Pharmacokinetics of Superselective Intra-Arterial and Intravenous [^{11}C]BCNU Evaluated by PET

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The pharmacokinetics of i.v. and superselective intra-arterial carbon-11 1,3-bis-(2-chloroethyl)-1-nitrosourea ([^{11}C]BCNU) were directly compared for the first time in ten patients with recurrent gliomas using positron emission tomography (PET). Intra-arterial administration of [^{11}C]BCNU achieved concentrations of the drug in the tumor that averaged 50 times higher than with a comparable i.v. dose. These preliminary results suggest that the degree of early metabolic trapping of BCNU in tumor correlates with the clinical response to this chemotherapy.

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Gliomas make up ~50% of primary intracranial tumors; of these, about half are grade III or grade IV. Systemic chemotherapy of these highly malignant lesions has been disappointing, and the addition of i.v. chemotherapy to surgical resection and radiotherapy has not improved survival significantly (*1,3*). Of those agents now available for the treatment of intracerebral gliomas, 1,3-bis- (2-chloroethyl)-1-nitrosourea (BCNU), a lipophilic alkylating agent, has proven the most effective (*1–3*).

Recently it has been suggested that the intra-arterial administration of chemotherapeutic drugs can improve their efficacy (*4–11*). Theoretically, selective arterial injection into a major feeding artery of a glioma would be preferable to the more general administration of the drugs into the carotid or vertebral artery systems. Using this approach, we have obtained in some instances striking clinical responses.

Cerebral imaging of carbon-11-labeled BCNU ([^{11}C] BCNU) using positron emission tomography (PET) made it possible to characterize the in vivo pharmacokinetics of BCNU, to compare the pharmacokinetics of i.v. and superselective intra-arterial administration of BCNU, and to correlate the clinical response with the predictive capability of these studies.

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METHODS

Study Protocol

Patients initially had dynamic PET scans following the i.v. injection of ~10 mCi [^{11}C]BCNU. Subsequently, an angiographically placed two French silastic catheter with a radio-opaque tip was advanced through the internal carotid artery on the side of the tumor into a major tumor feeding vessel (*12*). This resulted in catheter placement either in the middle cerebral artery (MCA) or one of its branches. After correct catheter placement, an injection of ~ 500 μCi of [^{11}C]BCNU was made through this superselective catheter, and a second dynamic study was performed. Finally, once proper catheter position again had been confirmed by examining the intra-arterial [^{11}C]BCNU study and an x-ray film of the skull, a therapeutic dose of nonradioactive BCNU (150 mg/m^2 body surface area), diluted in 5% dextrose, was infused through the superselective catheter.

Patient Population

All patients had malignant gliomas of grade III or grade IV that had been previously proven by biopsy. All had undergone surgical resection of their tumors, and had received maximal radiotherapy to the tumor (6,000 rad). One patient (Patient 1) had received i.v. BCNU chemotherapy (80 mg/m^2 on three consecutive days) 1 yr before this study. All patients had evidence of tumor recurrence on serial computed tomographic (CT) studies. All patients had angiograms demonstrat-

ing a tumor arterial supply from the middle cerebral artery circulation; no angiogram demonstrated a hypervascular tumor "blush." Informed consent was obtained from all patients before entry into the protocol.

Radiopharmaceutical Synthesis

BCNU labeled with ^{11}C was produced on site by the ^{14}N (p,α) ^{11}C reaction. The method of synthesis, previously reported in detail (*13–16*), involves the reaction of 2-chloroethyleneamine HCl with ^{11}C-labeled phosgene in dioxane at room temperature to yield ^{11}C-labeled 1,3-bis-(2-chloroethylene) urea. Nitrosation of this compound with $NaNO_2$ in formic acid produced BCNU labeled with ^{11}C in the carbonyl position. The radiolabeled compound had a specific activity of 30 mCi/mmol or 140 mCi/mg. For i.v. studies, 10–15 mCi of [^{11}C]BCNU were injected; for intra-arterial studies 300–500 μCi were used.

This method of [^{11}C]BCNU synthesis, resulting in the introduction of the radiolabel on the carbonyl atom of the molecule ensures that, with BCNU decomposition, the ^{11}C label remains attached to the isocyanate fraction, which is thought itself to have antitumor action (*14*).

This method of BCNU labeling was chosen in preference to placement of an ^{13}N label on the nitroso group of BCNU. It has been shown that the presence of ^{13}N label in the plasma after chloroform extraction indicates oxidative metabolism or denitrozation, and loss of the radiolabel from the pharamceutical (*14*).

Scanning Procedures

Images were obtained on the Therascan-3128, a two-ring tomographic positron emission scanner (*17,18*), with a full width at half maximum resolution in the dynamic mode of 17 mm. Scans were started immediately following the injection of the [^{11}C]BCNU intravenously or intra-arterially. The scanning schedule was as follows: ten scans of 30 sec each, five scans of 2 min each, five scans of 5 min each, and finally one scan of 10 min. At the completion of an intra-arterial study, 5 mCi of gallium-68 ethylenediaminetetraacetic acid were injected intravenously. The patient was then scanned for 10 min to localize activity in the skull, so that the edge-finding algorithm during reconstruction could determine the correct skull boundary.

Images were reconstructed using the Therascan standard software package, that includes automatic correction of random coincidences, cross-calibration with the NaI (Tl) well-counter used to measure plasma radioactivity, normalization of detector sensitivity, attenuation correlation (*19*), and scatter correction (*20,21*).

Data Analysis

Multiple sequential images were obtained after both i.v. and intra-arterial injections of [^{11}C]BCNU. Circular regions of interest 3 cm^2 in size were placed over tumor tissue and over a corresponding region in the contralateral hemisphere, and time-activity curves were generated. The curves were analyzed using a curve stripping technique. A slow exponential component was determined by fitting the clearance curve data to the terminal flat portion of the time-activity data; this slow component was subtracted and the remaining activity at early times fitted with a single exponential curve.

The count rates obtained from brain tissue in the contralateral hemisphere were too low after upper-selective intra-arterial injection to permit statistically significant curve analysis. Typical results obtained after i.v. (Fig. 1A) and superselective intra-arterial (Fig. 1B) [^{11}C]BCNU administration are presented.

Chemotherapy

Following the intra-arterial [^{11}C]BCNU study, the superselective catheter was left in place, and the patients received BCNU chemotherapy, 150 mg/m^2 body surface area, diluted in a dextrose water solution (*22*) over a continuous 3-hr infusion.

RESULTS

Results are presented for 12 completed procedures in ten patients: two females and eight males, ranging in age from 37 to 70 yr.

In the half-life clearance curves of ^{11}C radioactivity from the brain, two distinct components can be identified in each clearance curve (Table 1). After i.v. injection, an initial fast curve component is seen with a $T_{1/2}$ of 3.42 ± 0.95 min in tumor, and 3.08 ± 0.96 min in a homologous region in the contralateral hemisphere. The difference is not statistically significant ($p = 0.40$). After intra-arterial injection, a fast component is also seen with a $T_{1/2}$ of 2.79 ± 1.38 min. Again, there is no significant difference in this fast component in tumor when the i.v. and intra-arterial studies are compared ($p = 0.20$).

The second component of the i.v. ^{11}C radioactivity clearance curve differed significantly in tumor tissue, where the $T_{1/2}$ = 219 ± 130 min, compared with contralateral brain tissue, in which the $T_{1/2}$ = 52 ± 21 min. Despite the large standard deviations, especially in tumor tissue, this difference is significant ($p = 0.005$). These findings are in keeping with clearance curve results previously reported (*23*). It is believed that this slow second component of the curve represents the breakdown products of [^{11}C]BCNU; radioactivity bound to amino groups in proteins or nucleic acids in tissue (*24*). After 30 min, the majority of the ^{11}C radioactivity that is measured represents protein-bound breakdown products of BCNU rather than the intact drug.

The second component of the tumor clearance curve

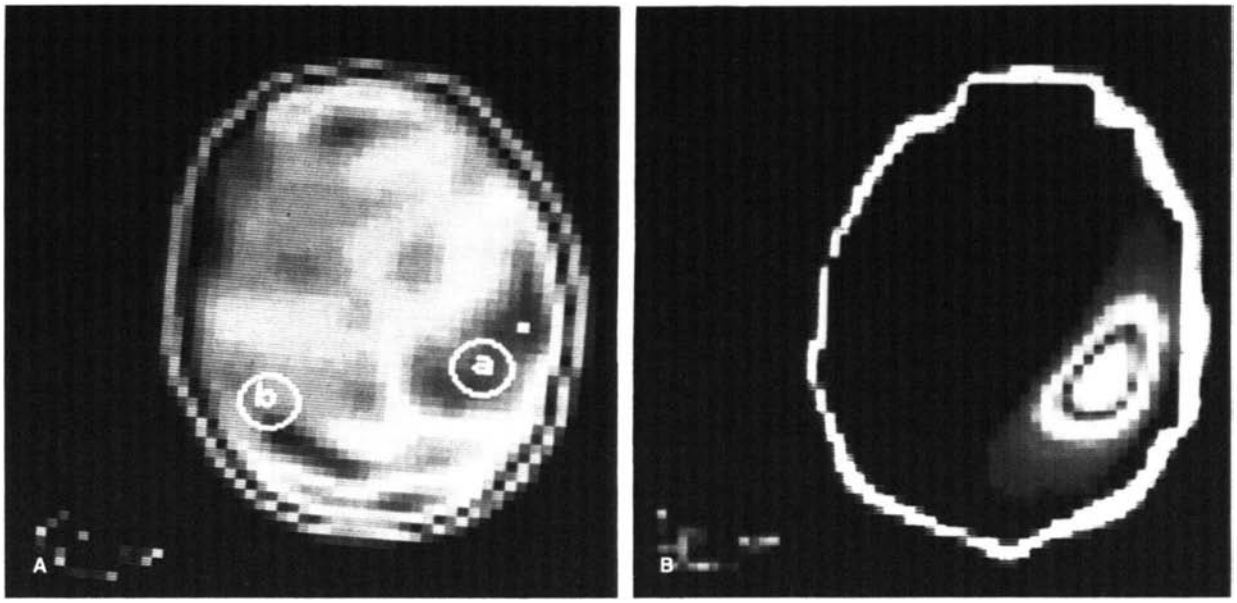

FIGURE 1
Images obtained at 40 min after injection of [^{11}C]BCNU by i.v. (A) and superselective intra-arterial (B) routes. ^{11}C activity is observed to accumulate in right parietal tumor after i.v. injection (a = 9,009 Bq/cc, b = 6,149 Bq/cc). However, IA injection achieves both high tumor concentrations of activity as well as very low activity in surrounding and contralateral brain

after intra-arterial injection of [^{11}C]BCNU is much shorter ($T_{1/2}$ = 20 ± 5 min) than the slow component after i.v. injection (p = 0.001). The longer second component seen after i.v. injection may be due at least in part to the circulating [^{11}C]BCNU breakdown products binding to proteins, and leakage of this radioactivity into the region of altered permeability in and around the tumor (*23–27*).

Although quantitative measurements of blood flow were not made in this study, relative tumor blood flow can be estimated by comparing the heights of the peaks of the time-activity curves in normal tissue and in tumor after i.v. injection of a bolus (Table 2). The peak height tumors (tumor/normal tissue) ranged form 0.53 to 1.66, with a mean of 1.02 ± 0.37. It is interesting to note that in two patients (1 and 3) who were treated twice with intra-arterial BCNU, the peak ratios decreased by 37% and by 34%, respectively, after the first treatment, suggesting a relative diminution of tumor blood flow after the superselective intra-arterial chemo-

TABLE 1
Half-Life Clearance of ^{11}C Radioactivity from Brain

	Intravenous		Intra-arterial
Patient no.	Tumor	Normal tissue	Tumor
1	3.05	4.62	1.42
	399.43	50.00	20.12
1a	2.97	3.71	1.26
	207.89	34.87	10.99
2	3.91	3.14	3.60
	288.18	110.73	19.66
3	2.80	3.84	2.61
	147.60	57.89	21.84
3a	3.38	2.70	1.12
	190.03	38.20	26.98
4	2.54	2.57	5.34
	84.05	31.81	15.79
5	5.40	4.66	3.58
	82.05	33.99	19.43
6	3.60	1.51	5.04
	435.64	63.97	14.85
7	4.70	2.88	2.47
	401.16	35.02	29.09
8	3.28	2.57	1.80
	180.90	57.85	15.62
9	1.81	2.59	2.52
	90.40	58.60	20.50
10	3.54	2.19	2.67
	122.82	51.20	26.20
Mean ± s.d.	3.42 ± 0.95	3.08 ± 0.96	2.79 ± 1.38
	219 ± 130	52 ± 21	20 ± 5

TABLE 2
Ratio of Curve Peak Heights: Tumor/Normal Tissue

Patient no.	Ratio
1	1.51
1a	0.95
2	0.82
3	0.80
3a	0.53
4	1.12
5	1.66
6	0.92
7	1.54
8	0.71
9	0.95
10	0.71

therapy. When a paired t-test was applied to the peak heights in tumor and in normal tissue in these 12 cases, no significant difference was found ($p = 0.50$).

The ratio of peak heights (tumor/normal tissue) after bolus intra-arterial injection demonstrated that significantly increased first-pass concentrations could be achieved by this injection route. These values were quite variable, however, (range 2.42–419.34) and did not correlate with the relative tumor/normal tissue blood flow as indicated by the i.v. peak height ratios. It should be noted that this ratio represents only the amount of the radiopharmaceutical extracted by the tumor on the first-pass and total-body distribution of the [^{11}C]BCNU reaching the contralateral brain.

When comparing radioactivity achieved in tumor tissue relative to brain of the contralateral hemisphere, the intra-arterial injection gave an increase of up to 389 times (mean = 48.9 times). The i.v. injection only achieved an increase of a maximum 1.7 times (mean = 1.2 times).

Since it is known that BCNU is rapidly broken down into a variety of products (*26,27*), the initial portions of the clearance curves were carefully examined. At 10 min after injection, the tissue radioactivity in tumor after i.v. and after intra-arterial injection were compared (Table 3). Two cases (Patients 4 and 7) in which striking tumor regression was seen after the BCNU chemotherapy, had 10-min values that were significantly greater (mean = 90.0 ± 13.0) than the values in the other ten cases. Patient 7, a 37-yr-old female with a left anterior temporal glioblastoma multiforme, had substantial reduction in the size of her tumor 2 wk after treatment. Patient 4, a 66-yr-old female with a right parieto-occipital grade III mixed glioma (Fig. 2A), had virtual disappearance of her tumor on computed tomography scan 4 wk after treatment (Fig. 2B). Patient 7 died 4 mo later as a complication of spinal cord metastases. Patient 4 had a recurrence of her tumor 6 mo after intra-arterial treatment. Superselective catheterization of a tumor-feeding vessel was again performed, and she again received 150 mg/m^2 BCNU through this route. Her CT scans subsequently showed almost complete regression of the tumor, and scans remain without visible tumor 2 mo after that second treatment.

TABLE 3
Tumor ^{11}C Radioactivity Concentration

Patient no.	Intra-arterial study/ intravenous study*
1	12.27
1a	19.16
2	35.64
3	39.56
3a	12.15
4	81.32
5	8.71
6	2.46
7	99.11
8	13.41
9	12.10
10	26.89

*Activity normalized per mCi/dose.

In three cases (Patients 2, 3, and 10) intermediate ratios were seen at 10 min (mean = 34.0 ± 6.0). After the BCNU intra-arterial chemotherapy, these patients had a significant decrease in the size of their tumors, though less marked than the changes seen in the former two patients. In the remaining seven cases, low ratios were found (mean = 11.0 ± 5.0). These patients had either no change or only a slight decrease in size of their tumors.

DISCUSSION

Gliomas of high grade malignancy are uniformly fatal. Conventional treatment with surgery, maximal radiotherapy, and i.v. chemotherapy achieves a median survival of only 51 wk (*2*). Recently, theoretic models and experimental studies (*4–11*) have demonstrated that intra-arterial administration of chemotherapeutic agents can give much higher tumor concentrations of drug, without increasing systemic toxicity (*11*). It would be logical to extrapolate from this that a more selective arterial injection into a major tumor vessel would achieve an even more favorable benefit/risk ratio.

In the present study, trace doses of [^{11}C]BCNU were injected through such a superselective arterial catheter, dynamic PET images obtained, and the data then compared to results after i.v. injection. Tissue ^{11}C time-activity curves were generated for both studies, and these results (Table 1) were in good agreement with previous work (*14,23–25,28*). The initial fast components of the clearance curve were proportional to blood flow. Half-lives for the first component were similar in tumor and in tissue in the contralateral hemisphere and were independent of route of injection. In contrast, half-lives obtained for the second curve components differed significantly from one another in length. This suggests a difference between tumor and normal brain in the chemical and metabolic decomposition of BCNU. Since ^{11}C radioactivity cleared more slowly from tumor than from normal brain, decomposition of BCNU probably occurred at a higher rate in the tumor itself, resulting in "metabolic trapping" of the [^{11}C] BCNU breakdown products. Intact [^{11}C]BCNU, due to its high lipid solubility, is free to diffuse out of normal tissue. The decomposition process, yielding such products as 2-chloroethyl isocyanate (*25,29*), results in the tissue trapping of the breakdown products by virtue of their binding to proteins and/or nucleic acids. These decomposition products of BCNU have been shown to

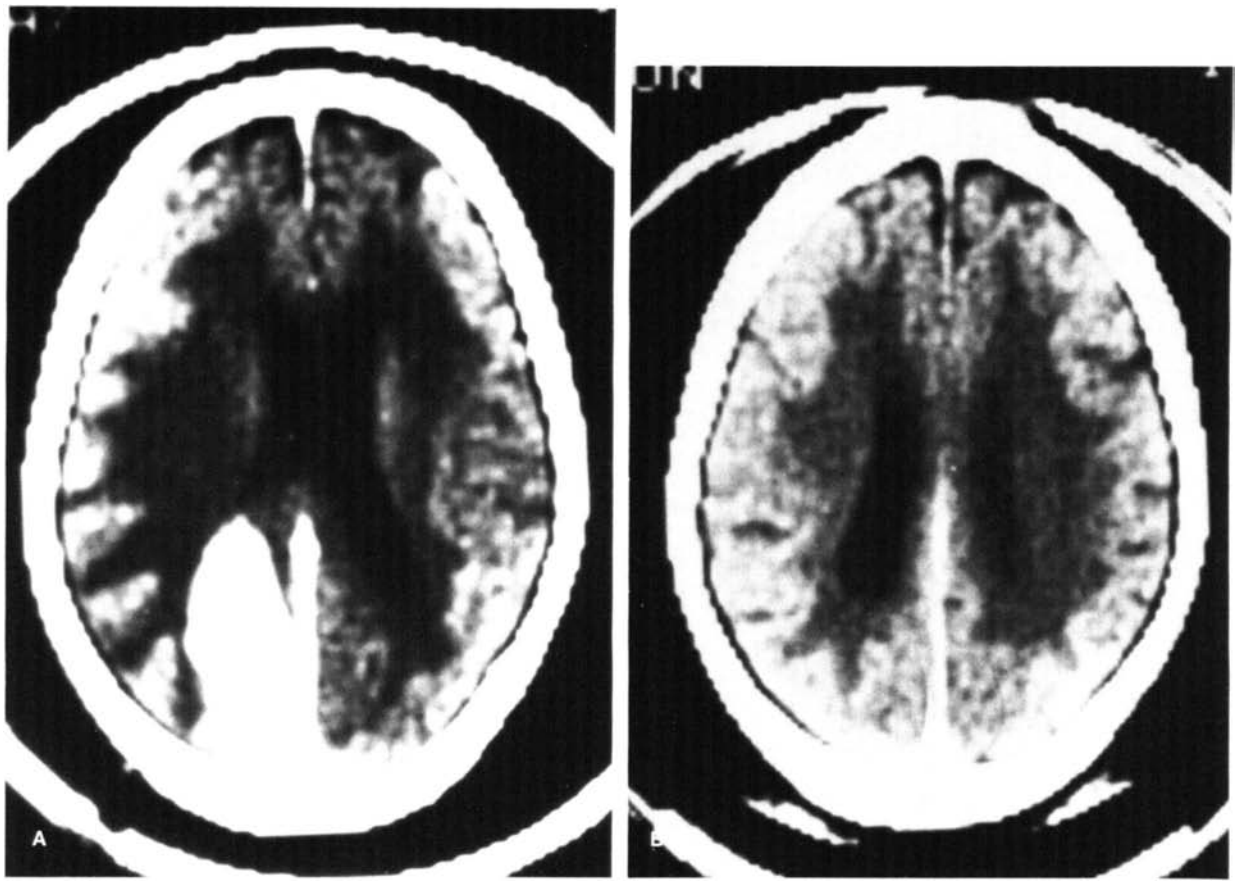

FIGURE 2
Computed tomography brain scans of Patient 4 prior to (A) and 4 wk after (B) superselective intra-arterial BCNU chemotherapy

have antineoplastic properties (*30–33*). Rapid BCNU decomposition in tumor could produce a concentration gradient between tumor and the surrounding brain, resulting in greater absolute amounts of BCNU reaching the tumor.

As shown in Table 2, increased tumor blood flow cannot explain the accumulation of ^{11}C radioactivity in tumor since the peak heights on i.v. injection did not differ significantly in tumor, and in normal tissue ($p = 0.50$). Neither can decreased tumor blood flow be cited as a cause of delayed clearance of activity from the tumor.

Intravenous administration of [^{11}C]BCNU achieved a mean tumor:normal tissue ^{11}C radioactivity concentration of 1.2:1, matching our previous finding (*23*). As predicted, comparable doses of [^{11}C]BCNU given by the superselective intra-arterial route achieved much higher ratios, in the order of 50:1. Thus, for a given dosage of BCNU, the superselective administration results in greatly increased delivery of drug to the tumor, and consequent sparing of normal brain from the chemical agent.

Due to the unstable nature of BCNU and its rapid decomposition, it is necessary to examine early tissue activity for an index of the "metabolic trapping" of BCNU. The tissue concentrations of ^{11}C radioactivity at 10 min after injection (Table 3) demonstrate that two of the seven cases (4 and 7) differed significantly by having increased metabolic trapping of BCNU after the superselective intra-arterial injection. These two patients differed significantly from the others in having marked tumor regression or disappearance after BCNU chemotherapy. Further PET studies of cerebral glucose metabolism, oxygen utilization, protein synthesis, and cerebral pH may identify those patients for whom a significant response to this treatment may be predicted.

CONCLUSION

Preliminary results have shown significant advantages of superselective intra-arterial as compared to i.v. routes of [^{11}C]BCNU injection, with higher tumor concentrations of BCNU and sparing of normal tissue. Two cases with striking tumor regression showed higher degrees of initial metabolic trapping of [^{11}C]BCNU, indicating that this may prove useful in predicting a favorable clinical response.

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