Reduced systemic drug exposure by combining intra-arterial chemotherapy with hemoperfusion of regional venous drainage

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Four patients with malignant cerebral gliomas received 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) into the internal carotid artery (ICA) while the ipsilateral jugular drainage was pumped extracorporeally through a hemoperfusion cartridge containing a nonionic adsorbant resin. Each patient received 220 mg/sq m BCNU, infused over 45 minutes through a toposcopic catheter positioned with the tip in the ICA beyond the origin of the ophthalmic artery. Jugular blood was pumped extracorporeally at 300 ml/min through a large-bore catheter in the jugular bulb. Plasma samples were obtained for BCNU measurement at frequent intervals from the right atrium. During a separate treatment, 6 weeks before or after the hemoperfusion treatment, the same dose of BCNU was infused into the ICA and atrial samples were obtained on a similar schedule.

Hemoperfusion of the jugular blood during intracarotid infusion reduced the systemic exposure by 56% to 87% and increased total body clearance of BCNU by two- to eightfold. The calculated pharmacokinetic advantage (brain:body exposure ratio) was between 21 and 55:1 when the combined treatment was used.

Key Words • BCNU • intracarotid artery infusion • drug delivery • chemotherapy • brain tumor • hemoperfusion • venous drainage

Due to the low therapeutic index of contemporary anticancer therapies, toxicity to sensitive normal tissues frequently limits the tolerable dose. To increase the delivery of cytotoxic therapy to tumor while limiting toxicity to normal tissues, regional therapies, such as radioactive implants and intraperitoneal, intrathecal, or intra-arterial chemotherapy, have been used. Intra-arterial administration is being used to treat tumors of the head and neck, extremities, liver, and brain. Despite intra-arterial delivery, systemic toxicity, not toxicity to the tissues harboring the neoplasm, often limits the tolerable dosage. Previous attempts to limit exposure of the body by vascular isolation during intracarotid delivery did not perform optimally, possibly because of ineffective drugs and limitations of available technology. Recent advances in drug development and technological progress encouraged us to reassess this technique.

We have previously demonstrated in rhesus monkeys that brain exposure 18 to 69 times greater than systemic exposure can be achieved by combining intracarotid BCNU infusion with drug removal from the ipsilateral jugular blood by hemoperfusion. These brain exposures favorably with exposures associated with very high kill of human malignant glioma cells as suggested by in vitro cytotoxicity. We now report a comparison of the systemic exposures to BCNU and of the regional pharmacokinetic advantage after internal carotid artery (ICA) infusion and after ICA infusion combined with extracorporeal hemoperfusion of the ipsilateral jugular blood in four patients with malignant cerebral gliomas.
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Clinical Material and Methods

Patient Population

Four patients, aged 17 to 32 years (three women and one man), with malignant gliomas of the left cerebral hemisphere were treated by ICA infusions of BCNU at intervals of 6 weeks. During one of the treatments, the ipsilateral internal jugular vein was catheterized and the venous blood was aspirated at 300 ml/min and channeled extracorporeally through a hemoperfusion circuit for BCNU removal and back into the iliac vein. During the treatment with hemoperfusion and the one treatment without hemoperfusion, samples for BCNU measurement were obtained from the right atrium at frequent intervals for 6 hours after infusion was begun.

All subjects participated in the study after informed consent was obtained as required by a National Institutes of Health institutional review board (Protocol 83N90).

Procedure

The patients received 5.0 mg droperidol intramuscularly 60 minutes before the procedure was begun. Transfemoral catheterization of the ICA ipsilateral to the tumor was performed using Seldinger's technique. Arteriography demonstrated the distribution of ICA flow and ensured that the tumor was perfused by blood from the ICA. The catheter was then withdrawn to the proximal segment of the common carotid artery and heparin was infused through it (500 units/hr) for the remainder of the procedure. The distribution of the cerebral venous drainage was assessed by intravenous digital subtraction angiography the day before the treatment with hemoperfusion.

For BCNU administration, transfemoral catheterization of the ICA with a No. 5 French toposcopic catheter was performed via the contralateral femoral artery. The toposcopic catheter was a No. 3 French flexible polyurethane catheter attached to a No. 5 French introducer. The lead catheter advances by continuously turning itself inside out to negotiate complex vascular curves. The toposcopic catheter was advanced through the carotid siphon, and its tip was positioned distal to the ophthalmic artery, between the origin of the posterior communicating artery and the intracranial carotid bifurcation into the middle cerebral and anterior cerebral arteries. Infusion of BCNU, 220 mg/sq m, was performed into the distal intracranial ICA over a period of 45 minutes from a syringe infusion pump. Blood was sampled from the right atrium for measurement of plasma BCNU concentrations at frequent intervals for 6 hours after the infusion was begun.

During one ICA treatment, the ipsilateral jugular blood was channeled extracorporeally for BCNU removal. A No. 10 French thin-walled Teflon catheter with multiple large side-holes was introduced transfemorally, and its tip positioned in the bulb of the internal jugular vein ipsilateral to the tumor. Blood was returned from the extracorporeal circuit to the contralateral iliac vein via a No. 9 French catheter. Blood from the jugular bulb was pumped through an extracorporeal hemoperfusion circuit at 300 ml/min for BCNU removal.

The hemoperfusion circuit contains inflow and outflow lines equipped with drip chambers and pressure monitoring lines (Fig. 1). The inflow line contains a heparin administration line, a roller pump chamber, and a negative-pressure pillow to which an automatic shutoff switch was fitted. The roller pump, which was used to propel the blood through the extracorporeal circuit, would automatically stop if the negative pressure in the inflow line was less than −50 mm Hg. Pressures in the inflow and outflow lines were monitored with sphygmomanometers. The hemoperfusion cartridge contains approximately 310 g dry weight of a nonionic adsorbant resin, a copolymer of divinyl benzene and polystyrene (Amberlite XAD-4 resin).

* Syringe infusion pump manufactured by Medrad, Pittsburgh, Pennsylvania.
† Hemoperfusion circuit, Model XR-010, manufactured by Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania.
‡ Roller pump manufactured by Sarns, Inc., Ann Arbor, Michigan.
§ Hemoperfusion cartridge, Model XR-004, manufactured by Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania.
TABLE 1
Pharmacokinetics of intracarotid BCNU infusion with and without hemoperfusion*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Peak BCNU in Systemic Plasma (µg/ml)</th>
<th>Brain Exposure† (µg/min/ml)</th>
<th>Systemic Exposure (µg/min/ml)</th>
<th>% Less Exposure With ICA+</th>
<th>Total-Body BCNU Clearance (ml/min/kg)</th>
<th>Brain:Body Exposure†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICA</td>
<td>ICA+</td>
<td>ICA</td>
<td>ICA+</td>
<td>ICA</td>
<td>ICA+</td>
</tr>
<tr>
<td>1</td>
<td>3.01</td>
<td>0.59</td>
<td>1338</td>
<td>1313</td>
<td>97.6</td>
<td>26.3</td>
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<tr>
<td>2</td>
<td>3.95</td>
<td>0.91</td>
<td>1338</td>
<td>1263</td>
<td>201.6</td>
<td>32.9</td>
</tr>
<tr>
<td>3</td>
<td>3.90</td>
<td>0.52</td>
<td>1338</td>
<td>1230</td>
<td>178.3</td>
<td>22.7</td>
</tr>
<tr>
<td>4</td>
<td>3.56</td>
<td>1.77</td>
<td>1664</td>
<td>1532</td>
<td>163.7</td>
<td>72.0</td>
</tr>
<tr>
<td>Mean ±</td>
<td>3.61 ± 0.22</td>
<td>0.95 ± 0.29</td>
<td>1444 ± 74</td>
<td>1335 ± 68</td>
<td>160.3 ± 22.3</td>
<td>43.5 ± 11.7</td>
</tr>
</tbody>
</table>

* ICA = internal carotid artery BCNU infusion only; ICA+ = internal carotid artery BCNU infusion combined with extracorporeal hemoperfusion of blood from the ipsilateral jugular vein at 300 ml/min; SEM = standard error of the mean.
† Brain exposure based on the assumptions of an internal carotid artery flow of 300 ml/min and equal plasma and red blood cell concentrations.

For treatments of ICA infusion of BCNU combined with hemoperfusion, the patients received 5000 units of heparin sulfate intravenously 15 to 30 minutes before extracorporeal circulation began, then 1500 units/hr was infused into the inflow line of the hemoperfusion circuit during hemoperfusion, and 500 units/hr was infused into the proximal portion of the common carotid artery. The extracorporeal circuit was primed (priming volume 500 to 550 ml) with a 0.9% NaCl solution or with human plasma protein fraction (USP), containing 1500 units/liter heparin. Hemoperfusion began at 50 ml/min and was increased slowly until a rate of 300 ml/min was reached, 7 to 10 minutes before the BCNU infusion was started. Hemoperfusion was continued for 5 to 15 minutes after completion of BCNU infusion. The blood within the hemoperfusion system was reinfused, and 50 mg of protamine sulfate was administered intravenously at the completion of the procedure.

Platelet counts were obtained before hemoperfusion was started and at 30, 60, and 360 minutes after initiation. Platelet counts and complete blood counts were obtained the day before the treatment and at 24 and 48 hours and weekly for 6 weeks following each BCNU infusion.

**BCNU Analysis**

The BCNU used in these patients was obtained from the Drug Development Branch of the National Cancer Institute. It was mixed with absolute ethanol and sterile water to yield a solution of BCNU in 4% ethanol, so that 220 mg/sq m could be administered over 45 minutes at 2 or 3 ml/min. A sample of the BCNU infusate was measured for BCNU concentration at each treatment to ensure full BCNU potency.

Analysis of plasma samples for BCNU content was performed by high-performance liquid chromatography. Whole-blood samples were cooled in an ice bath immediately after being drawn. They were then centrifuged at 2000 G for 8 minutes, plasma was removed (0.5 to 1.0 ml), pH was adjusted to 4 with 4% (v/v) glacial acetic acid, and the samples were frozen until analysis. Standards were made in fresh acidified plasma. Propyl paraben was added as an internal standard. Samples and standards were extracted with 1.25% (v/v) ethyl alcohol in diethyl ether. The extracts were separated, evaporated until dry, and refrigerated for later analysis. Chromatography was performed on a reverse phase C-18 analytical column preceded by a guard column. The mobile phase consisted of 35% (v/v) acetonitrile and 0.1% glacial acetic acid in water, pumped at 1.2 ml/min. Detection was by ultraviolet absorbance at 230 nm. Concentrations were determined by comparison of peak height ratios (BCNU/internal standards analyzed by weighted least-squares linear regression (weight = 1/measured concentration2)). The sensitivity of the assay is 0.050 µg/ml (0.025 µg/ml if 1.0 ml plasma is used).

**Statistics**

Systemic exposure was calculated by determining the area under the plasma concentration-time curve by the trapezoidal method with extrapolation to infinite time based on a BCNU half-life of 60 minutes. Brain exposures were calculated with the assumption of an ICA flow of 300 ml/min.

**Results**

In all four patients the tumor was located in an area perfused by the ICA. Angiography suggested symmetrical drainage of cerebral blood into the transverse sinuses and internal jugular veins in three patients and asymmetrical drainage to the side opposite the tumor in one patient.

Hemoperfusion of the jugular blood during ICA infusion of BCNU reduced systemic BCNU exposure, increased total-body BCNU clearance, and resulted in lower peak plasma BCNU levels compared to levels measured with ICA infusion alone (Table 1, Fig. 2). The combined treatment reduced systemic exposure by 73% to 87% in the patients with symmetrical venous...
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**MINUTES**

**FIG. 2.** Systemic plasma BCNU levels for each of the four patients during the two types of treatment: intracarotid BCNU infusion combined with extracorporeal hemoperfusion of the jugular blood (solid line), and intracarotid delivery of the same dose without hemoperfusion (broken line). Time is measured from the start of the infusion. ACU = area under the concentration-time curve.

Drainage and by 56% in the patient whose major pathway for cerebral venous drainage was contralateral to the hemisphere harboring the tumor. Extracorporeal drug removal increased total-body BCNU clearance from 39.2 ± 8.5 ml/min/kg (mean ± standard error of the mean) after ICA infusion alone to 173.2 ± 52.3 ml/min/kg after ICA delivery combined with hemoperfusion. Based on an assumed ICA flow of 300 ml/min, the pharmacokinetic advantage (brain:body exposure ratio) was between 7 and 14:1 following ICA infusion.
alone and between 21 and 55:1 following the combined treatment. The calculated brain exposures are based on the assumption that the BCNU concentration in the plasma is equal to that in the red blood cells. The actual role of the red blood cells in transporting BCNU is unknown. Peak systemic plasma BCNU concentrations were reduced to 13% to 50% of those during the treatment without hemoperfusion.

Several patients experienced moderate frontal and retro-orbital pain during BCNU infusion. The discomfort disappeared 5 to 10 minutes after completion of the infusion. In all patients, as the rate of extracorporeal circulation increased to 300 ml/min, the systolic blood pressure dropped transiently (by 20 to 30 mm Hg) and the pulse rate increased (by 30 to 55 beats/min). These responded promptly to a 200-ml intravenous bolus of colloid. All patients returned to their normotensive state after 5 to 9 minutes, and were hemodynamically stable throughout the remainder of the treatment. The circulating platelet count dropped during hemoperfusion, reaching a nadir of 28 to 57 x 10^9/cu mm at 60 minutes, then gradually returning to > 100 x 10^9/cu mm by 48 hours following the treatment. There was no significant difference in weekly white blood cell or platelet counts following treatments with or without hemoperfusion.

One patient developed delayed hemiparesis 4 months following the fourth ICA infusion and 2 months after completing radiation therapy. Cerebral computerized tomography scanning revealed focal radioluency of the deep and superficial tissue of the left cerebral hemisphere, but there was no evidence of increased size of the contrast-enhancing tumor mass. This patient's neurological deficit has been stable in the 6 months since the onset of weakness.

**Discussion**

A basic tenet of cancer chemotherapy is that tumor response should increase with increased drug exposure. However, toxicity to tissues other than that containing the neoplasm frequently limits the tolerable dose. The intra-arterial delivery technique has been developed to increase tumor exposure while maintaining tolerable levels of systemic exposure. If the system is linear and the perfused region does not eliminate a significant amount of drug, the pharmacokinetic advantage (R_d) of intra-arterial infusion compared to intravenous administration is a function only of the total-body clearance (Cl_{tb}) of the drug being used and the blood flow perfusing the region of interest (Q):\(^1\,2,6\)

\[
R_d = 1 + \frac{C_{lb}}{Q}.
\]  

For a specific artery (or blood flow), the kinetic advantage can be increased by selection of a drug with a high Cl_{lb} or by the application of techniques that increase Cl_{lb}. The clearance and R_d can be increased by removing drug from circulating blood in an extracorporeal device. A greater increase can be obtained by removing drug from the venous drainage of the infused region because the drug is more concentrated, and the equivalent of a pharmacological first-pass effect can be obtained. Dedrick, et al.,\(^4\) have recently analyzed the pharmacokinetics of drug removal from the venous blood draining the infused region during intra-arterial infusion. They derived an equation analogous to Equation 1, which is:

\[
R_d = \frac{1 + EQ + C_{lb}}{Q(1 - fE)},
\]

where f is the fraction of the blood flow Q infused by drug which is pumped through the extracorporeal device, E is the fraction of drug entering the device which is removed on a single pass, and Q, is the blood flow rate from the systemic circulation which serves to dilute the drug entering the device. It is apparent that the pharmacokinetic advantage (R_d), resulting from arterial infusion alone can be greatly increased if a substantial fraction of the vascular drainage of the infused region can be processed in an effective device.

We previously examined the pharmacokinetic advantage obtained by combining intracarotid infusion and drug removal from the ipsilateral jugular blood in rhesus monkeys.\(^{13}\) Initially, an in vivo assessment of a hemoperfusion circuit similar to the one used in this study showed removal of all the BCNU (400 mg over 30 minutes) from whole blood flowing through the circuit at 300 ml/min. A study in rhesus monkeys then demonstrated an increase in the brain:body exposure ratio from 4 to 9:1 with ICA infusion alone to 18 to 69:1 by extracorporeal hemoperfusion of blood from the ipsilateral jugular vein during ICA infusion.\(^{13}\) Brain BCNU exposures comparable to those associated with very high glioma cell cytotoxicity in vitro were achieved without permanent brain injury.

BCNU, an alkylating agent with short plasma half-life and a rapid total-body clearance of 13 to 56 ml/min/kg,\(^{11,16}\) has tumoricidal activity against gliomas in vitro\(^{15}\) and in vivo.\(^20\) However, pulmonary and renal toxicity limit the cumulative doses of intravenous BCNU to approximately 1500 mg/sq m.\(^{10,17,19}\) Minimal in vitro cytotoxicity is achieved with exposures comparable to those occurring after the dose currently used intravenously. Levin, et al.,\(^12\) demonstrated a four- to fivefold increase in radioactivity derived from carbon-14 labeled BCNU in areas perfused by the middle cerebral artery of squirrel monkeys ipsilateral to common carotid infusion compared to the opposite side.

The maximum dose of BCNU that the human cerebrum can tolerate by ICA infusion without immediate or delayed damage is unknown, but doses as high as 600 mg/sq m have been delivered into the cervical segment of the ICA without neurological deficit (A. Pruitt, et al., unpublished data). This is equivalent to about 0.7 mg/gm whole brain. Doses of the order of 1 mg/gm whole brain have been administered to rhesus
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monkeys without focal brain injury. However, the possibility of delayed toxicity was not assessed. Since intraspecies brain weight varies little with body size, the brain exposure occurring after ICA administration varies greatly between individuals when doses are based on body mass or surface area. Part of the variability of the calculated brain exposures for the patients reported here is a result of using a dose (220 mg/sq m) based on body surface area consistent with pharmacological practice to control systemic toxicity. If the distribution of the ICA is comparable among subjects and the infusion is performed into the same ICA segment, a given dose to the ICA results in similar brain exposures in adults of the same species and is relatively independent of body size.

The clearance of BCNU during the treatments without hemoperfusion, 39.2 ± 8.5 ml/min/kg, was generally in accordance with those previously reported for BCNU in humans. The total-body clearance was increased to between 63 and 285 ml/min/kg and the total-body exposure was reduced by 56% to 87% by the combined treatment (Table 1). This suggests that a two- to eightfold dose increase would have been possible while maintaining systemic exposures at the levels occurring after ICA infusion alone. Such an increase in dose would result in brain exposures in the range of 3200 to 11,500 µg/min/ml, which greatly exceed the exposures to BCNU associated with significant response of malignant gliomas in vitro. In a microcytotoxicity assay of monolayer cultures, with an initial BCNU concentration of 33 µg/ml and 1 hour of incubation, Kornblith, et al., found that the cytotoxic index reached 98% or over in glioblastomas in 42 of 58 patients. The calculated exposure under the conditions of the assay is 2400 µg/min/ml. Using a clonogenic assay, found less consistent decreases in cell survival in vitro, although a dramatic response of the cell cultures was seen with 10 to 25 µg/ml BCNU and 2 hours of incubation (calculated exposure 1028 to 2570 µg/min/ml) in clinically responsive patients. The in vitro responses suggest that sterilization of the tumor in situ might occur in some patients if tumor exposures in excess of 2500 to 3000 µg/min/ml could be safely achieved.

One of our patients experienced focal brain injury after supraophthalmic ICA infusion of BCNU, but patients receiving comparable doses into the cervical segment of the ICA infrequently suffer cerebral injury. The mechanism of the difference in toxicity after infusion of similar doses into different levels of the ICA is unclear. This must be resolved before routine supraophthalmic administration of BCNU in the doses used here or consideration of higher doses.

Finally, in this communication we have described hemoperfusion of jugular drainage during intracarotid infusion of chemotherapy. The same pharmacokinetic principles apply to tumors and other diseases affecting any organ in which arterial drug delivery and collection of venous blood for drug removal can be performed.

Acknowledgments

We thank Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania, for donating the hemoperfusion systems and the roller pump used in this study. We also thank Mrs. Ellie Frishman and Miss Elsa Bray for preparing this manuscript with their customary precision.

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*Stroke* 14:256–266, 1983


Manuscript received October 22, 1984. Accepted in final form April 1, 1985.

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