Yang MB, Tamargo RJ, and Brem H. "Controlled delivery of 1,3-Bis(2-chloroethyl)-1-nitrosourea from ethylene-vinyl acetate copolymer. Cancer Research, 49(18):5103-5107, 1989.

[CANCER RESEARCH 49, 5103–5107, September 15, 1989]

Controlled Delivery of 1,3-Bis(2-chloroethyl)-1-nitrosourea from Ethylene-Vinyl Acetate Copolymer[1]

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ABSTRACT

1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) has been found to be an effective chemotherapeutic agent against brain tumors. However, because it has a very short half-life in plasma, the exposure of neoplastic cells to BCNU is very brief. The delivery of BCNU may be enhanced by using controlled release polymers. We measured the release of BCNU from ethylene-vinyl acetate copolymer (EVAc) into blood, phosphate buffer, and brain tissue. BCNU-EVAc cylinders that weighed 60 mg were implanted in the peritoneum of rats, and BCNU was detected in blood for 6 days. Studies carried out *in vitro* showed that BCNU was released from EVAc at a decreasing rate for 195 h. BCNU-EVAc cylinders that weighed 15 mg were implanted either intracranially (i.c.) or i.p. in Fischer 344 rats. Controlled release of BCNU from the i.c. BCNU-EVAc implants was observed over 9 days, with peak drug levels of 49.6 μg/g of brain tissue in the implanted hemisphere. The BCNU levels in the contralateral hemisphere and the peripheral circulation were much lower and were detectable for only 1 day. By contrast, peak BCNU levels in the brain from the i.p. BCNU-EVAc implants were 2.7–3.0 μg/g for only 12 h, accompanied by peak BCNU levels in blood of 1.0 μg/ml tapering over 1 day. These results demonstrate the controlled release of intact BCNU from EVAc *in vitro* and *in vivo*. Furthermore, the i.c. implants resulted in localized, prolonged, high levels of the drug in the implanted hemisphere. Hence, the i.c. controlled delivery of BCNU may be more efficacious for the treatment of localized brain tumors.

INTRODUCTION

Systemically administered chemotherapeutic agents must cross the blood-brain barrier to be effective against brain tumors. To achieve this exchange by passive diffusion, the drug should show high lipid solubility, low ionization at physiological pH, and low plasma binding (1). 1,3-Bis(2-chloroethyl)-1-nitrosourea possesses these properties (2). However, because BCNU[3] in plasma has a half-life of about 15 min *in vivo* (3), the exposure of neoplastic cells to intact BCNU is very brief.

Controlled release polymers have been used to achieve the sustained delivery of drugs, proteins, and macromolecules (4). Among these, ethanol-washed ethylene-vinyl acetate copolymer, which is being used clinically for birth control and the treatment of glaucoma (5), has been shown to be noninflammatory in a rabbit cornea assay (6). Hence, EVAc could be used to achieve the controlled delivery of BCNU.

In our laboratory, EVAc that was loaded with BCNU, when implanted in rats, significantly delayed the growth of 9L gliosarcoma growing in the flank, when compared to the systemic administration of BCNU (7). This and other experiments suggested that chemotherapeutic agents were being released from EVAc over a prolonged period of time *in vivo*, but the concentration of the drug in blood and the duration of release were unknown. Therefore, the first experiments in the present study were designed to measure the rate of release of BCNU from EVAc *in vitro* and the blood concentration of BCNU released from EVAc *in vivo*.

Having established that BCNU is released in a controlled fashion over a prolonged period of time, we hypothesized that implanting the polymer i.c. would increase the concentration of BCNU in local brain tissue, while minimizing the amount of BCNU reaching the peripheral tissues. Indeed, implanting the polymer at the site of a brain tumor should increase the exposure of neoplastic cells to BCNU and reduce the systemic toxicity due to BCNU. Therefore, we compared the effects of i.c. controlled release and systemic controlled release on the concentration of BCNU in brain tissue and in the peripheral circulation.

MATERIALS AND METHODS

Polymer Preparation. Ethylene-vinyl acetate, 40% vinyl acetate by weight (ELVAX 40 W E4902-30 V51212; DuPont), was cleaned as described by Langer *et al.* (6). The EVAc used was noninflammatory, as determined by the rabbit cornea assay (6). To make EVAc with or without BCNU, respectively, EVAc and BCNU (Drug Synthesis and Chemistry Division, National Cancer Institute), in a 7:3 ratio, or EVAc alone were dissolved in methylene chloride (Baker) (10%, w/v). Small volumes of the solutions were pipeted into glass cylindrical molds (5- x 27-mm) that were previously cooled on dry ice. The mixtures froze and were removed from the glass molds with a cold spatula. The methylene chloride was allowed to evaporate for 1 week in a freezer at −40°C, during which time the polymers shrank to half their original size. The polymers were cut to cylinders of desired weight and sterilized by UV irradiation for 30 min. Although BCNU is sensitive to light (8), drug beneath the surface of the polymer should be protected from decomposition.

Reagents. Phosphate buffer was prepared by adding 0.1 mol of monobasic, monohydrate sodium phosphate (Baker Lot 424124) to 4 ml of gentamicin sulfate (GIBCO Lot 12K7744) and diluting to 1 liter to make a 0.1 M solution. The solution was titrated to pH 7.4 with sodium hydroxide and filter sterilized (Corning No. 25942). For the sulfanilamide reagent, 2.5 g of sulfanilamide (Baker Lot 619738) were added per 100 ml of 2 *N* HCL. The Bratton-Marshall reagent contained 3 mg of *N*-(1-naphthyl)ethylenediamine dihydrochloride (Baker Lot 106F-0042) per ml of distilled water and was made fresh before each assay.

Animals. Male Fischer 344 rats (Charles River Research Primates Co., Long Island, NY), weighing between 153 and 195 g (mean, 170 g), were used in the *in vivo* release experiment. The rats used in the study comparing i.c. *versus* systemic release weighed between 169 and 262 g (mean, 225 g). They were housed five to a cage in standard animal facilities and given free access to Certified Rodent Chow No. 5002 (Ralston Purina Co., St. Louis, MO) and water.

Anesthesia. The anesthesia solution, Xylaket, was made by mixing 25 ml of ketamine (100 mg/ml; Ketalar; Parke-Davis, Morris Plains, NJ), 2.5 ml of xylazine (100 mg/ml; Rompun; Mobay Co., Shawnee, KS), 14.2 ml of 100% ethanol, and 58.3 ml of 0.9% NaCl solution and was filter sterilized (Corning 25932). For all animals, 3.0 to 3.5 ml of Xylaket/kg of animal weight were used.

Received 6/30/88; revised 1/5/89, 6/2/89; accepted 6/13/89.

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[1] This investigation was supported in part by an Association for Brain Tumor Research Fellowship in Memory of Steven Lowe, NIH Grant NS01058-01, American Cancer Society Grant IN-11W, and an Andrew W. Mellon Foundation Johns Hopkins University Faculty Development Award.

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[3] The abbreviations used are: BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; EVAc, ethylene-vinyl acetate copolymer; i.c., intracranial; i.a., intraarterial.

Surgery. Surgery was performed under aseptic conditions. For i.p. implantation, the abdomens of the rats were shaved and rinsed with 70% ethanol and Prepodyne solution (AMSCO, Erie, PA). An incision was made in the peritoneum wall, and the polymer was placed in the lower right quadrant of the abdominal cavity, about 3 cm from the hole. Softgut (4–0) (Davis & Geck) was used to close the peritoneum wall, and a 9-mm MikRon autoclip applier (Becton Dickinson) was used to close the skin.

For i.c. implantation, an incision was made in the scalp and a burr hole about 3 mm in diameter was made in the skull overlying the left brain, centered 3.5 mm from the sagittal suture and 3.5-mm anterior to the coronal suture. An incision 3-mm deep was made in the cortex, and the polymer was inserted. A piece of Gelfoam was placed over the exposed cortex. The scalp was closed with a 9-mm MikRon autoclip applier.

Assay for Intact BCNU. A spectrophotometric assay devised by Bratton and Marshall (9) and modified by Loo and Dion (10) was used to determine the amount of intact BCNU present in phosphate buffer, in brain tissue, and in whole blood. Standard curves of absorbance *versus* BCNU concentration were constructed for phosphate buffer, brain tissue, and whole blood, with sensitivities of 0.2, 0.2, and 0.05 μg/ml, respectively.

In the *in vitro* studies, 4 ml from the 5-ml samples were pipetted to test tubes that contained 1 ml of the sulfanilamide solution and were placed in a water bath at 50°C for 45 min, followed by an ice bath for 5 min. The Bratton-Marshall reagent (0.2 ml) was added, and the sample was left for 10 min at room temperature to permit complete color formation. The absorbance at 540 nm was measured with an LKB Ultrospec 450 spectrophotometer (LKB Instruments), and the amount of BCNU present was determined by comparison with standards.

To determine the concentration of BCNU in whole blood, a 2-ml sample of blood was extracted with 4 ml of anhydrous ether in capped polypropylene tubes (Falcon 2006). The sample was centrifuged at 5000 rpm (3020 relative centrifugal force) for 2 min at −10°C in a Sorval Superspeed RC-2B. Then, 2.5 ml of the ether layer were transferred to 13- x 100-mm glass test tubes (Pyrex). The ether was evaporated over a 10- to 12-min period under a gentle flow of nitrogen. Then, 0.5 ml of the sulfanilamide solution and 1 ml of water were added to the residue. The remaining steps were as described for the *in vitro* studies, with the following exceptions: (*a*) only 0.1 ml of the Bratton-Marshall reagent was added to each sample; (*b*) after complete color formation, the samples were filtrated by using 3-ml syringes fitted with GF/B glass microfibre filters (Whatman) in 13-mm syringe filter assemblies (Gelman).

To determine the concentration of BCNU in brain, the polymer was removed, and the cerebrum was divided, weighed, and homogenized after the addition of enough distilled water to make 2 ml. Then, 1.5 ml of the homogenate were pipeted into polypropylene tubes, extracted with 4 ml of ether, and assayed as described for blood.

***In Vitro* Release Kinetics Study.** Five cylinders (2.5- x 3-mm, weighing 20.0 to 20.5 mg) containing BCNU were placed in separate vials, each containing 5 ml of phosphate buffer, at 37°C. The following procedure was used for each cylinder. After allowing drug release for 1 h, the cylinder was transferred by forceps to fresh buffer solution. During the transfers, excess buffer solution on the cylinder was removed by blotting on sterile Topper dressing sponges (Johnson and Johnson). Then, the cylinder was transferred into a 5-ml vial containing fresh buffer and was allowed to release for 1 h if the solutions were to be assayed at the end of the hour. Solutions of 15 ml were used if the pellets were allowed to release for several hours before assay. The 15-ml buffer solutions were not analyzed and merely served to provide "infinite sink" conditions; only 5-ml buffer solutions were analyzed. Samples were thus analyzed for each of the first 9 h and at 11, 24, 33, 50, 75, 98, 124, 146, 170, and 195 h.

Loo *et al.* (3) calculated that the half-life of BCNU in 0.1 M phosphate buffer at pH 7.4 and 37°C was 52 min. To determine the half-life of BCNU under our conditions, the same amount of BCNU was placed in tubes containing phosphate buffer at 37°C. One sample was analyzed every 5 min. These results were used to calculate the rate of release of BCNU from EVAc.

***In Vivo* Release Study.** Cylinders containing BCNU (2.5 x 9 mm; weight range, 58.2–61.0 mg; mean, 60 mg) were surgically implanted in the peritoneums of 39 rats. At 1, 4, 12, 24, 49, 72, 96, and 120 h postoperatively, groups of four animals were anesthetized and weighed; at 148 h (6 days), two animals were used. The rats were exsanguinated by direct cardiac puncture. Blood samples of 2 ml were obtained from each rat and stored at −60°C until assay, which was always within 30 min.

Intracranial *versus* Systemic Release of BCNU. Thirty rats received polymer implants. The size of the BCNU-EVAc cylinders was about 2.5 x 2.5 mm; the weight of the polymers ranged from 14.0 to 15.6 mg (mean, 15 mg). The empty EVAc cylinders were similar in size and weight. Twenty-one rats were implanted with BCNU-EVAc cylinders i.c. and empty EVAc cylinders i.p. Nine rats received empty EVAc cylinders i.c. and BCNU-EVAc cylinders i.p. At 4, 12, and 24 h and 3, 5, 7, and 9 days after implantation for the rats that had received BCNU-EVAc i.c. and at 4, 12, and 24 h after implantation for the rats that had received BCNU-EVAc in the peritoneum, groups of three rats were anesthetized and weighed. The rats were exsanguinated, and the concentration of BCNU in blood was assayed. Immediately after the rat was exsanguinated, the brain was removed and the concentration of BCNU in brain tissue was determined.

RESULTS

***In Vitro* Release Study.** The rate of drug release was determined by a method of signal analysis, the convolution integral. Our analysis assumes constant release of BCNU over 1-h periods and involves the half-life of BCNU in phosphate buffer, which we found to be 65.6 min. Although constant release does not actually occur, making that assumption simplifies the analysis and the approximation is not unreasonable, considering the overall duration of release. The derivation is as follows. $y(t)$ is the output, i.e., the amount of BCNU present in buffer, $x(t)$ is the input, i.e., the rate of constant BCNU release from polymer, and $h(t)$ is the exponential which characterizes the decay of BCNU in phosphate buffer.

$$x(t) = au(t)$$

where $u(t)$ is a unit step.

$$h(t) = e^{-kt}u(t)$$

$$k = -\ln 0.5/T_{½} = 0.010566 \text{ min}^{-1}$$

where $T_{½} = 65.6$ min.

$$y(t) = x(t) * h(t) = h(t) * x(t)$$

$$= \int_{-\infty}^{+\infty} h(\tau)x(t - \tau)\, d\tau$$

For a specific time T,

$$y(T) = a \int_0^T e^{-k\tau}\, d\tau$$

From this, an expression for a may be derived.

$$y(T) = a(1 - e^{-kT})/\text{k}$$

$$a = y(T)/[(1 - e^{-kT})/\text{k}]$$

Knowing the half-life of BCNU and choosing T as 60 min, we can evaluate the denominator on the right side. Therefore, a, the rate of release of BCNU, is simply y(60 min) divided by a

constant.

$$a = y(60)/(44.44 \text{ min})$$

In reality, the rate of release decreases over time. Therefore, the value of constant release we calculated slightly overestimates the actual rate of release at the end of the 1-h period.

The release rate of BCNU from EVAc over time can be seen in Fig. 1. There was a burst of drug released in the first day. The release rate fell from 11.7 μg/min at 1 h to 1.53 μg/min by 24 h. The rate of release then decreased slowly, relative to the burst phase, and was not measurable at 195 h (8.2 days). Thus EVAc releases BCNU for at least 7 days *in vitro*.

***In Vivo* Release Study.** The concentration of BCNU in whole blood dropped from 3.5 μg/ml at 1 h to 0.33 μg/ml by 24 h (Fig. 2). It remained between 0.28 and 0.37 μg/ml until day 5, when it increased to 0.48 μg/ml. The mean drug concentration for the two rats on day 6 was 0.50 μg/ml. Hence, EVAc releases BCNU for at least 6 days *in vivo*.

Fig. 3 shows the decrease in animal weight, presumably due to drug toxicity. For the five animals that died before their blood could be assayed, the average value for the percentage of their original weight at time of death was 66.9% ± 1.8 SE). The time of death was 5.8 days (±0.2 SE).

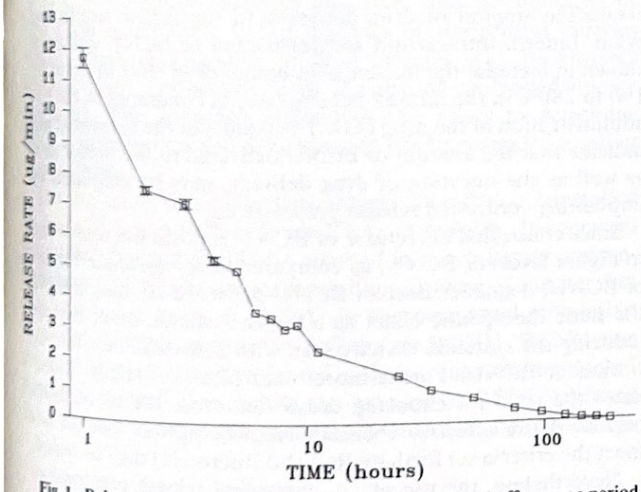

Fig. 1. Release rates of BCNU from EVAc into phosphate buffer over a period of 195 h. The time scale is logarithmic (five polymers; *bars*, SE).

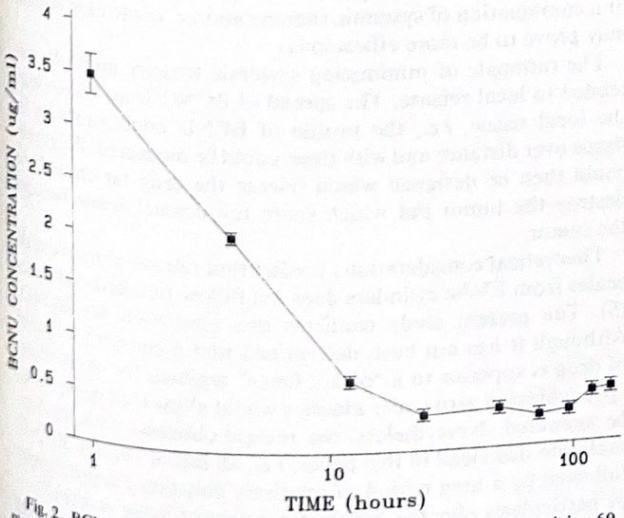

Fig. 2. BCNU concentration in the peripheral circulation of rats receiving 60-mg BCNU implants i.p. The results were normalized for animal weight (170 g). The time scale is logarithmic (four rats; *bars*, SE).

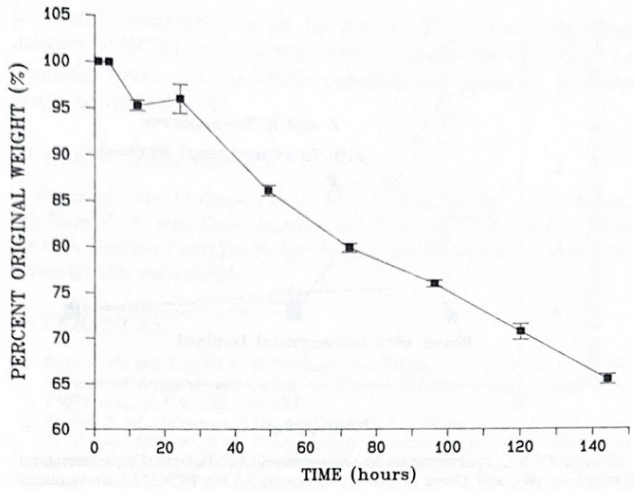

Fig. 3. Weight loss of animals that received 60-ms BCNU-EVAc implants i.p., plotted as percentage of animal weight at time of implantation (four rats, except for day 6, where two rats were used; *bars*, SE).

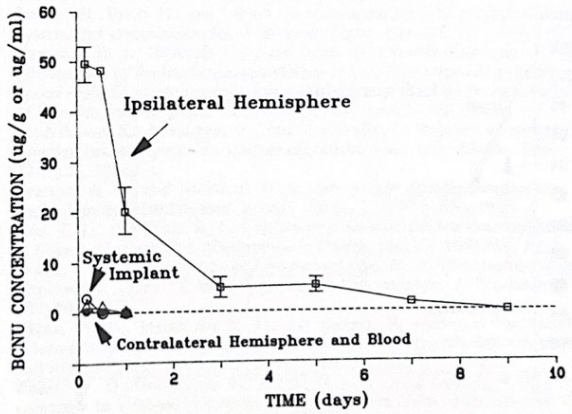

Fig. 4. BCNU concentration in the ipsilateral hemisphere (□), contralateral hemisphere (△), and blood (●) of rats receiving 15-mg BCNU-EVAc implants i.c. In a separate experiment, BCNU concentration was measured in the left hemisphere (○) of rats receiving 15-mg BCNU-EVAc implants i.p. Similar or lower concentrations were measured in the right hemisphere and blood. The results were normalized for animal weight (225 g) and polymer weight (15 mg) (three rats; *bars*, SE).

Intracranial *versus* Systemic Release of BCNU. For the group receiving BCNU-EVAc i.c. and empty EVAc i.p. (Fig. 4), the concentration of BCNU in the ipsilateral hemisphere decreased from 49.6 μg of BCNU/g of brain tissue at 4 h to 20.1 μg/g at 24 h, remained at 2 to 5 μg/g through day 7, and was undetectable by day 9. The BCNU concentration in the contralateral hemisphere dropped from 1.14 μg/g at 4 h to 0 at 24 h. In blood, the BCNU concentration dropped from 0.38 μg/ml at 4 h to 0 at 24 h.

For the group receiving BCNU-EVAc i.p. and empty EVAc i.c. (Fig. 5), the BCNU concentration in the ipsilateral and contralateral hemispheres dropped from 2.7 and 3.0 μg/g, respectively, at 4 h to 0 at 12 h. The blood levels of BCNU dropped from 1.0 μg/ml at 4 h to less than 0.04 μg/ml by 24 h.

The i.c. controlled release of BCNU resulted in much higher concentrations of BCNU in the ipsilateral (left) hemisphere, as compared to systemic controlled delivery of BCNU (Fig. 4). On the other hand, i.c. delivery resulted in a lower BCNU concen-

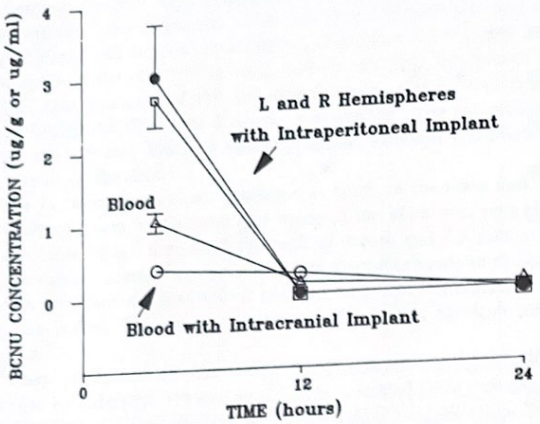

Fig. 5. BCNU concentration in the ipsilateral hemisphere (□), contralateral hemisphere (●), and blood (△) of rats receiving 15-mg BCNU-EVAc implants i.p. In a separate experiment, BCNU concentration was measured in the blood (○) of rats receiving 15-mg BCNU-EVAc implants i.c. The results were normalized for animal weight (225 g) and polymer weight (15 mg) (three rats; *bars*, SE).

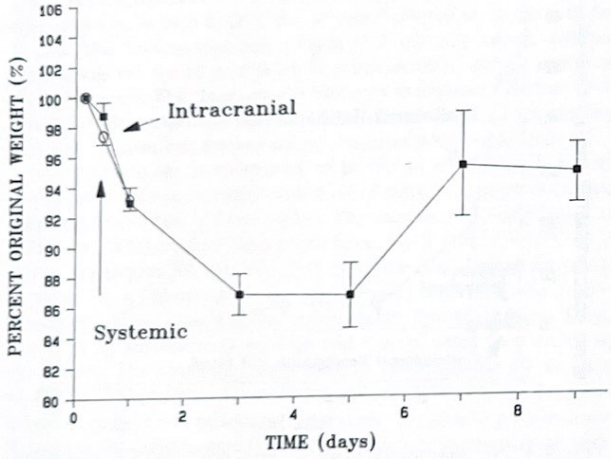

Fig. 6. Weight loss of animals that received 15-mg BCNU-EVAc implants i.c. (■) or i.p. (○), plotted as percentage of animal weight at time of implantation (three rats; *bars*, SE).

tration in blood at 4 h than did systemic delivery (Fig. 5). Although the BCNU level in blood for i.c. release exceeded that of systemic release at 12 h, it was undetectable by day 1. The decrease in animal weight during the experiment is shown in Fig. 6. The three measurements of animal weight during the first day were about the same for rats with i.c. or systemic BCNU-EVAc implants.

DISCUSSION

This study shows that the antitumor drug BCNU can be released in a controlled fashion from ethylene-vinyl acetate copolymer. EVAc cylinders that are loaded with BCNU may be implanted in the brain to achieve the i.c. controlled release of the drug. Controlled release i.c. delivered significantly higher concentrations of BCNU to the implanted hemisphere of Fischer 344 rats and lower levels of BCNU to the peripheral circulation, as compared to the systemic controlled delivery of BCNU.

In the rats receiving 15-mg BCNU-EVAc cylinders i.c., intact BCNU was detected in the implanted hemisphere up to 9 days and in the contralateral hemisphere and peripheral circulation for 1 day. (Cylinders weighing 15 mg were used because the size of an i.c. implant is limited.) The drug concentration in the implanted hemisphere was initially 40 times higher than were the drug levels in the contralateral hemisphere and the peripheral circulation.

For those animals receiving 15-mg BCNU-EVAc cylinders i.p., a minimal amount of drug was delivered to both hemispheres of the brain for 1 day. This is not surprising, considering that BCNU was delivered in a systemic fashion. The BCNU concentration in blood was higher for the first 12 h for systemic delivery than for i.c. delivery. The total dose of BCNU was the same, regardless of the route of administration, perhaps leading to the similar weight loss for both groups.

The *in vivo* study of BCNU concentration in whole blood when rats were implanted with 60-mg BCNU-EVAc cylinders in the peritoneum showed that BCNU was continuously delivered for at least 6 days. (Cylinders weighing 60 mg were used because of the sensitivity limit of the assay for BCNU.) Release of BCNU into phosphate buffer at pH 7.4 and 37°C, showed that BCNU was released from EVAc at a decreasing rate for at least 7 days. This is consistent with the drug levels detected *in vivo* in both brain and blood.

One rationale for i.a. administration of BCNU was to increase the amount of drug delivered to the tumor site in the brain. Indeed, intracarotid administration of BCNU has been shown to increase the nucleic acid-bound drug level in brain by 190 to 280% in the infused hemisphere, as compared to the i.v. administration of the drug (11). The results of the present study indicate that the amount of BCNU delivered to the tumor site, as well as the duration of drug delivery, may be increased by implanting controlled release polymers i.c.

Since controlled i.c. release of BCNU exposes the tumor site to higher levels of BCNU, as compared to the systemic release of BCNU, a smaller dose of BCNU delivered i.c. may achieve the same therapeutic effect as a larger systemic dose, thereby reducing the systemic toxicity seen with conventional administration of BCNU. Furthermore, controlled i.c. release eliminates the need for choosing drugs that cross the blood-brain barrier. More effective chemotherapeutic agents that do not meet the criteria set forth by Rall and Zubrod (1) may be tested.

Nevertheless, the use of i.c. controlled release presupposes that the lesion is localized and, hence, amenable to regional chemotherapy. For poorly localized tumors, systemic therapy or a combination of systemic therapy and i.c. controlled release may prove to be more efficacious.

The rationale of minimizing systemic toxicity might be extended to local release. The spread of BCNU from EVAc into the local tissue, *i.e.*, the profile of BCNU concentrations in tissue over distance and with time, could be measured. Polymers could then be designed which release the drug far enough to destroy the tumor but which spare the normal tissue beyond the tumor.

Theoretical considerations predict that release of macromolecules from EVAc cylinders does not follow zero-order kinetics (5). The present study confirms this prediction for BCNU. Although it has not been determined that a constant infusion of drug is superior to a "picket fence" regimen for chemotherapy, achieving zero-order kinetics would allow that question to be answered. Nevertheless, the release obtained with the formulation described in this paper, *i.e.*, an initial burst of BCNU followed by a long period of relatively constant release, might be particularly effective for the treatment of brain tumors.

The rate of release of macromolecules from EVAc is affected by the percentage of loading and the molecular weight of the

macromolecules (12). When using BCNU and a cylindrically shaped EVAc polymer, a release rate closer to zero-order kinetics may be obtained by manipulating the percentage of loading. Previous *in vitro* studies with other macromolecules have shown that increasing the percentage of loading of the substance to be released increases the initial rate of release of the substance (12). Therefore, reducing the percentage of loading of BCNU should increase the period of sustained drug delivery while reducing the initial amount of drug released.

Matrix geometry also plays a role in the kinetics of release of drug from diffusion-controlled matrix systems, and it has been demonstrated theoretically that an inwardly releasing hemisphere is better able to achieve near zero-order kinetics than other polymer shapes (13). The inwardly releasing hemisphere is impermeable to solvents except at a small concavity in the center of the planar surface. By increasing the amount of drug exposed to the solvent over time, the inwardly releasing hemisphere compensates for increasing diffusion distance between drug and solution and, consequently, achieves zero-order kinetics.

The use of controlled release polymers is not restricted to chemotherapeutic agents. The efficacy of other antineoplastic agents or biological response modifiers may be enhanced by this form of delivery. Other diseases of the central nervous system that are amenable to drug therapy, *e.g.*, Parkinson's disease, may also benefit from the use of controlled release polymers. The approach utilized in this study to determine brain concentration and drug kinetics can be extended to other applications.

In conclusion, this study demonstrates that the i.c. controlled delivery of intact BCNU from EVAc is feasible. Intracranial controlled delivery of BCNU resulted in much higher concentrations of BCNU in the ipsilateral hemisphere of Fischer 344 rats and lower levels of BCNU in the peripheral circulation than did systemic controlled delivery of BCNU. BCNU was released from the i.c. implanted polymer into the implanted hemisphere for 9 days, while the amount of BCNU released into the implanted hemisphere from polymers implanted i.p. fell below detectable levels by day 1. Thus, i.c. controlled delivery of BCNU may be more efficacious for the treatment of localized brain tumors, while reducing the systemic toxicity resulting from BCNU.

ACKNOWLEDGMENTS

We would like to thank Dr. O. Michael Colvin, Dr. John Hilton, Dr. Kam W. Leong, Dawn Borsi, Carla Reinhard, and Michael Pinn for their assistance and Dr. Robert Langer and Dr. Pamela Talalay for reviewing this manuscript.

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