Disposition and tumour concentrations of platinum in hypoalbuminaemic patients after treatment with cisplatin for cancer of the head and neck

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- 1 Platinum concentrations in the tumour reached a peak of $3.8 \pm 1.5 \mu\text{g g}^{-1}$ wet weight tissue at the end of an 8 h intravenous infusion of cisplatin. The tumour concentrations of platinum were higher than the corresponding plasma concentrations ($2.5 \pm 0.9 \mu\text{g ml}^{-1}$) and declined more slowly.
- 2 Patients with squamous carcinoma of the head and neck had a significantly shorter median survival time if they had low plasma albumin concentrations ($< 40 \text{ g l}^{-1}$) compared with patients in the normal range, 133 days and 768 days respectively ($P < 0.05$) after treatment with cisplatin.
- 3 No changes in the pharmacokinetics of platinum were detected to account for this poor response of hypoalbuminaemic patients, but plasma albumin concentration was found to be negatively correlated with the first order elimination rate constant.
- 4 The cumulative urinary excretion of platinum in the first 24 h was not altered by lowered plasma albumin.
- 5 The concentration of platinum in the tumour did not correlate with the survival time of the patient, but was found to be correlated with the volume of distribution in the post-distributive phase.

Keywords cisplatin head and neck cancer hypoalbuminaemia

Introduction

Patients undergoing palliative chemotherapy with cisplatin respond to treatment less well if they are hypoalbuminaemic as defined by the WHO (plasma albumin 35 g l^{-1} or less; Morton *et al.*, 1985). Furthermore, they are more likely to suffer serious nephrotoxicity (Nanji *et al.*, 1986).

Cisplatin becomes extensively and covalently bound to plasma proteins (Gullo *et al.*, 1980; Repta & Long, 1980), so that the pharmacokinetics of the drug may be altered in patients with low albumin concentrations, possibly accounting for the differences in response and toxicity. Most authorities regard 35 g l^{-1} as the lower limit of normal albumin concentrations. However, Phillips *et al.* (1989) recently demonstrated an increased risk of mortality in men with plasma albumin concentrations below 40 g l^{-1} , and they suggest that albumin concentrations below this higher limit may also constitute hypoalbuminaemia. Therefore, we investigated hypoalbuminaemic patients ($< 35 \text{ g l}^{-1}$), patients with low

albumin concentrations ($35\text{--}39 \text{ g l}^{-1}$) and patients in the normal range ($> 40 \text{ g l}^{-1}$). Lowered albumin concentrations are common in cancer patients, especially those with a poor Karnofsky status, and a correlation between these two factors has been demonstrated by Morton *et al.* (1985). The incidence of hypoalbuminaemia in patients with advanced cancer of the head and neck is about 30%.

Despite the many studies of the pharmacokinetics of platinum after administration of cisplatin, there is little information about the amount of platinum which reaches the tumour *in vivo*. A tissue distribution study in humans (using post-mortem samples and including tumour tissue) showed that platinum concentrations in tumours were generally lower than those in the organ in which the tumour lay (Stewart *et al.*, 1982). Platinum concentrations have been measured in biopsies of tumours of the head and neck after intravenous and intra-arterial infusions of cisplatin. The platinum concentrations found

were in the range 0.71 to 7.9 $\mu\text{g g}^{-1}$ tumour (Gouyette *et al.*, 1986; Hecquet *et al.*, 1985).

Thus, there is little known about the relationships between the dose and tumour concentration of platinum and between the tumour concentration of platinum and the response. Until such information becomes available selection of dosage is largely empirical. Furthermore, the concentration of drug which should be used for experimental investigation *in vitro* is a matter of conjecture. We have therefore measured the platinum concentration in needle biopsies from patients treated with cisplatin for tumours of the head and neck in order to investigate these relationships and also the relationship between tumour concentration and the pharmacokinetics of the drug with regard to the possible effects of lowered plasma albumin concentration.

Methods

Patients and treatment

A total of 27 patients who had given informed consent were investigated. All had histologically proven end-stage squamous cell carcinoma of the head and neck and were undergoing palliative chemotherapy with cisplatin in the Department of Oto-rhino-laryngology at the Royal Liverpool Hospital. The patients included 24 men and three women and their ages ranged from 33 to 79 years (median 62 years). They were all previously untreated with cisplatin or any other chemotherapy, but eight had previously received radiotherapy and/or surgery. Twelve patients were treated with cisplatin alone, while 15 also received other drugs namely methotrexate (7), 5-fluorouracil (6) or adriamycin (2).

The dose of cisplatin given depended upon renal function. If the latter was adequate (creatinine clearance $> 60 \text{ ml min}^{-1}$) a full dose of 100 mg per square metre of body surface area (100 mg m^{-2}) was given. Half of this dose was used if creatinine clearance was between 50 and 60 ml min^{-1} , while those patients with poor renal function (creatinine clearance $< 50 \text{ ml min}^{-1}$) were excluded from cisplatin treatment.

Cisplatin was given according to a standard protocol, involving pre- and post-hydration and administration of a diuretic. Patients were prehydrated with isotonic saline (2 l) given intravenously over 36 h and then cisplatin was given in 1 l saline containing 12.5 g mannitol over 8 h. Metoclopramide (5 mg kg^{-1} in 500 ml saline) was given intravenously during this stage in five divided doses every 2 h over a 15 min period. Treatment was completed by post-hydration with 1 l saline given over 8 h, and this treatment schedule was repeated every 4 weeks. Tumour responses were assessed by standard UICC/WHO criteria.

Patients were divided into three groups according to their plasma albumin concentration: $< 35 \text{ g l}^{-1}$ (hypoalbuminaemic), $35\text{--}39 \text{ g l}^{-1}$ (low albumin), $> 40 \text{ g l}^{-1}$ (normal). These terms will be used to refer to each group of patients hereafter.

Collection of samples

Blood samples were taken before, and at 2 hourly intervals during the infusion and then at 2, 4, 8, 12, 24 and

48 h after the infusion, with further samples taken at 24-hourly intervals whilst the patient remained in hospital. Blood was collected into lithium-heparin blood-tubes (LIP Equipment and Services Ltd, Shipley, W. Yorks) and plasma was separated by centrifugation in a Gallenkamp bench centrifuge and then stored at -20°C until analysed.

Urine was collected over 24 h periods up to 5 days after treatment, and in some cases, where clinically feasible, the urine voided during the infusion was collected separately. After collection into 2.5 l polypropylene bottles an aliquot (10 ml) was taken and stored in blood-tubes without anticoagulant (LIP Equipment and Services Ltd) at -20°C .

Tumour biopsies were taken in most cases with a 'Tru-cut needle' (punch forceps were used on some accessible tumours) at the end of the infusion and also 24 and 48 h later. Biopsies were also taken from two patients before the second course. Biopsy samples were stored at -20°C in polypropylene microcentrifuge tubes until prepared for analysis. Approval for the study was obtained from the Ethics Committee of the Royal Liverpool Hospital.

Measurement of platinum in plasma, urine and tissue

Platinum concentrations were measured by flameless atomic absorption spectrometry with a Perkin-Elmer 2280 instrument used in conjunction with an HGA-300 furnace and an AS-40 autosampler. The furnace was fitted with pyrocoated graphite tubes containing L'vov platforms and argon was the inert gas. The hollow cathode lamp was operated on a continuous current of 30 mA and the absorbance was measured at 265.9 nm with a slit band-width of 0.7 nm. Measurements were made in the peak height mode for a sample volume of 20 μl while the gas flow was stopped (stage 6). Deuterium-arc background correction was employed throughout and baseline correction was performed during stage 5. The heating programme used is shown below:

Stage	1	2	3	4	5	6	7
Temperature ($^\circ\text{C}$)	90	130	650	1600	1600	2600	2650
Ramp(s)	5	5	10	10	1	0	1
Hold(s)	15	15	10	5	5	3	5

All samples were diluted with at least an equal volume of 0.5% (v/v) Triton X-100. Urine and plasma measurements were calibrated by standard additions and the detection limits for the two media were 0.10 ng and 0.14 ng, respectively. Tumour biopsies were digested in 1 ml of concentrated nitric acid at 110°C for 30 min. The digests were then evaporated to dryness and resuspended in a known volume of 0.2% v/v nitric acid. Tissue digests were calibrated by reference to a standard curve (PtCl_6 , 'Spectrosol' BDH Ltd) diluted in 0.2% v/v nitric acid. A comparison of the results obtained with this method and using a DC plasma technique for measurement of platinum in a series of plasma and urine samples demonstrated a high degree of correlation (McLoughlin *et al.*, 1988).

Pharmacokinetic analysis and statistics

Individual post-infusion data were fitted with a bi-exponential decay function using BMDPAR, an iterative

non-linear regression program. The zero time intercepts were then corrected for the time of the infusion as described by Loo & Riegelman (1970). The parameters of a two-compartment model with elimination from the central compartment were derived by standard calculations (Fracasso *et al.*, 1987; Gibaldi & Perrier, 1982). The area under the concentration-time-curve from the beginning of the infusion until 24 h later (AUC(0,24)) was calculated by the linear trapezoidal rule. Differences in parameters between the three patient groups were analysed by analysis of variance and correlations were examined by determination of Spearman's rank correlation coefficient. Differences in survival were analysed by the logrank test (Peto *et al.*, 1977).

Results

Clinical results

Six of the 27 patients had a plasma albumin concentration of less than 35 g l^{-1} , 12 of $35\text{--}39 \text{ g l}^{-1}$ and 9 of 40 g l^{-1} or above. The Karnofsky status of patients did not differ significantly between groups, the median (range) values being 70 (40–80), 70 (50–90) and 80 (60–90) for the hypoalbuminaemic, low albumin and normal groups, respectively. Three patients were treated with a half-dose, because of their reduced renal function, and had the lowest plasma platinum concentrations and AUC(0,24) values. These patients were omitted from some calculations.

A previous trial (Liverpool Head and Neck Oncology Group, 1990), which included some of the patients involved in this study, showed that cisplatin in combination with 5-fluorouracil or methotrexate offers no advantage over cisplatin alone. Therefore, patients treated with combination chemotherapy were assessed as if they had received cisplatin alone.

Pharmacokinetics of platinum

Computer fits were obtained with data from 15 patients; in the remainder too few samples were taken to allow detailed analysis. Of these 15 patients two were hypoalbuminaemic, seven had low albumin concentrations and six were in the normal range. The low number of hypoalbuminaemic patients obviously reduced the like-

lihood of finding any statistically significant differences between the groups and so the data were analysed by calculation of Spearman's rank correlation coefficient in addition to analysis of variance. No differences were found by analysis of variance for any of the pharmacokinetic parameters, nor the peak plasma Pt concentration, plasma Pt concentration 24 h after the end of the infusion or AUC(0,24)—all of which were derived from the whole group of patients (Table 1). Spearman's rank test also failed to show any correlations with the exception of a negative one between plasma albumin and k_{10} , the first order elimination rate constant from the central compartment ($P < 0.05$) (Table 1).

Urinary excretion

Urine was collected from 22 patients and in four of them the urine voided during the cisplatin infusion was collected separately. However, none of these patients was hypoalbuminaemic and only one was in the low albumin group. In the group of patients as a whole, excretion of platinum was initially rapid with $11.5 \pm 8.0\%$ of the dose excreted during the infusion (Table 2). Twenty-four hours after the start of the infusion $23.3 \pm 9.5\%$ had been excreted, but subsequent excretion was much lower with $3.1 \pm 1.1\%$ and $3.2 \pm 1.4\%$ being recovered on the second and third days. The cumulative excretions were thus $28.1 \pm 10.0\%$ and $36.7 \pm 9.0\%$, respectively (Table 2). Excretion over subsequent days was measured in a small number of patients (three on day 4, and one on day 5) and was found to continue at a similar rate to that seen on the second and third days (Table 2).

When the patients were divided into three groups on the basis of plasma albumin concentration no differences were found in the cumulative urinary excretion of platinum over the first 24 h (A_e) by analysis of variance. The A_e values for the three groups were $22.3 \pm 5.8\%$, $24.4 \pm 12.0\%$ and $22.5 \pm 8.5\%$ for the hypoalbuminaemic, low albumin and normal groups, respectively (Table 1). The excretion of platinum on subsequent days was also similar for each group.

Tumour concentrations

Sequential tumour biopsies were taken two or three times from 12 patients. The tumour platinum concentration was at or near its peak at the end of the cisplatin infusion (Figure 1). Therefore, only one biopsy was

Table 1 Pharmacokinetic parameters determined in patients receiving an 8 h intravenous infusion of cisplatin (100 mg m^{-2})

Parameter	Plasma albumin (g l^{-1})		
	< 35	35–39	> 40
Plasma Pt concentration ($\mu\text{g ml}^{-1}$)			
Peak (end-infusion)	2.25 ± 0.77 (5)	2.91 ± 0.66 (9)	2.64 ± 0.49 (8)
24 h post-infusion	1.57 ± 0.57 (5)	1.85 ± 0.32 (10)	1.77 ± 0.60 (7)
$t_{1/2,z}$ (h)	100 ± 25 (5)	116 ± 52 (10)	133 ± 61 (7)
AUC(0,24) ($\text{mg l}^{-1} \text{ h}$)	29.8 ± 7.1 (5)	40.2 ± 11.9 (11)	43.3 ± 9.7 (7)
V_z (l)	69.5 (2)	56.1 ± 15.7 (7)	50.8 ± 11.9 (6)
k_{10} (h^{-1})	0.022 (2)	0.026 ± 0.017 (7)	0.014 ± 0.004 (6)
A_e (% dose)	22.3 ± 5.8 (4)	24.4 ± 12.0 (9)	22.5 ± 8.5 (8)

Values are mean $\pm$ s.d. Figures in parentheses are number of patients.

taken at the end of the infusion from each subsequent patient and this part of the study was expanded to include 20 patients. One patient was lost to follow up and his survival time is unknown; in another, blood was drawn from a vein in the same arm as the drip and so contained misleadingly high plasma concentrations of platinum during the infusion. Therefore, these patients have been excluded from some calculations.

The concentrations of platinum found in the sequential biopsies are shown in Figure 1. In most cases the concentration varied only slightly over the first 48 h after a cisplatin infusion (Figure 1) and the wider variation in some patients probably reflects a non-homogenous distribution of platinum in the tumour. The tumour concentration of platinum was higher than the plasma concentration at the end of the infusion, and it declined more slowly. It was not possible to take all of the third biopsies at exactly 48 h so the data are presented as the range, for which the median concentration in tumours was $2.8 \mu\text{g g}^{-1}$ and for plasma $1.3 \mu\text{g ml}^{-1}$ (Table 3). The difference between the plasma and tumour concentration at the end of the infusion was statistically significant ($P < 0.05$) by analysis of variance (differences at the other times were not tested). No differences in the tumour platinum concentrations were found between hypoalbuminaemic patients ($3.9 \pm 1.4 \mu\text{g Pt g}^{-1}$, $n = 4$), patients with low albumin ($3.1 \pm 1.4 \mu\text{g Pt g}^{-1}$, $n = 9$) and patients in the normal range ($4.4 \pm 1.5 \mu\text{g Pt g}^{-1}$, $n = 7$) by analysis of variance. In two patients biopsies were taken before their second course of chemotherapy, 4 weeks after the first, and platinum was still present at levels of 13% and 39% of the concentration at the end of the first infusion.

We found no evidence of a relationship between tumour platinum concentration and tumour response. In two patients the disease progressed and the tumour platinum concentrations at the end of the infusion in these patients were 1.6 and $3.6 \mu\text{g g}^{-1}$. In eight patients the disease remained stable and the mean tumour platinum concentration was $4.8 \pm 1.5 \mu\text{g g}^{-1}$. Five patients showed a partial response and they had a mean concentration of $3.0 \pm 0.8 \mu\text{g g}^{-1}$ while one patient had a complete response but a tumour platinum concentration of only $3.1 \mu\text{g g}^{-1}$. Figure 2 is a log-log plot showing the relationship between the tumour platinum concentration at the end of the infusion and survival time. The median survival for the whole group was 195 days, and the median survival times for hypoalbuminaemic, low albumin and patients in the normal range were 385, 100 and 768 days, respectively. When these data were analysed with the logrank test it was found that patients with a plasma albumin concentration of less than 40 g l^{-1} (the hypoalbuminaemic and low albumin groups combined) had a significantly shorter survival time than the patients in the normal range, 133 days compared with 768 days, respectively ($\chi^2 = 4.70$, $P < 0.05$). When all of the patients were divided into two groups on the basis of their tumour platinum concentration, those with a platinum concentration above $3.4 \mu\text{g g}^{-1}$ (the median concentration) had a survival time of 351 days ($n = 10$), while those below $3.4 \mu\text{g g}^{-1}$ had a median survival of 195 days ($n = 10$). This difference was not significant when tested with the logrank test ($\chi^2 = 0.17$). Previous treatment with radiotherapy or surgery did not affect

Table 2 Urinary platinum excretion during and after an 8 h intravenous infusion of cisplatin (100 mg m^{-2})

Period (h)	Pt excreted		Cumulative excretion	n
	(mg)	(% dose)	(% dose)	
Infusion	12.8 ± 9.4		11.5 ± 8.0	4
0–24	23.4 ± 11.9		23.3 ± 9.5	22
24–48	3.0 ± 1.7	3.1 ± 1.1	28.1 ± 10.0	13
48–72	2.8 ± 2.0	3.2 ± 1.4	36.7 ± 9.0	7
72–96	3.3 ± 1.7	3.4 ± 1.0	33.7 ± 4.8	3

Values are mean $\pm$ s.d.

Figure 1 Concentrations of platinum in biopsies from tumours of the head and neck after an 8 h intravenous infusion of cisplatin (100 mg m^{-2}).

Table 3 Tumour and plasma platinum concentrations after an 8 h intravenous infusion of cisplatin (100 mg m^{-2})

Time after infusion (h)	Tumour ($\mu\text{g g}^{-1}$ wet weight tissue)	Plasma ($\mu\text{g ml}^{-1}$)	n
0	3.8 ± 1.5	2.5 ± 0.9	19
24	3.7 ± 1.5	1.6 ± 0.6	12
41–64	$0.8\text{--}4.3$ (2.8) ^a	$0.6\text{--}1.9$ (1.3) ^a	9
500	0.3	0.1	1
700	1.5	0.2	1

Values are mean $\pm$ s.d.

^aMedian value.

Figure 2 Relationship between survival time and tumour platinum concentration at the end of the infusion. All patients had end-stage head and neck cancer of squamous cell origin and were treated with an 8 h intravenous infusion of cisplatin (100 mg m^{-2}). Data from those patients with an albumin concentration $< 40 \text{ g l}^{-1}$ are indicated by unfilled squares.

either tumour uptake of platinum or survival. In most cases the tumour biopsy was taken from the main tumour mass which was irradiated in those patients who received such treatment. The mean tumour platinum concentration for previously treated patients was $3.7 \pm 1.7 \mu\text{g g}^{-1}$ ($n = 11$) compared with $3.7 \pm 1.3 \mu\text{g g}^{-1}$ ($n = 9$) for those who had not been previously treated, while the respective median survival times were 133 days and 622 days. These differences were not significant when tested with the logrank test ($\chi^2 = 2.85$).

The relationships between tumour platinum concentration and plasma albumin, AUC(0,24) and various pharmacokinetic parameters were analysed by Spearman's rank test. A significant association ($P < 0.01$) was found between tumour platinum concentration and V_z , the volume of distribution in the post-distributive phase. No other significant correlations were found.

Discussion

Hypoalbuminaemia and pharmacokinetics

The persistence of platinum derived from cisplatin in tissues means that patients who have been pretreated with the drug should not be included in a pharmacokinetic investigation. It has been shown in both guinea pigs (Litterst & Schweitzer, 1984) and in man (Leone *et al.*, 1987) that a second course of cisplatin is excreted more slowly resulting in higher AUC values and tissue deposition. Therefore, it was important that all patients in whom the pharmacokinetics of the drug were evaluated were on their first course of treatment.

Despite the extensive covalent protein binding of cisplatin the effect of hypoalbuminaemia on its kinetics has not previously been investigated in detail. In a study of the pharmacokinetics of intra-arterially administered cisplatin Stewart *et al.* (1983) reported that hypoalbuminaemia (plasma albumin $< 35 \text{ g l}^{-1}$) was associated with a shortening of the terminal half-life. They found no other differences related to hypoalbuminaemia although investigation of the effect of this condition was not the primary aim of the study. In the present work the effect of hypoalbuminaemia on the disposition of platinum after administration of cisplatin as an 8 h intravenous infusion has been studied specifically. No alteration of the pharmacokinetics of total platinum caused by lowered plasma albumin concentrations was detected. A wide variation between patients in many of the pharmacokinetic parameters was observed and this may reflect variability in the disease state. This variation is also apparent in other reports (Crom *et al.*, 1981; Fracasso *et al.*, 1987; Leone *et al.*, 1987; Preiss *et al.*, 1988).

No reduction of the terminal elimination half-life of platinum in hypoalbuminaemic patients was observed, in contrast to the finding of Stewart *et al.* (1983). The half-lives, however, were in most cases considerably longer than those reported by Stewart *et al.* (1983). Gormley *et al.* (1979) found that a two compartment model with a terminal half-life of 67 h could not accurately predict the plasma platinum concentration at 21 days and postulated a further phase with a longer half-life. In order to define this plasma samples would have to be

taken over an extended period, which is difficult unless the patients are in hospital for a considerable time. In this study it was not possible to obtain blood samples for more than about 100 h after the infusion and so a two compartment-model was used. However, in four patients blood samples were taken before the second course of therapy, that is about 500 to 700 h after the first. When these data were used in the computer analyses in three out of four cases the terminal half-lives were increased from between 93 to 126 h to 181 to 223 h. In the fourth patient the terminal half-life was 177 h in both analyses. Thus a terminal half-life of around 100 h does not adequately describe the true terminal phase, and the actual half-life is nearer to 200 h.

Unbound platinum

In recent studies of the pharmacokinetics of cisplatin attention has focussed on the disposition of unbound platinum (Belt *et al.*, 1979; Erlichman *et al.*, 1987; Reece *et al.*, 1987; Vermorken *et al.*, 1982, 1986), including the parent compound as well as any metabolites, spontaneous transformation products and platinum bound to low molecular weight species such as methionine. However, the interruption of the cisplatin infusion caused by the intermittent administration of metoclopramide resulted in sizeable fluctuations in the concentration of platinum in plasma ultrafiltrate during the infusion (data not shown). In view of this the unbound concentrations were not considered further.

Urinary excretion

The excretion of platinum in the urine by hypoalbuminaemic patients did not differ from that of other patients, at least over the first 24 h after the start of the infusion. It is possible that the excretion rate during the infusion may have been different in hypoalbuminaemic patients but this possibility was not investigated. The excretion rate during the infusion accounted for between 40 and 84% of the total platinum excreted in the first 24 h in patients with normal plasma albumin concentrations. Therefore, any differences in hypoalbuminaemic patients are unlikely to have been significant.

The urinary excretion of platinum indicates the extent of renal exposure to the drug. In view of the greater susceptibility of hypoalbuminaemic patients to nephrotoxicity a higher renal exposure and amount of excretion might have been expected. This hypothesis is supported by the work of Campbell *et al.* (1983) who reported that patients who achieved the highest plasma concentrations of platinum during a 24 h infusion of cisplatin were more likely to suffer nephrotoxicity. It has also been shown in a study based on autopsy material that the renal toxicity of cisplatin correlates with the kidney concentration of platinum (Stewart *et al.*, 1985). Similarly, Nanji *et al.* (1988) reported that the incidence of nephrotoxicity was related to urinary platinum excretion and earlier work by this group showed that hypoalbuminaemic patients were predisposed to cisplatin nephrotoxicity (Nanji *et al.*, 1986). They considered that this may be due to either the effect of hypoalbuminaemia on renal haemodynamics, or the lower availability of albumin to bind the drug. Cisplatin is converted to at least seven products *in vivo*

(Daley-Yates & McBrien, 1983, 1984) and since different entities are responsible for the toxicity and efficacy of the drug future investigation should attempt to identify and follow these species individually. In the work reported here, no attempt was made to relate the pharmacokinetics or excretion of platinum to nephrotoxicity but an attempt was made, however, to relate the pharmacokinetics to tumour response.

Tumour platinum concentrations

Although there have been many clinical and laboratory investigations of cisplatin there have been few measurements of the amount of drug that reaches the tumour *in vivo*. Stewart *et al.* (1982) reported the results of an analysis of tumour tissue from post-mortem samples, while Vennin *et al.* (1985) took sequential biopsies after treatment from patients with cancers of the uterine cervix. The latter group also reported measurements in head and neck and breast tumours (Hecquet *et al.*, 1985). Gouyette *et al.* (1986) in a comparison of intra-arterial and intravenous administration also reported tumour concentrations in head and neck cancer patients. In all four of these investigations similar tumour concentrations of platinum were reported (range 1–5 $\mu\text{g g}^{-1}$) but in no case was any attempt made to relate the tumour concentration to response. In a study of tumours of the uterine cervix Vennin *et al.* (1985) found wide intra-tumour variation in the platinum concentration. This may partly reflect a non-homogenous distribution of platinum within the tumours. In the present study some variation was found (Figure 1) but it was not as extreme as that seen by Vennin *et al.* (1985) and so the concentration of platinum in the tumour at the end of the infusion was taken as being representative and was used to examine the relationship between the response to treatment and drug concentration.

Since the aim of treatment in our patients was palliation rather than cure, the survival time from the first treatment with cisplatin was used as an index of response. There was no evidence of a relationship between tumour response and tumour platinum concentration. All of the patients were end-stage when they entered the trial with a similar prognosis. Therefore, this objective method of measuring the efficacy of the treatment was considered better than the measurement of tumour size which is more subjective and in many cases is hampered by restricted access to the tumour mass.

The spread of the data seen in Figure 1 was not unexpected. While all of the patients had squamous cell carcinomas, the tumours arose from various different sites so that tumour uptake of the drug may be expected to vary depending on how well the tumour is perfused with blood. Previous surgery or radiotherapy could alter the vasculature of the tumour, but in this study prior treatment was not found to have an effect on the tumour concentration or on survival. Similarly, concurrent chemotherapy with methotrexate, adriamycin or 5-fluorouracil did not affect tumour uptake and, as shown by the Liverpool Head and Neck Oncology Group (1990), combination chemotherapy does not improve the efficacy of cisplatin in comparison with its use as a single agent. As expected, the survival time of patients with lowered albumin concentrations (albumin $< 40 \text{ g l}^{-1}$) was shorter than that of patients with albumin in the normal range ($P < 0.05$), despite there being no significant difference in the Karnofsky status of the two groups. However, tumour uptake of platinum in these patients showed no significant difference and so a lowered albumin concentration does not appear to impair survival by lowering tumour uptake of the drug.

The tumour concentration of platinum was found to be associated with its volume of distribution in the post-distributive phase. The correlation was negative indicating that the smaller the volume the remaining platinum is distributed in the higher the concentration achieved. This indicates, as expected, that the tumour lies in the 'peripheral compartment'. Furthermore, the tumour platinum concentration was always higher than the plasma concentration and it declined more slowly. Thus, platinum binds to tissues and is only slowly released from its cellular targets, probably as a result of protein turnover.

No effect on any of the parameters studied was observed in hypoalbuminaemic patients which could account for their decreased response to cisplatin therapy. The poor response of hypoalbuminaemic patients to cisplatin may not be due simply to a decreased tumour response: the increased susceptibility to nephrotoxicity of such patients could negate any therapeutic effect of treatment and decrease survival time.

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