, suggesting that besides undergoing glomular filtration, cisplatin or a metabolite is secreted by the human kidney. Studies in rats suggest that renal elimination of cisplatin involves an active secretory mechanism, whereas carboplatin is eliminated by glomerular filtration alone [12].

Many studies of carboplatin pharmacokinetics have been carried out. The results concerning renal handling of carboplatin have been obtained by comparison of the GFR as measured by [^{51}Cr]-EDTA clearance or creatinine clearance with measurements of the total renal clearance of carboplatin over long periods (4–24 h) [2, 6, 8, 9, 11].

The aim of the present study was to evaluate the mechanisms underlying the renal handling of carboplatin by simultaneous measurements of renal carboplatin and [^{51}Cr]-EDTA clearances at short intervals.

Patients and methods

Patients. In all, 17 patients with epithelial ovarian cancer received carboplatin and cyclophosphamide in a randomized phase II study. None of the subjects had received prior cytostatic treatment. Their age ranged from 39 to 67 years (mean, 54.9 years). Informed consent was obtained from all patients. The pretherapeutic GFR level as determined by [^{51}Cr]-EDTA plasma clearance [1] was in the range of 49.3–118.4 ml/min. Patients with GFR values of >60 ml/min were randomized to one of the following doses of carboplatin: 250, 375, or 500 mg/m^2. One individual with a GFR value of <60 ml/min was given 250 mg/m^2. All patients received 500 mg/m^2 cyclophosphamide dissolved in 75 ml isotonic saline as a 15-min i.v. infusion. Immediately thereafter, carboplatin dissolved in 300 ml isotonic saline was infused over 60 min. A model 281 IVAC infusion pump (IVAC Corporation, San Diego, Calif.) was used to ensure a constant infusion rate. Urine samples were obtained from all

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Table 1. Time-table for plasma and urine sampling

Time after [^{51}Cr]-EDTA injection (h)	[^{51}Cr]-EDTA		Carboplatin		Event
	Plasma	Urine	Plasma	Urine	
o	x				Injection of [^{51}Cr]-EDTA
1.50					Start of the cyclophosphamide infusion
1.75			x		Start of the carboplatin infusion
2.75	x	o	x	o	
3.00			x		
3.50	x	o	x	o	
5.50	x	o	x	o	
7.50	x	o	x	o	
9.50	x	o	x	o	
11.50			x	o	
24.75			x	o	

patients via a urethral catheter. Treatment was repeated at monthly intervals. No adjustment was made in patients, usual medication prior to their entry into the study. Most subjects received antiemetic treatment with prednisone and metoclopramide.

[^{51}Cr]-EDTA analysis. Carboplatin and [^{51}Cr]-EDTA clearances were measured simultaneously on the day of chemotherapy. At 90 min before the start of cytostatic treatment, an i. v. bolus injection of 8 MBq [^{51}Cr]-EDTA was given. Plasma and urine samples for [^{51}Cr]-EDTA analysis were drawn as shown in Table 1.

The renal clearance (C_R) of [^{51}Cr]-EDTA was calculated as:

$C_R = V \times U/AUC_{t_1-t_2}$,

where V represents the volume of urine, U indicates the concentration of [^{51}Cr]-EDTA in the urine, and AUC represents the area under the [^{51}Cr]-EDTA plasma concentration versus time curve during the interval t_1-t_2.

Assuming that the clearance of [^{51}Cr]-EDTA is monoexponential at 3 h after injection, the AUC can be calculated as:

$$AUC = \int_{t_1}^{t_2} c_0 \times \exp(-k_c t)dt,$$

where c_0 represents the plasma concentration of [^{51}Cr]-EDTA at the beginning of the sampling interval $t = 0$, c_t is the plasma concentration of [^{51}Cr]-EDTA at the end of the sampling interval, and k_c is the rate constant determined as $\ln(c_0/c_t)/t$.

Carboplatin analysis. Blood and urine samples for carboplatin analysis were collected at the time points shown in Table 1. Blood samples were collected in sodium heparin-coated tubes and were immediately cooled and centrifuged. Plasma and urine samples were stored at –70° C until analysis. Samples were stored for a maximum of 4 months before being analysed.

Carboplatin concentrations in plasma ultrafiltrate and urine were determined by high-performance liquid chromatography (HPLC) using the method described by Duncan et al. [4]. Within- and between-day coefficients of variation were 5.3% and 7.7% at 10 μg/ml, respectively. The detection limit was 0.2 μg/ml (coefficient of variation, <25%). To ensure the stability of carboplatin in plasma, plasma samples containing 10 μg/ml were stored at –70° C; every time an analysis was performed, one plasma sample from the pool was thawed, ultrafiltered, and analyzed along with the patients' plasma samples. No decrease in carboplatin concentration was observed in the pool over 6 months.

In vitro stability of carboplatin in urine. Carboplatin was added to urine samples to obtain a final concentration of 200 μg/ml. The urine was incubated at 37° C. Samples were taken at 1, 2, 3, 4, 5, and 24 h and immediately analyzed for carboplatin.

Pharmacokinetic analysis. Postinfusion carboplatin plasma concentration versus time curves were fitted by the computer program GraphPad Inplot (GraphPAD Software, San Diego, Calif.) to a biexponential equation, assuming a two-compartment model for distribution and elimination of carboplatin [6]:

$$c(t) = A' \times e^{-\alpha t} + B' \times e^{-\beta t},$$

where c stands for the concentration at time t, A' and B' represent concentration constants, and α and β represent rate constants.

The AUC value from the beginning of the carboplatin infusion to infinity was calculated using the following equation [7]:

$$AUC_{0-\infty} = \frac{A'T}{1 - \exp(-\alpha T)} + \frac{B'T}{1 - \exp(-\beta T)},$$

where T represents the infusion time. The carboplatin plasma clearance was calculated as:

$$C_P = D/AUC_{0-\infty},$$

where D represents the dose. During the short intervals after the end of the carboplatin infusion, the AUC value was calculated as:

$$AUC_{(t_1, t_2)} = \int_{t_1}^{t_2} (A' \times e^{-\alpha t} + B' \times e^{-\beta t})\, dt.$$

Renal clearance (C_R) was defined as the cumulative urinary excretion (CUE) divided by the AUC measured during the same intervals.

Statistical methods. After several measurements of R had been obtained in one patient, i.e., for repeated treatments and during up to four short intervals per treatment, it was necessary to test whether all of these results could be used in the overall evaluation of R. F-tests were performed to determine whether interpatient variations exceeded intertreatment variations and whether the intertreatment variation was larger than the variation between the short intervals. A t-test was used to determine whether R was significantly different from 1. To test whether there was an association between the R value and the carboplatin plasma concentration, we used linear regression analysis.

Results

At 37° C, carboplatin degraded in urine at a mean $t_{1/2}$ value of 41.7 h (range, 37.7–47.3 h); during the collection interval (45–120 min), a maximal degradation of 4% was expected.

Simultaneous measurements of the renal clearance of carboplatin and [^{51}Cr]-EDTA during the short intervals (0–0.75, 0.75–2.75, 2.75–4.75, and 4.75–6.75 h) were performed in 17 patients during a total of 35 chemotherapy courses. In all, 131 sampling intervals were evaluable for analysis.

Carboplatin renal clearances ranged from 12 to 224 ml/min (mean, 75 ml/min), and the corresponding [^{51}Cr]-EDTA renal clearances ranged from 30 to 283 ml/min (mean, 99 ml/min). An important question arises as to whether a given patient should be used several times, i.e. during three treatments, in the overall evaluation of R. The variation in R values observed from one short

Table 2. Analysis of variance

	Sum of squares	DF	Mean square	*P* value
Between patients	1.71	16	0.107	<0.0001
Between treatments	2.32	18	0.129	<0.0001
Error	2.38	96	0.025	
Totals	6.41	130		

The test for equal variation between treatments and patients yields $F = 1.206$ (DF = 18.16), for a one-sided P-value of approximately 0.30

interval to another within the same treatment was significantly smaller than that found between different treatments and different patients. The variation in R values observed between two patients was not significantly larger than that found between two treatments for the same patient. This means that a given patient can be evaluated anew for every treatment (see analysis of variance, Table 2). Consequently, the calculation of an average R value for each course yielded 35 observations for the study of R. The mean R value was 0.77 (range, 0.45–1.32). The *t*-test for mean (R) = 1 (DF = 34) yielded a t value of 5.5 ($P < 0.001$). The distribution of R values is shown in Fig. 1. No significant correlation could be found between the R value and the carboplatin plasma concentration (range, 0–35 μg/ml).

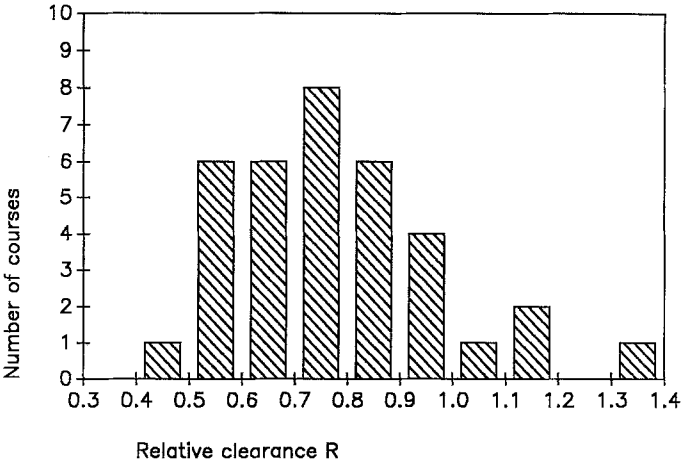

Fig. 1. Distribution of average R values calculated for 35 treatments

Discussion

We found considerable intraindividual variation across the short intervals in the renal clearance of both [^{51}Cr]-EDTA and carboplatin; this variation may have been caused by our difficulties in achieving accuracy in urine sampling. Such inaccuracy, however, affects [^{51}Cr]-EDTA and carboplatin renal clearances in the same way. Thus, the ratio between carboplatin and [^{51}Cr]-EDTA renal clearances (R) adequately describes the mechanism underlying the renal elimination of carboplatin; a value of R>1 would indicate tubular secretion of carboplatin, and a value of R<1 would indicate that tubular secretion has been balanced and exceeded by tubular backward diffusion.

The results of the present study indicate that the mechanism of renal elimination of carboplatin is mostly effected by glomerular filtration. Our finding of a mean R value that was significantly lower than 1 shows that any tubular secretion was exceeded by tubular reabsorption. In 4 of 35 treatments, the average R value was >1, indicating an element of tubular secretion. Although we do not consider this finding to represent an experimental error, we have no explanation for it, as these subjects did not differ from the other patients in terms of their medical history, medication, renal function, or hydration.

The clearance of substances that are subjected to tubular backward diffusion usually tends to increase with the urinary flow. However, proper analysis of this aspect requires very accurate urine-collection procedures (e.g., using nephrostomy catheters). As such methods were not available during the present study, any associations found cannot be regarded as reliable.

We found no correlation between the plasma concentration of carboplatin and the value of R; therefore the occurrence of strongly dose-dependent pharmacokinetics would have been unlikely at the present dose levels.

In terms of the evaluation of carboplatin renal clearance values, it should be borne in mind that carboplatin may have degraded into substances that cannot be detected by the HPLC method used in the present study. If so, this would lower the calculated clearance values and produce a R value that lies below its true level. The in vitro studies carried out by Harland et al. [9] on the stability of carboplatin in urine at 37° C demonstrated a $t_{1/2}$ value for carboplatin that ranged between 20 and 460 h. Our stability studies revealed a mean $t_{1/2}$ value for carboplatin in urine of 41.7 h at 37° C. Correction for a possible decay of carboplatin at a $t_{1/2}$ value of 20 h yielded a mean R value of 0.83; this value was also significantly less than 1 ($P < 0.01$).

Harland et al. [9] have demonstrated a ratio of 0.7 between the renal clearance of free platinum and the GFR as measured by pretreatment [^{51}Cr]-EDTA clearance. This supports the present results, as we found a ratio of 0.77 by simultaneous measurements of renal and [^{51}Cr]-EDTA clearances. The aforementioned authors conclude that the renal clearance of carboplatin does not involve a concentrative mechanism. Siddik et al. [12] have performed a study very similar to ours on the renal handling mechanism of carboplatin in rats. From their study, it appears that the ratio between the renal clearance of carboplatin and that of inulin is very close to 1, indicating that the renal elimination of carboplatin in rats does not involve net tubular secretion or reabsorption. On the basis of the present results, we conclude that carboplatin renal elimination in humans occurs via glomerular filtration followed by net tubular reabsorption.

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