Review

Clinical Pharmacokinetics of Oxaliplatin: A Critical Review

Martin A. Graham,[1] Graham F. Lockwood, Dennis Greenslade, Silvano Brienza, Martine Bayssas, and Erick Gamelin

Department of Clinical Pharmacokinetics and Drug Metabolism, Sanofi-Synthelabo Research, Malvern, Pennsylvania 19355 [M. A. G., G. F. L., D. G.]; Debiopharm SA, 1003 Lausanne, Switzerland [S. B., M. B.]; and Center Paul Papin, 49033 Angers, France [E. G.]

Abstract

Oxaliplatin (*cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N*,*N*′] oxalato(2-)-*O*,*O*′] platinum; Eloxatine) is a novel platinum coordination complex used for the treatment of metastatic colorectal carcinoma in combination with fluoropyrimidines. The objective of this review is to integrate the key data from multiple studies into a single, comprehensive overview of oxaliplatin disposition in cancer patients. The pharmacokinetics (PKs) of unbound platinum in plasma ultrafiltrate after oxaliplatin administration was triphasic, characterized by a short initial distribution phase and a long terminal elimination phase ($t_{1/2}$, 252–273 h). No accumulation was observed in plasma ultrafiltrate after 130 mg/m^2 every 3 weeks or 85 mg/m^2 every 2 weeks. Interpatient and intrapatient variability in platinum exposure (area under the curve$_{0-48}$) is moderate to low (33 and 5% respectively). In the blood, platinum binds irreversibly to plasma proteins (predominantly serum albumin) and erythrocytes. Accumulation of platinum in blood cells is not considered to be clinically significant. Platinum is rapidly cleared from plasma by covalent binding to tissues and renal elimination. Urinary excretion (53.8 ± 9.1%) was the predominant route of platinum elimination, with fecal excretion accounting for only 2.1 ± 1.9% of the administered dose 5 days postadministration. Tissue binding and renal elimination contribute equally to the clearance of ultrafilterable platinum from plasma. Renal clearance of platinum significantly correlated with glomerular filtration rate, indicating that glomerular filtration is the principal mechanism of platinum elimination by the kidneys. Clearance of ultrafilterable platinum is lower in patients with moderate renal impairment; however, no marked increase in drug toxicity was reported. The effect of severe renal impairment on platinum clearance and toxicity is currently unknown. Covariates such as age, sex, and hepatic impairment had no significant effect on the clearance of ultrafilterable platinum, and dose adjustment due to these variables is not required. Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation and is not subjected to CYP450-mediated metabolism. Up to 17 platinum-containing products have been observed in plasma ultrafiltrate samples from patients. These include several proximate cytotoxic species, including the monochloro-, dichloro-, and diaquo-diaminocyclohexane platinum complexes, along with several other noncytotoxic products. Oxaliplatin does not inhibit CYP450 isoenzymes *in vitro*. Platinum was not displaced from plasma proteins by a variety of concomitant medications tested *in vitro*, and no marked PK interactions between oxaliplatin, 5-fluorouracil, and irinothecan have been observed. These results indicate that the additive/synergistic antitumor activity observed with these agents is not due to major alterations in drug exposure, and the enhanced efficacy is likely to be mechanistically based. Together, these PK, biotransformation, drug-drug interaction analyses and studies in special patient populations provide a firm scientific basis for the safe and effective use of oxaliplatin in the clinic. These analyses also reveal that the pharmacological activity of oxaliplatin may be attributable, at least in part, to the unique pattern of platinum disposition observed in patients.

Introduction

Oxaliplatin (*cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N*,*N*′] oxalato (2-)-*O*,*O*′] platinum; Eloxatine; Fig. 1) is a novel platinum coordination complex recently approved in Europe, Asia, and Latin America for the treatment of metastatic colorectal carcinoma in combination with fluoropyrimidines. Oxaliplatin is more potent than cisplatin *in vitro*, requiring fewer DNA adducts to achieve equivalent cytotoxicity (1–4). Oxaliplatin has demonstrated efficacy in preclinical studies against a broad spectrum of experimental tumors, including some cisplatin- and carboplatin-resistant cell lines (2, 5–11). Clinically, the safety and efficacy of a variety of dosing regimens with 5-FU and leucovorin have been evaluated, and the combination has demonstrated marked antitumor efficacy in patients with a favorable toxicity profile (12–18). As part of the clinical development program, the PKs[2] of oxaliplatin have been evaluated by several investigators in several different laboratories. The main objectives of this review, therefore, are to: (*a*) provide a critical assessment of the various PK studies conducted to date; (*b*) integrate the key data from these investigations into a single, comprehensive overview of oxaliplatin disposition in patients; and (*c*) identify the PK characteristics of the drug relevant to the safe and effective use of oxaliplatin in the clinic.

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[1] To whom requests for reprints should be addressed, at Department of Clinical Pharmacokinetics and Drug Metabolism, Sanofi-Synthelabo, 9 Great Valley Parkway, Malvern, PA 19355. Phone: 610-889-6025; Fax: 610-889-6356.

[2] The abbreviations used are: PK, pharmacokinetic; AUC, area under the curve; CI, confidence interval; CYP 450, cytochrome P450; DACH, diaminocyclohexane; FAAS, flameless atomic absorption spectroscopy; 5-FU, 5-fluorouracil; GFR, glomerular filtration rate; HPLC, high-pressure liquid chromatography; ICPMS, inductively coupled plasma mass spectrometry; ALT, alanine transaminase; CPT-11, irinothecan.

Fig. 1 Molecular structure of oxaliplatin.

Overview

An overview of the design of the various PK and metabolism studies cited in this review is summarized in Tables 1 and 2. The most comprehensive PK studies were conducted in multiple matrices (plasma, ultrafiltrate, and blood) and originate from three main studies (19–23). In the PK studies reported by Graham *et al.* (19, 20), the multiple dose PKs of platinum were analyzed in six patients treated with 130 mg/m^2 oxaliplatin every 3 weeks for five cycles. This study provided detailed kinetic data in a variety of matrices with PK monitoring over a 3-week period and enabled platinum accumulation to be assessed after multiple dosing. In other studies reported by Allen *et al.* (21, 22), the single dose PKs, biotransformation, and excretion of platinum were explored in a total of 20 patients receiving 130 mg/m^2 oxaliplatin. In these studies, the first five patients were enrolled for the assessment of oxaliplatin biotransformation and excretion (with limited PK sampling). The remaining 15 patients then underwent a full PK analysis. As an extension to this study, the multiple dose PKs of oxaliplatin were investigated in six additional patients after a 2-h infusion at 85 mg/m^2 every 2 weeks for three cycles (24). All of the above studies were supported by fully validated ICPMS bioanalytical method for platinum in ultrafiltrate, plasma, and blood (25, 26). The PKs of platinum (expressed as oxaliplatin equivalents) after a 4-h infusion schedule has also been reported by Kern *et al.* (23) in plasma and ultrafiltrate. Supportive PK studies, generally limited to measuring total plasma platinum levels, have also been conducted by a number of other investigators using a variety of FAAS and ICPMS methods (27–30).

The P450-mediated metabolism of oxaliplatin by human liver microsomes and the effect of oxaliplatin on CYP450 enzyme activity *in vitro* have been investigated in two studies (31, 32). Two further studies characterized the major platinum degradation products after the nonenymatic biotransformation of [^{3}H]oxaliplatin in human plasma ultrafiltrate, blood, and urine samples *in vitro* by liquid chromatography-mass spectrometry (33, 34). These results support the *in vivo* biotransformation studies in patients (21).

A comprehensive characterization of the major routes of oxaliplatin biotransformation and elimination in patients receiving a single i.v. infusion of oxaliplatin at 130 mg/m^2 has been reported by Allen *et al.* (21, 22). These studies investigated the major oxaliplatin biotransformation products in plasma ultrafiltrate and urine samples from patients by liquid chromatography-mass spectrometry. These studies also examined platinum excretion in the urine and feces of cancer patients receiving oxaliplatin. Other supportive platinum mass balance results in urine and feces using nonvalidated bioanalytical methods have been reported by several investigators, with good agreement in the derived estimates across all studies (19, 20, 23, 28, 30).

The PKs of platinum in special patient populations have

Table 1 Overview of oxaliplatin PK, distribution, and P450 metabolism studies

Study type	Dose (mg/m^2)	No. of cycles	No. of PK patients	5-FU[a]	Matrices evaluated	No. of PK samples (duration)	Method (validation)	Ref.
PK	130	5	6	−5-FU	UF, P, BC[b]	12 (1–22 days)	ICPMS (validated)	Graham *et al.* (19, 20)
	130	1	15	−5-FU[c]	UF, P, BC, B	14 (1–22 days)	ICPMS (validated)	Allen *et al.* (21, 22)
	130	1	13	+5-FU	UF, P	15 (0–24 h)	FAAS (validated)	Kern *et al.* (23)
	85	3	3[d]	+5-FU	UF, P, BC, B	12 (1–14 days)	ICPMS (validated)	Graham (24)
	20–180	1	20	−5-FU	P	7 (0–24 h)	FAAS	Taguchi (27)
	135–200	1	16	−5-FU	P	7 (0–24 h)	FAAS	Marty (28)
	130	6	16	+5-FU	P, BC (limited PK)	6 (1–22 days)	ICPMS (validated)	Gamelin and Allain (40)
	130	1	6–7	−5-FU	P, BC	12 (1–22 days)	ICPMS (validated)	Misset and Allain (30)
Distribution *in vitro*								
Protein binding	NA	NA	NA	NA	P, B, Alb, AGP, GG, VLDL, LDL, HDL, S	NA	Ultrafiltration, FAAS	Uriens and Tillement (44)
Erythrocyte binding	NA	NA	NA	NA	BC	NA	FAAS	Pendyala and Creaven (7)
Distribution *in vivo*	130	1–3	6	−5-FU	WBC	4 (1–5 days)	ICPMS	Misset *et al.* (45)

[a] PK assessments made in the presence (+) or absence (−) of 5-FU.
[b] P, plasma; UF, ultrafiltrate; BC, blood cells; B, blood; Alb, albumin; AGP, α-1 acidic glycoprotein; GG, gamma globulin; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; S, serum; NA, not applicable.
[c] 5-FU administration delayed for 48 h during blood sampling.
[d] Interim PK analysis on three of six patients.

Table 2 Overview of oxaliplatin biotransformation, excretion, special population, and drug interaction studies

Study type	Dose (mg/m^2)	No. of cycles	No. of PK patients	5-FU[a]	Matrices evaluated[b]	No. of PK samples (duration)	Method (validation)	Ref.
Biotransformation								
In vitro	NA	NA	NA	NA	UF, P, B	NA	HPLC-UV, MS (validated), radiochemical	Shackleton and Allen (53)
	NA	NA	NA	NA	UF, U	NA	HPLC-UV, MS (validated), radiochemical	McDougall and Allen (34)
In vivo	130	1	5	−5-FU[c]	UF U	5 (0–48 h) 1–5 (1–5 days)	ICPMS (validated)	Allen *et al.* (21, 22)
Excretion								
Urine & feces	130	1	5	−5-FU	U Fe	5 (1–5 days) 1 (1–5 days)	ICPMS (validated)	Allen *et al.* (21, 22)
	130	1	6–7	−5-FU	U Fe	9 (1–11 days) 8 (1–21 days)	ICPMS	Misset and Allain (30)
	130	5	6	−5-FU	U	2 (0–48 h)	ICPMS (validated)	Graham *et al.* (19, 20)
	135–200	1	16	−5-FU	U	1 (0–24 h)	FAAS	Marty (28)
	130	2	13	+5-FU	U	1 (0–24 h)	FAAS (validated)	Kern *et al.* (23)
Special populations								
Renal impairment	130	1	24	−5-FU	UF, P, U	19 (0–144 h)	FAAS	Massari *et al.* (35)
Age, sex, hepatic, renal impairment	130	1	11–27	−5-FU	UF, U	NA	NA	Graham *et al.* (36)
Drug interactions								
5-FU *in vivo*	85	1–7	18	±5-FU	P (5-FU)	6–8 (0–1 h)	HPLC-UV (validated)	Papamichael *et al.* (37, 38)
CYP450 metabolism *in vitro*	NA	NA	NA	NA	Microsomes	NA	P450 assays (validated)	Shackleton and Allen (31)
CYP450 inhibition *in vitro*	NA	NA	NA	NA	Microsomes	NA	P450 assays (validated)	Brandl and Brian (32)
Con. meds. *in vitro*	NA	NA		Con. meds.	S	NA	Ultrafiltration FAAS	Uriens and Tillement (44)

[a] Pharmacokinetic assessments made in the presence (+) or absence (−) of 5-FU.
[b] P, plasma; UF, ultrafiltrate; B, blood cells; U, urine; Fe, feces; S, serum; Con. meds, concommitant medications.
[c] 5-FU administration delayed for 48 h during blood sampling for biotransformation and PK.

been examined in two studies by Massari *et al.* (35) and Graham *et al.* (36). Massari *et al.* (35) investigated the effect of moderate renal impairment on the clearance of platinum and toxicity of oxaliplatin in cancer patients after a single dose at 130 mg/m^2. In the study by Graham *et al.* (36), a meta-analysis of oxaliplatin PKs was conducted to investigate the effect of age, sex, and renal and hepatic function on the clearance of ultrafilterable platinum in cancer patients.

Finally, potential PK interactions after a single 2-h infusion of oxaliplatin at 130 mg/m^2 and 5-FU (de Gramont regimen) have been examined by Papamichael *et al.* (37, 38) in a one-way interaction study. Details of other *in vivo* and *in vitro* drug-drug interaction studies are also reviewed in this article.

Selection of Analyte and Matrix for PK Studies

Oxaliplatin rapidly forms a variety of reactive intermediates in blood and plasma, including the monochloro-, dichloro-, and diaquo-platinum species. These reactive platinum complexes can bind irreversibly to various constituents in the blood and/or cellular macromolecules. Ultimately, the products of these reactions are eliminated as nonreactive small molecular weight conjugates. Given the rapidity of these reactions both *in vitro* and *in vivo*, investigating the PKs of intact parent compound or one of the transient intermediates is technically difficult and not feasible for routine PK assessment. Hence monitoring platinum PKs rather than intact parent compound (or a metabolite) is a generally accepted approach that has been adopted for the analysis of other platinum complexes published in the literature (for a review, see Ref. 39).

For a full description of platinum PKs, it is useful to discriminate between bound and free platinum in blood and plasma. Ultrafilterable platinum (comprising nonprotein bound drug and biotransformation products in plasma water) is thought to represent all the platinum species with antitumor and toxic properties in the circulation. Unbound platinum is cleared from the systemic circulation by a combination of irreversible binding to plasma/blood constituents, tissue uptake, and urinary elimination. Platinum irreversibly bound to plasma proteins and erythrocytes is generally considered to be pharmacologically inactive (39). Therefore, plasma ultrafiltrate represents the most relevant matrix when considering pharmacological activity.

The most comprehensive PK studies presented in this review were conducted in plasma ultrafiltrate, as well as plasma, blood, and blood cells (19–24). In a number of earlier studies,

Table 3 Comparison of mean (±SD) plasma platinum PKs across studies following a single 1–4-h infusion of oxaliplatin at 130 mg/m^2 (cycle 1)

Ref.	Infusion duration (h)	C_{max} (μg/ml)	AUC_{0-48} (μg/ml·h)	AUC_{0-inf} (μg/ml·h)	Terminal $t_{1/2}$ (h)	Method
Marty (28)	1	4.81 ± 1.83[a]	ND	ND	36.5 ± 8.70[b]	FAAS
Taguchi (27)	1	3.23 ± 0.85	ND	ND	31.5 ± 4.80[b]	FAAS
Graham *et al.* (19, 20)	2	3.20 ± 0.34	59.1 ± 11.4	207 ± 60.9	239 ± 54.4	ICPMS
Allen *et al.* (22)	2	2.96 ± 0.57	71.5 ± 13.3	278 ± 81.0	237 ± 53.0	ICPMS
Misset and Allain (30)	2	3.22 ± 0.54	ND	290	189	ICPMS
Gamelin and Allain (40)	2	3.20 ± 0.61	ND	ND	ND	ICPMS
Massari *et al.* (35)	2	2.59 ± 0.37[c]	50.4 ± 12.2[c]	92.7 ± 22.1[c]	37.5 ± 8.24	FAAS
Kern *et al.* (23)	4	1.52 ± 0.45[c]	ND	780 ± 2477[c]	47.0 ± 64.0[b]	FAAS

[a] C_{max} determined following a 1-h infusion at doses between 135 and 150 mg/m^2.
[b] $t_{1/2}$ value estimated over 24 h only.
[c] Values derived from oxaliplatin equivalents using the molecular weight correction factor 0.49.
ND, not determined.

platinum measurements were only obtained in plasma and blood samples (27–30, 40). Therefore, plasma platinum measurements were used to make PK comparisons across all studies.

PKs of Oxaliplatin

A summary of the main PK parameters in plasma across all studies conducted to date is presented in Table 3. The studies provided consistent parameter estimates for plasma platinum C_{max} and AUC (Table 3). After a dose of 130 mg/m^2 infused over 2 h, mean C_{max} values were in the range of 2.59–3.22 μg/ml and mean AUC_{0-48} values were in the range of 50.4–71.5 μg/ml·h (Table 3).

Dose Proportionality

Assessment of dose proportionality for total plasma platinum was conducted as part of the Phase I study reported by Taguchi (27). Oxaliplatin was administered as single 1-h infusion in a total of 17 patients over the dose range 20–180 mg/m^2. The mean C_{max} and AUC_{0-24} increased in a dose related manner up to 180 mg/m^2. The relationship between plasma platinum AUC and dose is presented in Fig. 2.

Infusion Duration

The effect of infusion duration on plasma platinum C_{max} was investigated as part of study by Marty *et al.* (28). Prolongation of the infusion from 2 to 6 h has been used to circumvent the acute laryngopharyngeal dysestheias observed in certain patients.

Analysis of plasma platinum C_{max} values after a 1-h infusion (dose normalized to 130 mg/m^2) indicated that prolonging the infusion from 1 to 6 and 12 h decreased the mean C_{max} by approximately 56 and 71%, respectively (Fig. 3). Although 2-h infusion data were not included in this study, the levels at 1 and 6 h encompass the typical mean plasma C_{max} values after a 2-h infusion (2.96 ± 0.57 μg/ml; Table 3). The percentage of decrease in C_{max} produced by increasing the duration of infusion from 2 to 6 h was estimated to be approximately 32%.

Multiple Dose PKs at 130 mg/m^2 and 85 mg/m^2

Multiple dose PK analysis of platinum in plasma ultrafiltrate, plasma, and blood cells has been investigated after oxaliplatin infusions at 85 and 130 mg/m^2 (19, 20, 24).

Platinum PKs have been monitored in six patients receiving five consecutive cycles of treatment at 130 mg/m^2 every 3 weeks (19, 20). The multiple dose PK data at 130 mg/m^2 in ultrafiltrate, plasma, and blood cells are presented in Fig. 4. No accumulation was observed in plasma ultrafiltrate after 3–5 cycles of treatment. Limited platinum accumulation (≤2-fold) was observed in plasma and blood cells (Fig. 5).

An interim PK analysis has been conducted in three of six patients receiving three consecutive cycles at 85 mg/m^2 every 2 weeks in combination with 5-FU (300 mg/m^2/day continuous infusion for 12 weeks; Ref. 24). The multiple dose PK data at 85 mg/m^2 in ultrafiltrate, plasma and blood cells are presented in Table 4. No accumulation was observed in ultrafiltrate and plasma after three cycles of treatment and platinum only accumulated to a limited extent in blood cells (<2 fold) after multiple doses at 85 mg/m^2 (Fig. 5). Similar clearance values after a dose of 85 mg/m^2 have also been reported by Lokiec *et al.* (41) after PK studies with oxaliplatin in combination with CPT-11.

Peak Platinum Exposure (C_{max})

After a 2-h infusion of oxaliplatin at 130 mg/m^2 every 3 weeks, mean (±SD) C_{max} values in plasma ultrafiltrate on cycle 5 were approximately 1.21 ± 0.10 μg/ml. Mean C_{max} values in plasma and blood cells were approximately 3.61 ± 0.43 and 3.25 ± 0.49, μg/ml respectively (cycle 5; Refs. 19 and 20). Mean C_{max} values in plasma ultrafiltrate, plasma, and blood cells after a 2-h infusion of oxaliplatin at 85 mg/m^2 every 2 weeks for three cycles were 0.681 ± 0.077, 1.92 ± 0.338, and 2.67 ± 0.798 μg/ml, respectively, on cycle 3 (24).

Platinum Exposure (AUC)

After a 2-h infusion of oxaliplatin at 130 mg/m^2, AUC_{0-inf} values in plasma ultrafiltrate (cycle 1) were 11.9 ± 4.60 μg·h/ml. AUC_{0-inf} values in plasma and blood cells (cycle 1) were typically 207 ± 60.9 and 1326 ± 570 μg·h/ml, respectively (19, 20, 22).

Mean (±SD) AUC_{0-inf} values (cycle 1) in plasma ultrafiltrate, plasma, and blood cells after a 2-h infusion of oxaliplatin at 85 mg/m^2 were 4.25 ± 1.18, 118 ± 8.97, and 252 ± 34.6 μg/ml·h, respectively (24).

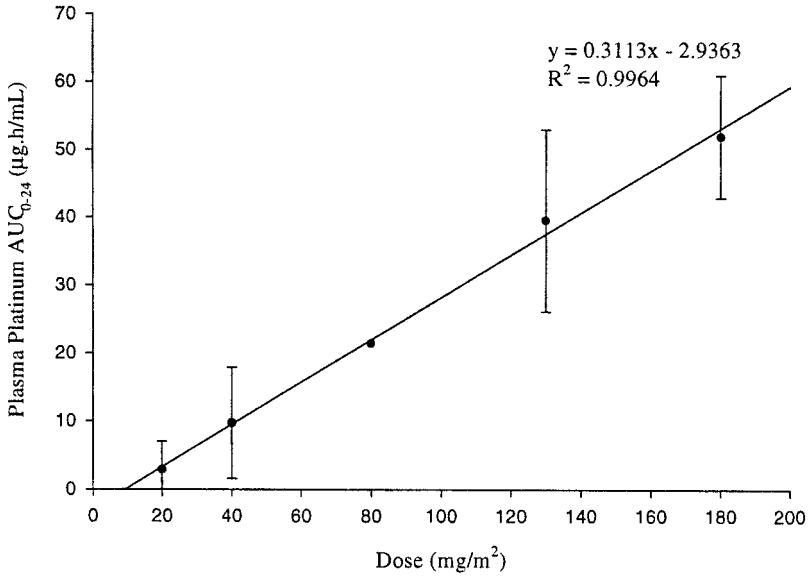


Fig. 2 Relationship between oxaliplatin dose and plasma platinum AUC_{0-24} values (n = 2–6 patients per dose level; Ref. 27). *Data points,* mean; *bars,* SD.

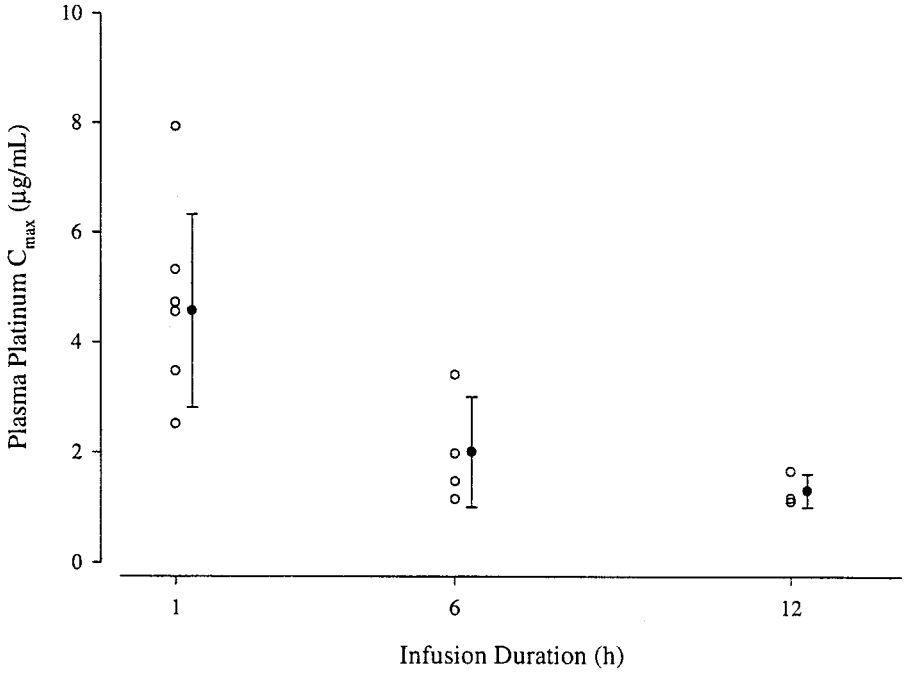


Fig. 3 Effect of infusion duration on plasma platinum C_{max} values (oxaliplatin doses normalized to 130 mg/m^2; n = 3–7 patients per group; Ref. 28). *Data points,* mean; *bars,* SD.

Platinum Half-life ($t_{1/2}$)

In the studies monitoring PK of platinum over 2–3 weeks posttreatment, the PKs of platinum in ultrafiltrate were triexponential, characterized by short initial α and β distribution phases (0.28 and 16.3 h, respectively) followed by a long terminal γ-phase (273 h; Refs. 19 and 20).

The short initial half-life of platinum in plasma ultrafiltrate probably represents the rapid clearance of intact oxaliplatin and the reactive dichloro-, monochloro-, and diaquo-DACH platin intermediates into tissues and/or removal from the systematic circulation via glomerular filtration. The long terminal half-life of unbound platinum in plasma ultrafiltrate probably represents the slow release of low molecular weight platinum-amino acid conjugates after the degradation of cellular macromolecules, such as proteins (19, 20).

The apparent differences in the terminal half-life estimates between studies for total plasma platinum and ultrafiltrate (Tables 3 and 4) is likely to be due to two main contributory factors: first, differences in the frequency and duration of sample collection (Table 1); and second, differences in detection limits

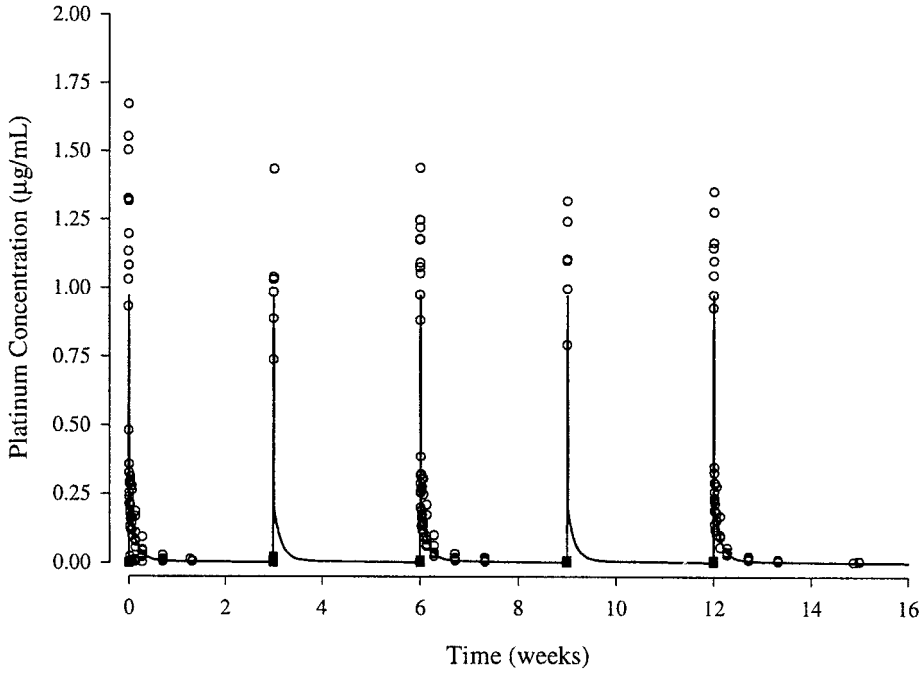


Fig. 4 Multiple dose PKs of platinum in plasma ultrafiltrate showing lack of accumulation after a 2-h infusion of oxaliplatin at 130 mg/m^2 every 3 weeks (n = 6 patients). *Line* represents mean platinum concentration; ○, individual platinum concentrations; ■, trough platinum concentrations (19, 20).

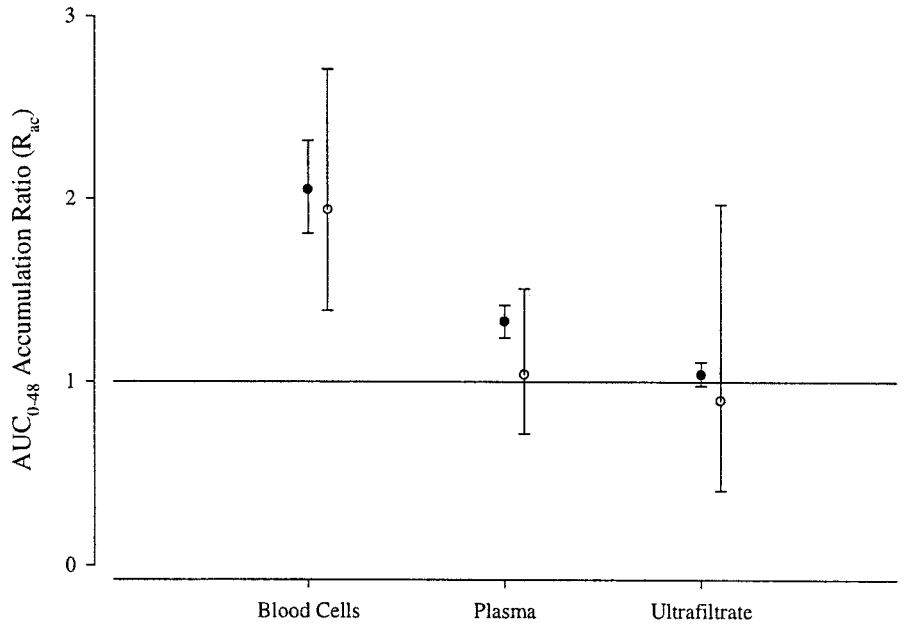


Fig. 5 Platinum AUC_{0-48} accumulation ratios in blood cells, plasma, and ultrafiltrate, after multiple doses of oxaliplatin at 85 mg/m^2 (cycle 3/cycle 1; ○) and 130 mg/m^2 (cycle 5/cycle 1; ●; Refs. 19 and 20). *Data points*, mean; *bars*, SD.

between FAAS and ICPMS (approximately 50 and 1 ng/ml, respectively). For example, the terminal half-life of platinum estimated by Kern *et al.* (23) was approximately 27.3 ± 10.6 h in plasma ultrafiltrate. However, blood sampling was only conducted over a 24-h period, which results in an imprecise estimate of the terminal elimination phase. In contrast, in studies in which complete PK monitoring was conducted 2–3 weeks posttreatment and using a more sensitive ICPMS method, the terminal half-life of platinum in ultrafiltrate was estimated to be 273 ± 19.0 h (19, 20).

The latter half-life estimate of 273 h represents a more rigorous and precise evaluation of the terminal half-life of platinum after oxaliplatin administration. However, the half-lives of the shorter α and β phases (0.28 and 16.3 h, respectively) probably represent the more clinically relevant $t_{1/2}$ values of pharmacologically active platinum, given that the platinum in

Table 4 Comparison of mean (±SD) ultrafilterable platinum PKs across studies following dosing of oxaliplatin at 85 and 130 mg/m^2 following a 2- or 4-h infusion

Mean C_{max} values were calculated on cycle 5 for Refs 19 and 20, cycle 1 for Ref. 22, and cycle 3 for Ref. 24. Mean AUC_{0-inf}, V_{ss}, and Cl terms were calculated on Cycle 1. $t_{1/2}$ was calculated as mean value over all cycles using compartmental analysis.

Ref.	Dose (mg/m^2)	Infusion duration (h)		C_{max} (μg/ml)	AUC_{0-inf} (μg/mL·h)	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	$t_{1/2}\gamma$ (h)	V_{ss} (liters)	Cl (liters/h)
Graham (24)	85	2	Mean	0.681	4.25	NC[a]	NC	NC	295	18.5
			(SD)	(0.077)	(1.18)				(142)	(4.71)
Graham *et al.* (19, 20)	130	2	Mean	1.21	11.9	0.28	16.3	273	582	10.1
			(SD)	(0.10)	(4.60)	(0.06)	(2.90)	(19.0)	(261)	(3.07)
Allen *et al.* (22)	130	2	Mean	0.825	13.6	0.21	15.1	252	812	9.34
			(SD)	(0.359)	(4.50)	(0.10)	(3.6)	(82)	(369)	(2.85)
Kern *et al.* (23)	130	4	Mean	0.790	9.88	0.09	0.72	27.3	349	13.3
			(SD)	(0.271)	(3.42)	(0.08)	(0.54)	(10.6)	(132)	(3.9)

[a] NC, not calculated.

the terminal elimination phase will comprise almost entirely of inactive platinum conjugates (21, 42).

Platinum Clearance

The clearance of ultrafilterable platinum was relatively high, with estimates ranging from 9.34 ± 2.85 to 10.1 ± 3.07 liters/h at 130 mg/m^2 (20, 22) to 18.5 ± 4.71 liters/h at 85 mg/m^2 (24; Table 4). Platinum clearance was similar to or exceeded the average human glomerular filtration of approximately 7.5 liters/h. The renal clearance of ultrafilterable platinum has been shown to be significantly correlated with GFR, indicating that glomerular filtration is a principal mechanism of platinum clearance after oxaliplatin administration (36).

Clearance of platinum from plasma and blood cells was relatively low, which is probably a reflection of the covalent binding of platinum to these matrices (19, 20).

Platinum Volume of Distribution (V_{ss})

Platinum has a high volume of distribution from plasma ultrafiltrate ranging from 349 ± 132 to 812 ± 369 liters (Refs. 19 and 20; Table 4). This high volume of distribution may be due to the lipophillic nature DACH platinum complexes and the subsequent irreversible binding of platinum to proteins, DNA, and other cellular macromolecules.

Platinum Accumulation (R_{ac})

No significant accumulation has been observed in plasma ultrafiltrate after multiple dosing at 130 mg/m^2 every 3 weeks (19, 20, 29) or 85 mg/m^2 every 2 weeks (24). The AUC_{0-48} accumulation ratios in ultrafiltrate, plasma and blood cells at 130 mg/m^2 every 3 weeks are shown in Fig. 5. Although platinum has a long terminal half-life in ultrafiltrate (273 h), the lack of accumulation in this matrix is probably due to the fact that the terminal portion of the curve contributes little to the overall AUC and there is negligible carryover into the next cycle.

Negligible accumulation of platinum was observed in plasma at 130 mg/m^2 [cycle 5/cycle 1 AUC_{0-48} accumulation ratio = 1.33 (95% CI = 1.24–1.42); Refs. 19, 20, and 29]. Similar results were also obtained after multiple dosing at 85 mg/m^2 every 2 weeks [cycle 3/cycle 1 AUC_{0-48} accumulation ratio = 1.04 (95% CI = 0.72–1.51); Ref. 24].

Statistically significant accumulation in blood cells [cycle 5/cycle 1 AUC_{0-48} accumulation ratio = 2.05 (95% CI = 1.81–2.32)] was observed after oxaliplatin administration at 130 mg/m^2 every 3 weeks (19, 20, 29). Some accumulation was also observed in blood cells with the 85 mg/m^2 every 2-week dosing regimen [cycle 3/cycle 1 AUC_{0-48} accumulation ratio = 1.94 (95% CI = 1.39–2.71); Ref. 24].

Blood cell accumulation has been reported for other platinum complexes, but to a lesser degree (43).However, the pharmacological significance of blood cell accumulation is limited given the irreversible binding of platinum to this matrix and the lack of platinum efflux in *in vitro* experiments (7, 19, 20, 29).

Platinum Accumulation and Steady State (C_{ss})

Attainment of steady state was determined by measuring trough concentrations in plasma ultrafiltrate after five consecutive 3-week cycles of oxaliplatin at 130 mg/m^2. No accumulation of platinum was observed in ultrafiltrate, and steady state was achieved on cycle 1 (19, 20).

No formal analysis of steady state levels after multiple dosing at 85 mg/m^2 has been made, as only three cycles of treatment were evaluated (24). However, no accumulation was observed in plasma ultrafiltrate, an observation consistent with steady state being reached on cycle 1.

Variability in Ultrafilterable Platinum PKs

Moderate to low between-patient and within-patient variability was observed in ultrafilterable platinum levels over five cycles of treatment. The between- and within-patient variability in ultrafiltrate concentration at the end of infusion (C_{end}) was 18 and 13%, respectively, and 33 and 5% for the between- and within-patient variability in $AUC_{0-48.}$ (19, 20).

Platinum Distribution *In Vitro* and *In Vivo*

Binding of Platinum to Plasma Proteins. The extent of platinum binding to human plasma proteins has been investigated *in vitro* over the concentration range 0.3–20 μg/ml oxaliplatin after incubation at 37°C for 6 h (serum) or 24 h (purified protein solutions; Ref. 44). The binding kinetics were determined by ultrafiltration and platinum levels were assayed by FAAS.

The binding of platinum to serum was moderate (79–87%)

and time dependent. Equilibrium was attained after 6 h for serum and after 24 h for albumin. Most of platinum was found to be covalently bound. There was no evidence of saturable binding over the concentration range 0.3–20 μg/ml (44).

The main serum binding proteins were found to be albumin and gamma-globulins (44). Similar *in vitro* binding studies were performed by Pendyala and Creaven (7), except that plasma, rather than serum protein, was used. The binding of oxaliplatin derived platinum to plasma protein was found to be moderate, with 85–88% of the total platinum bound within 5 h.

The plasma protein binding of platinum has also been investigated in patients receiving 130 mg/m^2 oxaliplatin by 2-h infusion every 3 weeks for five cycles ($n = 6$ patients; Refs. 19 and 20). At the end of infusion at 2 h on cycle 5, the mean percentage of platinum bound to plasma protein was 65.5 ± 4.89%, which progressively increased to 90.3 ± 1.75% at 6 h and to 98.0 ± 0.42% by 3 weeks.

Similar *in vivo* protein binding results have also been reported by Misset and Allain (30). On day 1 at 2 h posttreatment, plasma protein binding was estimated at 70%. Five days posttreatment, with oxaliplatin at 130 mg/m^2, plasma protein binding was estimated to be >95%.

Binding of Platinum to Erythrocytes. Platinum has been shown to irreversibly bind to and accumulate in erythrocytes (7). The half-life of erythrocytic bound platinum is therefore likely to be determined by the rate of erythrocyte turnover (19, 20). Blood cell associated platinum is not considered to be a reservoir of pharmacologically active platinum due to the irreversible nature of the binding and the lack of platinum efflux in *in vitro* experiments (7, 19, 20).

Although platinum binds to blood cells, the blood cells only represent a minor compartment for drug distribution in patients (19, 20). At the end of infusion (2 h), approximately 15% of the administered platinum is present in the blood. The remaining 85% has undergone distribution from the plasma into tissues or has been subjected to urinary elimination. Therefore, platinum distribution to blood cells represents a relatively small component when consideration is given to the total body disposition of platinum.

Binding of Platinum to Lymphocytes. The uptake of platinum into peripheral lymphocytes of patients has been investigated after multiple doses of oxaliplatin at 130 mg/m^2 (45). Platinum was found in DNA extracts from all oxaliplatin treated patients 1 h after the end of infusion on cycles 1 and 3. The removal of platinum adducts was rapid. In four of six patients, no platinum was detected 24 h posttreatment on cycle 1, and platinum levels could only be detected in one of six patients on day 5.

Biotransformation and Metabolic Fate of Oxaliplatin

Metabolism and Biotransformation Overview. Oxaliplatin undergoes a series of spontaneous, nonenzymatic conversions in biological fluids, a process referred to as drug biotransformation. These reactions are mediated primarily through the displacement of the oxalate group by H_2O and endogenous nucleophiles, such as Cl^- and HCO_3^- ions. Several transient reactive species are formed, including dichloro-, monochloro-, and diaquo-DACH platin, which can complex with amino acids,

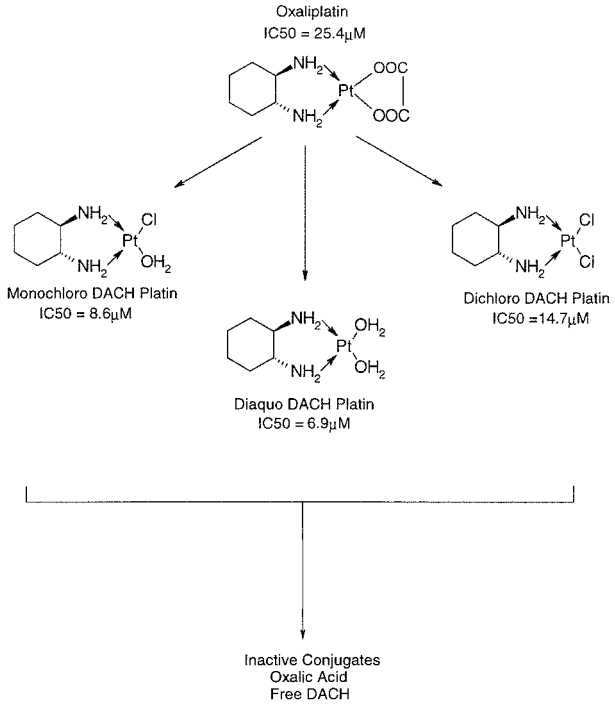


Fig. 6 Biotransformation of oxaliplatin and pharmacological activity of the major products (IC_{50} values in HT-29 human colon carcinoma cells *in vitro*; Refs. 21, 22, and 42).

proteins, DNA, and other macromolecules in plasma and tissues (Fig. 6; Refs. 21 and 22).

Studies to investigate the metabolism of oxaliplatin by human liver microsome extracts indicated that oxaliplatin was not a substrate for CYP450 *in vitro* (32).

Drug Metabolism Studies. The biotransformation of [^{3}H]oxaliplatin was investigated using human liver microsomal fractions *in vitro* (31). Human liver microsomes were prepared from three human livers with high CYP450 activity.

After a 30-min incubation of [^{3}H]oxaliplatin with human hepatic microsomes in the presence of NADPH, most of the radioactivity (67%) was associated with unchanged drug. Another major component, which comprised 17% of the total radioactivity, co-eluted with the diaquo-DACH platin standard. Several other minor products were also detected, each representing less than 1–3% of the radioactivity. Similar results were obtained in the absence of NADPH (71% co-eluting as unchanged drug and 17% as diaquo-DACH platin) and using heat-denatured microsomes, indicating that the biotransformation of oxaliplatin was nonenzymatic and occurred by chemical degradation.

In summary, no oxidative metabolism of the DACH group was detected *in vitro*. [^{3}H]Oxaliplatin was stable to oxidative CYP450-mediated metabolism and degraded nonenzymatically to a single major product, tentatively identified as diaquo-DACH platin (31, 32).

Biotransformation Studies *in Vitro*. The *in vitro* biotransformation and distribution of [^{3}H]oxaliplatin has been investigated in plasma ultrafiltrate, urine, and whole blood samples (33, 34).

Table 5 Urinary and fecal elimination of platinum following a single 2-h infusion at 130 mg/m^2

Dose (mg/m^2)	Sampling period	% Urinary elimination	% Fecal elimination	Ref.
130	0–120 h	53.8 ± 9.1	2.1 ± 1.9	Allen *et al.* (21, 22)
130	0–48 h	33.1 ± 5.2	ND[a]	Graham *et al.* (19, 20)
130	0–264 h	57.2	4.11	Misset and Allain (30)
135–150	0–24 h	35.9 ± 8.44	ND	Marty (28)

[a] ND, not determined.

[^{3}H]Oxaliplatin underwent extensive biotransformation in plasma ultrafiltrate and urine. At least 17 radioactive products were observed by HPLC in plasma ultrafiltrate at 24 h, the major ones of which chromatographed with DACH platinum adducts of methionine (6%), monochloro (37%), monochlorocreatinine (9%), dichloro (10%), and monocreatinine (4%). A major unidentified product (SP21; 10%) was also evident. A similar profile was observed at 24 h, and five additional products were also detected, one of which was tentatively identified by mass spectrometry as monochloro urea DACH platin (11%; Refs. 33 and 34).

At least 16 radioactive products were present *in vitro* in urine after incubation with oxaliplatin, the major ones of which were characterized by mass spectrometry and included dicreatinine (24%), methionine (6%), monochloro (2%), monochlorocreatinine (14%), dichloro (7%), and monocreatinine (11%) DACH platins. Diaquo-DACH platin (6%) was tentatively identified by HPLC (34).

In summary, the *in vitro* biotransformation studies in plasma ultrafiltrate, urine, and whole blood corresponded closely to the profile of oxaliplatin biotransformation products characterized in the ultrafiltrate and urine samples of patients undergoing oxaliplatin therapy (21, 22).

Biotransformation Studies *in Vivo*. Allen *et al.* (21, 22) have demonstrated that oxaliplatin undergoes extensive biotransformation in cancer patients, with evidence of nucleophilic substitution of the oxalate-leaving group and dissociation of the platinum complex from the carrier ligand, DACH. The major routes of biotransformation to active species is depicted in Fig. 6. Oxaliplatin was below the limit of detection in plasma ultrafiltrate at the end of infusion (2 h) at 130 mg/m^2 and could not be detected in urine. Up to 17 platinum-containing products were observed in the plasma ultrafiltrate, the major one of which, in four of five patients, corresponded by HPLC to monochloro-DACH platin (31–100% sample platinum). Other putative DACH platinum complexes of dichloro (2–8%), diaquo (2–26%), methionine (8–24%), monochlorocreatinine (2–11%), and glutathione (12%) appeared to be present in plasma ultrafiltrate. A number of unknown products were also observed (21, 22).

Up to 21 products were resolved by HPLC in urine, a number of which were characterized by mass spectrometry. These included dicreatinine (1–4% platinum dose), methionine (1–7%), monochloro (2%), monochlorocreatinine (1–20%), and monocreatinine (1–10%) DACH platins. In addition, glutathione DACH platin (2–18% dose) and a number of unidentified products were also resolved by HPLC (21, 22).

Preclinical cytotoxicity studies indicate that the monochloro-, dichloro-, and diaquo-DACH platin represent the principal cytotoxic platinum species in the systemic circulation, whereas the conjugated platinum complexes were devoid of cytotoxic activity (42).

Platinum Elimination

Urinary and Fecal Elimination of Platinum. The elimination of platinum occurs mainly in urine rather than in feces (Table 5).

A mass balance study was performed to determine the major route of platinum elimination in patients after a single dose of oxaliplatin at 130 mg/m^2 (21, 22). Urine and fecal samples were collected over 5 days from five patients. Over the 5-day study period, the majority of the platinum dose (53.8%) was excreted in the urine, with only 2.1% in feces (Table 5) Between 2 and 12% of the administered dose was excreted in urine as free DACH carrier ligand.

Similar mass balance results have also been reported by other investigators (19, 28, 30) and are summarized in Table 5.

PKs in Special Patient Populations

Platinum Clearance and Renal Function. The clearance of platinum in patients with normal renal function and moderate renal impairment has been investigated by Massari *et al.* (35). Twenty-four patients were evaluated (10 with moderate renal impairment and 14 with normal renal function) after a single dose of oxaliplatin at a dose of 130 mg/m^2 given as a 2-h infusion. The median creatinine clearance in the normal group was 78.00 (± 19.63) ml/min. One patient in this group had a calculated creatinine clearance <60 ml/min but was still included in the normal group due to the absence of any history of renal failure. The median creatinine clearance in the renally impaired group was 42.20 (± 10.63) ml/min.

There was no statistically significant difference between the two groups with respect to ultrafilterable platinum $C_{max.}$ There was, however, a significant increase in AUC in patients with moderate renal impairment and a significant decrease in clearance of ultrafiltrate platinum (35). Clearance in the group with moderate renal impairment was 14.23 ± 6.04 liters/h. This was significantly lower ($P = 0.005$) than clearance in the group with normal renal function (25.70 ± 8.53 liters/h). Although there was a significant decrease in the clearance of ultrafilterable platinum, no additional toxicity was observed in the renally impaired patients (35).

Platinum Clearance. Typically the clearance of ultrafilterable platinum has been shown to range from 9.34 ± 2.85 to 13.3 liters/h at 130 mg/m^2 (Table 4). The apparently higher clearance at 85 mg/m^2 (18.5 ± 4.71) and in the study by Massari *et al.* (35) quoted above is likely to be due to underestimation of the AUC.

Renal clearance at 130 mg/m^2 (4.66 liters/h) contributed to approximately half of the total clearance of platinum and was close to the average human GFR of approximately 7.5 liters/h. The clearance of ultrafilterable plasma platinum and platinum renal clearance was also significantly correlated with GFR (36). These results indicate that glomerular filtration is a major mech-

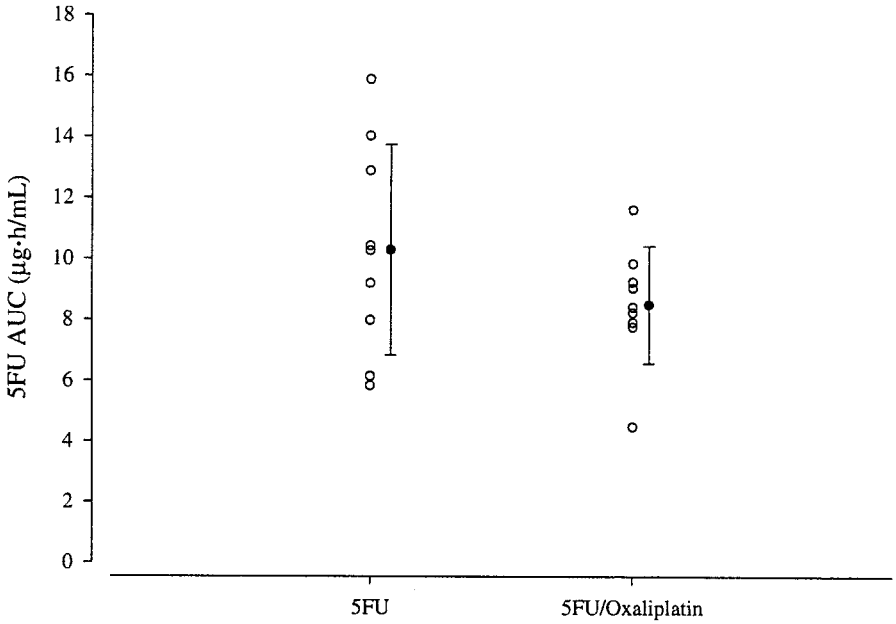


Fig. 7 5-FU AUC values in plasma after the administration of 5-FU alone (de Gramont regimen) or in combination with oxaliplatin at 85 mg/m^2 (n = 9 patients per group; not significant: P = 0.299; Ref. 38). ●, mean; *bars*, SD.

anism of platinum elimination from the body after oxaliplatin administration.

Clearance of platinum from plasma and blood cells was relatively low (19, 20), which is probably a reflection of the covalent binding of platinum to these matrices.

Platinum Clearance and the Effect of Hepatic Function, Sex, and Age. A meta-analysis in 26 patients pooled from two studies (n = 26 subjects) was performed by Graham *et al.* (36) to investigate the relationship between hepatic function (baseline ALT) and ultrafilterable platinum clearance. There was no statistically significant difference (P = 0.507) in platinum clearance in patients with normal ALT values (2–47 units/liter) or in patients with mild to moderate elevations in ALT values (48–126 units/liter; Ref. 36).

In the same meta-analysis, no statistically significant differences (P = 0.0657) were observed between males and females with respect to the clearance of ultrafilterable platinum (36). Similarly, no statistically significant correlation (P = 0.618) was observed between the clearance of ultrafilterable platinum and age (26–72 years; Ref. 36).

Drug-Drug Interactions

Effect of Oxaliplatin on 5-FU Clearance. The effect of oxaliplatin on the PKs of 5-FU has been studied in 18 patients with colorectal carcinoma (37, 38). 5-FU was administered to these patients according to the de Gramont regimen (200 mg/m^2 leucovorin, 400 mg/m^2 5-FU as an i.v. bolus injection on day 1 followed by 600 mg/m^2 5-FU by 22 h of continuous infusion).

The study adopted a parallel group design (n = 9 patients per group) with or without a single infusion of oxaliplatin at 85 mg/m^2. The PKs of 5-FU were compared in the presence and absence of oxaliplatin after 1–7 cycles of treatment with the combination.

Table 6 PKs of 5-FU alone or following a single 2-h infusion of oxaliplatin at 85 mg/m^2 (de Gramont regimen; Ref 38)

Evaluation	No. of patients	C_{max} (μg/ml)	AUC (μg·h/ml)
5-FU	9	36.2 ± 11.5	10.3 ± 3.45
5-FU/oxaliplatin	9	37.2 ± 7.70	8.58 ± 1.83
t test (P)[a]		0.683	0.299

[a] $P \geq 0.05$; not significant.

Although an early interim analysis of the data in limited number of patients reported a significant PK interaction between oxaliplatin and 5-FU (37), the final analysis of the full data set in 18 patients indicated no significant differences in 5-FU exposure in the presence and absence of oxaliplatin (38; Fig. 7; Table 6).

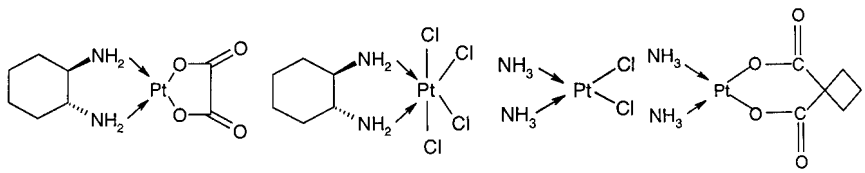
PK analyses of oxaliplatin (85–130 mg/m^2) in combination with CPT-11 (150–350 mg/m^2) have also demonstrated no statistically significant PK interactions between the drugs with respect to clearance (41).

Effect of 5-FU on Platinum Clearance. The effect of 5-FU on oxaliplatin PKs has not been studied directly; however, comparison of platinum levels when oxaliplatin is combined with 5-FU (weekly infusion regimen) show that oxaliplatin exposure in the presence of 5-FU is within the normal range of the values derived from single agent studies in the absence of 5-FU (30).

Drug-Drug Interaction Assessments *In Vitro*

CYP450 Interactions. Oxaliplatin did not significantly inhibit (defined as a decrease in enzyme activity to <70% of control rate) CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP3A4, CYP2D6, or CYP2E1. Therefore, metabolically me-

Table 7 Comparative PKs of oxaliplatin, tetraplatin, cisplatin and carboplatin

	Oxaliplatin[a]	Tetraplatin[b]	Cisplatin[c]	Carboplatin[d]
Molecular Structure				
Reactivity	Intermediate	High	High	Low
Total platinum				
$t_{1/2}\alpha$ (h)	7.30 ± 4.9	0.16	0.22 ± 0.15	0.37 ± 0.17
$t_{1/2}\beta$ (h)	239 ± 54.4	25.8	0.72 ± 0.4	1.93 ± 0.23
$t_{1/2}\gamma$ (h)	NA[e]	NA	130 ± 24	139 ± 38.4
AUC/D (min·m^2/liter)	125 ± 28	35.0 ± 7.21	299 ± 28	83.0 ± 32.0
V_{ss} (liters)[f]	93.4 ± 16.8	ND	52.0 ± 13	176 ± 58.0
Cl (liters/h)[f]	0.96 ± 0.17	3.05 ± 0.06	0.35 ± 0.03	1.38 ± 0.36
Ultrafiltrable platinum				
$t_{1/2}\alpha$ (h)	0.28 ± 0.06	0.14	0.10 ± 0.03	0.38 ± 0.13
$t_{1/2}\beta$ (h)	16.3 ± 2.90	14.9	0.60 ± 0.02	2.00 ± 0.18
$t_{1/2}\gamma$ (h)	273 ± 19.0	ND	NA	NA
AUC/D (min·m^2/liter)	5.49 ± 2.12	4.84 ± 1.20	5.10 ± 0.50	17.4 ± 4.00
V_{ss} (liters)[f]	582 ± 261	378 ± 240	19.2 ± 2.00	17.0 ± 2.00
Cl (liters/h)[f]	10.1 ± 3.071	22.4 ± 5.30	21.2 ± 1.98	6.42 ± 1.14
Clr (ml/min)[f]	77.7 ± 26.8	59.5 ± 17.8	74.0 ± 29.0	81.0 ± 17.0
Blood cell platinum (%D)	4–15[g]	ND	1.20 ± 0.20	0.40 ± 0.10
Urinary elimination (Ae over 24 h; %D)	36.8 ± 6.6	11–32	28.0 ± 4.00	77.0 ± 5.00

[a] Refs. 19–22.
[b] Refs. 46 and 47.
[c] Ref. 48.
[d] Ref. 49.
[e] NA, not applicable; ND, not determined; Cl, clearance; Cl_r, renal clearance.
[f] Normalized to 1.73 m^2.
[g] % Platinum dose in blood cells over range of concentrations between C_{min} and C_{max}.

diated drug-drug interactions of oxaliplatin on co-administered drugs cleared by these CYP450 isoforms are not anticipated in the clinic (32). Additionally, because the biotransformation of oxaliplatin is not dependent on CYP450, induction or inhibition of CYP450 activity by medications concomitantly administered with oxaliplatin is not expected to affect platinum clearance.

Plasma Protein Binding Interactions. Drug-drug interaction studies have been performed *in vitro*, to investigate the ability of selected concomitant medications, including erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel (Taxol), to displace oxaliplatin from plasma proteins (44). Oxaliplatin (20 μg/ml) was incubated at for 6 h with human serum protein in the presence of erythromycin (7 μg/ml), salicylate (300 μg/ml), sodium valproate (100 μg/ml), granisetron (100 ng/ml), and paclitaxel (5 μg/ml). Any displaced platinum was then assayed in plasma ultrafiltrate by FAAS.

No significant displacement of platinum from plasma protein was observed with any of the concomitant medications tested, with the exception of a small (2.85%) increase in free platinum concentrations in the presence of erythromycin (44). This small increase is not considered to be clinically significant, and no protein binding displacement reactions are anticipated in patients.

Comparative PKs of Oxaliplatin, Cisplatin, Carboplatin, and Tetraplatin

The comparative PKs of oxaliplatin, tetraplatin, cisplatin, and carboplatin are presented in Table 7. The PKs of platinum complexes are determined by two major factors. First, the stability of the leaving ligand largely determines the chemical reactivity and intrinsic cytotoxicity of the complex. Second, the nature of the carrier ligand may influence the tissue distribution characteristics of the molecule. These two factors combined will determine the unique chemical reactivity and disposition properties of a given platinum complex. Among the most striking differences between the DACH platin complexes compared to cisplatin and carboplatin are the differences in the volume of distribution from plasma ultrafiltrate. Oxaliplatin and tetraplatin have very large volumes of distribution (582 and 378 liters) compared to 19.2 and 17.0 liters for cisplatin and carboplatin, respectively (Table 7). This observation implies that the DACH moiety may confer some advantages in terms of enhanced tissue penetration that may be due altered cell membrane permeability. This hypothesis is supported by the observation that oxaliplatin accumulates more readily into erythrocytes compared to cisplatin and carboplatin, a feature that cannot be explained solely on the basis of chemical reactivity and covalent binding of platinum. To date, however, no direct measurements of platinum

concentrations in normal or tumor tissue have been made after oxaliplatin administration to substantiate this hypothesis.

The urinary elimination of platinum within 24 h of treatment differs markedly across the various platinum compounds. For example, the more chemically reactive platinum complexes, such as cisplatin and tetraplatin, exhibit relatively low platinum recovery in urine (approximately 11–32%) within 24 h of treatment. This observation probably reflects the extensive binding of these reactive platinum compounds to tissues and implies that renal elimination is relatively unimportant, at least during the initial phases of platinum clearance from plasma. In contrast, carboplatin is considerably less chemically reactive than cisplatin and tetraplatin by virtue of the carboxylato-leaving ligand. Carboplatin is extensively cleared unchanged, with platinum urinary recovery values up to 77%. In contrast to cisplatin and tetraplatin, clearance is predominantly driven by GFR, and carboplatin doses are now routinely adjusted based on a prospective evaluation of GFR. Oxaliplatin appears to be cleared equally by tissue distribution and glomerular filtration. The clearance of ultrafilterable platinum from plasma after a dose of oxaliplatin administration at 130 mg/m^2 is in the range of 9.34–10.1 liters/h. Renal clearance (approximately 4.66 liters/h) accounts for approximately half of the total plasma clearance, implying that distribution into tissues is also an important clearance mechanism for oxaliplatin. Given that tissue distribution and GFR appear to play equal roles in the clearance of oxaliplatin, it is predicted that a prospective evaluation renal function alone (GFR) is unlikely to be a useful predictor of platinum exposure and toxicity after oxaliplatin administration.

Conclusions

The PKs of unbound platinum in plasma ultrafiltrate after oxaliplatin administration are typically triphasic, characterized by a short initial distribution phase and a long terminal elimination phase ($t_{1/2}$, 252–273 h). No accumulation was observed in plasma ultrafiltrate after 130 mg/m^2 every 3 weeks or 85 mg/m^2 every 2 weeks. Interpatient and intrapatient variability in platinum exposure (AUC_{0-48}) was moderate to low (33 and 5%, respectively). Platinum bound irreversibly to plasma proteins (predominantly serum albumin) and erythrocytes. Erythrocytes did not serve as a reservoir for platinum in the systemic circulation, and accumulation of platinum in blood cells is not considered to be of clinical significance. Platinum was rapidly cleared from plasma ultrafiltrate (9.34–18.5 liters/h) at a rate that was similar to or exceeded the average human GFR (7.5 liters/h). The renal clearance of platinum significantly correlated with GFR, indicating that renal filtration is a major mechanism of platinum clearance. Tissue distribution is also an equally major mechanism of platinum elimination from systemic circulation.

Clearance of ultrafilterable platinum was decreased in patients with moderate renal impairment; however, there was no increase in drug toxicity. The effect of severe renal impairment on platinum clearance and toxicity is unknown. There was no significant effect of age, sex, or moderate hepatic impairment on the clearance of ultrafilterable platinum. Oxaliplatin underwent rapid and extensive nonenzymatic biotransformation in plasma ultrafiltrate and urine *in vitro* and *in vivo*. There was no evidence of CYP450-mediated metabolism *in vitro*. Up to 17 platinum-containing products were observed in plasma ultrafiltrate samples, including several putative cytotoxic species (including monochloro-, dichloro-, and diaquo-DACH platin). A number of noncytotoxic products (methionine, monochlorocreatine, and glutathione DACH platins), together with some unknown products, were also observed. Urinary elimination (53.8 ± 9.1%) was the predominant route of platinum elimination, with fecal excretion accounting for only 2.1 ± 1.9% of the administered dose 5 days postadministration. No significant PK interaction between oxaliplatin, 5-FU, and CPT-11 have been observed in patients. Oxaliplatin did not inhibit CYP450 isoenzymes *in vitro*, and platinum was not displaced from plasma proteins by selected concomitant medications. No metabolism-based drug-drug interactions or plasma protein binding displacement interactions are therefore anticipated in patients.

Analysis of platinum PKs after oxaliplatin, tetraplatin, cisplatin, and carboplatin administration reveals marked differences in the platinum disposition characteristics between the drugs. This may be attributable to differences in the stability of the various leaving ligands, which in turn determine the chemical reactivity of the complex. In addition, the nature of the various carrier ligands also appears to profoundly alter the disposition characteristics of platinum, with the DACH platinum species exhibiting substantially higher volumes of distribution compared to cisplatin and carboplatin.

In conclusion, these PK, biotransformation, mass balance, and drug-drug interaction studies provide a firm scientific basis for the safe and effective use of oxaliplatin in the clinic. These analyses also reveal that the pharmacological activity of oxaliplatin may be attributable, at least in part, to the unique pattern of platinum disposition in observed patients.

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