Cancer Chemother Pharmacol (1991) 27: 347–353

0344570491000191

Cancer Chemotherapy and Pharmacology

Intratumoural administration of cisplatin in slow-release devices: II. pharmacokinetics and intratumoural distribution

Marc J. M. Deurloo[1,2], Wim Kop[1], Olaf van Tellingen[1], Harry Bartelink[1], and Adrian C. Begg[1]

[1] Department of Experimental Therapy, The Netherlands Cancer Institute, Plesmanlaan 21, 1066 CX Amsterdam, The Netherlands
[2] *Present address:* Pharmaceutical RDL, Organon Int. B.V., PO Box 20, 5340 BH Oss, The Netherlands

Received 1 May 1990/Accepted 24 September 1990

Summary. The pharmacokinetics of cisplatin in mice with s.c. RIF 1 tumours was studied after intratumoural (i.t.) administration of drug in solution and in different slow-release devices. The data were compared with those obtained after i.p. administration of cisplatin. The slow-release devices under test were manufactured from either starch (ST) or polymeric hydrogels with different water uptakes (named T1, T2 and T3). In vitro release from these devices was approximately 100% in 2 h for starch rods, 100% in 24 h for T3 hydrogels, 45% in 4 days for T2 hydrogels and <10% in 4 days for T1 hydrogels. In vivo release rates agreed well with the in vitro data for T1 and T2 rods and were slightly slower in vivo for the T3 rods. The ST rods released the drug 6 times slower in vivo than in vitro. Plasma concentrations after i.t. administration were lower than those measured after i.p. administration. Systemic exposure to both total and free platinum was reduced to 70% for i.t. as compared with i.p. administration. Tumour concentrations were 4 times higher after i.t. than after i.p. administration. Tumour and peak plasma levels of platinum increased with increasing release rates. With the faster-releasing formulations (ST and T3), tumour platinum concentrations were 100 times higher than after i.p. administration. With the slower releasing formulations (T1 and T2), total tumour platinum concentrations were 2 and 9 times higher, respectively, than after i.t. administration of cisplatin in solution. Platinum distribution within the tumour was homogeneous after i.p. administration. After i.t. administration of cisplatin in solution, platinum concentrations in the centre of the tumour were approximately 4 times higher than in peripheral tumour tissue. Implantation of cisplatin in T2 and T3 hydrogel rods resulted in large concentrations of platinum in the centre of the tumour (the site of implant), which decreased steeply towards the tumour periphery. In summary, i.t. administration of cisplatin solution produced better results than did systemic (i.p.) administration in terms of tumour versus plasma drug-concentration ratios. Administration of drug in slow-release rods proved even more advantageous, although this was offset by inhomogeneous drug distributions within the tumour.

Offprint requests to: A. C. Begg

Introduction

A number of authors have shown that in experimental models the intratumoural (i.t.) administration of cisplatin has a greater effect on the tumour and produces reduced toxicity as compared with systemic routes of administration [2, 4, 15, 23, 24]. This makes direct administration into the tumour an attractive way to increase the therapeutic ratio. Pharmacokinetic studies on a number of drugs have consistently shown larger tumour concentrations and/or reduced plasma concentrations after i.t. administration as compared with systemic routes [3, 15, 19, 22]. Drug distribution within the tumour, however, was found to be non-uniform after i.t. administration of hematoporphyrin derivative (HPD) [1, 9]. The i.t. administration of cisplatin solution resulted in i.t. platinum concentrations 2–5 times higher than those obtained after i.p. administration, whereas total platinum levels in plasma were reduced [15]. However, these authors did not measure free platinum levels in plasma, which are believed to represent active cisplatin metabolites [16, 21], nor did they investigate the distribution of platinum within the tumour.

Slow-release formulations administered i.t. enable prolonged local exposure to cytostatic drugs. A number of slow-release formulations have been described for cisplatin, including viscous fluid formulations [2, 23, 24], implants [4, 7, 8], microcapsules [6] and microspheres [18]. In a previous report, we demonstrated that i.t. implantation of slow-release implants containing cisplatin could result in higher tumour responses, depending on the release rate, than were obtained after i.t. injections of cisplatin solution [4].

Table 1. Characteristics of slow-release rods

	Starch	Hydrogel		
	ST	T3	T2	T1
Water uptake (% w/w)	–	40	14	4
Length (mm)	4.6	5	5	5
Diameter (mm)	1.2	1.6	1.6	1.6
Weight (mg)	7.86	13.47	13.16	12.42
Cisplatin (% w/w)	9.27	5	4.9	5
mg/rod	0.73	0.67	0.64	0.62
Dose (mg/kg)[a]	24	22	21	21

[a] Calculated for a mouse weighing 30 g

The aim of the present investigation was to study the pharmacokinetics of cisplatin after i.t. administration with and without slow-release devices and to compare the results with those obtained using cisplatin given by systemic administration, with emphasis on free platinum concentrations in plasma and on the distribution of platinum within the tumour.

Materials and methods

Formulations. Cisplatin was obtained from Ventron (Karlsruhe, FRG) as a crystalline powder and was either dissolved in saline (0.9% NaCl) for i.p. and i.t. injections or dispersed in slow-release matrices. Solid slow-release rods were based either on starch (in collaboration with the University of Groningen, the Netherlands) or on a new type of hydrogel (see [17]) based on polyether polymers (in collaboration with TNO, Delft, the Netherlands). Characteristics of the slow-release rods are summarized in Table 1. The starch rods were prepared by direct compression of a powder mixture containing 9.27% cisplatin by weight. For the hydrogel rods, three formulations with different water uptakes were studied, i.e. 4%, 14%, and 40% (w/w) for formulations named T1, T2 and T3, respectively. The hydrogels were prepared as rods with a diameter of 1.6 mm and a length of 5 mm.

In vitro release. In vitro release of cisplatin from the slow-release devices was studied at 37° C in flat-bottomed vials on a shaker. The release medium (10 ml) consisted of phosphate-buffered saline (PBS, 0.01 M; pH 7.4). Samples (100 µl) were taken at regular intervals and analyzed for platinum (Pt) concentration using flameless atomic absorption spectrometry (FAAS).

Mice and tumours. Female C3H/Km and C2H/HeA mice, 8–12 weeks old and weighing 25–35 g, were used. The mice were obtained from the animal department of the Netherlands Cancer Institute and were bred under specific pathogen-free (SPF) conditions. The animals were kept on a 12-h light12-h dark schedule and were fed standard mice chow and tap water ad libitum. RIF1 murine fibrosarcomas were grown s.c. on the lower back. The tumour was maintained by the protocol described by Twentyman et al. [20]. Tumours were obtained by s.c. inoculation of 2×10^4 cells in 0.1 ml PBS. The mice were treated when the mean diameter of the tumour reached approximately 8 mm.

Drug administration. Solutions of cisplatin in saline were injected i.p. or i.t. The cisplatin solutions were freshly prepared on each day. Injection volumes were 0.01 ml/g body weight for the i.p. route and 0.1 ml/tumour for the i.t. route. Cisplatin concentrations in the i.p. and i.t. solutions were 0.57 and 1.7 mg/ml, respectively, giving a dose of 5.7 mg/kg in both cases, assuming a mouse weight of 30 g. Prior to i.t. drug administration, the mice were lightly anaesthetized with an enflurane-oxygen mixture. The hair over the tumours was shaved and the skin, disinfected with 70% ethanol. For i.t. administration, cisplatin was given by a single injection in the centre of the tumour. The slow-release rods were implanted in a small hole in the centre of the tumour that was made using a 21-gauge needle. The small size of the insert hole obviated the need for sutures, and little or no bleeding or other problems resulted from the procedure.

In vivo release and pharmacokinetics. At predetermined times after drug administration, the mice were anaesthetized with an enflurane-oxygen mixture. Blood was collected in heparinized tubes by ocular puncture. The animal was then killed while still under anaesthesia and the tumour was removed. The heparinized blood was centrifuged immediately after collection so as to obtain plasma, which was then stored at 4° C. Ultrafiltrate was obtained as soon as possible, usually within 30 min after blood collection, by centrifugation (15 min; 2,000 *g*) of 200 µl plasma over Amicon ultrafiltration membranes (mol. wt. cutoff, 10 kDa). Residues of the slow-release implant were then removed from the tumour. Plasma, ultrafiltrate, tumour tissue and slow-release devices were stored at –20° C until analysis for platinum concentration using FAAS.

Drug distribution within tumours. At several times after drug administration, tumours were also collected for determination of the i.t. distribution of total platinum. The tumours were excised and immediately frozen on dry ice, and then cut with a scalpel into six slices of approximately equal thckness (≈ 1.3 mm). If present, the embedded slow-release rods were removed and the tumour slices were individually analyzed for platinum content by FAAS.

Flameless atomic absorption spectroscopy. Platinum concentrations were determined in plasma, ultrafiltrate, tumour tissue and the remainder of the slow-release devices using a model AA40 atomic absorption spectrometer with a GTA 96 graphite tube atomiser with Zeeman background correction (Varian; Victoria, Australia). Plasma and ultrafiltrate samples were diluted with solutions containing HCl and 0.15 *N* NaCl, giving a final concentration of 0.2 *N* HCl. Residues of the slow-release rods and tumours were digested in 65% HNO_3 at 170° C in Parr Teflon-lined acid-digestion bombs for 2 h. After cooling, excess NaCl (5–10 mg) was added and the liquid was evaporated under a stream of air at 100° C. Residues were dissolved in 0.2 *N* HCl and 0.15 *N* NaCl. All standards were treated in the same way as the samples, either diluted with or digested in the appropriate matrix. A four-stage heating program was used, consisting of drying at 110° C for 65 s, ashing at 1,400° C for 75 s, atomizing at 2,650° C for 3 s and conditioning at 2,550° C for 5 s. Nitrogen was used as the inert gas.

Data analysis. Both total and free plasma platinum concentrations after i.p. and i.t. injection of cisplatin solution were fit to a two-compartment open model. Parameters were estimated by non-linear regression using the Simplex method (Nelder-Mead Algorithm). The area under the concentration-time curves (AUCs) were calculated using the linear trapezoidal rule. For the i.t. implanted slow release devices, plasma platinum concentrations were analyzed in terms of maximal time (T_{max}) maximal concentration (C_{max}) and AUC. Apparent elimination half-lives were estimated from the terminal part of the concentration-time curves [5]. The platinum distribution within tumours was calculated by averaging the values for the two centre, intermediate and peripheral slices. These individual tumour values were then averaged for each group. For statistical evaluation of the results, Student's one-tailed *t*-test for either similar or non-similar variances was used after testing for similarity of variance had been done using the F-test [11]. Differences were assumed to be statistically significant at $P < 0.05$.

Results

Release rates

In vitro release from the slow-release rods is shown in Fig. 1. The starch data have been replotted from a previous publication [4] and are shown for direct comparison with in

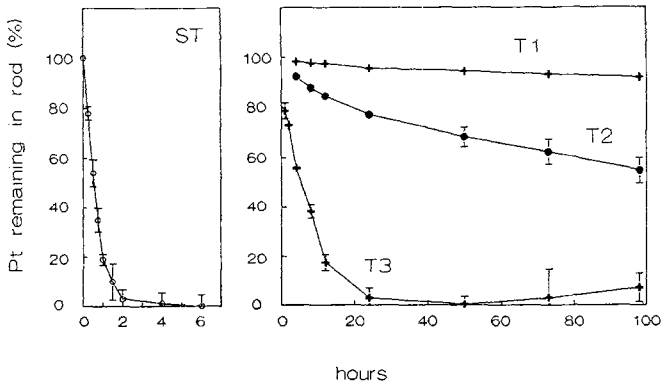

Fig. 1. In vitro release rate of cisplatin from slow-release devices. Amount of platinum remaining in starch rods (*left panel*) or hydrogel rods with low (*T1*), medium (*T2*) or high (*T3*) water uptakes (*right panel*). Average of 3 rods; bars represent ± 1 SEM

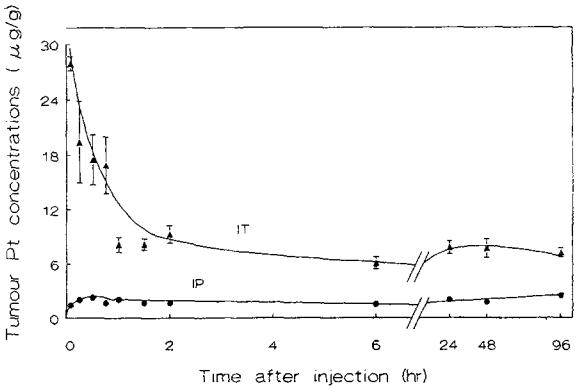

Fig. 3. Platinum concentrations in s.c. RIF1 tumours after i.t. (*triangles*) or i.p. (*circles*) injection of 5.7 mg/kg cisplatin in saline. Average of 3–4 mice per point; bars represent ± 1 SEM

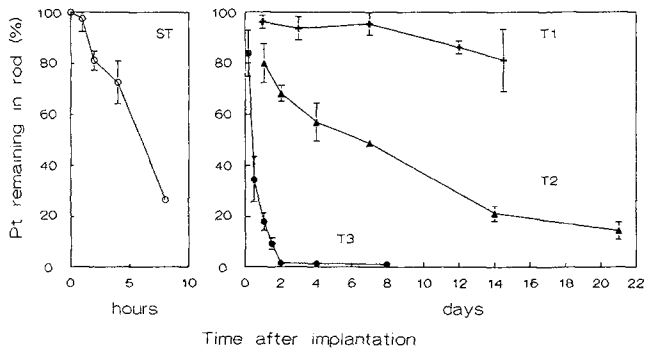

Fig. 2. In vivo release rate of cisplatin from slow-release devices. Amount of platinum remaining in slow-release rods after i.t. implantation of cisplatin in starch rods (*left panell*) or hydrogel rods (*right panel*). Average of 3–4 rods; bars represent ± 1 SEM

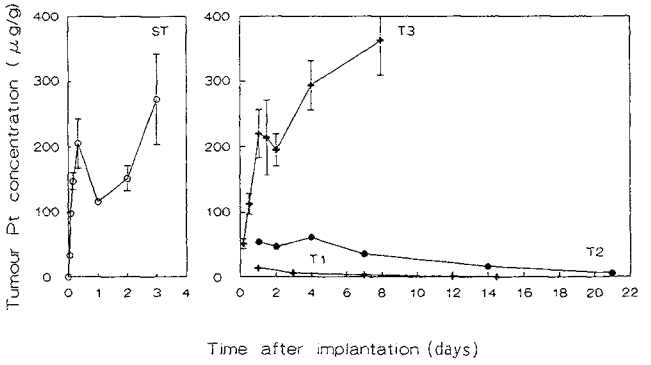

Fig. 4. Platinum concentrations in s.c. RIF1 tumours after i.t. implantation of cisplatin in slow-release rods made of starch (*ST, left panel*) or hydrogel with different water uptakes (*T1, T2, T3; right panel*). Cisplatin dose was 21–24 mg/kg. Average of 2–4 mice per point; bars represent ± 1 SEM

vivo release data. In vitro release of platinum from the starch rods was rather fast, with almost 100% release occurring within 2 h (Fig. 1, left panel). For the three hydrogel preparations, release rates ranged from 97% in 1 day for the formulation with the greatest water uptake (T3) to 8% in 4 days for the rods with the least water uptake (T1).

The same batch of rods was used for i.t. implantation. The amount of platinum remaining in the slow-release rods in vivo as a function of time is shown in Fig. 2. Extrapolating the data for the starch rods, 100% release would be achieved in vivo after approximately 12 h (Fig. 2), which was much longer than the equivalent time in vitro of approximately 2 h (Fig. 1). In vivo release fom the T3 hydrogel rods was slightly slower than in vitro release, whereas in vivo release from T2 and T1 rods correlated well with the in vitro release data.

Tumour concentrations

Cisplatin in solution. Tumour platinum concentrations after i.p. and i.t. administration of 5.7 mg/kg cisplatin are shown in Fig. 3. Tumour platinum concentrations after i.t. administration were markedly higher than those after i.p. administration at all time points. Platinum concentrations were 20 times higher after 5 min and decreased rapidly within the 1st hour for i.t. cisplatin. The amount of platinum recovered from the tumour at 5 min after i.t. administration of 0.1 ml cisplatin solution corresponded to only 15% of the delivered dose, i.e. 85% of the drug left the tumour either during injection or shortly thereafter. After 1 h, tumour platinum levels remained approximately 4-fold those obtained following i.p. administration.

Slow-release devices. The highest tumour platinum concentrations were obtained after i.t. implantation of cisplatin (22–24 mg/kg) in the fastest-release formulations, ST and T3 (Fig. 4). For both formulations, tumour platinum levels were 100 times those obtained after i.p. administration and 30 times the concentrations determined after i.t. injection of cisplatin in solution (5.7 mg/kg; Fig. 3). The platinum levels per gram of tumour increased after 2 days, when the ST and T3 rods were empty; this was caused by a decrease in tumour mass resulting from the killing and loss of cells. The absolute amount of platinum in the tumour reached a maximum of 160 μg/tumour 2 days after implantation of the starch rods, which was approximately 1/3 of the delivered dose (approximately 0.7 mg cisplatin or 0.43 mg platinum). For T3 hydrogel rods, equally high amounts of platinum were recovered from the tumour after

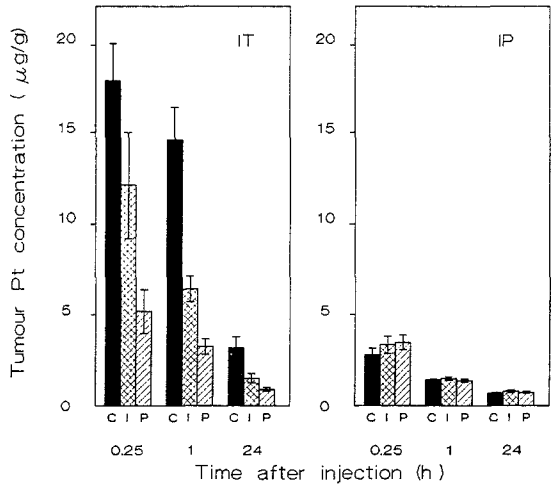

Fig. 5. Platinum concentrations in the centre (*C*), intermediate (*I*) and peripheral (*P*) regions within RIF1 tumours after i.t. (*left panel*) or i.p. (*right panel*) injection of 5.7 mg/kg cisplatin in saline. Average of 3–5 mice per point; bars represent ± 1 SEM

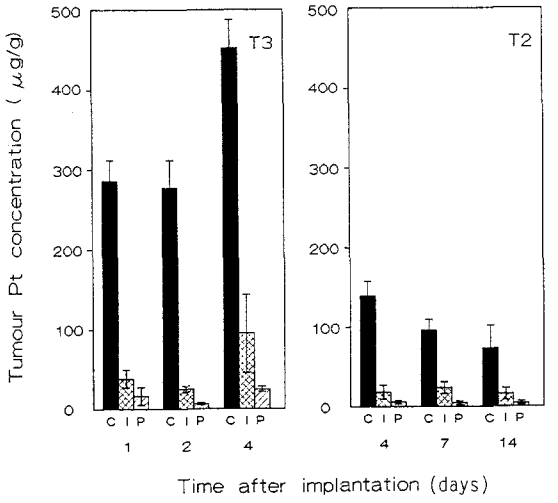

Fig. 6. Platinum concentrations in the centre (*C*), intermediate (*I*) and peripheral (*P*) regions within s.c. RIF1 tumours after i.t. implantation of cisplatin in slow-release hydrodrogel rods with 40% (*T3, left panel*) and 14% water uptake (*T2, right panel*). The cisplatin dose was 21–22 mg/kg. Average of 4 mice per point; bars represent ± 1 SEM

1.5 days. After the implantation of T1 and T2 rods, maximal tumour levels were lower, but the respective values remained 2- and 9-fold those observed after i.t. drug administration solution.

Platinum distribution within the tumour

Cisplatin in solution. The distribution of platinum within tumours is shown in Fig. 5. After i.t. injection of drug in solution, the concentrations in the centre of the tumour were 3.5–4.5 times those measured in the periphery of the tumor. This concentration gradient remained for at least 24 h. After i.p. administration, platinum was homogeneously distributed in the tumour (Fig. 5). Platinum concentrations in the rim of the tumour at 60 min after i.t. injection were significantly higher than the overall tumour platinum concentrations reached after i.p. administration.

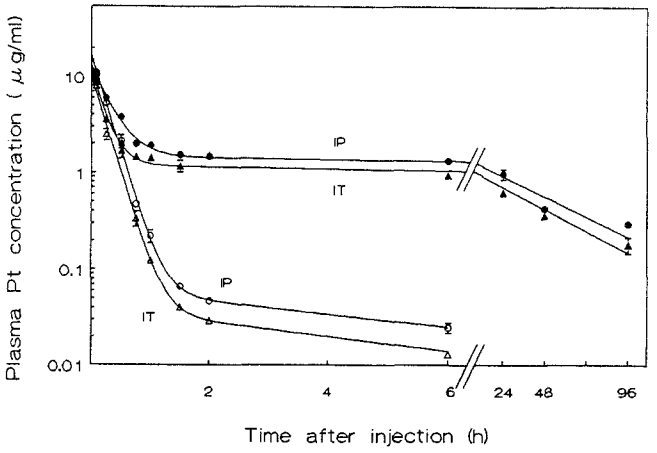

Fig. 7. Platinum concentrations in murine plasma (total platinum, *closed symbols*) and ultrafiltrate (free platinum; *open symbols*) after i.p. (*circles*) or i.t. (*triangles*) injection of 5.7 mg/kg cisplatin in saline. Average of 3–4 mice per point; bars represent ± 1 SEM

After both 15 min and 24 h, platinum concentrations in the rim of the tumour remained higher than those obtained after i.p. administration, although statistical significance was not reached.

Slow-release devices. Platinum distribution within the tumour after i.t. implantation of cisplatin in slow-release devices is shown in Fig. 6. After administration of the hydrogel T3, platinum levels in the centre of the tumour, excluding the rod itself, were 20–40 times those in the peripheral parts of the tumour. As measured from the centre to the intermediate regions, platinum concentrations decreased from approximately 400 μg/ml to 40 μg/g (Fig. 6). Concentrations in the different parts of the tumour increased after 4 days due to the killing and loss of cells, but the concentration gradient between centre and peripheral parts remained approximately constant. For the hydrogel T3, platinum concentrations in peripheral tumour slices were of the same magnitude as those obtained after i.t. administration of cisplatin solution (Fig. 5).

For T2 rods, the platinum distribution was also inhomogeneous, with concentrations in the centre of the tumour being approximately 20 times those in the periphery (Fig. 6). The levels in the different tumour slices were lower than those measured after administration of cisplatin in T3, which is in accordance with the lower total platinum levels found in the tumour (Fig. 4). Platinum concentrations in the different tumour slices after 14 days were lower than those obtained after 4 days, although the amount of platinum per tumour had increased; this was caused by tumour regrowth. After administration of the slower-releasing hydrogel T2, platinum concentrations in the peripheral slices were lower than those observed after i.t. administration, although the differences were not statistically significant.

Plasma concentrations

Cisplatin in solution. The concentration-time curves for total and free platinum in plasma after both i.p. and i.t. injection had similar shapes (Fig. 7), which could be de-

Table 2. Pharmacokinetics after i.t. and i.p. administration of cisplatin in solution (5.7 mg/kg)

	Total Pt		Free Pt	
	i.p.	i.t.	i.p.	i.t.
A (μg/ml)	11.67±2.67[1]	10.69±2.76	16.77±2.09	9.89±2.21
α (h^{-1})	3.59±0.72	5.32±1.1	4.71±0.01	4.64±0.42
B (μg/ml)	1.48±0.17	1.19±0.1	0.064±0.01	0.04±0.014
β (h^{-1})	0.02±0.003	0.022±0.002	0.16±0.05	0.17±0.083
AUC (μg h ml^{-1}):				
0–96 h	66.7	47.9		
0– 6 h	11.46	9.11	3.38	2.19

Data represent the mean ± SE. Plasma platinum data were fit to a two-compartment open model. A, zero time intercept, first compartment; B, zero time intercept, second compartment;
α, elimination rate constant, first compartment;
β, elimination rate constant, second compartment

Table 3. Pharmacokinetics of platinum in murine plasma after i.t. administration of cisplatin in slow-release devices

	Dose (mg/kg)	T_{max} (h)	C_{max} (μg/ml)	AUC (interval) (μg h ml^{-1})
Total plasma Pt:				
ST	24	8	2.11±0.08	93 (0–72 h)
T3	22	36	1.14±0.21	118 (0–192 h)
T2	21	48	0.44±0.16	101 (0–504 h)
T1	21	72	0.28±0.09	35 (0–348 h)
Free Pt:				
ST	24	4	0.45±0.09	6.1 (0–24 h)
T3	22	4	0.34±0.09	4.4 (0–48 h)
T2	21	48	0.02	–
T1	21	–	<0.016	–

Data represent the mean ± SE

scribed by a two-compartment open model (Table 2). No absorption phase was observed after administration by either route, indicating that uptake in the systemic circulation from each site was rapid. Platinum plasma concentrations were consistently lower after i.t. administration than after i.p. administration, resulting in a reduced AUC. Systemic exposure to total and free platinum after i.t. administration of cisplatin was calculated from the AUC values to be approximately 65% and 75%, respectively, of the i.p. values (Table 2).

Slow-release devices. Plasma platinum concentrations after i.t. implantation of slow-release devices with cisplatin are shown in Fig. 8. The highest peak plasma concentrations were obtained using the fast-release formulations ST and T3. Although plasma levels were initially lower after the implantation of T2, the AUC for total plasma platinum was approximately the same as that found for T3 (Table 3). The AUC for T1 was much lower. This indicates that the total platinum exposure obtained with T2 and T3 was similar, although the exposure duration was markedly different. The lower values observed for T1 are in agreement with the high level of platinum remaining in this formulation at 14 days, at which time the animals had to be killed because of regrowing tumour.

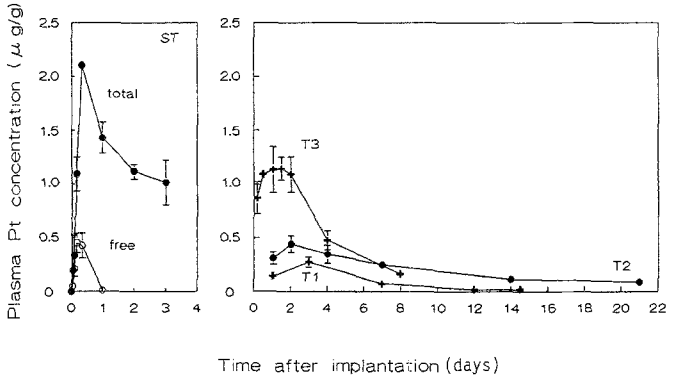

Fig. 8. Platinum concentrations in murine plasma after i.t. implantation of cisplatin in slow-release rods. *Left panel;* total (*closed symbols*) and free (*open symbols*) platinum concentrations after implantation of starch (*ST*) rods. *Right panel:* total platinum after i.t. implantation of cisplatin in hydrogel rods. Cisplatin dose was 21–24 mg/kg. Average of 2–4 mice per point; bars represent ± 1 SEM

Ultrafiltrate (free) platinum levels could be measured at day 1 and 2 after administration of ST and T3, with maximums of 0.45 and 0.34 μg/ml, respectively, being achieved. Ultrafiltrate platinum concentrations obtained with the slower formulations (T2 and T1) were very low, being either of the same magnitude as or lower than the detection limit of the FAAS procedure.

Discussion

The rationale for i.t. drug administration is the simultaneous achievement of higher drug concentrations in the tumour and decreased systemic exposure. The present study found that tumour platinum concentrations after i.t. injection of cisplatin were 3 times those measured after i.p. administration. This is in agreement with the 2–5 times higher tumour platinum concentrations reported by others, who also measured decreased total serum platinum concentrations [15]. These authors did not discriminate between total and free platinum, the latter being believed to represent active (i.e. cytotoxic) platinum species [16, 21]. In the present study, both total and free plasma platinum concentrations were reduced after i.t. administrations, resulting in a reduction in systemic exposure to active platinum species to 70% of the value observed after i.p. injection. These pharmacokinetic data are consistent with the increased tumour response and reduced animal toxicity previously reported for i.t. cisplatin solutions [2, 4, 15, 23, 24].

Tumour platinum concentrations after i.t. implantation of the faster-release ST and T3 rods (100% release within 24 h) reached levels 100 and 30 times those measured after i.p. or i.t. administration of drug in solution, respectively. The cisplatin dose given to the mice in slow-release rods was only 3.9 times higher. The slower-release formulations (duration of drug release, >3 weeks) resulted in lower tumour concentrations. Tumour response and animal toxicity data obtained after i.t. implantation of these slow-re-

lease devices in s.c. RIF1 murine tumours have been reported elsewhere [4]. For equal doses of cisplatin, both tumour response and animal toxicity were found to decrease with decreasing release rate. The maximum tolerated dose therefore increased with decreasing release rate. It is apparent that there is a threshold of release rate below which no biological effect is achieved. The slowest-releasing T1 rods produced a significant plasma AUC (Table 3) without inducing weight loss [4]. Peak plasma levels may correspond better with toxicity, since T1 rods were the only formulation that produced neither measurable free-platinum levels in plasma nor toxicity.

At maximum tolerated doses delivered with i.t. implanted slow-release devices, the tumour responses observed were greater than those noted after i.t. and i.p. injections. This is consistent with the relative plasma and tumour levels achieved for these two modes of treatment. For the hydrogel rods, the doses used in the present study were well below the maximum tolerable doses, whereas that for the ST rods was approximately equal to the maximum tolerated dose for this treatment [4].

In the present study, platinum distribution within the tumour was found to be non-uniform after i.t. administration of cisplatin, whether in solution or in slow-release implants, whereas uniform i.t. distribution of platinum was found after i.p. drug injection. Whereas i.t. injection of dissolved cisplatin resulted in platinum concentrations in the centre of the tumour that were 3.5–4.5 times those observed in the outer rim, i.t. implantation of slow-release devices resulted in a much larger platinum-concentration gradient. These data represented average values obtained in tumour slices of 1.3 mm thickness at early time points. Platinum-concentration gradients on a sub-millimeter scale would probably be larger. These data are consistent with the limited distance reported for cisplatin diffusion into i.p. tumours after i.p. chemotherapy [12, 13]. They are also consistent with the platinum-concentration profile obtained after microinfusion of cisplatin in rat brain [10], which was modelled as a linear diffusion-reaction-permeation process [14]. In this model, the rapid reaction of cisplatin with macromolecules produces bound platinum species that diffuse very poorly and is one of the major reasons for the steep concentration profile obtained [14].

The improved platinum distribution within the tumour after i.t. administration of cisplatin in solution as compared with that observed after i.t. implantation of cisplatin in slow-release devices may have been caused by the relatively large volume of aqueous fluid that was injected with the drug solution (0.1 ml in a tumour volume of 0.5 ml); thus, convective fluid flow may have subsequently contributed to drug distribution. These factors were obviously not involved after implantation of the show-release devices.

The studies on platinum distribution indicate that in the RIF1 tumour model, drug distribution within the tumour is not a problem after administration of cisplatin via a systemic route, but that tumour response is indirectly limited by systemic toxicity (i.e. the drug dose). With the slow-release implants, it is not clear whether the platinum concentration in the periphery of the tumour was caused by exposure to platinum through its direct diffusion within the tumour or by exposure via the systemic circulation. The lowest platinum level within the tumour, i.e. in the outer rim after i.t. implantation of slow-release devices in the centre, determines the overall tumour response. This might explain why no effect on the tumour was obtained with the T1 hydrogel rods [4], although the latter produced average tumour platinum concentrations that were higher than those observed after i.t. administration of cisplatin in solution. Experiments are under way to address this question.

The results of this work show that i.t. administration of cisplatin results in tumour drug concentrations higher than those obtained after i.p. administration, even in peripheral parts of the tumour. After i.t. implantation of slow-release devices containing cisplatin, tumour drug concentrations can increase further and plasma levels can decrease, but the drug distribution within the tumour may become the limiting factor.

References

1. Amano T, Prout GR, Lin C-W (1988) Intratumor injection as a more effective means of porphyrin administration for photodynamic therapy. J Urol 139: 392
2. Begg AC, Bartelink H, Stewart FA, Brown DM, Luck EE (1988) Improvement of differential toxicity between tumor and normal tissues using intratumoral injection with or without a slow-drug-release matrix system. NCI Monogr 6: 133
3. Bier J, Benders P, Wenzel M, Bitter K (1979) Kinetics of [^{57}Co]-bleomycin in mice after intravenous, subcutaneous and intratumoral injection. Cancer 44: 1194
4. Deurloo MJM, Bohlken S, Kop W, Hennink W, Lerk CF, Bartelink H, Begg AC (1990) Intratumoral administration of cisplatin in slow-release devices: I. Tumour response and animal toxicity. Cancer Chemother Pharmacol (in press)
5. Gibaldi M, Perrier D (1982) Pharmacokinetics. Drugs and the pharmaceutical sciences. Marcel Dekker, New York Basel
6. Hecquet B, Fournier C, Depadt G, Cappelaere P (1986) Preparation and release kinetics of microencapsulated cisplatin with ethylcellulose. J Pharm Pharmacol 36: 803
7. Hecquet B, Chabot F, Delatorre Gonzalez JC, Fournier C, Hilali S, Cambier L, Depadt G, Vert M (1986) In vivo sustained release of cisplatin from bioresorbable implants in mice. Anticancer Res 6: 1251
8. Kaetsu I, Yoshida M, Asano M, Yamanaka H, Imai K, Yuasa H, Mashimo T, Suzuki K, Katakai R, Oya M (1987) Biodegradable implant composites for local therapy. J Controlled Release 6: 249
9. Kostron H, Bellnier DA, Lin C-W, Swartz MR, Martuza RL (1986) Distribution, retention, and phototoxicity of hematoporphyrin derivative in a rat glioma. J Neurosurg 64: 768
10. Kroin JS, Penn RD (1982) Intracerebral chemotherapy: chronic microinfusion of cisplatin. Neurosurgery 10: 349
11. Letner C (ed) (1982) Geigy scientific tables, vol 2. Ciba-Geigy, Basle
12. Los G, Mutsaers PHM, Vijgh WJF van der, Baldew GS, Graaf PW de, McVie GJ (1989) Direct diffusion of *cis*-diamminedichloroplatinum(II) in intraperitoneal tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. Cancer Res 49: 3380
13. Los G, Mutsaers PHM, Lenglet WJM, Baldew GS, McVie JG (1989) Platinum distribution in intraperitoneal tumors after intraperitoneal cisplatin treatment. Cancer Chemother Pharmacol 25: 389
14. Morrison PF, Dedrick RL (1986) Transport of cisplatin in rat brain following microinfusion. J Pharm Sci 75: 120
15. Nagase M, Nomura T, Nakajima T (1987) Effects of intralesional versus IP administration of cisplatin on squamous cell carcinoma in mice. Cancer Treat Rep 71: 825

16. Patton TF, Himmelstein KJ, Belt R, Bannister SJ, Sternson LA, Repta AJ (1978) Plasma levels and urinary excretion of filterable platinum species following bolus injection and IV infusion of *cis*-diamminedichloroplatinum(II) in man. Cancer Treat Rep 62: 1359
17. Pedley DG, Skelly PJ, Tighe BJ (1980) Hydrogels in biomedical applications. Br Polym J 12: 99
18. Spenlehauer G, Vert M, Benoit J-P, Chabot F, Veillard M (1988) Biodegradable cisplatin microspheres prepared by the solvent evaporation method: morphology and release characteristics. J Controlled Release 7: 217
19. Takahashi H, Nakazawa S, Shimura T (1985) Evaluation of postoperative intratumoral injection of bleomycin for craniopharyngioma in children. J Neurosurg 62: 120
20. Twentyman PR, Brown JM, Gray JW, Franko AJ, Scoles MA, Kallman RF (1980) A new mouse tumor model system (RIF-1) for comparison of endpoint studies. J Natl Cancer Inst 64: 595
21. Vermorken JB, Van Der Vijgh WJF, Klein I, Gall HE, Van Groningen CJ, Hart GHM, Pinedo HM (1986) Pharmacokinetics of free and total cisplatin species after rapid and prolonged infusion of cisplatin. Clin Pharmacol Ther 39: 136
22. Wenzel M, Schneider M, Bier J, Benders P, Schachschneider G (1979) Concentrations of cytostatic drugs in organs and tumors: comparison after intravenous and intratumoral injection. J Cancer Res Clin Oncol 95: 147
23. Wenzel M, Schneider M, Bier J (1980) Toxicity and cytostatic effect of $PtCl_2(NH_3)_2$ after i. v. and i. t. injection. Z Naturforsch 35 c: 838
24. Yu NY, Conley FK, Luck EE, Brown DM (1988) Response of murine tumors to matrix associated cisplatin intratumoral implants. NCI Monogr 6: 137