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CONTROLLED RELEASE POLYMERS TO DELIVER DRUGS TO THE BRAIN

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Delivery of drugs to the brain is hampered because of the blood-brain barrier and the need to achieve high, systemic concentrations in order to obtain adequate brain tissue concentrations. In particular, brain tumors have been resistant to treatment because they are locally invasive and require high concentrations of drugs which have considerable systemic toxicity. To obviate these problems, we have developed a polymeric system for delivering high concentrations of drugs over a sustained period of time directly to the brain.

Before 1973 there were no chemical methods of prolonged controlled release of molecules greater than molecular weight of 500 that were biocompatible in vivo. In 1976 Langer and Folkman reported the release kinetics of macromolecules from ethylene vinyl acetate (EVAc) and several other polymers.[1] The EVAc polymer has been used extensively for biological applications including contraception, insulin delivery, cancer chemotherapy, glaucoma treatment, dental caries prevention, and asthma therapy.[2] The limitations of the EVAc delivery system for the brain are that, despite it being predictable and reproducible, it is non-biodegradable and hydrophilic which will not protect certain unstable drugs (such as BCNU). Furthermore, EVAc released by bulk erosion, which has the potential for a burst release of chemotherapeutic drug in the brain, could cause significant toxicity.

By contrast, the development in Langer's laboratory of poly(bis(p-carboxyphenoxy)propane-sebacic acid) (PCPP-SA) has a number of advantages for use in the brain. It is biodegradable over periods ranging from days to years. It is hydrophobic, thereby protecting unstable compounds. The PCPP-SA is available in a variety of forms ranging from nanospheres to wafers and sheets.

Leong et al, have demonstrated that the PCPP-SA polymer is non-mutagenic, non-cytotoxic, and non-teratogenic.[3] Endothelial cell and smooth muscle cell growth in tissue culture was unaffected when plated on a layer of polyanhydride polymer.

In our laboratory at Johns Hopkins, we have carried out a number of experiments to demonstrate the biocompatibility of the PCPP-SA, the drug distribution of a chemotherapeutic agent from the polymer implanted in the brain, and the intracranial efficacy of BCNU PCPP-SA against brain tumor implants. Specifically we showed in the rabbit cornea that the polyanhydride polymer was free of an inflammatory response.[4] The polymers were then tested in the rat brain and compared to the tissue reaction of that seen with absorbable gelatin sponge (Gelfoam®) and with oxidized regenerated cellulose (Surgicel®).[5] None of these animals showed any behavior changes or neurological deficits suggesting other systemic or localized toxicity from the biodegradable polyanhydrides. The histological results were similar to that seen with the currently used clinical implants listed above. In the rabbit brain, the polyanhydride similarly was minimally reactive and without toxicity.[6]

We then proceeded to evaluate the safety of the implants in the monkey brain.[7] Fifteen adult Cynomologous monkeys were randomized into one of three groups of five monkeys. Group 1 had empty polymer disks; group 2 had polyanhydride polymers impregnated with BCNU chemotherapy; group 3 had a sham operation with no implant. There was no systemic or local toxicity demonstrated in any of these groups. The monkey brains were also evaluated radiologically, and there was no demonstrable deleterious effect seen.[8]

In summary, in all of the animal systems tested, there was no systemic toxicity or localized toxicity of significance.

Release kinetic studies were then carried out demonstrating very high sustained local concentrations of the impregnated nitrosourea chemotherapeutic agent BCNU.[9]

We then evaluated the effectiveness of PCPP-SA loaded with BCNU as a treatment for a 9L gliosarcoma. Our first series of experiments evaluated the effectiveness of the nitrosourea released from the controlled-release polymer against a brain tumor growing in the flank as compared to systemic treatment.[10] We showed that it effectively treated the tumors with release of active drug. We then began a series of experiments where we implanted 9L gliosarcomas in the brain of rats and treated them with polymers--treatment beginning simultaneously or five days after tumor implantation.[10] In the groups treated with BCNU polymers, the median survival was significantly prolonged, and there was a large percentage of cures of the brain tumors implanted in the rat brain. None of the controls demonstrated any cures.

We therefore concluded that, based on these laboratory studies: (1) PCPP-SA was biocompatible and could be implanted safely in the brains of rodents and primates; (2) BCNU incorporated into PCPP-SA could be released in a sustained controlled fashion; and (3) delivery of BCNU in this fashion could effectively inhibit the growth of an experimental malignant glioma in a manner superior to the standard systemic administration of BCNU.

Based on these results, three clinical trials with BCNU impregnated polymers have been undertaken. The first was a Phase I-II study carried out at five medical institutions, utilizing escalating doses of BCNU-impregnated polyanhydride polymers for the treatment of recurrent malignant brain tumors.[11] Twenty-one patients were evaluated. Based on the safety and effectiveness of the BCNU impregnated polymer, a Phase III placebo-controlled study was carried out. This study involved implantation of polymers in 220 patients and will be completed soon. Once the code is broken, we will have determined the effectiveness of this specific dose of BCNU with this type of polymer for patients who have failed standard therapy for malignant gliomas. However, we have already learned that the technique itself is safe, and therefore we have initiated a 22-patient study of three institutions utilizing the BCNU-impregnated polymers as the initial therapy for malignant primary brain tumors. The results of this study are currently being evaluated.

In addition to the application described above for the polyanhydride polymers, we are developing in the laboratory a number of other chemotherapeutic drugs for brain tumors. For example, 4-Hydroperoxycyclophosphamide and carboplatin are drugs which on an experimental basis should be highly effective against brain tumors, but are not currently utilized because of the difficulty in delivery. Using biodegradable polymers in experimental animals, we have shown these drugs to be highly effective in treating brain tumors.[12] Further studies are underway in order to prepare for eventual clinical testing.

We have also utilized polymers to deliver glucocorticoids directly into brain tissue in order to optimally control brain swelling.[13] We are also utilizing polymers over laminectomy sites to see if we can better control adhesions related to post-surgical scarring.

A major effort is underway in our laboratory to utilize controlled-release polymers for novel biological response modifiers, such as angiogenesis inhibitors. Future applications for drug delivery in the brain may include local treatments for Parkinson's disease and Alzheimer's disease utilizing sustained high levels of selective compounds in the brain.

1. Langer R. and Folkman J. "Polymers for the sustained release of proteins and other macromolecules, Nature. 263:797, 1976.
2. Langer R and Wise D., (Eds). "Medical Applications of Controlled Release." Vols. I and II. CRC Press, Boca Raton, Florida, 1986.
3. Leong KW, D'Amore P, Marletta M, and Langer R. "Bioerodible polyanhydrides as drug-carrier matrices. II." J Biomed Mat Res. 20:51, 1986.

4. Langer R, Brem H, and Tapper D. "Biocompatibility of polymeric delivery systems for macromolecules." Journal of Biomedical Materials Research 15:267-277, 1981.

5. Tamargo RJ, Epstein JI, Reinhard CS, Chasin M, and Brem H. "Brain biocompatibility of a biodegradable, controlled release polymer in rats." Journal of Biomedical Materials Research, 23(2):253-266, 1989.

6. Brem H, Kader A, Epstein JI, Tamargo R, Domb A, Langer R, and Leong, K. "Biocompatability of a biodegradable, controlled- release polymers in the rabbit brain." Selective Cancer Therapeutics, 5(2):55-65, 1989.

7. Brem H, Tamargo RJ, Pinn M, and Chasin M. "Biocompatibility of a BCNU-loaded biodegradable polymer: A toxicity study in primates." American Association of Neurological Surgeons, Toronto, Canada, April 24, 1988, p. 381.

8. Brem H, Ahn H, Tamargo RJ, Pinn ML, and Chasin M. "A biodegradable polymer for intracranial drug delivery: A radiological study in primates." American Association of Neurological Surgeons, Toronto, Canada, April 24, 1988, p. 349.

9. 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.

10. Tamargo RJ, Myseros JS, and Brem H. "Growth inhibition of the 9L gliosarcoma by the local sustained release of BCNU: A comparison of systemic versus regional chemotherapy." American Association of Neurological Surgeons, Toronto, Canada, pp 212-214, April 24, 1988.

11. Brem H, Mahaley MS, Vick NA, Black K, Schold SC, Burger PC, Friedman AH, Ciric IS, Eller TW, Cozzens JW, and Kenealy JN. "Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas." J Neurosurgery, 74:441-446, 1991.

12. Judy KD, Olivi A, Domb A, Colvin OM, Brem H. "Controlled release of a cyclophosphamide derivative with polymers is effective against rat gliomas." Congress of Neurological Surgeons, Orlando, Florida, Oct. 1991.

13. Tamargo RJ, Sills AK, Reinhard CS, Pinn ML, Long DM, and Brem H. "Interstitial delivery of dexamethasone in the brain for the reduction of peritumoral edema." J Neurosurgery, 74:956-961, 1991.