Eur J Cancer Clin Oncol, Vol. 24, No. 4, pp. 621–627, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

Pharmacokinetics of Free and Total Platinum Species After Rapid and Prolonged Infusions of Aqua(1,1-bis(aminomethyl)cyclohexane) sulfatoplatinum (II) (Spiroplatin) During a Phase I Trial

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Abstract—*The pharmacokinetics of the second generation platinum complex aqua(1,1-bis-(aminomethyl)cyclohexane)sulphatoplatinum(II) (spiroplatin, TNO-6) were studied during a phase I evaluation. Thirty patients received 49 cycles of spiroplatin by short term (≤ 10-min), 1-, 3- or 6-h infusion. Dosages given ranged from 5 to 40 mg/m². Platinum determinations were performed by atomic absorption spectrometry.*

Up to 5 days after administration platinum concentrations in plasma decayed triexponentially. Pharmacokinetic parameters of total platinum in plasma after short-term and prolonged infusion were similar in terms of terminal half-life (3.7 ± 1.1 and 3.6 ± 0.5 days), AUC/dose (548 ± 106 and 616 ± 278 min.m²/l), volume of distribution (20 ± 6 and 27 ±8 l) and total body clearance (2.9 ± 1.0 and 3.4 ± 1.8 ml/min), whereas peak plasma concentrations were two times lower after prolonged infusion. The cumulative urinary platinum excretion after short-term infusion was 20 ± 6%, 30 ± 6% and 47 ± 7% of the administered dose after 6, 24 and 120 h, respectively. These values are comparable to those after administration of cisplatin. The half-life of ultrafilterable platinum was 4.4 ± 0.7 min. The curves of free and total platinum diverged rapidly, reflecting the high reactivity of spiroplatin towards plasma proteins. This high reactivity, most likely caused by the abundant presence of aquated compounds in the injection fluid, may also account for severe and unpredictable nephrotoxicity induced by spiroplatin.

INTRODUCTION

SPIROPLATIN (aqua(1,1-bis(aminomethyl)cyclohexane)sulphatoplatinum(II), TNO-6, Fig. 1) was synthesized as a member of the interesting class of 1,1-bis(aminomethyl)cyclohexaneplatinum(II) complexes [1]. It was recognized as a highly active analogue of the successful antitumour drug cisplatin in *in vitro* screening experiments [2–4]. In mice and rats spiroplatin also showed antitumour activity and appeared to be less nephrotoxic than cisplatin [4–6]. In dogs, however, nephrotoxicity of spiroplatin was higher than that of cisplatin [5, 7]. The promising preclinical results and the high solubility in water of spiroplatin (>10 mg/ml) were reasons to perform clinical phase I and phase II trials [8–14]. The maximum tolerated doses of spiroplatin were determined as 35 and 9 mg/m² for short-term single dose [10] and a daily times 5 schedule [11], respectively. Prolonged infusion times (1–6 h) were used at doses of 25 mg/m² and higher [8–10] in an attempt to reduce proteinuria. Dose limiting

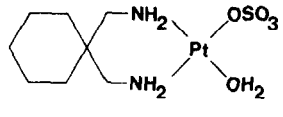

Fig. 1. Structural formula of aqua(1,1-bis(aminomethyl)cyclohexane)-sulfatoplatinum(II) (=spiroplatin).

Accepted 30 September 1987.
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This study was supported by The Netherlands Cancer Foundation (KWF), grant No. AUKC VU 83-7, and Bristol Myers Co. Spiroplatin was supplied by Bristol Myers, Weesp, The Netherlands.

Table 1. Peak plasma concentrations (C_p, not corrected for infusion time) half-lives, areas under the curve (AUC) and amounts involved in enterohepatic circulation (EC) of total Pt *after a short-term infusion (≤10 min) of spiroplatin*

Patient	Dose (mg/m²)	T (min)	C_p (μM)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	$t_{1/2\gamma}$ (days)	Final sample (day)	AUC (min.mM)	EC (%D)
1*	20	2	18.3	1.5	167	4.6	2	39	—
2†	20	2	13.8	3.0	—	2.5	2	30	—
3	25	8.5	11.3	2.6	—	2.9	5	32	2.6
4*	25	10	9.3	2.0	56	3.5	5	38	1.1
5	25	7	8.9	1.7	628	3.8	5	28	3.7
6*	25	7	20.2	3.1	51	2.9	5	70	1.2
7*	30	2	18.6	2.0	91	2.7	5	52	1.8
8	30	1	48.6	1.3	—	2.4	5	27	3.1
9*	30	7.5	16.4	2.7	779	5.2	5	61	0.1
10	35	10	16.1	3.0	393	4.5	3	55	4.1
11	35	5	16.6	2.1	197	5.4	4	54	2.6

*Creatinine clearance <60 ml/min.
†Second cycle.

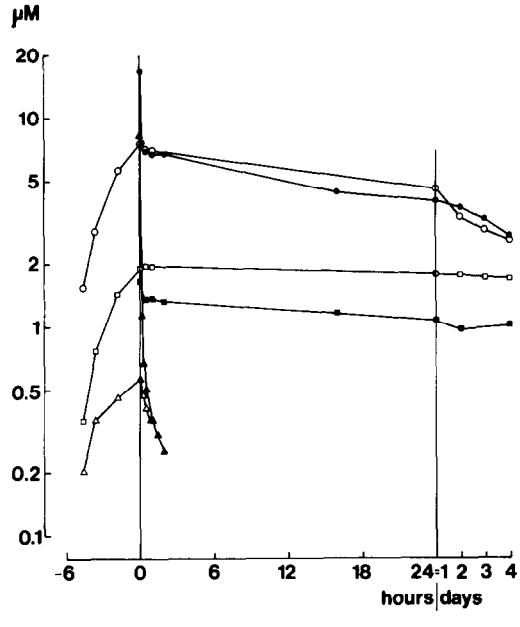

Fig. 2. Semilogarithmic concentration vs. time plots of total Pt (●,○) *and free* Pt (▲,△) *in plasma and* Pt *in RBCs* (■,□) *after short term (patient 11, closed symbols) and 6 h infusion (patient 14, open symbols) of 35 mg/m² spiroplatin.*

toxicities were myclosuppression and nephrotoxicity. The purpose of this study was to investigate the pharmacokinetics of platinum after bolus injection and 1-, 3- or 6-h infusions of spiroplatin during a phase I study and to compare the results with those obtained after the administration of cisplatin.

PATIENTS AND METHODS

Patients and materials

Pharmacokinetic studies were performed in 30 patients with advanced solid tumours. Twenty-one received 40 cycles of spiroplatin at 3 week-intervals by short-term (≤10 min) intravenous (i.v.) infusion. The doses ranged from 5 to 40 mg/m². The other nine patients received nine cycles of spiroplatin (dose range 30–40 mg/m²) by 1-, 3- or 6-h infusion. The median age of the patients (15 females, 15 males) was 56 years (range 21–74 years). All patients had normal liver function. Creatinine clearance was decreased (25–60 ml/min) at the start of 17 of the 49 cycles. Spiroplatin was supplied by Bristol Myers (Weesp, The Netherlands) in ampoules containing an aqueous solution of 10 mg/ml (23 mM). The appropriate amount of this solution was diluted in 20–500 ml of 5% glucose within 1 h before administration. Concentrations of the administered solutions ranged from 0.17 to 5.6 mM.

Sampling and analysis

Blood samples (5 ml) were collected in heparinized tubes prior to the administration of spiroplatin, at the end of the infusion and at 10, 20, 30, 60, 90, 120, 150, 180, 210, 240, 360, 480 min and at 1, 2, 3, 4, and 5 days after the end of the infusion. Some patients were sampled only daily up to 5 days. Additional samples were taken on an hourly basis during prolonged infusions. Samples were processed immediately after collection. Blood was centrifuged and plasma was frozen. In 11 courses 1-ml plasma samples were ultrafiltrated in the MPS-1 micropartition system provided with YMT filters (Amicon, Oosterhout, The Netherlands) [15] up to 60 min after administration. Red blood cells (RBCs) were washed twice with an equal volume of normal saline. Urine was collected in portions of 6 h during the first day and daily up to day 5. This sampling scheme could not be performed in all patients, therefore different groups of patients were used to calculate the various pharmacokinetic parameters. All samples were stored at −25°C and thawed just prior to analysis. Platinum concentrations in plasma (total Pt), plasma ultrafiltrate (free Pt), RBCs and

Table 2. Pharmacokinetic parameters of total Pt [*mean ± S.D.* (n)] *after short-term and* 3- *or* 6-h *infusions of spiroplatin*

Parameter		Short-term infusion CL_{cr}* > 60		Short-term infusion CL_{cr}* < 60		3- or 6-h infusion	
$t_{1/2\gamma}$	days	3.6 ± 1.2	(6)	3.8 ± 1.1	(5)	3.6 ± 0.5	(5)
AUC/D	min.m²/l	548 ± 106	(6)	870 ± 207	(5)	616 ± 278	(6)
V_c†	l	4.9 ± 1.6	(6)	4.5 ± 1.1	(5)	—	
V_{ss}†	l	23.4 ± 6.1	(6)	16.0 ± 4.9	(5)	27 ± 8	(6)
CL†	ml/min	3.3 ± 0.7	(6)	2.1 ± 0.4	(5)	3.4 ± 1.8	(6)

*CL_{cr} = creatinine clearance (ml/min) before administration of the drug.
†Normalized to 1.73 m² body surface area.

urine were determined by atomic absorption spectrometry (AAS) as described before [16].

Pharmacokinetic data analysis

Postinfusion plasma concentration vs. time curves of total Pt after both short-term and prolonged infusions were fitted to a polyexponential equation $C = \Sigma Y_i \exp(-\lambda_i t)$ by the NONLIN computer program [17]. Y_i values of bolus injections were corrected for infusion time (T): $C_i = (-\lambda_i T Y_i)/(\exp(-\lambda_i T) - 1)$. From the obtained coefficients C_i and exponents λ_i half-life, area under the concentration vs. time curve (AUC = $\Sigma C_i/\lambda_i$) and area under the first moment of the plasma curve (AUMC = $\Sigma C_i/\lambda_i^2$) were determined [18]. The AUC and AUMC during 1-, 3- and 6-h infusion were determined by the linear trapezoidal rule and after infusion from $\Sigma Y_i/\lambda_i$ and $\Sigma Y_i/\lambda_i^2$. Total body clearance (CL = D/AUC, D = dose) and volumes of distribution ($V_c = D/\Sigma C_i$, only after short-term infusion, and V_{ss} = CL × AUMC/AUC) were determined [18]. Additionally, the half-life of total Pt over the time interval 1–5 days was calculated by a linear fit of the semilogarithmic C–t plot with the least squares method. This method was also used to calculate the first part of the biphasic decay of free Pt. The relative amount of platinum involved in enterohepatic recycling was calculated by the curve stripping procedure described earlier [19]. Renal clearance (Cl_R) of free Pt was determined during prolonged infusions by the cumulative urinary excretion (CUE) divided by the AUC, both measured over the same time-interval.

Values of clearance and volume of distribution were normalized to 1.73 m² body surface area. The Student's t and Spearmans rho tests were used for statistical evaluation.

RESULTS

Short-term infusions

As an example, Fig. 2 shows the concentration vs. time curves of total Pt and free Pt in patient 11 after a short-term infusion. The very short distribution phase of total Pt was followed by a long elimination phase. The total Pt concentration vs. time data of 11 patients, who could be completely sampled for at least 2 days, were fitted to a polyexponential curve by NONLIN. Peak plasma concentrations, half-lives and AUCs are shown in Table 1. In three patients the decline of total Pt could only be described by two phases, while in the other eight a 3-exponential decay was observed. The half-lives of the second phase in the latter patients varied widely around a median value of 182 min (mean 295 ± 277 min). The $t_{1/2\alpha}$, which could only be observed during the first 10 min after administration, was very short (2.2 ± 0.6 min), indicating a very rapid distribution to the tissues, from which Pt was slowly released as indicated by the long terminal half-life. The intercept of the elimination phase of total Pt during first cycles only (n = 12), as calculated by the linear least squares method, correlated with the dose ($P < 0.05$), dose range 15–40 mg/m²), indicating linear pharmacokinetics.

A secondary peak between 1 and 3 h after administration was observed in 14 out of 21 curves, from patients extensively sampled for at least the first 24 h after infusion, indicating a second influx of platinum into the plasma compartment probably due to enterohepatic recirculation. Eleven of these 21 curves comprised 3 or more days, which allowed an estimation of the amount of platinum involved in this process [19]: 2.3 ± 1.2% of the dose. Most individual values are given in Table 1.

Mean values of the main pharmacokinetic parameters of total Pt are shown in Table 2. These values were separately calculated for patients with a normal and reduced creatinine clearance. The mean final half-life calculated over days 1–5 by means of the linear least squares method was 4.0 ± 0.6 days (n = 17), being similar to the NONLIN-values. A decreased creatinine clearance had no influence on $t_{1/2\gamma}$ and V_c, but clearly increased AUC/D and decreased V_{ss} and CL. The values of V_c corresponded with the volume of intravascular fluid, while the low values of V_{ss} indicated that a large amount of spiroplatin is bound to plasma proteins.

Table 3. Cumulative urinary excretion [CUE, mean ± S.D. (n)] after short-term and 3- or 6-h infusions of spiroplatin

Time interval	Short-term infusion		3- or 6-h infusion
	CL_{cr}* > 60	CL_{cr}* < 60	
0–6 h	20 ± 6 (11)	10 ± 5 (10)	15 ± 8 (5)
0–24 h	30 ± 6 (23)	23 ± 9 (10)	28 ± 11 (4)
0–5 days	47 ± 7 (12)	46 ± 14 (6)	42 ± 12 (3)

*CL_{cr} = creatinine clearance (ml/min) before administration of the drug.

Table 4. Peak plasma concentrations (C_p), half-lives and areas under the curve (AUC) of total Pt after 3- or 6-h infusions of spiroplatin

Patient	Dose (mg/m²)	T (h)	C_p (μM)	$t_{1/2\beta}$ (min)	$t_{1/2\gamma}$ (days)	AUC (min.mM)
12*	35	3	8.7	220	4.3	54
13	35	3	7.2	221	3.1	31
14*	35	6	7.5	539	9.6	87
15	35	6	9.2	412	3.6	54
16*	35	6	9.2	165	3.7	52
17	40	6	5.6	164	3.1	25

*Creatinine clearance < 60 ml/min.

Ultrafilterable platinum concentrations rapidly dropped to concentrations far below total Pt concentrations, indicating a rapid binding of platinum to plasma proteins and tissues. The decline was biphasic. A second phase generally appeared after 20 min. The half-life of the second phase was strongly dependent on the time over which the patient was sampled (<4 h). Therefore, consistent $t_{1/2\beta}$-values could not be obtained for free Pt (range 52–115 min). For that reason, only the concentration–time points of the first linear part of the curves (0–10 min) were used to calculate $t_{1/2\alpha}$ (4.4 ± 0.7 min, $n = 6$).

The cumulative urinary excretion of platinum (CUE) measured over the time-intervals 0–6 h and 0–24 h (Table 3) was lower in patients with a decreased creatinine clearance than in patients with a normal kidney function ($P < 0.01$ and $P < 0.05$, respectively). After 5 days the CUE became similar for patients with a normal and a reduced renal function.

1–6 h *infusions*

Table 4 shows the peak concentrations (C_p), half-lives and AUCs of total Pt in six patients, who received spiroplatin as an infusion of 3 or 6 h. Peak plasma concentrations were lower than after short term infusion of comparable doses. A distribution phase, as observed after short-term infusion, was absent after prolonged infusion, due to the fast distribution that already occurred during the infusion. The mean half-life of the second phase was 287 ± 154 min (median 220 min) and again a long terminal half-life was observed. Mean values of half-life, AUC/D, volume of distribution and clearance of total Pt were comparable with those after short-term infusion (Table 2). No distinction was made between patients with decreased creatinine clearance and those with normal kidney function because of the small number of patients. The cumulative urinary excretion of Pt (Table 3) and the final half-life calculated over day 1–5 by means of the linear least squares method (3.5 ± 0.5 days, $n = 8$) were also comparable with those after short-term infusions.

Figure 2 shows the concentration vs. time curves of total and free Pt in the plasma of patient 14 during and after a 6-h infusion. From 10 min after administration onwards the curve of total Pt vs. time ran parallel to that after short-term infusion of spiroplatin. During infusion free Pt concentrations were about ten times lower than total Pt concentrations. The AUC/D (min.m²/l) of free Pt increased with increasing duration of infusion: 0.91 ± 0.15 ($n = 6$) for short-term infusion and 1.34 ($n = 1$), 1.47 ± 0.28 ($n = 4$) and 1.81 ± 0.09 ($n = 4$) for 1-, 3- and 6-h infusions, respectively. Renal clearance was determined during infusion, because only then were free Pt concentrations in plasma and urine available over the same time interval. The mean renal clearance of free Pt during infusion was

Table 5. Pharamcokinetic parameters of total and free Pt [*mean ± S.D.* (n)] *after short-term i.v. infusions of spiroplatin and cisplatin*

Parameter		Spiroplatin		Cisplatin	
Total Pt					
$t_{1/2\alpha}$	min	2.3 ± 0.6	(11)	14 ± 4	(7)*
$t_{1/2\gamma}$	day	4.0 ± 0.6	(17)	5.4 ± 1.0	(7)*
AUC/*D*	min.m²/l	548 ± 106	(6)	332 ± 66	(7)*
EC	%*D*	2.3 ± 1.2	(11)	1.4 ± 0.5	(7)*
Free Pt					
$t_{1/2\alpha}$	min	4.4 ± 0.7	(6)	24 ± 6	(5)†
AUC/*D*	min.m²/l	0.9 ± 0.2	(6)	4.9 ± 0.5	(3)§
CL_R	ml/min	86 ± 47	(4)	70 ± 26	(7)§
CUE (0–6 h)	%*D*	20 ± 6	(11)	24 ± 5	(7)*
CUE (0–5 d)	%*D*	47 ± 7	(12)	40 ± 4	(7)§

*Ref. [19].
†Without correction for subsequent phases.
‡Ref. [31].
§Ref. [16].

86 ± 47 ml/min (n = 4), while the mean total body clearance was 878 ± 64 ml/min (n = 5). A non-renal (metabolic) clearance of 803 ± 52 ml/min (n = 4) was estimated by subtracting both values.

Platinum was rapidly taken up by RBCs. Plateau values were obtained immediately after administration of the drug, although sometimes (and especially after short-term infusions) small peaks could be observed for a very short time (< 30 min) probably caused by contamination with plasma. Plateau values after a dose of 35 mg/m² were 1.6 ± 0.2 μM (n = 3) and 1.7 ± 0.2 μM (n = 5) after short-term and prolonged infusions, respectively. This concentrations means that about 2.4% of the dose is bound to RBCs [20]. Pt in RBCs declined in a monoexponential way with a half-life of 8.7 ± 3.0 days (n = 13) as measured over 5 days after infusion.

DISCUSSION

The second generation platinum complex spiroplatin was clinically evaluated in phase I and II trials [8–14]. In this study we investigated the pharmacokinetics of total and free Pt during a phase I study, in which spiroplatin was given as an i.v. bolus injection or by prolonged infusion (1–6 h) once every 3 weeks. If possible, samples were obtained over 5 days in accordance to the scheme used earlier for cisplatin [16, 19], which facilitates comparison of the main pharmacokinetic parameters between the two compounds as shown in Table 5. The analytical methodology for the determination of spiroplatin and derivatives was under development during and after the clinical studies [21, 22]. Therefore, the original compounds could not be quantitated in body fluids during the study. However, the chemical findings [22] appeared to be important for possible explanations of (pre)clinical and pharmacokinetic observations.

Free platinum concentrations concern (a) injected platinum species, (b) low molecular weight metabolites and (c) degradation products from Pt–protein complexes. In the case of spiroplatin, each of the three categories consists of several platinum compounds. The spiroplatin solutions administered to the patients did not contain a well defined single component but rather a mixture of aquated platinum complexes in mutual equilibrium [22], e.g. a 2.3 mM solution of spiroplatin contained only 17% of the original drug (monoaqua-monosulphato complex), and 70% was hydrolysed to the diaqua form. The remaining part consisted of dimer, trimer, monoaqua–monochloro and dichloro complexes. After dilution with water a further hydrolysation of the monosulphato complex was observed [22]. All aqua complexes are highly reactive, the diaqua complex having the highest reactivity [22]. Low molecular weight metabolites are ultrafilterable molecules formed between the injected Pt-species and low molecular weight endogenous compounds containing strong nucleophilic groups. The injected platinum species also react with macromolecules in plasma and tissues from which low molecular weight platinum complexes are released by breakdown of the macromolecules. These breakdown products, which should be present over the time that Pt is retained by the body, could not be observed due to the low dose and the detection limit of the assay.

Just like after cisplatin, decay of total Pt after spiroplatin in plasma could be described by a tri-exponential equation. The initial half-life of distribution was much shorter than that of cisplatin, while the terminal half-life was equivalent to that of cisplatin (Table 5). The short initial half-life

together with the very early divergence of the free and total platinum curves are indicative for the high reactivity of the injected platinum species towards plasma proteins and tissues. The faster protein binding of spiroplatin compared to cisplatin, which was also observed *in vitro* [15, 23], resulted in a lower AUC/*D* of free Pt and in a higher AUC/*D* of total Pt (Table 5). The volume of distribution of total Pt was also lower after spiroplatin than after cisplatin (62 ± 17 l [19]). This small volume of distribution of total Pt suggests that binding of spiroplatin species principally took place in plasma and in organs with a high blood flow. The similarity of the final half-lives can be explained by the degradation of the same plasma proteins to which platinum, originating from either compound, is similarly bound in both cases and the subsequent excretion of comparable Pt-containing degradation products.

Secondary peaks of total Pt indicated enterohepatic recirculation. This phenomenon was also observed in man after short-term infusions of cisplatin [19]. The amounts of Pt involved in enterohepatic circulation were higher after the administration of spiroplatin than after cisplatin (Table 5). This is in agreement with the observation in rats that biliary excretion of Pt was higher after spiroplatin than after cisplatin [24].

The AUC/*D*-value of free Pt increased with increasing infusion time. This effect could not be observed for AUC/*D* of total Pt. This finding is in contrast to the AUC/*D*-values of free Pt after the administration of cisplatin, being independent of infusion time [16]. A possible explanation might be the change in constitution of the infusion fluid occurring during the time of infusion, due to shifts in the equilibria between the Pt-compounds originating from spiroplatin after preparation of the infusion fluid [22]. The diminished proteinuria obtained after prolonged infusions [7, 8] may be the result of decreased peak plasma concentrations. Generally, proteinuria was unpredictable and more severe than after other platininum compounds like cisplatin, carboplatin or JM-40 [13, 14, 25–27]. This may be caused by varying amounts of hydrolysed spiroplatin present in the infusion fluid [22] and can probably be overcome—at least in part—by the addition of sodium sulphate to the infusion fluid, as was observed in rats [28].

Renal clearance and CUE of free Pt were comparable with those of cisplatin (Table 5). The relation of the renal Pt excretion with the creatinine clearance (Table 3), which was also observed for carboplatin [29], and the value of the renal clearance measured after prolonged infusion (86 ml/min) suggest that spiroplatin derived platinum species are principally excreted by glomerular filtration. Understandably, this does not rule out the possibility that tubular excretion and reabsorption may occur at the same time.

The more rapid and extensive binding of spiroplatin to RBCs compared to the values obtained after cisplatin (2.6 vs. 0.6 %*D*) [20] also reflects its high reactivity. In fact, of several analogues studied in the clinic spiroplatin is the only one with a higher chemical reactivity than the parent compound [30]. Although spiroplatin induced some partial responses [13, 14], it was withdrawn from the clinic because of its unpredictable nephrotoxicity. The abundant presence of hydrolysed platinum compounds in the infusion fluids may explain—at least in part—the clinical and pharmacokinetic data obtained.

Acknowledgements—F. Varossieau is acknowledged for technical assistance.

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