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ORIGINAL ARTICLE

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Atypical pharmacokinetics and excretion of new platinum analogues in rodents

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Abstract *Purpose*: Two new series of platinum complexes with cytotoxic activity in vivo are $[Pt(NRCH_2)_2L_2]$, (R = polyfluorophenyl, L = pyridine or substituted pyridine) and $[Pt(NRCH_2CH_2NR'_2)_2L(X)]$, (R, L as before; R′ = Me or Et, X = halogen). The aim of this study was to determine the pharmacokinetics and excretion in mice and in isolated perfused rat livers of a representative compound from each class, respectively: Pt103 (R = *p*-HC_6F_4, L = pyridine) and Pt109 (R, L as for Pt103, R′ = Et, X = I). *Methods*: Mice were given intraperitoneal injections of active doses of Pt103, Pt109, or cisplatin in a variety of vehicles. Blood was sampled at several times to 48 h. Some mice were placed in metabolic cages where urine and feces were collected. In isolated, perfused rat livers, perfusate and bile were collected following a dose of Pt103, cisplatin or carboplatin. Platinum was measured in blood, urine, feces, or perfusate by atomic absorption spectroscopy. Three vehicles used were peanut oil, dimethyl sulphoxide, and saline/Tween 20. *Results*: In contrast to renal excretion of over 70% for cisplatin in saline, urinary excretion of platinum was less than 24% of a dose of Pt109 in peanut oil, less than 21% of Pt103 in DMSO, and only 4% for Pt103 in peanut oil. Over 60% of Pt103 was eliminated in mouse feces, and 57% was excreted in bile from rat liver. Plasma protein binding of Pt109 was greater than 90% at 6 h following administration in mice. *Conclusion*: In contrast to cisplatin and carboplatin, representatives of two new classes of platinum anticancer agents undergo minimal renal elimination, but are excreted mainly in the bile and feces. If a platinum complex with a similar excretion profile was introduced into the clinic, there might be a therapeutic advantage in terms of drug toxicity and combination therapy with other cytotoxics.

Keywords Platinum · Pharmacokinetics · Excretion · Biliary clearance

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Introduction

Cisplatin (*cis*-diamminedichloroplatinum(II)) is widely used for the treatment of many cancers including breast, lung, head and neck, ovary and testes [5]. Although the dose-limiting renal toxicity of cisplatin can be avoided by the use of its less-toxic analogue carboplatin (diammine(1,1-cyclobutanedicarboxylato)platinum(II)), many tumour types do not respond to either drug, and the development of resistance remains a significant clinical problem. Many research groups are therefore focusing on the development of platinum analogues with more activity and an acceptable toxicity profile [4, 12]. Two unique series of fluorocarbon-stabilized platinum(II) organoamides have recently been synthesized [1, 2, 3]. The general structures of these compounds are $[Pt(NRCH_2)_2L_2]$ (R = polyfluorophenyl, L = pyridine or substituted pyridine) with a lead compound known as Pt103 (R = *p*-HC_6F_4, L = pyridine), and $[Pt(NRCH_2CH_2NR'_2)_2L(X)]$ (R, L as before; R′ = Me or Et, X = halogen) with a lead compound known as Pt109 (R, L as for Pt103, R′ = Et, X = I; Fig. 1).

Previous studies with Pt103 and Pt109 have shown anticancer activity both in vitro and in vivo against a variety of tumour models, including activity against

platinum-resistant cell lines in vitro [9, 14]. We now report the pharmacokinetics and excretion in mice of platinum from Pt103, Pt109 and cisplatin at selected doses using various vehicles. We also examined the hepatic elimination and biliary excretion of platinum from Pt103, cisplatin and carboplatin using the isolated perfused rat liver model.

Materials and methods

Chemicals

Pt103 and Pt109 were prepared by previously reported methods [1, 2, 3]. Cisplatin and carboplatin were generous gifts from the Institute of Drug Technology, Melbourne, Australia. Triton X-100, and DMSO (dimethyl sulphoxide) were from BDH (Kilsyth, Victoria, Australia), and platinum chloride standard was from BDH (Poole, UK). Tween 20, peanut oil and benzethonium hydroxide were from Sigma Chemical Co., St Louis, Mo.

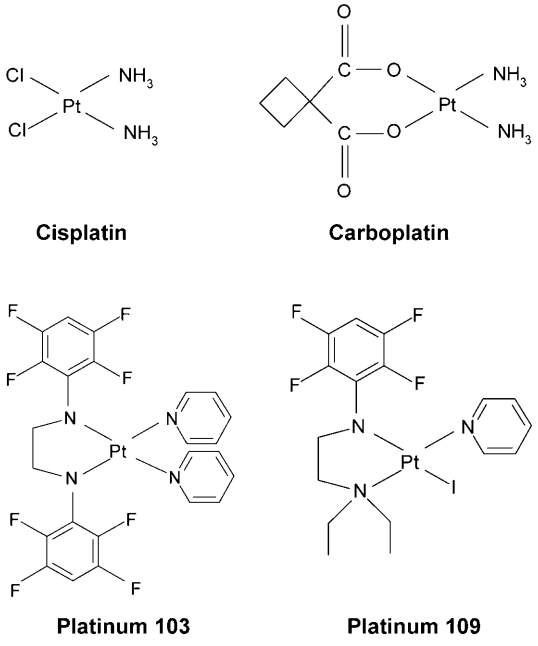

Fig. 1 Structures of cisplatin, carboplatin, Pt103 and Pt109

Pharmacokinetics and excretion in mice

All animal protocols were approved by the Institute's Animal Experimentation Ethics Committee. Animals had free access to food and water throughout all experiments, and were housed in a clean conventional facility with specific pathogen-free status with 12-h light/dark cycle. Female Balb/c or $B_6D_2F_1$ mice aged 8 to 14 weeks were used.

Doses were chosen to reflect the active dose as determined previously in studies of antitumour activity (Table 1). Doses were non-toxic as determined by weight loss unless otherwise noted. Cisplatin was dissolved in saline (0.9% NaCl). Pt103 and Pt109 are water-insoluble, and were either dissolved in DMSO or suspended in 1% Tween 20/saline (1:9 v/v), or ethanol/1% Tween 20/saline (1:10:90), or sonicated in peanut oil. Drugs were injected i.p. (intraperitoneally) at a volume of 10 ml/kg except when in DMSO, which was toxic above 2.5 ml/kg. Oral administration of Pt109 in peanut oil (10 ml/kg) was also investigated.

For pharmacokinetic studies, blood (20 μl) was sampled from a tail vein using a heparinized capillary tube following puncture with an 18 gauge needle, just prior to dosing and at 9 to 12 time-points up to 48 h later. The sample was expelled into 200 μl of a 1:1 (v/v) solution of 0.1% Triton-X-100 and sodium heparin (40 U/ml) and stored at 4°C until analysis. To investigate plasma protein binding, mice were given 150 μmol/kg Pt109 in peanut oil, and three mice at each of several time-points from 30 min to 6 h were anaesthetized and bled by axillary dissection. From each sample, 50 μl blood was treated as above, and plasma was obtained from the remaining blood by centrifugation, followed by ultrafiltration with Ultrafree (Millipore) units with a molecular weight cut-off of 30,000 Da to obtain ultrafiltrate, which was stored at 4°C until analysis.

For excretion studies, mice were placed in Nalgene metabolic cages for 48 h following dosing. Every 24 h, the collected urine and feces were weighed, and the cage was washed with two 10-ml volumes of warm water that were collected to recover urine that remained on the cage. All samples were stored at –20°C prior to analysis.

Isolated perfused rat liver studies

Non-fasting male Sprague-Dawley rats (200–280 g) were anaesthetized with sodium pentobarbitone (60 mg/kg i.p.) and their livers

1% Tween 20 with a mortar and pestle and nine parts saline added to achieve an appropriate concentration; *ethanol/saline/Tween* drug dissolved in ethanol to final concentration of 1%, followed by 1% Tween 20 and saline (1:10:90); *peanut oil* drug sonicated to form a suspension (*ND* not done, *MTD* maximum tolerated dose; top active dose was generally close to the MTD)

Drug	Vehicle	P388[a]		ADJ/PC6[b]	
		Dose (μmol/kg)	Activity	Dose (μmol/kg)	Activity
Pt103	Saline/Tween	70–170	Active	ND	
	Saline/ethanol	56–113	Active	ND	
	DMSO	226	Inactive	ND	
	Ethanol/saline/Tween	ND		170	Very active
	Peanut oil	ND		141	Moderately active
Pt109	Saline/Tween	75–300	Active	ND	
	Ethanol/saline/Tween	ND		300	Inactive
	Peanut oil	ND		226 (MTD)	Activity not tested
Cisplatin[c]	Saline	21	Very active	21	Very active

[a]Drug schedule: every 4 days ×3
[b]Single dose
[c]21 μmol/kg = 6 mg/kg

surgically isolated by standard techniques and perfused as previously described [13]. The portal vein, thoracic inferior vena cava and bile duct were cannulated and the liver was connected to a recirculating, oxygenated perfusion circuit at 15 ml/min at a constant temperature of 37°C. Total perfusate volume was 80 ml, consisting of 20% (v/v) washed human red blood cells, 4% (w/v) bovine serum albumin (Fraction V, Commonwealth Serum Laboratories, Melbourne, Australia) and 0.1% (w/v) D-glucose in a modified Krebs Henseleit buffer (pH 7.4). Sodium taurocholate was infused into the perfusate reservoir at 30 μmol/h to maintain bile flow. Liver viability was confirmed for the duration of the 3-h experiments by normal values for bile flow (greater than 0.5 ml/h), perfusion back pressure (less than 8.0 cm water), oxygen consumption (2.0–4.0 μmol/g liver per min) and homogeneous appearance.

All drugs were given as a 2.8 μmol bolus dose to the perfusate reservoir to simulate systemic administration. Pt103 was dissolved in DMSO (40 μl), cisplatin was delivered in 0.9% saline, and carboplatin in water. Perfusate samples (750 μl) for drug estimation were taken from the reservoir at ten time-points between 2 and 180 min after addition of drug, and the volume replaced with fresh perfusate. Drug amounts lost through sampling were less than 5% of the dose. Red blood cells were removed by centrifugation. Bile was collected in preweighed vials at 30-min intervals. All samples were stored at –20°C prior to assay.

Platinum analyses

Platinum concentrations were measured in biological fluids by graphite furnace atomic absorption spectroscopy (Perkin Elmer 3030) using our previously reported method [6] for plasma, blood, and urine. Bile was diluted with a matrix modifier consisting of 0.11% w/v EDTA-diammonium salt, 0.33% w/v ammonium dihydrogen orthophosphate (both from BDH, Poole, UK), 0.1% w/v Triton X-100, with pH adjusted to 6.5 using ammonia solution. Feces were digested with benzethonium hydroxide (1 ml plus 200 mg feces) by heating for 24 h at 55°C. Samples were further diluted to 2.3% benzethonium hydroxide by addition of 0.1 *M* HCl. Calibration was against a standard curve of 0.64 to 5.13 μ*M*, and samples were diluted if out of range using 0.1% Triton-X-100 for blood, and 0.1 *M* HCl for urine, perfusate and plasma ultrafiltrate. The minimum quantifiable concentration was 0.15 μ*M*.

Pharmacokinetic analyses

Cmax (maximum plasma platinum concentration) and Tmax (time of maximum platinum concentration) were tabulated from the data. The area under the plasma-concentration versus time curve (AUC) was calculated with the trapezoidal rule using the measured platinum concentrations in plasma, ultrafiltrate or perfusate. For unbound platinum, elimination half-life was calculated by linear regression of the log-linear concentration-time plot. For the perfused liver studies, perfusate clearance was calculated as dose/AUC(0–180 min), and biliary clearance was the amount excreted in bile/perfusate AUC.

Results

Pharmacokinetics

Although absorption of Pt103 in saline/Tween was rapid, with a Tmax less than 30 min (the first time-point for this study), the AUC was sevenfold lower than the identical dose in peanut oil, and the Cmax was also reduced (Fig. 2; Table 2). Pt109 was more rapidly absorbed from peanut oil than Pt103, and when dissolved in DMSO Pt109 was absorbed at a rate similar to that from peanut oil, but achieved double the Cmax and

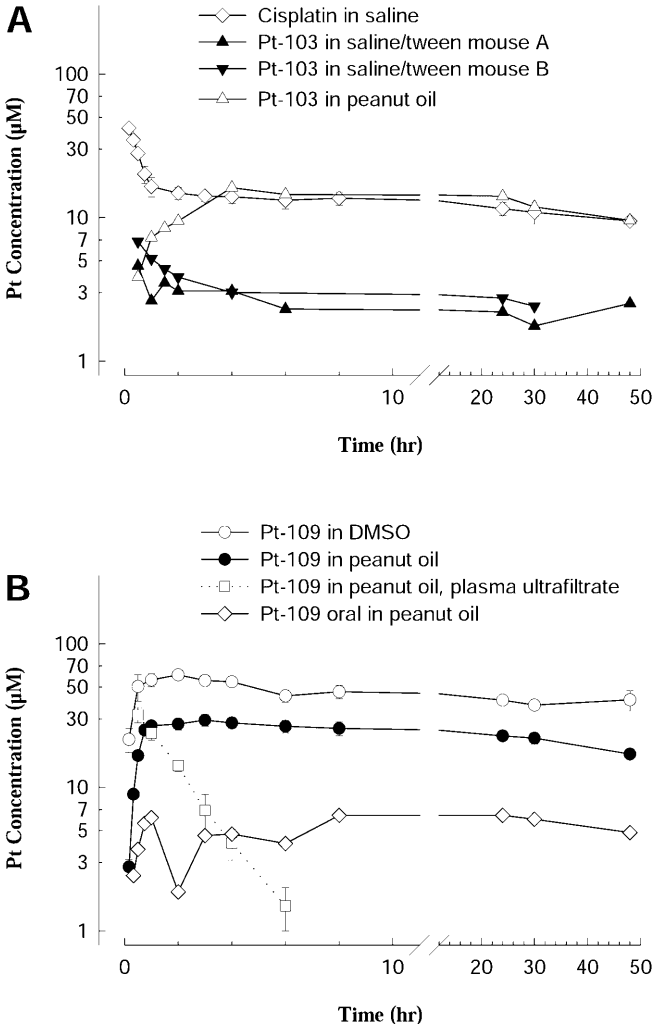

Fig. 2A, B Semilogarithmic plots of platinum concentrations in blood (or plasma where indicated) of mice following drug administration in various vehicles. **A** 27 μ*M* cisplatin ($n=3$ mice) and 141 μ*M* Pt103 (representative plots from individual mice). **B** 150 μ*M* Pt109 ($n=3$ mice per plot) and for plasma ultrafiltrate ($n=3$ mice per point). All doses given i.p. except oral Pt109 where indicated. Values are means ± SEM, $n=3$

AUC. Absorption of an oral dose of 150 μmol/kg Pt109 in peanut oil was erratic, with multiple peaks, and a relatively low AUC (Fig. 2B). In addition, despite the higher molar doses of both platinum complexes, both Cmax and normalized AUC from delivery in peanut oil were lower than for cisplatin in saline (Table 2). The extent of absorption of cisplatin when delivered in peanut oil was less than half that of an identical dose in saline, as indicated by the AUC (Table 2). The dose-normalized AUC was identical for both 90 and 150 μmol/kg Pt109, indicating dose-independent pharmacokinetics in this range. The terminal elimination half-life of total platinum for all drugs was similar and was longer than could be determined by the 48-h sampling schedule. Plasma protein binding was investigated for Pt109, and following a dose of 150 μmol/kg in peanut oil to three mice per time-point, unbound platinum

in plasma declined monoexponentially with a half-life of 2.7 ± 0.4 h and AUC of 71 ± 12 μM·h (mean ± SD) (Fig. 2B). By 6 h, 90% of the platinum was bound.

Whole animal excretion studies

The most notable feature of the elimination from mice was the lower renal excretion of both Pt103 and Pt109 compared with cisplatin (Table 3). Less than 2% of a dose of Pt103 in saline/Tween was recovered in urine, and only 4% from peanut oil, compared with over 70% for cisplatin in saline. From three doses of Pt103 in DMSO, roughly 20% was recovered in urine. Again in contrast to cisplatin, the majority of the dose of Pt103 was recovered in feces. The lack of feces produced at the high dose in DMSO reflects toxicity seen in that group of mice. Pt109 in peanut oil was excreted in urine to a fivefold greater extent than Pt103 in the same vehicle. Renal excretion of cisplatin suspended in peanut oil was approximately half that from saline, while 84% of cisplatin in DMSO was recovered in urine, and total recovery was very high at 96%. Less than 6% of an oral dose of Pt109 was excreted in urine (data not shown). Over 90% of the urinary and fecal excretion for all drugs occurred in the first 24 hr.

Hepatic elimination studies

The elimination profiles of cisplatin, carboplatin or Pt103 in the isolated perfused rat liver demonstrate that Pt103 was rapidly eliminated from perfusate in the first 30 min, followed by a plateau, suggestive of irreversible protein binding (Fig. 3). In contrast, both cisplatin and carboplatin remained at relatively constant perfusate concentrations. Biliary excretion of platinum from Pt103 was high, accounting for 57% of the dose, and this occurred within the first hour (Table 4). Only small amounts of the dose of platinum from either cisplatin (3%) or carboplatin (1%) were recovered in the bile. Liver function (oxygen consumption, bile flow) remained normal throughout all the experiments.

Discussion

This study showed that two platinum complexes with antitumour activity in animals have platinum excretion profiles notably different from those of both cisplatin and carboplatin. This was evidenced by the low renal excretion in mice of both Pt103 and Pt109 compared with cisplatin, as well as the high biliary clearance of Pt103 in the isolated perfused rat liver compared with both cisplatin and carboplatin. The results for cisplatin and carboplatin are in agreement with previous findings. For example, Siddik et al. found 50% and 90% of a dose of cisplatin and carboplatin, respectively, was excreted in the urine in mice [8], and biliary excretion in rats is less than 1.2% of the dose for both drugs [7]. In humans, 42% of a dose of cisplatin [11], representing 90% of total drug eliminated from the body, and 70% of a dose of carboplatin [10], are eliminated as platinum in the urine.

Table 2 Pharmacokinetics of total platinum in blood from mice receiving intraperitoneal cisplatin, Pt103, or Pt109, or oral Pt109. Drug preparation and vehicles same as in Table 1 Mean ± SEM

Drug	Vehicle	*n*	Dose (μmol/kg)	Pt Cmax (μM)	Tmax	Pt AUC_{0-48h} (μM·h)	Pt AUC normalized[a]
Pt103	Saline/Tween	2	141	5.7 ± 1.1	< 30 min	99 ± 10	0.7
	Peanut oil	2	141	17.3 ± 1.1	4–6 h	663 ± 67	4.7
Pt109	DMSO	3	150	60.9 ± 2.5	2 h	2039 ± 165	14
	Peanut oil	5	150	29.4 ± 1.3	2–3 h	1032 ± 49	7
	Peanut oil	3	90	23.5 ± 3.0	2 h	655 ± 80	7
Pt109, oral	Peanut oil	3	150	6.9 ± 0.3	2–8 h	255 ± 14	1.7
Cisplatin	Saline	3	27	42.0 ± 0.7	< 10 min	570 ± 51	21
	Peanut oil	3	27	16.7 ± 2.1	< 20 min	264 ± 27	10

[a]AUC divided by dose

Table 3 Excretion of platinum drugs following intraperitoneal administration in mice. Values are means ± SEM. Drug preparation and vehicles same as in Table 1 (*XX* no feces excreted in 48 h, *ND* not done)

Drug	Vehicle	*n*	Dose (μmol/kg)	Pt excreted 0–48 h (%)	
				Urine	Feces
Pt103	Saline/Tween	3	141	1.5 ± 0.5	ND
	Peanut oil	3	141	4 ± 1	61 ± 6
	DMSO	5	14	16 ± 1	66 ± 9
	DMSO	6	56	21 ± 1	60 ± 5
	DMSO	3	113	21 ± 5	XX
Pt109	Peanut oil	4	90	24 ± 1	ND
	Peanut oil	6	150	21 ± 2	ND
Cisplatin	Saline	3	21	72 ± 4	6 ± 0.2
	DMSO	4	21	84 ± 2	12 ± 2
	Peanut oil	6	27	40 ± 2	ND

Platinum anticancer drugs with a route of excretion different from traditional platinum agents might have significant clinical advantages if it can be demonstrated that the toxicity profile is different. It could be expected that the high biliary excretion reflects differences in structure and metabolism of the compounds that might result in less renal damage than cisplatin. Non-overlapping side effects with other established anticancer agents may potentially lead to alternative platinum-based drug combinations.

Following i.p. administration, drugs are taken up by the liver prior to reaching the systemic circulation. For a drug that is highly excreted into the bile, the bioavailability may thus be decreased, as reflected by either the extent of urinary excretion or the AUC in plasma, relative to an i.v. dose. In the present studies, the doses, vehicles and routes of delivery were chosen to include those producing antitumour activity [9, 14]. For activity, higher molar doses of Pt103 (113 to 170 μmol/kg) and Pt109 (75 to 300 μmol/kg) were required than of cisplatin (21 to 27 μmol/kg), and thus dose-normalized AUC was used for comparisons. Drugs were either suspended in saline/Tween or peanut oil, or dissolved in DMSO, or in saline for cisplatin. It was expected that more drug would reach the systemic circulation by dissolving the complexes, and indeed there was evidence that more drug was absorbed from solutions than from suspensions, as shown by the higher urinary excretion and AUC of cisplatin dissolved in saline or DMSO than of cisplatin suspended in peanut oil. Similarly, the AUC for Pt109 in DMSO was double that in peanut oil, and the renal excretion of Pt103 in DMSO was fivefold greater than that in peanut oil. However, despite Pt103 in saline/Tween having the lowest dose-normalized AUC and the lowest Cmax, the best antitumour activity was seen with this vehicle. In contrast, when dissolved in DMSO, Pt103 was inactive.

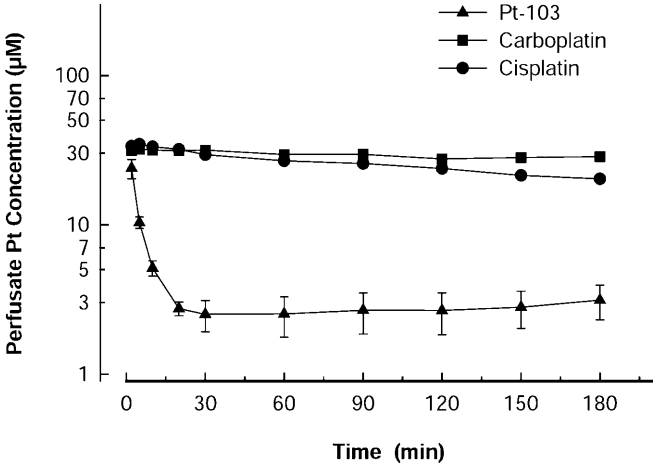

Fig. 3 Semilogarithmic plots of platinum concentrations in perfusate from isolated perfused rat livers following 2.8 μmol doses of cisplatin, carboplatin or Pt103. Values are means ± SEM, $n = 3$

It is important to remember that this study measured only the platinum from each compound, and that this may consist of both active and inactive metabolites as well as the parent drug. The platinum from Pt103 when delivered in DMSO was absorbed, as indicated by the 20% excretion in urine, but this may have been in an inactive form. For example, the lack of activity against P388 mouse leukaemia may be due to a chemical reaction, such as a substitution of either or both pyridine rings by DMSO, resulting in an inactive complex. However, substitution in Pt103 by DMSO requires light, and the resulting mono-DMSO Pt103 complex in saline/Tween retains activity against P388, with a tenfold lower toxic dose (unpublished results).

One explanation for the activity of Pt103 in saline/Tween may be related to its short Tmax, and the consequent rapid absorption into the circulation of unbound, active drug. Platinum reached the systemic circulation in less than 30 min, much faster than from peanut oil or DMSO. Plasma protein binding of cisplatin is mostly irreversible, and occurs quickly, with a half-life of unbound platinum of 3.3 h, and it is extensive, with roughly 90% bound by 8 h [8]. This compares well with our finding for Pt109, for which 90% was bound by 6 h, and the elimination half-life was 2.7 h. As protein binding for Pt103 is likely to be similar to that for Pt109, it is possible that a vehicle-dependent slower absorption into the circulation results in more drug becoming protein-bound prior to reaching the active site.

We demonstrated a different route of excretion for representatives of two new classes of platinum anticancer agents, compared with the traditional platinum drugs cisplatin and carboplatin. These new classes of active compound are of interest because of their unusual elimination, and further work is aimed at making similar compounds with improved solubility profiles. It is important to examine the pharmacokinetics, protein binding, excretion and toxicity of active new compounds in order to develop better drugs and to design appropriate clinical trials. If a platinum complex with an

Table 4 Pharmacokinetics and biliary excretion following equimolar doses (2.8 μmol) of platinum compounds in the isolated perfused rat liver at a perfusate flow rate of 15 ml/min. Values are means ± SD, $n = 3$

	Perfusate platinum		Biliary platinum	
	AUC 0–180 min (μ*M*·min)	Clearance (ml/min)	Content 0–180 min (nmol)	Clearance (ml/min)
Cisplatin	4652 ± 53	0.60 ± 0.01	99 ± 14	0.021 ± 0.003
Carboplatin	5291 ± 420	0.53 ± 0.04	28 ± 12	0.005 ± 0.002
Pt103	630 ± 257	4.93 ± 1.83	1592 ± 482	2.95 ± 1.89

excretion profile similar to these new compounds was introduced into the clinic, there might be a therapeutic advantage in terms of drug toxicity and combination therapy with other cytotoxics.

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