Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain

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Sustained drug delivery by biodegradable polymer devices can increase the therapeutic efficacy of drugs by producing high local tissue concentrations over extended periods of time. It has been shown previously that implantation of controlled-release polymers impregnated with the nitrosourea carmustine (BCNU) extended the period of survival in rats bearing the 9L glioma compared with similar rats treated with systematically administered BCNU. This study evaluated the effect on the monkey brain of interstitial delivery of BCNU by the biodegradable poly(anhydride copolymer poly[bis(p-carboxyphenoxy)propane]anhydride (PCPP) and sebacic acid (SA) in a 20:80 formulation (PCPP:SA). The effect of combining interstitial BCNU with radiation therapy was also evaluated. Eighteen male cynomolgus monkeys were randomly assigned to one of four groups: a control group; a group with implantation of empty polymer; a group with implantation of BCNU-loaded polymer; and a group with implantation of empty polymer in the right hemisphere and BCNU-loaded polymer in the left hemisphere, followed by irradiation. The effects were evaluated radiologically and histologically at specified times. A local reaction by the brain to the polymer was found, which was greater when the polymer contained BCNU. Local cerebral edema was observed radiographically on postoperative Day 14 and had resolved by Day 72. Histologically, a subacute cellular inflammatory response was seen on postoperative Day 16, which had changed to a chronic inflammatory response by Day 72. In the group with radiation therapy administered to the hemisphere bearing BCNU-loaded polymer, only localized pathological changes were detected. In all animals, brain distant from the polymer implantation site was normal. No neurological or general deleterious effects were seen in any of the animals. It is concluded that the interstitial delivery of BCNU by the poly(anhydride polymer PCPP:SA is safe in the primate brain and that concomitant radiation therapy did not lead to any adverse effects. These experimental findings are important to an understanding of the clinical effects of PCPP:SA implants in treating brain diseases.

KEY WORDS • implantable polymer • glioma • drug delivery • BCNU • radiation therapy • drug implant • monkey

Drug delivery by controlled-release polymers has many potential clinical applications. Certain drugs that, when administered by the intravenous route, would not penetrate the blood-brain barrier can be effectively delivered directly to the brain by means of implantable polymers. In the brain, drug delivery by controlled-release polymers allows sustained high local drug levels while avoiding systemic toxicity. We have investigated the efficacy of the nitrosourea carmustine (BCNU)-impregnated controlled-release polymers as a treatment for brain tumors. Using a rat intracranial 9L gliosarcoma model, we found that treatment with BCNU-impregnated controlled-release polymers resulted in extended survival of animals compared to those receiving systemic treatment with BCNU and to control animals. On the basis of these results, clinical trials evaluating the efficacy of BCNU-impregnated polymers as a treatment for malignant gliomas have been initiated. The objective of this study was to determine the effects on the monkey brain of interstitial BCNU delivered by the poly(anhydride copolymer poly[bis(p-carboxyphenoxy)propane]anhydride (PCPP) and sebacic acid (SA) in a 20:80 formulation (PCPP:SA). We also
evaluated the effect of BCNU-impregnated polymers in conjunction with radiation therapy on the monkey brain. Using this primate model, we were able to assess the effect of the polymer on normal brain by computerized tomography (CT) and magnetic resonance (MR) imaging at specified intervals after implantation, and pathologically at autopsy. We also observed the monkeys for neurological or systemic effects of the implants.

Materials and Methods

Animal Groups

Eighteen adult male cynomologous monkeys (Macaca fascicularis), aged about 2 years old and each weighing 3.5 to 4.5 kg, were quarantined until found to be in good health by the veterinary staff, then transferred to standard primate housing facilities. The monkeys were caged individually with free access to Agway Prolab Primate 18 Formula and Baltimore city water.

The monkeys were randomly assigned to one of four experimental groups (Table 1). The first three groups consisted of five animals each; three were sacrificed on or near postoperative Day 16 and two on or near Day 72. Group 1 animals (controls) underwent a right-sided frontal lobectomy without an implant; Group 2 animals received a frontal lobectomy followed by implantation of 2.5-cm wafers of PCPP:SA, and Group 3 animals underwent a frontal lobectomy followed by implantation of PCPP:SA wafers containing BCNU. In the three monkeys in Group 4, bilateral frontal lobectomies were performed with placement of PCPP:SA wafers containing BCNU in the bed of the left lobectomy and PCPP:SA wafers without BCNU in the bed of the right lobectomy, followed by whole-brain radiation therapy.

Polymer

The PCPP:SA disks measured 2.5 cm in diameter and 1 mm in thickness and weighed about 660 mg. Two types of disks were used: an empty polymer and a polymer with 12.5 mg BCNU (1.9% loaded by weight). The disks were sterilized by exposure to gamma irradiation, shipped in sterile bags from the manufacturer, and kept at -30°C until the day of surgery.

Anesthesia

For both the surgical procedure and the radiological studies, food was withheld from the animals for at least 12 hours prior to treatment, although water was made available. The animals were anesthetized with ketamine hydrochloride (12.5 mg/kg) and atropine sulfate (0.0125 mg/kg) and transferred to the operating suite. An intravenous catheter was introduced into a calf vein through which lactated Ringer's solution was infused throughout the procedure. For the radiological studies, the animals were maintained on thiamylal sodium (7.5 mg/kg), administered as an intravenous bolus and supplemented with 5 mg/kg as needed throughout the procedure. For the craniotomy, the animals were intubated under direct vision with a 4.0-mm endotracheal tube and maintained on halothane inhalation anesthesia. The Group 4 animals were sedated with 70 mg intramuscular ketamine before radiation treatment.

Polymer Implantation

The animal was placed in a prone position and the scalp was shaved and prepared with Prepodyne solution. The procedure was carried out in an operating room under sterile conditions with optical loupes for magnification. The animal’s head was draped, leaving the right hemicranium exposed. A C-shaped incision was made and the skin retracted to reveal the underlying musculature. The temporal muscle was incised in a similar pattern using a Bovie cautery. The periosteum was elevated and the skull exposed. Four burr holes were made defining a rectangle measuring 1.0 to 1.5 cm in the anteroposterior dimension and 0.7 to 1.0 cm in the lateral dimension. The anterior border of the triangle was 1.0 cm from the supraorbital ridge and the medial border was 1.0 cm from the midline. The burr holes were connected with fine rongeurs and the bone flap was maintained in normal saline.

Furosemide (1.0 mg/kg) was administered intravenously for brain relaxation, and the dura was incised in a cruciate fashion. The surface cortical vessels were coagulated with the bipolar cautery. A cortical incision was made in a gyrus, and the pial layer on both sides of the incision was coagulated. While the brain tissue was aspirated, hemostasis was achieved with the bipolar cautery. A defect measuring about 2 cu cm was

### Table 1

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Monkeys</th>
<th>Computerized Tomography</th>
<th>Magnetic Resonance Imaging</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (control)</td>
<td>5</td>
<td>Day 14</td>
<td>Day 42</td>
<td>Day 72</td>
</tr>
<tr>
<td>2 (empty polymer)</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3 (BCNU-loaded polymer)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4 (BCNU-loaded polymer + radiation therapy)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* Monkeys obtained from Primate Imports, Port Washington, New York.

† Disks supplied by Nova Pharmaceutical Corp., Baltimore, Maryland.
Chemotherapy-loaded polymers in monkey brains

created and, after absolute hemostasis was obtained, the polymer was injected into the lobeecto
cavity by stacking fragments of the wafer transversely within the
defect against the exposed white matter. The wafer was
broken into several fragments because it was too large
to fit into the cortical defect.

The dural flaps were closed over the polymer implant
with 5-0 Prolene sutures. A piece of Gelfoam was
placed over the dura, the bone flap was replaced over
the Gelfoam, and a second piece of Gelfoam was
placed over the bone flap. The five monkeys that did
not receive polymer implants (Group 1) were treated
identically except that the cavity was left empty. The
temporal muscle fascia was repaired with 3-0 Vicryl
suture, the subcutaneous tissue was approximated with
3-0 Vicryl inverted-mattress stitches, and the skin was
closed with surgical staples.

In the three Group 4 animals, the frontal craniotomy
was extended to the contralateral hemisemion. Lobec-
tomy was performed as described previously but in
ecluded both the right and left frontal lobes. A PCPP:SA
wafer impregnated with BCNU wa implanted in the
bed on the left side and a PCPP:SA wafer without
BCNU was implanted similarly on the right side. The
dura, bone flap, and skin were closed as before.

The animals were extubated as they awoke and were
then transferred to a recovery room, where they were
observed by the veterinary staff for at least 24 hours
before being returned to the standard facilities. The ani-
mal were evaluated daily by two independent observ
ers for evidence of systemic or neurological deterio-
ration.

Radiation Therapy

Beginning on Day 21 after polymer implantation and
while under ketamine sedation, the monkeys in Group
4 received conventional external beam radiation treat-
ment to the entire brain, with a total dose equal to the
standard course given to patients with high-grade gli-
omas. The total midasial plane dose was 6000 cGy
(200 cGy/day, 5 days/wk). Each animal was treated
with 4 MeV photons using a parallel opposed lateral
technique; each portal was treated on alternate days.
The portal subtended the entire calvaria with shielding
of the anterior half of each globe. Port film verification
was used to ensure field placement accuracy. The ani-
mals tolerated the radiation well, sustaining only scalp
hair loss.

Imaging Studies

For the CT and MR studies, the animals were placed
prone and coronal sections of the head were obtaiined.
Contiguous CT scans were obtained, in slices 4 mm
thick, first without contrast enhancement, followed by
enhancement with either Hypaque 60 or Angiovist 60
injected intravenously (2.0 ml/kg body weight). Mag-
netic resonance imaging was conducted on a 0.6-tesla
superconducting unit, and both T1- and T2-weighted
spin-echo pulse sequences were used.

The times of postoperative evaluation are shown in
Table 1. The five animals in Groups 1, 2, and 3 un-
derwent CT first without and then with contrast me-
dium on Day 14, MR imaging on Day 14 (three animals
per group), MR imaging on Day 28 (one animal per
group), and CT on approximately Day 72 (one animal
in Groups 1 and 2 and two animals in Group 3). Two
Group 4 animals underwent CT midway through ra-
diation therapy (Day 42).

Pathological Evaluation

At the end of the experiment, the animals were sac-
ificed by an overdose of intravenous sodium pento-
barbital. In Groups 1, 2, and 3, three animals were sac-
ificed on or near Day 16 and two animals on or near
Day 72. One Group 4 animal was sacrificed on Day
72 and the other on Day 196 (one animal died on Day
2). Full autopsies were performed at time of death
(Table 1). The brains were examined grossly and his-
topathologically by hematoxylin and cosin staining.

Results

All animals tolerated the surgical procedures and ra-
diologic studies well. There were two surgical com-
lications. Because posterior extension of the frontal
lobectomy involved the motor strip, the first monkey
to undergo surgery (a Group 2 animal, empty polymer
implant) developed hemiplegia and homonymous
hemianopsia which resolved quickly to mild hemi-
paresis. The surgical procedure was subsequently
modified and there were no further neurological com-
lications in any of the experimental groups. One
Group 4 monkey died on Day 2, and complete autopsy
revealed intracerebral hemorrhage. There was no evi-
dence of either systemic or neurological disease in
any animal throughout the course of the experiment,
except for the two operative complications described
above.

Radiological Evaluation

The five control animals (Group 1) had evidence of
mild edema on both CT and MR imaging performed
14 days after surgery. A small amount of blood at the
resection site was evident in two animals, causing mini-
mal mass effect in one. No enhancement with contrast
material was seen. The MR images at 28 days and the
CT scans at 72 days showed resolution of edema and
a decrease in the size of the low-density area which
correlated with the lobectomy resection. The changes
seen in this group are attributable to the surgery.

In the five Group 2 animals (receiving empty poly-
mer), the wafer was visible on both CT and MR im-
aging; it appeared opaque on the CT scan and as a dark
area on the MR image (Fig. 1). On both, the polymer
was surrounded by evidence of edema suggesting brain
reaction to the wafer. One animal had a small mass
effect associated with the edema. No enhancement was
seen when contrast material was administered. On Day
28 after surgery, brain reaction to the polymer on the
MR image was still evident. On Day 72, the polymer
was not visible on CT and there was no evidence of
ongoing brain reaction in the implant area.

In the five Group 3 animals (BCNU-polymer group),

J. Neurosurg. / Volume 80 / February, 1994
the results of CT and MR imaging on Day 14 after surgery were similar to those of the Group 2 (empty polymer) animals. The polymer wafer was visible on both CT (opaque area) and MR imaging (dark area). The area surrounding the polymer appeared as a low signal on CT and high signal on T₂-weighted MR images, consistent with brain edema. Four Group 3 animals had minimal shift of intracranial structures across the midline. No enhancement was seen when contrast material was administered. On MR imaging 28 days after surgery, brain reaction to the polymer was still evident; on CT 72 days after surgery, one animal had no evidence of the polymer while another had an opaque area that was consistent with blood or dissolved wafer. The brain reaction to the polymer had improved significantly, with one animal having some residual low density on CT in the area of the implant.

In two Group 4 animals (receiving irradiation), CT revealed the bilateral craniotomies, but was otherwise normal. There was no difference between the hemisphere receiving the empty polymer and that containing the BCNU-loaded polymer. The third animal in this group died on Day 2.

Pathology

Autopsies with histopathological analysis were performed on all animals. In Groups 1, 2, and 3 three animals were sacrificed around Day 16 and two on Day 72. One surviving animal in Group 4 was sacrificed on Day 72 and the other on Day 196.

Groups 1, 2, and 3. There was no gross evidence of the effect of treatment on the brains except at the implant site. In the animals implanted with empty polymer (Group 2) or BCNU-loaded polymer (Group 3), fragments of polymer were present on both Day 16 and Day 72 (Fig. 2).

Microscopic evaluation of specimens from Groups 2 and 3 showed a narrow zone of brain parenchymal necrosis which was not present in the control group (Group 1) (Fig. 3). The width of the necrosis was 0.5 to 1.0 mm in the empty polymer group (Group 2) and 2.0 to 3.0 mm in the BCNU-polymer group (Group 3). An early subacute cellular inflammatory response was seen on Day 16 in both groups, with a greater response in the BCNU-polymer group (Fig. 3). A zone of gliosis and neovascularization formed around the polymer which was not seen in the control animals and which was wider in the BCNU-polymer group compared to the empty-polymer group. Furthermore, there appeared to be less phagocytic activity in the BCNU-polymer group compared to the empty-polymer group (possibly due to the BCNU). Intimal hyperplasia of vessels in the adjacent parenchyma and in the zone of cellular reactivity was seen more often in the BCNU-polymer group.

By Day 72, the tissue reaction had evolved into a chronic inflammatory response. In the empty-polymer group, a narrow zone of gliosis, neovascularization, and hemosiderin-laden macrophages was present at the polymer-brain interface (Fig. 4). In the BCNU-polymer group, one animal had only mild gliosis of the brain.

**Fig. 1.** Imaging studies of a monkey brain 2 weeks after implantation of a polymer disk. **Left:** Computerized tomography scan of a monkey brain implanted with an empty PCPP-SA polymer. The polymer appears opaque (arrow), with a low-density area surrounding it which represents edema. **Right:** T₂-weighted magnetic resonance image of a monkey brain implanted with a PCPP-SA polymer containing BCNU. The polymer appears dark (arrow).

**Fig. 2.** Photomicrographs of monkey brain section on Day 72 after polymer implantation. H & E, × 160. **Left:** Pale foamy histiocytes containing polymer debris are observed throughout the field. **Right:** Under polarized light, the polymer material is clearly seen within the histiocytes.
Chemotherapy-loaded polymers in monkey brains

adjacent to the polymer, while the second continued to have a zone of cellular reactivity with a moderate foreign body cellular reaction. This zone was characterized by neovascularization, mild gliosis, and necrotic parenchyma with hemosiderin- and polymer-filled glial macrophages.

**Group 4.** In the animal sacrificed on postoperative Day 72, the BCNU-polymer implantation area was surrounded by a 6-mm region of necrosis, which was not present around the empty polymer. A narrow zone of intense histiocytosis measuring 5 mm was found around both polymers. Outside the zone of histiocytes, the brain showed a moderate gliotic response measuring 1 mm in the hemisphere containing BCNU-polymer and 2 mm in the hemisphere containing empty polymer, with a perivascular lymphocytic infiltration (Fig. 5). Vascular changes, wall thickening, and hyalinization consistent with radiation effects were found in several vessels at the edge of the reaction in the hemisphere implanted with BCNU-loaded polymer. At both implantation sites the area of reaction was less than 1 cm in diameter, and outside this area the brain appeared normal.

In the animal sacrificed on Day 196, the abnormal zone at the empty polymer implantation site measured 1.2 cm in diameter. This zone comprised a 4-mm area of dense fibrosis with hemosiderin-laden macrophages, thick-walled vessels, and recent hemorrhage. The remaining 8 mm of the reaction consisted of edema, perivascular lymphocytes, and gliosis. The reaction in the hemisphere implanted with BCNU polymer measured 1.5 mm in diameter, and showed mild gliosis and edema. No inflammatory infiltrate or abnormal vessels were found.

In both hemispheres, the brain beyond the reaction zone was normal. Material consistent with degraded polymer was found on Day 72 at the empty polymer implantation site. No polarizable polymer was seen in either hemisphere on Day 196.

**Discussion**

**Study Rationale**

Carmustine-impregnated polymers are currently being evaluated in patients to treat recurrent malignant glioma. In this study, the objectives were to systematically evaluate in a controlled laboratory environment the effects of PCPP:SA polymer with and without BCNU, both by itself and in conjunction with irradiation using neurological, radiological, and pathological techniques.

**Interstital Delivery of BCNU**

The present study was designed to examine the safety of delivering BCNU interstitially with PCPP:SA polymers in the primate brain. The animals with implanted polymers had no systemic or neurological problems. The brain reaction to the polymer involved

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**Fig. 3.** Photomicrographs of brain sections from monkeys in Groups 2 and 3 sacrificed on Day 16 after polymer implantation, H & E, × 60. *Left:* Section from a Group 2 animal (empty polymer) showing superficial necrosis with neutrophils and histiocyte infiltration. *Right:* Section from a Group 3 animal (BCNU-loaded polymer) showing superficial necrosis with neutrophils and histiocyte infiltration. Note the accumulation of cells at the base of the necrosis.
When edema, the changes, an early cellular inflammatory reaction which had become chronic by Day 72. Beyond the local histological changes, the brain appeared normal. Radiographically, the early brain reaction was consistent with brain edema, with minimal shift of intracranial structures when BCNU was present in the polymer. This edema response, which disappeared by Day 72, could be managed with steroid therapy in patients receiving a polymer implant.

Effects of Irradiation Combined With BCNU-Polymer

When radiation therapy was administered in conjunction with empty-polymer and BCNU-loaded polymer implantation, no deleterious neurological effects were seen and only localized pathological changes were detected. At 72 days after surgery (2 months after starting radiation therapy), a zone of necrosis was evident surrounding the BCNU-polymer that was not present around the empty polymer or around the BCNU-polymer in the nonirradiated animals (Group 3). On postoperative Day 196 (6 months after irradiation was begun), no necrosis was evident and only a mild gliotic reaction remained. The brain outside the reaction zone was normal on both Days 72 and 196 after implantation. The lack of pathological changes in the surrounding brain of the irradiated monkey is consistent with the results of Wakisaka, et al., who found that, 6 months after starting radiation therapy, only one of three monkeys treated with 6000 cGy in 30 fractions developed necrotic white-matter lesions characteristic of radiation injury. Whether BCNU-impregnated polymers will affect the delayed radiation injury to the monkey brain seen at 1 and 2 years cannot be determined from this study. However, neither empty-polymer nor BCNU-polymer implantation produced the regional radiation necrosis that occurs when radiation is administered to brain with previous local damage.

Polymers for Drug Delivery

Biodegradable polyanhydrides, which have been shown to be biocompatible in the rabbit and rat brain, can be used to deliver a variety of drugs to a target site, such as the brain, in a predictable and sustained

![Figure 4](image1.png)

**Fig. 4.** Photomicrograph of a brain section from a Group 2 monkey sacrificed on Day 72 after polymer implantation. Brain gliosis with numerous histiocytes is present. On polarization, these histiocytes contain polymer material. Findings were similar in animals from Group 3, with the exception of necrosis seen in one BCNU-treated animal. In Group 1 animals (no polymer implanted), there was minimal surface fibrosis with hemosiderin-laden macrophages. H & E, × 78.

![Figure 5](image2.png)

**Fig. 5.** Photomicrographs of brain sections from a Group 4 monkey sacrificed on Day 72 after polymer implantation. H & E, × 13. **Left:** Right hemisphere implantation site (empty polymer). An intense zone of histiocytes is demonstrated with a moderate gliotic response in the surrounding brain. **Right:** Left hemisphere implantation site (BCNU-loaded polymer). Surface necrosis with histiocytic infiltration can be seen.
Chemotherapy-loaded polymers in monkey brains

Polymers release drug primarily by surface erosion. The polyanhydride in this study is made of two monomer units in a 20% PCPP to 80% SA (w/w) ratio. The PCPP subunit is relatively hydrophobic and thus degrades very slowly, whereas the SA subunit is hydrophilic and degrades rapidly. By varying the ratio of the two subunits, the degradation rate of the polymer and thus the drug release can be altered.17

Successful treatment of malignant gliomas is limited by local tumor recurrence.11 Surgical resection and adjuvant treatments such as radiation therapy are aimed primarily at local control of the tumor. The need for high systemic doses of chemotherapeutic agents to penetrate the blood-brain barrier is a major limitation in the chemotherapeutic treatment of these tumors. Biodegradable polymers can deliver drugs locally, thereby bypassing the limitation of the blood-brain barrier and achieving high concentrations in a sustained fashion.

Carmustine is the first-line chemotherapeutic agent used against malignant gliomas.12-26 Its effectiveness is limited by its systemic toxicity and its short half-life. When placed in a controlled-release polymer, intact BCNU is measurable over a sustained period of time at high local concentrations without systemic effects.11,27 Furthermore, BCNU released locally via a polyanhydride polymer extended survival in a rat glioma brain tumor model longer than did systemic BCNU.1,2,22 On the basis of these findings, clinical trials to test the use of a polyanhydride polymer (PCPP:SA) containing BCNU to treat malignant gliomas have been started.4 This method of drug delivery is also being explored as a means to improve delivery of other chemotherapeutic drugs (carboplatin, 4-hydroperoxy-cyclophosphamide, taxol, and camptothecin) to brain tumors.

By allowing sustained high local tissue concentrations, drug delivery by biodegradable polymers has many potential clinical applications, especially for treatment of local diseases. Such uses include delivery of chemotherapeutic agents to tumors in other body areas; biological response modifiers such as angiogenesis inhibitors21 or radiosensitizers; steroids to control cerebral edema;19,25 dopamine to the striatum in patients with Parkinson’s disease;10 nerve growth factor to the striatum to improve the survival of adenomedullary tissue transplants;7,18 and antibiotics for chronic infections such as osteomyelitis.16

Conclusions

In summary, BCNU can be safely delivered interstitially by biodegradable polymers. Furthermore, irradiation can be safely administered when a BCNU-loaded polymer has been implanted. Based in part on the results presented in this paper, multi-institutional clinical trials with BCNU-impregnated PCPP:SA polymers have been initiated. The safety and efficacy of this approach may allow a variety of drugs to be administered locally: interstitially for brain tumors, as well as local application to cancers in other specific locations.

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References

18. Powell EM, Sobarzo MR, Saltzman WM: Controlled re-

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lease of nerve growth factor from a polymeric implant. 
**Brain Res** 515:309–311, 1990

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