Eur J Cancer Clin Oncol, Vol. 22, No. 3, pp. 257–263, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00

Pharmacokinetics of Intra-arterial and Intravenous Cisplatin in Head and Neck Cancer Patients

ALAIN GOUYETTE,*†‡ ANNIE APCHIN,§ MARIA FOKA* and JEAN-MARIE RICHARD§

*Laboratoire de Biochimie-Enzymologie (LA 147 CNRS and U 140 INSERM) and §Head and Neck Cancer Department, Institut Gustave Roussy, Villejuif Cedex, France

Abstract—*After administration of cisplatin* (50 mg/m^2 *on days* 1 *and* 2) *by intra-arterial or intravenous infusions over* 1 *or* 6 hr *to a total of* 24 *patients with head and neck cancer, the main pharmacokinetic parameters of platinum were determined according to a multicompartmental analysis. Elimination half-life of total platinum is* >3 days, *the amount of platinum recovered in the urine over* 7 days *accounting for* 15–50% *of the administered dose. The half-life of filterable platinum species was calculated from the urinary excretion data:* 39 ± 17 min (*i.a.*/1 hr), 37 ± 24 min (*i.a.*/6 hr), 58 ± 17 min (*i.v.*/1hr) *and* 51 ± 22 min (*i.v.*/6 hr). *Biopsies of the tumor were also analyzed on day* 3 *for their platinum content. The mean concentrations of platinum in biopsies were:* 2.72 μg/g (*i.a.*/1 hr), 3.89 μg/g (*i.a.*/6 hr), 1.27 μg/g (*i.v.*/1 hr) *and* 1.38 μg/g (*i.v.*/6 hr). *Tumor regression, based upon clinical and histological data, was only moderate after this single chemotherapy course.*

INTRODUCTION

CISPLATIN (CDDP) is now a well-known anticancer agent with nephrotoxic side-effects, but it gives a 20% response rate in head and neck cancers [1]. Other authors have also found some activity in these kinds of malignancies [2, 3]. More recently, a study by Wittes *et al.* [4], including a total of 73 patients with advanced head and neck cancer treated with CDDP alone (120 mg/m^2, i.v.) or in combination with bleomycin or methotrexate, indicated a tumor regression in 40% of previously untreated patients when cisplatin was given alone. The addition of bleomycin resulted in a higher response rate (70%) and responses were near-maximal after only one dose of CDDP. However, in another paper [5] Baker *et al.* wrote that response rates achieved with a single course of the cisplatin–bleomycin combination were somewhat less than those reported in trials with multiple-course therapy.

There is no unique administration protocol for this inorganic compound. Many pharmacokinetic studies have been carried out with i.v. injections over 15 min [6, 7], 1 hr [8], 6 hr [7, 9], 20 hr [8] and 5 days [10–12]. But to our knowledge there have been only a few results published using an intra-arterial infusion of cisplatin [13–15].

In this paper we report on the pharmacokinetics of platinum after intra-arterial (i.a.) and intravenous (i.v.) infusion of cisplatin over 1 or 6 hr, to 24 head and neck cancer patients divided into four groups of six subjects. Moreover, to avoid gastrointestinal toxicity (nausea and vomiting), we chose to administer cisplatin at doses of 50 mg/m^2 on days 1 and 2 accompanied with vigorous saline hydration to maintain urine output. Platinum levels were also measured in biopsies of the tumor on day 3.

MATERIALS AND METHODS

Patients

All 24 male patients had histologically confirmed epidermoid carcinoma from a primary site in the oral cavity or oropharyngeal area (Table 1). The patients were informed as to the investigational nature of the study in accordance with our institutional policy.

Protocol

Patients were divided into four groups with six subjects in each group. They were given cisplatin either intra-arterially over 1 (group A) or 6 hr (group B) or intravenously over 1 (group C) or 6 hr

Accepted 2 September 1985.
*To whom correspondence and requests for reprints should be addressed at: Pavillon de Recherche, Institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif Cedex, France.
‡Supported by the Institut Gustave-Roussy (grant CRC No. 80/A9).

Table 1. Patients' characteristics and tumor localization

	Patient No.	Age (yr)	Tumor localization	Other drugs*	Regression
	1	63	jaw	BLM, MTX	NE
	2	41	oropharynx	BLM, MTX	NE
i.a./1hr	3	61	oropharynx	none	none
	4	50	pelvilingual	none	20%
	5	50	jaw	none	30%
	6	40	oropharynx	none	30%
	7	48	jaw, gums	VCR, BLM	NE
	8	57	oropharynx	VCR, BLM	NE
i.a./6 hr	9	50	tongue	none	20%
	10	44	jaw	none	none
	11	49	oropharynx	none	none
	12	59	pelvilingual	VCR, BLM	NE
	13	43	tongue	VCR, BLM	NE
	14	59	oropharynx	VCR, BLM	NE
i.v./1 hr	15	51	oropharynx	VCR, BLM	NE
	16	66	floor of mouth	none	none
	17	48	oropharynx	none	20%
	18	35	oropharynx	VCR, BLM	NE
	19	53	pelvilingual	none	20%
	20	41	pelvilingual	none	20%
i.v./6 hr	21	52	oropharynx	none	30%
	22	46	pelvilingual	none	30%
	23	43	tongue	BLM, MTX	NE
	24	43	pelvilingual	BLM, MTX	NE

*BLM: bleomycin; MTX: methotrexate; VCR: vincristine, given 1 week after cisplatin chemotherapy. †NE: non-evaluable (combination chemotherapy).

(group D). Intra-arterial infusions were made through a catheter which was placed, under local anesthesia, into a temporal artery. At the same time, another catheter kept under heparin was inserted into the internal jugular vein (output of the blood flow from the tumor area). Intravenous administration was made into a cubital vein.

The dosage of CDDP was 50 mg/m^2 on days 1 and 2 (total dose 100 mg/m^2). Patients were hydrated for 3 days (3 l of water containing 4 g NaCl, 3 g KCl and 500 ml 20% mannitol per day).

Jugular and/or peripheral (cubital) blood samples were collected through catheters, rinsed from heparin with blood just before sampling. Those collections were made prior to drug administration, then every 15 min during the 1-hr infusions or every hour during the 6-hr infusions. After the end of the administration, samples were obtained at 5, 10, 15, 30, 60 and 90 min and 2, 3, 4, 6, 8 and 24 hr on days 1 and 2. On subsequent days (3, 4, 5 and 7) blood samples were also collected.

Urine was collected for 7 days: after each micturition during the infusion and for 6 hr following the cisplatin administration. Thereafter, urine was collected every 8 hr.

On day 3 biopsies of the tumor were analyzed for their platinum content.

Platinum analysis

Platinum assay in biological fluids and tissue samples was performed using a Perkin–Elmer 560 atomic absorption spectrophotometer (AS–1 injector and HGA 500 graphite furnace equipped with pyrocoated tubes), according to the technique described by LeRoy *et al.* [16]. Biopsies of the tumor (100–200 mg wet tissue) were digested in concentrated (≈14 N) nitric acid (0.5–1.0 ml) at 50°C. When dissolution was complete, the resulting mixture was then taken up in concentrated hydrochloric acid, transferred to a volumetric flask and adjusted to a known volume with 0.1 N HCl. This solution was analyzed for platinum content.

Pharmacokinetic analysis

Pharmacokinetic parameters were determined after fitting the experimental data (ADAPT program) according to a 3-(plasma data only) or 4-compartment model (plasma and urinary data fitted simultaneously), as described in Fig. 1. The ADAPT program has been developed by D'Argenio and Schumitzky [17] for parameter estimation of models arising from pharmacokinetic applications. It can accommodate linear and non-linear models with different inputs (no need to correct for infusion duration) and multiple outputs (plasma,

urine, etc.) defined by differential equations. The parameter values are determined using the Nelder–Mead simplex procedure. The clearance of free filterable platinum species was calculated according to the equation $Cl_{free} = V_{c\,free} \times k_{1u}$, where $V_{c\,free}$ is the apparent volume of distribution of the central compartment for the filterable species and k_{1u}, the urinary excretion rate constant of the same species.

Tumor regression

Some of the patients received cisplatin alone then subsequently underwent surgery or radiotherapy. Others received combination chemotherapy (bleomycin and vincristine or methotrexate) when our pharmacokinetic study was completed (Table 1). Tumor regression was only analyzed on the basis of clinical and histological data in the patients given CDDP alone.

RESULTS

Plasma concentrations

Peak plasma concentrations are summarized in Table 2. Total platinum plasma concentrations, measured by atomic absorption spectrophotometry, were fitted according to a 3-compartment model (Fig. 1). However, as much of this platinum is covalently bound to plasma proteins and is thus non-filterable through the kidneys, the use of a more complex model was necessary to fit simultaneously plasma concentrations and cumulative urinary excretion. On this basis we were able to estimate the plasma levels of free filterable platinum species. In Figs 2–5 we have drawn the experimental data and the results of curve fitting according to our models, for one patient in each group No. 5 (Fig. 2), No. 11 (Fig. 3), No. 16 (Fig. 4) and No. 20 (Fig. 5).

We found, as reported by several authors [8, 18], a very long terminal half-life (mean $t_{\frac{1}{2}} > 3$ days) for the elimination of total platinum. However, based upon urinary excretion, the half-life of the kidney-filterable platinum species is rather short (Fig. 2–5): $t_{\frac{1}{2}}$ = 39 ± 17 min (i.a./1 hr), 37 ± 24 min (i.a./6 hr), 58 ± 17 min (i.v./1 hr) and 51 ± 22 min (i.v./6 hr).

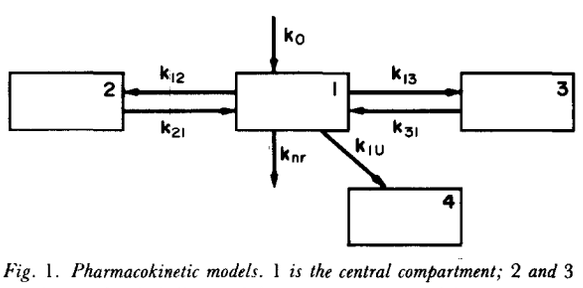

Fig. 1. Pharmacokinetic models. 1 is the central compartment; 2 and 3 are the peripheral shallow and deep compartments; and 4 is the urinary elimination compartment, k_0 is the infusion rate constant; k_{12}, k_{21}, k_{13}, k_{31} are the microscopic rate constants; k_{1u} is the urinary elimination rate constant of filterable species; and k_{nr} is the non-renal elimination rate constant.

In some patients given cisplatin i.a. we also collected several blood samples from the internal jugular vein to compare the platinum concentration profiles at the effluent of the tumor area to those in the peripheral blood. We could therefore conclude that there is a concentration gradient during the infusion period (Figs. 2 and 3).

Urinary excretion

The percentage of the dose eliminated in the urine within 7 days is given in Table 2. These figures are not different from those reported in the literature [7, 8]. Most of the amount eliminated was collected during the first hours following the infusions, which corresponded to the short half-life of the filterable species.

The renal clearance based upon the rate of excretion of the filterable species is calculated as the product of the apparent volume distribution of the central compartment for the free species and the rate constant of the renal elimination process. We found the following values: Cl_R = 63 ± 18 ml/min (i.a./1 hr), 30 ± 13 ml/min (i.a./6 hr), 57 ± 12 ml/min (i.v./1 hr) and 22 ± 16 ml/min (i.v./6 hr). Student's t test shows that there is a significant difference when the drug is administered over 1 or 6 hr ($P < 0.01$), the clearance being less when cisplatin is administered for a longer period.

Tumor biopsy platinum content

The results of the platinum assay in tumor biopsies are also given in Table 2. They are expressed in μg platinum/g wet tissue. There is a large interindividual variation so that, even if the means of platinum levels in the tumor tissue are greater when the drug is given i.a., they are not statistically different from those measured after i.v. infusions. Moreover, there is probably an heterogeneous distribution of platinum in the tumor since two biopsies were obtained from patient No. 23 at two different sites of the tumor and showed different tissue concentrations (0.89 and 1.14 μg/g).

Tumor regression

After this single chemotherapy course, for patients who received cisplatin alone, tumor regression was low (20–30% on the basis of clinical and histological data).

DISCUSSION

During this study we have investigated the pharmacokinetics of platinum after i.a. and i.v. infusions of cisplatin in head and neck cancer patients,

Table 2. Peak platinum concentrations, platinum levels measured in biopsies and urinary excretion after i.a. or i.v. infusion of CDDP

Patients	$C_{max(1)}$* jugular (μg/ml)	cubital	$C_{max(2)}$† jugular (μg/ml)	cubital	Half-life of free platinum (min)	Pt level in biopsy (μg/g)	Urinary excretion (% dose)
1	NS‡	1.11	NS	2.08	41.0	7.90	29.5
2	NS	1.16	NS	1.72	72.2	1.93	33.9
3	NS	1.46	NS	2.37	31.5	1.40	32.2
4	16.71	2.12	8.83	2.38	36.4	2.50	32.5
5	4.82	1.56	4.76	1.85	31.0	2.14	28.2
6	NS	1.93	NS	2.38	23.9	0.72	22.6
7	NS	0.70	NS	1.29	28.3	0.94	17.0
8	NS	0.78	NS	1.33	7.7	4.26	49.8
9	1.17	1.10	1.60	1.48	53.1	1.52	29.5
10	1.02	0.73	NS	1.14	23.1	2.45	23.6
11	1.45	1.17	3.02§	1.79	74.9	1.30	21.4
12	1.41	1.02	2.11	NS	33.1	1.15	25.3
13	2.03			2.50	75.5	1.67	47.2
14	2.13			2.67	38.8	1.50	44.5
15	2.01			2.68	—‖	1.22	—‖
16	1.74			2.44	39.6	1.50	30.8
17	1.68			2.17	68.2	1.03	29.0
18	2.01			2.26	66.0	0.71	38.3
19	0.94			1.58	55.7	1.38	27.3
20	1.00			1.28	84.2	1.18	21.4
21	1.45			2.01	61.3	2.16	16.3
22	1.61			1.48	26.1	1.47	14.7
23	0.83			1.40	25.1	0.89, 1.14	30.1
24	0.81			1.84	52.9	1.08	33.0

* $C_{max(1)}$:peak concentration at the end of the 1st infusion.
† $C_{max(2)}$: peak concentration after 2nd infusion.
‡ NS: no sample at the very end of the infusion.
§ 2nd infusion over 4 hr and 20 min.
‖ Loss of one urine sample on day 2.

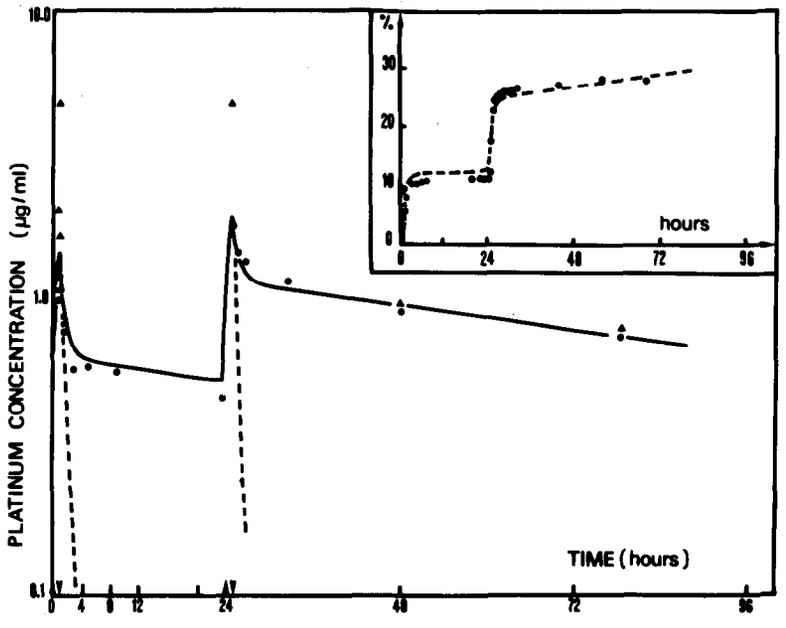

Fig. 2.

Figs. 2–5. Platinum plasma concentrations and urinary excretion (inset): after i.a. administration over 1 hr *in patient No.* 5 (*Fig.* 2); *after i.a. administration over* 6 hr *in patient* No. 11 (*Fig.* 3); *after i.v. infusion over* 1 hr *in patient No.* 16 (*Fig.* 4); *and after i.v. infusion over* 6 hr *in patient No.* 20 (*Fig.* 5). *The circles represent the experimental data, the triangles are the platinum levels measured in the jugular vein. The solid lines correspond to the fit of the total platinum concentration* (3-*compartment model*) *and the interrupted lines to the fit of the filterable species* (4-*compartment model*).

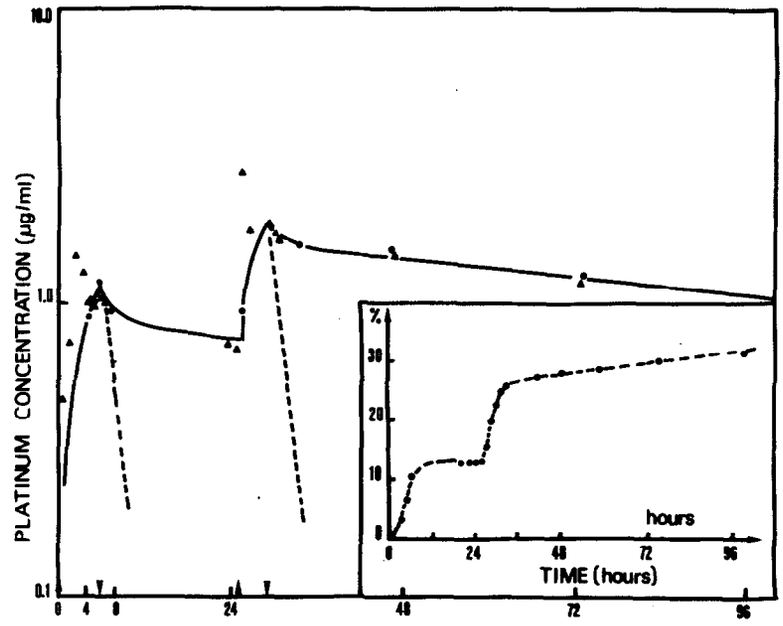

Fig. 3.

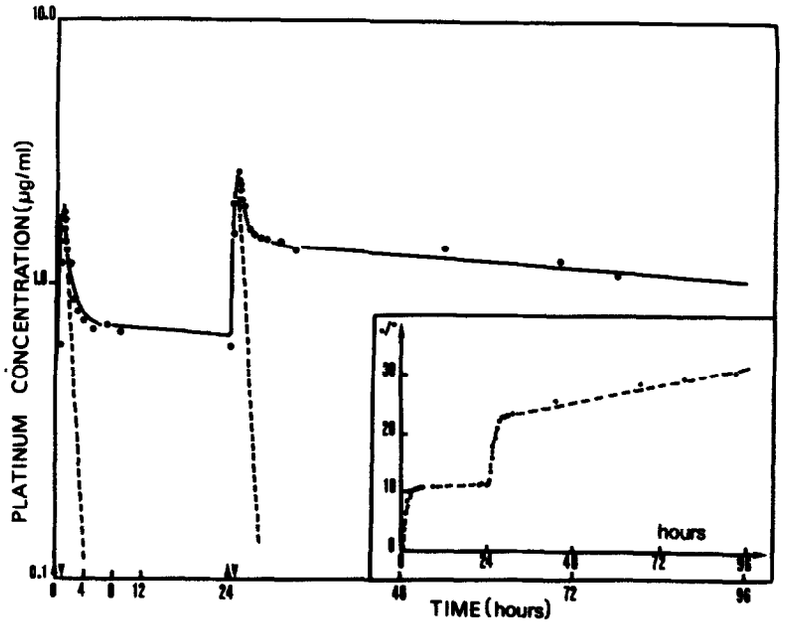

Fig. 4.

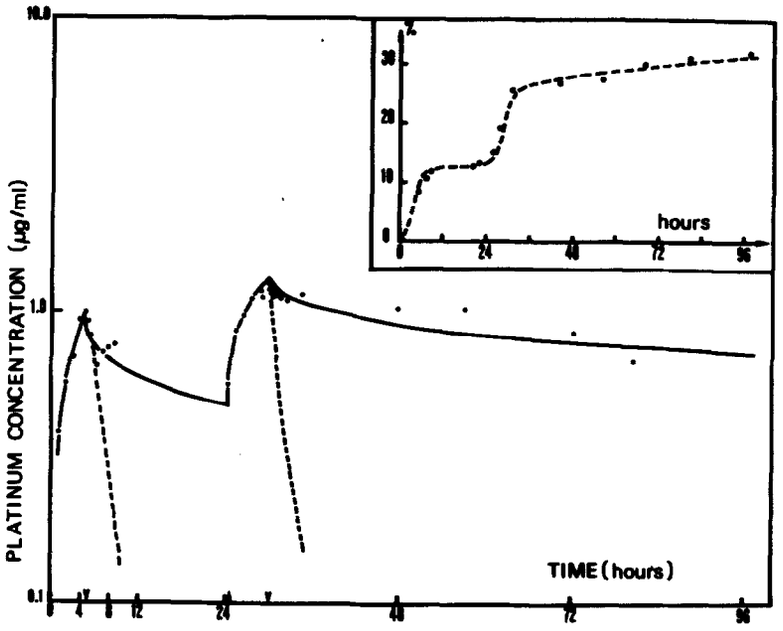

Fig. 5.

at doses of 50 mg/m^2 on days 1 and 2.

As reported by other authors [8, 18], the elimination half-life based upon total platinum concentrations is greater than 3 days. Urinary excretion followed over a period of 7 days is in the range of 15–50% of the total dose administered. No change was noticed in urinary elimination of platinum as a function of the protocol of administration. The same observation was made by Stewart *et al.* [14].

Many publications have indicated that the half-life of free platinum species in plasma measured by an ultrafiltration technique is rather short. Vermorken *et al.* [18] found half-lives of 17.4, 22.7 and 22.6 min after 15-min, 3-hr or 24-hr i.v. infusions of 100 mg/m^2, respectively. Belt *et al.* [19] reported a half-life of 28 min (range: 21.7–47.5 min) after a 1-hr i.v. infusion. These values are in the same order of magnitude as the figures given by Himmerlstein *et al.* [6] (24.6 min) or by Ribaud *et al.* [20] (32 min). However, the ultrafiltration technique using cones with protein weight cut-offs at 50,000 or 25,000 daltons is quite time-consuming. Thus during the processing of the samples the reactive platinum species may further react with plasma proteins, giving lower values for free filterable platinum concentrations and a relatively shorter half-life.

In our study careful collection of urine allowed us to fit plasma and urinary excretion data simultaneously. Based upon our model, calculated plasma concentrations of the free platinum species were superimposable upon the experimental data up to the end of the drug infusion. Thereafter, the estimated filterable species levels diverged from total platinum concentrations. The apparent half-life of these filterable species is short: 39 min (i.a./1 hr), 37 min (i.a./6 hr), 58 min (i.v./1 hr) and 56 min (i.v./6 hr), though the difference between i.a. and i.v. routes is not statistically different. These values are similar to those reported in the aforementioned literature and in a pharmacokinetic study of cisplatin in an anuric patient undergoing hemofiltration [21]. When the drug is given over 6 hr, the renal clearance of the filterable species is lower (i.a.: 30 ml/min and i.v.: 22 ml/min) than after 1-hr infusions (i.a.: 63 ml/min and i.v.: 57 ml/min). Campbell *et al.* [15], using an assay sensitive to only those forms of non-protein bound platinum capable of reaction with diethyldithiocarbamate, found no difference in plasma clearance after i.a. and i.v. administration of cisplatin to three patients at infusion rates of 5–15 mg/m^2/hr (range: 102–337 mg/m^2). And, after hepatic arterial infusion, the mean calculated plasma clearance, on the basis of steady-state concentrations, is in the range of 345 ml/min/m^2 — some 28-fold greater than the mean plasma clearance derived from measurements of total platinum (12.0 ± 4.2 ml/min/m^2) found by Stewart *et al.* [14]. Our results fall in between these extreme values based either on total platinum or on the platinum species reactive towards diethyldithiocarbamate, which may not be all native cisplatin. The renal clearance does not depend on the route of administration, in agreement with the results of Stewart *et al.* [14] and Campbell *et al.* [15], but seems to vary with infusion duration.

Based upon plasma concentration measurements in the jugular vein of some patients given cisplatin by the intra-arterial route, we oberved that, during infusion, the platinum concentration was consistently higher locally than peripherally and, after completion of the infusions, the local venous plasma levels fell rapidly to those found in peripheral venous plasma samples as observed by Stewart *et al.* [14]. This indicates that higher local concentrations of platinum can be achieved by i.a. administration. We also found higher platinum levels in tumor biopsies after i.a. administration. Although the differences are not statistically significant, it is quite possible that with a larger number of patients this trend would be confirmed.

Finally, after this single course of chemotherapy, tumor regression was moderate, but the use of cisplatin as an initial treatment did not give any incidence of complications when followed by surgery or radiation therapy. Ethical considerations precluded any further complete evaluation of cisplatin given alone.

Acknowledgements—We acknowledge the skilful technical assistance of Miss S. Colin, who carried out the platinum determination, and we thank the nursing staff for collecting the samples. This paper is dedicated to Prof. E.R. Garrett on his 65th birthday.

REFERENCES

1. Hayat M, Bayssas M, Brulé G *et al.* *Cis*-platinum-diamminodichloro (CDDP) in chemotherapy of cancers (phase II therapeutic trial). *Biochimie* 1978, **60**, 935–940.
2. Lippman AJ, Helson C, Helson L *et al.* Clinical trials of *cis*-diamminedichloroplatinum (NSC–119875). *Cancer Chemother Rep* 1973, **57**, 191–200.
3. Wittes RE, Brescia F, Young CW *et al.* Chemotherapy with *cis*-diamminedichloroplatinum(II) and bleomycin in tumors of the head and neck. *Oncology* 1975, **32**, 202–207.

4. Wittes RE, Heller K, Randolph VL *et al.* *Cis*-dichlorodiammineplatinum(II)-based chemotherapy as initial treatment of advanced head and neck cancer. *Cancer Treat Rep* 1979, **63**, 1533–1538.
5. **Baker SR, Makuch RW, Wolf GT. Preoperative cisplatin and bleomycin therapy in head** and neck squamous carcinomas. *Arch Otolaryngol* 1981, **107**, 683–689.
6. Himmerlstein KJ, Patton TF, Belt RJ *et al.* Clinical kinetics of intact cisplatin and related species. *Clin Pharmacol Ther* 1981, **29**, 658–664.
7. Patton TF, Himmerlstein KJ, Belt RJ *et al.* Plasma levels and urinary excretion of filterable platinum species following bolus injection and iv infusion of *cis*-dichlorodiammineplatinum(II) in man. *Cancer Treat Rep* 1978, **62**, 1359–1362.
8. Gullo JJ, Litterst CL, Maguire P *et al.* Pharmacokinetics and protein binding of *cis*-dichlorodiammineplatinum(II) administered as a one-hour or as a twenty-hour infusion. *Cancer Chemother Pharmacol* 1980, **5**, 21–26.
9. Casper ES, Kelsen DP, Alcok NW, Young CW. Platinum concentration in bile and plasma following rapid and 6-hr infusions of *cis*-dichlorodiammineplatinum(II). *Cancer Treat Rep* 1979, **63**, 2023–2025.
10. Lokich JJ. Phase I study of *cis*-diamminedichloroplatinum(II) administered as a constant 5-day infusion. *Cancer Treat Rep* 1980, **64**, 905–980.
11. Loo TL, Hall SW, Salem P *et al.* Clinical pharmacological and toxicological studies of *cis*-diamminedichloroplatinum(II) by continuous intravenous infusion. *Biochimie* 1978, **60**, 957–960.
12. Salem P, Hall SW, Benjamin RS *et al.* Clinical phase I–II study of *cis*-dichloroplatinum(II) given by continuous infusion. *Cancer Treat Rep* 1978, **62**, 1553–1555.
13. Mavligit GM, Benjamin R, Patt YZ *et al.* Intraarterial *cis*-platinum for patients with inoperable skeletal tumors. *Cancer* 1981, **48**, 1–4.
14. Stewart DJ, Benjamin RS, Zimmerman S *et al.* Clinical pharmacology of intraarterial *cis*-diamminedichloroplatine(II). *Cancer Res* 1983, **43**, 917–920.
15. Campbell TL, Howell SB, Pfeifle CE *et al.* Clinical pharmacokinetics of intraarterial cisplatin in humans. *J Clin Oncol* 1983, **1**, 755–762.
16. Leroy AF, Wehling ML, Sponseller HL *et al.* Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. *Biochem Med* 1977, **18**, 184–191.
17. D'Argenio DZ, Schumitzky A. A program package for simulation and parameter estimation in pharmacokinetic systems. *Comput Progr Biomed* 1979, **9**, 115–134.
18. Vermorken JB, Van der Vijgh WJF, Klein I *et al.* Pharmacokinetics of free platinum species following rapid, 3-hr and 24-hr infusions of *cis*-diamminedichloroplatinum(II) and its therapeutic implications. *Eur J Cancer Clin Oncol* 1982, **18**, 1069–1074.
19. Belt RJ, Himmerlstein KJ, Patton TF *et al.* Pharmacokinetics of non-protein-bound platinum species following administration of *cis*-dichlorodiammineplatinum(II). *Cancer Treat Rep* 1979, **63**, 1515–1521.
20. Ribaud P, Gouveia J, Bonnay M, Mathé G. Clinical pharmacology and pharmacokinetics of *cis*-platinum and analogs. *Cancer Treat Rep* 1981, **65** (Suppl. 3), 97–105.
21. Gouyette A, Lemoine R, Adhemar JP *et al.* Kinetics of cisplatin in an anuric patient undergoing hemofiltration dialysis. *Cancer Treat Rep* 1981,**65**, 665–668.