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ORIGINAL ARTICLE

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Pharmacokinetics of carboplatin administered with lobradimil to pediatric patients with brain tumors

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Abstract *Purpose*: To determine the pharmacokinetics of adaptively dosed carboplatin when administered in combination with the bradykinin agonist, lobradimil (RMP-7, Cereport), to pediatric patients with brain tumors. *Methods*: Carboplatin pharmacokinetic studies were performed on 21 of 25 children with primary brain tumors who received carboplatin and lobradimil on two consecutive days every 28 days in a phase I dose-escalation trial of lobradimil. Carboplatin was adaptively dosed, based on the radioisotopic glomerular filtration rate (GFR) to achieve a target plasma area under the concentration vs time curve (AUC) of 3.5 mg·min/ml per dose ×2 (2.5 mg·min/ml per dose ×2 in patients with prior craniospinal radiation or myeloablative chemotherapy). The adaptive dosing formula was: carboplatin dose (mg/m^2) = target AUC (mg·min/ml) × [0.93 × GFR (ml/min/m^2) + 15]. Carboplatin was infused over 60 min (n = 15) or 15 min (n = 6). The 10-min lobradimil infusion (100–600 ng/kg ideal body weight) began 5 min before the end of the carboplatin infusion. Frequent blood samples were drawn over 24 h after the first dose of carboplatin/lobradimil. Ultrafilterable platinum was measured by atomic absorption spectroscopy, and the AUC of ultrafilterable platinum was derived using the linear trapezoidal rule and extrapolated to infinity. *Results*: The median GFR was 65 ml/min/m^2(range 38–95 ml/min/m^2) and the median carboplatin doses for the 2.5 and 3.5 mg min/ml target AUCs were 154 and 276 mg/m^2/day (124–235 and 179–360 mg/m^2/day), respectively. The measured carboplatin AUC exceeded the target AUC in all 21 patients by a median of 35% (range 0.2–131%). The median carboplatin AUCs at the 2.5 and 3.5 mg·min/ml target AUCs were 3.4 and 4.8 mg·min/ml (2.51–5.8 and 3.9–7.7 mg·min/ml), respectively. Carboplatin clearance was lower than values previously reported in children and correlated poorly with GFR (r^2 = 0.14). *Conclusions*: Adaptive dosing of carboplatin based on GFR overestimated the dose required to achieve the target carboplatin AUC in pediatric patients with brain tumors treated with concurrent lobradimil. The degree to which the measured carboplatin AUC exceeded the target AUC appeared to be greater at higher doses of lobradimil, suggesting that the failure of the adaptive dosing method was related to an unexpected pharmacokinetic drug interaction.

Keywords Carboplatin · Pharmacokinetics · Pediatric · Brain · Lobradimil

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Introduction

The synthetic bradykinin analog, lobradimil (Cereport, RMP-7), is a potent and specific bradykinin B_2 receptor agonist [1, 2]. The B_2receptor is expressed on the luminal and abluminal surface of brain capillary endothelial cells, which is the anatomic site of the blood-brain barrier (BBB) [3]. The interaction of bradykinin or lobradimil with the B_2 receptor rapidly and reversibly increases the permeability of the BBB [1, 2, 4]. In rats implanted with RG2 gliomas, intracarotid or intravenous lobradimil significantly increased the uptake of carboplatin into brain tumors and brain tissue surrounding the tumor [5–7]. Tumor-bearing animals that received the combination of lobradimil and carboplatin survived longer than animals that received carboplatin alone [5]. Because the efficacy of chemotherapy in childhood brain tumors may be limited in part by the presence of the BBB, we studied the combination of

carboplatin with lobradimil in children with primary CNS tumors [8].

Carboplatin is eliminated primarily by renal excretion. Carboplatin clearance and area under the carboplatin plasma concentration vs time curve (AUC) are correlated with glomerular filtration rate (GFR) [9, 10], and carboplatin AUC is predictive of the severity of carboplatin-induced hematological toxicity [10]. Based on these observations, adaptive dosing formulas have been developed to individualize the dose of carboplatin from the GFR and the desired or target level of drug exposure (AUC). Adaptive dosing results in more uniform drug exposure and more predictable toxicity than dosing based on body surface area (BSA) [10, 11]. Adaptive dosing formulas have also been developed and prospectively validated in children [12–14].

In 15 children with solid tumors treated with adaptively dosed carboplatin in combination with ifosfamide and etoposide, GFR ranged from 33 to 122 ml/min/m^2 (median 79 ml/min/m^2) and carboplatin clearance ranged from 51 to 137 ml/min/m^2 (median 90 ml/min/m^2) [14]. Carboplatin clearance was highly correlated with GFR and the target AUC was achieved with good precision and minimal bias. The adaptively derived dose to achieve a target AUC of 8 mg·min/ml ranged from 362 to 1029 mg/m^2 in 14 subjects. A target AUC of 7–10 mg·min/ml produced tolerable toxicity levels in the pediatric trials of adaptively dosed carboplatin.

In adults with primary brain tumors treated with lobradimil and adaptively dosed carboplatin, the measured carboplatin AUC exceeded the target AUC by 4–89% [15]. We report the pharmacokinetics of adaptively dosed carboplatin (target AUC 2.5–3.5 mg·min/ml per day ×2 days) based on radioisotopically determined GFR administered with lobradimil in children with primary brain tumors.

Methods

Patient eligibility

Patients, 21 years of age and under, with histologically confirmed primary brain tumors refractory to standard therapy were eligible for a phase I dose-escalation trial of lobradimil given in combination with adaptively dosed carboplatin. Patients were required to have an ECOG performance status of 0, 1, or 2 and to have recovered from the toxic effects of prior therapy. Patients must not have received myelosuppressive chemotherapy within 3 weeks (6 weeks if prior nitrosourea) of entry into the study. Normal renal function was not required for study entry because carboplatin was adaptively dosed based on radioisotopically measured GFR, but patients were required to have a serum creatinine of ≤ 1.2 mg/dl if under 5 years of age, ≤ 1.5 mg/dl if aged 5–10 years, ≤ 1.8 mg/dl if aged 10–15 years, and ≤ 2.4 mg/dl if aged over 15 years. Serum creatinine was determined by the Jaffé method [16]. All patients were required to have a serum bilirubin and SGPT not more than twice the upper limit of normal. Patients who had not previously received craniospinal irradiation or myeloablative therapy with bone marrow or stem cell rescue were considered to be evaluable for hematologic toxicity and were required to have a granulocyte count $>1500/\mu l$, hemoglobin >8.0 g/dl, and a platelet count $>100{,}000/\mu l$. Patients treated with carboplatin within 6 months prior to study entry were ineligible. This trial was approved by our Institutional Review Board. Before study entry, written informed consent was obtained from the patient or his/her guardian.

Trial design

Carboplatin was adaptively dosed based on the radioisotopically measured GFR (^{99m}Tc-DTPA two-sample plasma method [17]) to achieve a target AUC of 3.5 mg·min/ml per dose (7.0 mg·min/ml per cycle). The target AUC was 2.5 mg·min/ml per dose (5.0 mg·min/ml per cycle) for patients who had previously received craniospinal radiation or myeloablative therapy. The adaptive dosing formula used [13] was:

$$\text{Carboplatin dose}\left(\text{mg/m}^2\right) = \text{Target AUC}\left(\text{mg•min/ml}\right) \times \left[0.93 \times \text{GFR}\left(\text{ml/min/m}^2\right) + 15\right]$$

The BSA was calculated using the actual body weight using the formula of Dubois and Dubois [18].

Lobradimil was provided by Alkermes (Cambridge, Mass.) as a sterile solution at a concentration of 0.02 mg/ml. The calculated dose was diluted in 0.9% sterile sodium chloride to a total infusion volume of 20 ml for all patients. Lobradimil was administered intravenously over 10 min without carboplatin on day 1 of the first treatment cycle to evaluate its toxicity and perform lobradimil pharmacokinetic sampling. On day 2 and day 3 of cycle 1, and day 1 and 2 of each subsequent cycle, lobradimil was administered intravenously over 10 min, beginning 5 min before the end of the carboplatin infusion. The starting dose of lobradimil was 100 ng/kg ideal body weight (IBW) with dose escalations to 300, 450, and 600 ng/kg IBW.

Carboplatin was infused intravenously over 60 min daily for 2 days every 28 days in the first 15 patients in whom pharmacokinetics were obtained. Pharmacokinetics were obtained in six additional patients who received the carboplatin infusion intravenously over 15 min daily for 2 days every 28 days after the recommended dose of lobradimil (600 ng/kg IBW) had been determined.

Blood samples were drawn for carboplatin pharmacokinetic evaluation from each patient on the first day of the carboplatin/lobradimil combination. Blood samples were drawn from the patients receiving the 60-min infusion immediately prior to the dose, and 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h after the

start of the carboplatin infusion. Blood samples were drawn for carboplatin pharmacokinetic evaluation from patients receiving the 15-min infusion prior to the dose, at the end of the infusion, and 0.75, 1.25, 1.75, 2.25, 3.25, 5.25, 7.25, 12 and 24 h after the start of the carboplatin infusion.

The 2–3 ml blood samples were collected in heparinized tubes (Becton Dickinson small Green Top) and immediately placed on ice. Plasma was rapidly separated by centrifugation (1200 *g* for 10 min) and a portion was subjected to ultrafiltration by centrifugation at 2500 *g* for 20 min in an Amicon Centrifree device (Millipore, Bedford, Mass.). The ultrafiltrate was frozen at −70°C until assayed. Total platinum concentration in the ultrafiltrate was measured by flameless atomic absorption spectroscopy [19]. The platinum AUC in the plasma ultrafiltrate was derived using the linear trapezoidal rule and extrapolated to infinity. Carboplatin clearance was derived from the definition: clearance = dose/$AUC_{0-\infty}$.

The nonparametric Mann–Whitney *U*-test was used to assess the significance of differences in nonpaired data sets, and simple regression analysis was used to assess the relationship between carboplatin clearance and GFR and between lobradimil dose level and degree of deviation of the measured AUC from the target AUC.

Table 1 Patient characteristics ($n = 21$). Patients are divided into two groups based on the duration of the carboplatin infusion (60 or 15 min)

	60-min infusion	15-min infusion
Number of patients	15	6
Age (years)		
Median	13	12.5
Range	4–18	4–18
Gender (M/F)	10/5	5/1
Target carboplatin AUC (mg min/ml)		
3.5	9[a]	2
2.5	5	4
Diagnosis		
High-grade glioma	7	2
Medulloblastoma/PNET	3	3
Brainstem glioma	4	–
Ependymoma	1	1
Number of prior chemotherapy regimens		
Median	1	3
Range	0–3	1–5
Prior chemotherapy (*n*)		
Carboplatin	2	1
Cisplatin	5	6
Radiation therapy	15	6
Craniospinal radiation	4	4

[a]One additional patient was dosed for a target AUC of 5.4 mg min/ml because of an error in the GFR calculation.

Results

Patient characteristics

Pharmacokinetics were performed on 21 of 25 patients entered on this pediatric phase I trial of lobradimil and carboplatin [8]. Patient characteristics are shown in Table 1. The patients ranged in age from 4 to 18 years (median 13 years). All patients had evidence of tumor progression or recurrence after standard therapy with radiation, chemotherapy, or both.

Dosing

The carboplatin dose ranged from 124 to 235 mg/m^2 per day (median 154 mg/m^2 per day) at the 2.5 mg·min/ml target AUC and 179–360 mg/m^2 per day (median 276 mg/m^2 per day) at the 3.5 mg·min/ml target AUC. Patient 10, who was in the 2.5 mg·min/ml per day ×2 days target AUC group, actually received only 62% of his carboplatin dose on the first day due to an infusion pump malfunction. The day-2 dose was adjusted to include the portion of the dose missed on day 1, yielding a carboplatin dose equivalent to a target AUC of 3.44 mg·min/ml on the day of pharmacokinetic sampling. Pharmacokinetic parameters from this patient are included in the 3.5 mg·min/ml target AUC cohort. Patient 21 received a carboplatin dose equivalent to a target AUC of 5.4 mg/m^2 per day because of an error in the GFR calculation.

The GFR, which was determined by a ^{99m}Tc-DTPA method, ranged from 38 to 95 ml/min/m^2 (median 65 ml/min/m^2). The median (range) GFR in the nine patients in the group receiving an adapted carboplatin dose targeting an AUC of 2.5 mg·min/ml per day ×2 days was 53 ml/min/m^2(38–86 ml/min/m^2), and the median (range) GFR in the 12 patients dosed for a target AUC of 3.5 mg·min/ml per day ×2 days was 74 ml/min/m^2(40–95 ml/min/m^2; $P = 0.065$). Six of nine patients who were treated at the 2.5 mg·min/ml target AUC had previously received cisplatin, whereas only five of 12 patients treated at the higher target AUC were pretreated with cisplatin; but there was no statistically significant difference between the GFR in the 11 patients who had previously received cisplatin (median GFR 63 ml/min/m^2) and the ten patients who were not pretreated with cisplatin (median GFR 68 ml/min/m^2; $P = 0.28$).

Carboplatin pharmacokinetics

As shown in Table 2 and Fig. 1, the measured carboplatin AUC exceeded the target AUC in all 21 patients by a median of 35% (range 0.2–131%). The median measured carboplatin AUC for the cohort of patients dosed to a target AUC of 2.5 mg·min/ml was 3.4 mg·min/ml (range 2.51–5.8 mg·min/ml). For the cohort of patients dosed to a target AUC of 3.5 mg·min/ml, the median measured carboplatin AUC was 4.8 mg·min/ml (range 3.9–7.7 mg·min/ml). The relationship between the dose level of lobradimil and the degree of deviation of the measured AUC from the target AUC is shown in Fig. 2.

Table 2 Lobradimil dose level, adapted carboplatin dose and carboplatin pharmacokinetic parameters

Patient no.	Lobradimil dose (ng/kg IBW)	GFR (ml/min/m^2)	Target AUC (mg min/ml)	Carboplatin dose		Carboplatin parameters		
				(mg/m^2/day)	(mg/day)	Measured AUC (mg min/ml)	Clearance (ml/min/m^2)	$T_{1/2}$(h)
1	300	67	2.5	192	200	3.5	55	3.0
2	600	48	2.5	148	240	4.8	31	1.8
3	600	86	2.5	235	280	5.8	41	1.6
4	600	65	2.5	194	120	3.0	65	1.6
5	600	38	2.5	124	210	3.7	34	1.7
6	600	53	2.5	157	220	3.2	49	1.3
7	600	48	2.5	149	200	2.51	60	1.4
8	600	47	2.5	150	240	3.1	48	2.2
9	100	70	3.5	279	410	4.0	69	1.9
10	300	67	3.44	264	370	3.9	67	1.9
11	300	84	3.5	330	300	6.0	55	1.5
12	300	87	3.5	328	600	4.7	70	1.6
13	450	40	3.5	179	280	4.6	39	2.0
14	450	63	3.5	258	490	7.7	34	1.9
15	450	80	3.5	313	360	5.9	53	1.6
16	600	95	3.5	360	360	6.9	52	1.6
17	600	53	3.5	222	410	3.9	57	1.9
18	600	87	3.5	273	300	4.9	56	1.5
19	600	62	3.5	258	170	4.7	55	2.4
20	600	79	3.5	308	400	5.8	53	1.6
21	100	57	5.4	367	540	6.1	60	1.5
Median		65					55	1.6
Range		38–95					31–70	1.3–3.0

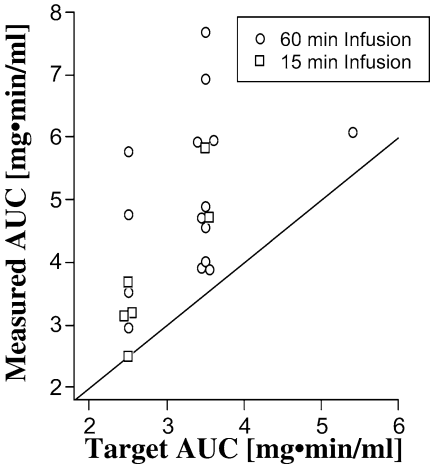

Fig. 1 The measured AUC of ultrafilterable carboplatin as a function of the target AUC used to derive the dose using the adaptive dosing formula. The *line* represents the line of unity. *Circles* represent patients receiving the carboplatin as a 60-min infusion and *squares* represent patients receiving carboplatin as a 15-min infusion

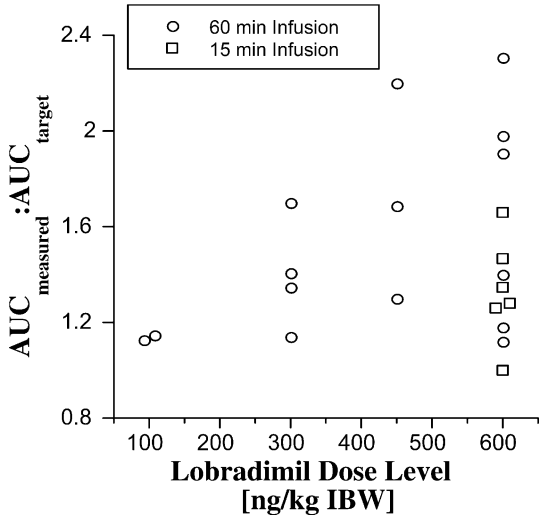

Fig. 2 The ratio of the measured AUC of ultrafilterable platinum to the target AUC used to derive the dose of carboplatin using the adaptive dosing formula as a function of the lobradimil dose level. A ratio greater than one indicates that the measured AUC exceeded the target. The regression analysis ($r^2 = 0.060$) was not statistically significant ($P = 0.28$). *Circles* represent patients receiving the carboplatin as a 60-min infusion and *squares* represent patients receiving carboplatin as a 15-min infusion

For the patients treated to achieve a target AUC of 2.5 mg·min/ml per day, the median carboplatin clearance was 49 ml/min/m^2 (range 31–67 ml/min/m^2), and for those treated to achieve a target AUC of 3.5 mg·min/ml, the median carboplatin clearance was 55 ml/min/m^2 (range 34–70 ml/min/m^2; $P = 0.15$). The carboplatin clearance correlated poorly with the GFR ($r^2 = 0.14$; Fig. 3).

We assessed the effect of adaptive dosing of carboplatin on interpatient variability using the coefficient of variation (CV) of the carboplatin clearance normalized to body weight, BSA, and GFR (Fig. 4). The CV of the clearance normalized to GFR (45%) was more than

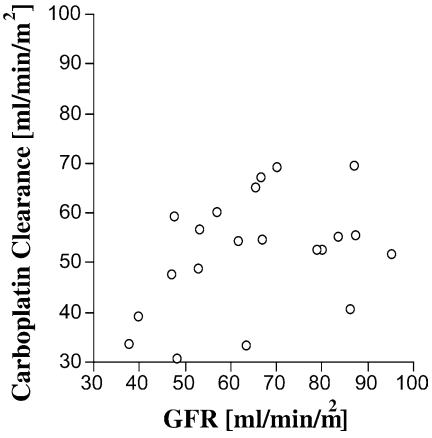

Fig. 3 Relationship between GFR and carboplatin clearance (regression analysis, $r^2 = 0.14$, $P = 0.091$)

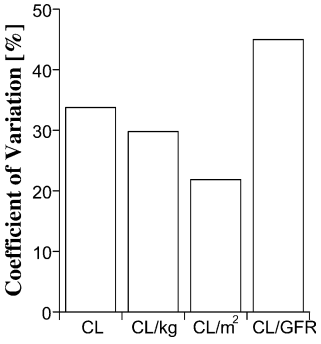

Fig. 4 The coefficient of variation (CV, measure of the degree of variability) for carboplatin clearance normalized to body weight, BSA, and GFR.(*CL* carboplatin clearance in ml/min, *CL/kg* clearance normalized to body weight in ml/min/kg, *CL/m²* clearance normalized to BSA in ml/min/m², *CL/GFR* carboplatin clearance in ml/min divided by the GFR in ml/min). The lower CV for CL/m² compared with CL/GFR suggests that dosing based on BSA would result in less-variable drug exposure than using the adaptive dosing formula in this instance

twofold higher than the CV of the clearance normalized to BSA (22%).

Toxicity

Myelosuppression was the primary toxicity from carboplatin. The median percentage drop in absolute neutrophil count at the nadir relative to the pretreatment value was 79% (range 33–97%), and the median nadir neutrophil count was 645 cells/μl. The median percentage drop in platelet count was 87% (range 31–97%), and the median nadir platelet count was 28,500 cells/μl. The relationship between percentage decline in platelet and neutrophil counts and the measured carboplatin AUC is shown in Fig. 5. Most patients fell on the plateau (upper end) of the concentration-effect curve, consistent with the pharmacokinetic observation that the measured carboplatin AUC exceeded the expected (target) level of

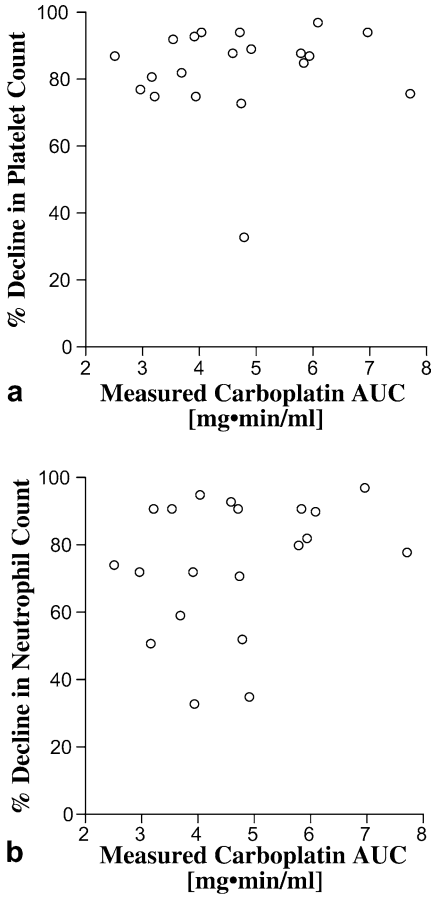

Fig. 5a, b Percentage decline in (**a**) platelet count and (**b**) neutrophil count at nadir relative to pretreatment levels on cycle 1 of therapy as a function of the measured carboplatin AUC

drug exposure. As a result, it is not feasible to assess the concentration-effect relationship in this population.

Discussion

Adaptive dosing of carboplatin based on the GFR overestimated the dose required to achieve the desired target carboplatin AUC, when administered in combination with lobradimil to pediatric patients with CNS tumors; and these patients experienced a greater than expected degree of myelosuppression. The GFR in our patient population (median 65 ml/min/m², range 38–95 ml/min/m²) was 18% lower than the GFR reported by Marina et al. (median 79 ml/min/m², range 33–122 ml/min/m²) in a heavily pretreated population of 15 pediatric patients with solid tumors; but the carboplatin clearance in our patient population (median 54 ml/min/m², range 31–70 ml/min/m²) was substantially lower than that measured in these solid tumor patients (median 90 ml/min/m², range 51–137 ml/min/m²) who received carboplatin in combination with ifosfamide and etoposide [14] and lower than the previously reported values of carboplatin clearance in

children, which generally range from 75 to 85 ml/min/m^2 [12, 20, 21]. A group of 18 adults with high-grade gliomas were treated with the combination of lobradimil and carboplatin (adaptively dosed using the Calvert formula). These patients had a median GFR of 71 ml/min/m^2 (range 39–110 ml/min/m^2) and a median carboplatin clearance of 69 ml/min/m^2 (range 45–90 ml/min/m^2), and their measured carboplatin AUC exceeded the target AUC by a median of 22%, compared to 35% in our patients, but they received lower doses of lobradimil (100–300 ng/kg) [15].

The results of our trial and the trial in adults suggest that lobradimil alters the clearance of carboplatin when the drugs are administered concurrently. This is supported by the observation in both studies that the degree to which the measured carboplatin AUC exceeded the target AUC appeared to be greater at higher doses of lobradimil (Fig. 2). If the ratio of measured to target carboplatin AUC as a function of lobradimil dose level from the two trials is combined, the median carboplatin $AUC_{measured}/AUC_{target}$ at the 100 ng/kg lobradimil dose level is 1.07 ($n = 5$), at the 300 ng/kg lobradimil dose level it is 1.27 ($n = 17$), and at the 600 ng/kg lobradimil dose level it is 1.38 ($n = 12$). The differences between the 100 ng/kg dose level and the two higher dose levels are statistically significant ($P < 0.02$).

Bradykinin has an effect on renal function primarily through interaction with its B_2 receptor [22], and lobradimil is specific for this receptor. However, in animals, bradykinin increases renal blood flow, urine volume, and sodium excretion, but does not alter the GFR [22–24]. Decreased carboplatin clearance would be expected to be associated with a decrease in GFR. Thomas et al. proposed a lobradimil-mediated alteration in renal tubular function as an explanation for the apparent drug interaction [15]. This might also explain the lack of correlation between carboplatin clearance and GFR in our patients.

Individualizing the dose of a drug by normalizing it to body weight or BSA or by using adaptive dosing formulas, such as those based on GFR that have been developed for carboplatin, is aimed at reducing interpatient variability in drug exposure (AUC) and achieving drug exposures that are within a range that is therapeutic and acceptably toxic. The twofold higher CV for carboplatin clearance normalized to GFR compared to carboplatin clearance normalized to BSA suggests that carboplatin AUC would be less variable when administered with lobradimil, if the dose were based on BSA rather than the adaptive dosing formula.

In conclusion, in this study of pediatric patients with primary brain tumors treated with the combination of carboplatin and concurrent lobradimil, adaptive dosing of carboplatin based on GFR overestimated the dose required to achieve the target carboplatin exposure, demonstrating that the more sophisticated adaptive dosing methods, such as those used to determining carboplatin dose, may not overcome an unexpected drug interaction.

References

1. Elliott PJ, Hayward NJ, Huff MR, et al (1996) Unlocking the blood-brain barrier: a role for RMP-7 in brain tumor therapy. Exp Neurol 141:214–224
2. Raymond JJ, Robertson DM, Dinsdale HB (1986) Pharmacological modification of bradykinin induced breakdown of the blood-brain barrier. Can J Physiol Pharmacol 13:214–220
3. Liu Y, Hashizume L, Chen Z, et al (2001) Correlation between bradykinin-induced blood-tumor barrier permeability and B2 receptor expression in experimental brain tumors. Neurol Res 23:379
4. Inamura T, Black KL (1994) Bradykinin selectively opens blood-tumor barrier in experimental brain tumors. J Cereb Blood Flow Metab 14:862–870
5. Matsukado K, Inamura T, Nakano S, et al (1996) Enhanced tumor uptake of carboplatin and survival in glioma-bearing rats by intracarotid infusion of bradykinin analog, RMP-7. Neurosurgery 39:125–133
6. Elliott PJ, Hayward NJ, Dean RL, et al (1996) Intravenous RMP-7 selectively increases uptake of carboplatin into rat brain tumors. Cancer Res 56:3998–4005
7. Inamura T, Nomura T, Bartus RT, et al (1994) Intracarotid infusion of RMP-7, a bradykinin analog: a method for selective drug delivery to brain tumors. J Neurosurg 81:752–758
8. Warren KE, Patel MC, Aikin AA, et al (2001) Phase I trial of lobradimil (RMP-7) and carboplatin in children with brain tumors. Cancer Chemother Pharmacol 48:275–282
9. Harland S, Newell D, Siddik Z, et al (1984) Pharmacokinetics of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum (II) in patients with normal and impaired renal function. Cancer Res 44:1693–1697
10. Egorin M, van Echo D, Tipping S, et al (1984) Pharmacokinetics and dosage reduction of *cis*-diammine (1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. Cancer Res 44:5432–5438
11. Calvert A, Newell D, Gumbrell L, et al (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756
12. Newell D, Pearson A, Balmanno K, et al (1993) Carboplatin pharmacokinetics in children: the development of a pediatric dosing formula. J Clin Oncol 11:2314–2323
13. Marina N, Rodman J, Shema S, et al (1993) Phase I study of escalating targeted doses of carboplatin combined with ifosfamide and etoposide in children with relapsed solid tumors. J Clin Oncol 11:554–560
14. Marina N, Rodman JH, Murry DJ, et al (1994) Phase 1 study of escalating targeted doses of carboplatin combined with ifosfamide and etoposide in treatment of newly diagnosed pediatric solid tumors. J Natl Cancer Inst 86:554
15. Thomas HD, Lind MJ, Ford J, et al (2000) Pharmacokinetics of carboplatin administered in combination with the bradykinin agonist cereport (RMP-7) for the treatment of brain tumors. Cancer Chemother Pharmacol 45:284–290
16. Spierto FW, MacNeil ML, Burtis CA (1979) The effect of temperature and wavelength on the measurement of creatinine with the Jaffe procedure. Clin Biochem 12:18
17. Russell C, Bischoff P, Kantzen F, et al (1985) Measurement of glomerular filtration rate: single injection plasma clearance method without urine collection. J Nucl Med 26:1243–1247
18. DuBois D, Dubois E (1916) Formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863
19. Ghazal-Aswad S, Calvert AH, Newell DR 1996) A single-sample assay for the estimation of the area under the free carboplatin plasma concentration versus time curve. Cancer Chemother Pharmacol 37:429–434
20. Thomas H, Boddy A, English M, et al (2000) Prospective validation of renal function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group trial. J Clin Oncol 18:3614–3621

21. Riccardi R, Riccardi A, Lasorella A, et al (1994) Clinical pharmacokinetics of carboplatin in children. Cancer Chemother Pharmacol 33:477–483
22. Matsumura Y, Tadano K, Yamasaki T (1999) Renal haemodynamic and excretory responses to bradykinin in anesthetized dogs. Clin Exp Pharmacol Physiol 26:645
23. Granger JP, Hall JE (1985) Acute and chronic actions of bradykinin on renal function and arterial pressure. Am J Physiol 248 (1 Pt 2):F87
24. Lortie M, Regoli D, Rhaleb NE, et al (1992) The role of B1- and B2-kinin receptors in the renal tubular and hemodynamic response to bradykinin. Am J Physiol 262 (1 Pt 2):R72