Beyond the Barrier: devices inside the brain
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The brain is usually thought of as an extremely sensitive part of the body, which should be entered only with great caution. However, it does appear to be amenable to intervention with treatment involving devices in a number of circumstances. This article describes on such application.

This column has discussed the problems of urinary incontinence in the context of a condition that is encountered frequently, but is not life threatening, and therefore has not achieved the level of progress in the development of treatments it deserves.[1] At the opposite end of the spectrum is the situation with brain tumors. Affecting a relatively small number of people, this is clearly a fatal rather than inconvenient condition. However, there appears to be a significant role for medical devices and materials technology in this area and this article attempts to address some of the key issues. There are two general reasons for considering this rather specialized condition and technology. The first is that it demonstrates the introduction of implantable devices into the brain is not as dramatic as may be thought, and suggests that many other, perhaps more widespread neurological conditions, may be considered for surgical intervention. The second is that this is an area at the interface between drugs and devices [2] and demonstrates the tremendous potential for the drug-device combination.

The problem

Malignant gliomas, that is, aggressive tumors within the brain, are particularly difficult to treat. Fifty per cent of patients die within four to six months of diagnosis and all die within two years. Although many tumors elsewhere in the body are treatable by chemotherapy, this method is largely inappropriate for the brain because of the difficulty of delivering drugs to the tumor. This arises because of the effect of the blood-brain barrier, a protective membrane that prevents access to the brain of exogenous substances, particularly those of high molecular weight. This, of course, is a very effective defense mechanism, but it has an undesirable consequence in situations where it is in the interests of the patient to have such a substance, for example a drug, delivered to the brain.

There are some drugs that are mechanistically effective against gliomas, but they have to be delivered to the patient in such high doses to reach therapeutic levels in the brain that the toxic side effects are just too great. BCNU is such a drug. It has been approved by the United States (US) Food and Drug Administration (FDA) for chemotherapy and not only has this problem with the blood- brain barrier, but also has a short half-life in vivo, typically a few minutes. There is no reason why this

drug could not be effective if it could gain access to the critical parts of the tumor for a long enough period.

Polymeric delivery systems

At the annual meeting of the US Society for Biomaterials held in San Francisco, California, USA, 19-23 March 1995, one of the solutions, and at this stage clearly the most promising solution, was discussed by Dr H. Brem, John Hopkins University Medical School (Baltimore, Maryland, USA).Working with Dr R. Langer, Massachusetts Institute of Technology (Cambridge, Massachusetts, USA) his team has developed a drug-delivery system for delivering chemotherapeutic agents to the brain by circumventing the blood-brain barrier and by protecting the drug for as long as possible from the metabolic activity that gives it such a short life span. A matrix-based interstitial delivery system has been developed with the specific purpose of releasing BCNU to intracranial sites.

The team has chosen a degradable polymer as the carrier, specifically a polyanhydride; the target was the prolonged delivery of the drug over a three-week period, with a minimum of systemic complications. Initial studies were directed at the demonstration of safety, drug distribution, and efficacy. A rodent model in which gliomas were implanted into hosts gave a mean survival time of 16 days if untreated, with no survivors at the end of the test. Systemic delivery of BCNU prolonged this slightly to 30 days, again with no survivors, but implantation of a BCNU-loaded polyanhydride depot intracranially extended the mean survival time to 60 days and produced a significant number of survivors at the end of the period.

At this stage, the team was given approval to implant these depots into humans. Phase I and II trials showed that the drug depot left the recipients no worse off than those without the device, which demonstrated essential safety. However, a couple of interesting points arise over the next stage, points that are relevant to many critical medical device trials. The FDA only gave approval to test these devices in patients who had recurrent malignant gliomas, that is, patients who had been diagnosed as having a brain tumor; who had been treated by radical surgery, radiotherapy, or chemotherapy; and in whom the tumor had recurred, probably because it had never been affected by the treatment. This, of course, presents a dilemma to scientists and regulators alike. With highly experimental treatments, a natural response is to restrict it to patients in whom all other treatment has failed, in order to minimize the possibility of unacceptable risks. Yet, patients with the poorest prognosis offer the poorest chance of the treatment actually working. This paradox was probably the key factor that prevented the total artificial heart from becoming more successful a decade or more ago.

An even more agonizing dilemma arises in clinical trials where it appears that the treatment being offered really does give patients a better chance. These trials have to be carried out with placebo controls and often have to take place over a period of time. For patients who are dying, when the results of the first parts of the trial provide a clear indication that the treatment is effective, it is very difficult for the clinical trials manager to continue to offer the placebo, yet without the proper statistical basis, the trial can never be complete.

Returning to the details of this case, several different formulations were assessed in which the drug was loaded into a simple matrix of the polyanhydride. This

degradable polymer releases all of the drug in vivo during a period of a few weeks simply through erosion. The patients, all of whom had been diagnosed as having a glioblastoma, the most malignant form of brain tumor, received radiation and/or chemotherapy first and then had the recurring tumor surgically removed, and a series of thin wafers of the drug-loaded polymer were implanted into the operative site. Bearing in mind the nature of these tumors, the significant increase in the number of survivors at six months, from 36% to 56% in one group, shows the possibilities of the treatment. More importantly, this has opened up the way for a new era in medical device technology where a simple concept, detailed materials engineering, and a complex system of preclinical experiment and clinical trial has shown how some of the most intractable and fatal conditions may be tackled.

Clearly, the results are not overwhelming in their significance and there is some way to go. It is likely that BCNU is not the most appropriate chemotherapeutic agent for this delivery mode and the team has already made progress with alternatives, particularly some other potent anticancer agents that are unable to get through the blood-brain barrier. Carboplatin and cyclophosphamides come into this category, but perhaps most exciting are the possibilities with topoisomerase inhibitors. These are highly potent drugs that showed much promise a number of years ago, but proved to be too toxic when delivered in the concentrations necessary to be effective. Early experiments show these to be the most effective agent under the conditions of release from the polymer depot.

Conclusions

Perhaps most importantly from the medical device point of view, these types of experiments and trials show that the brain is not as inaccessible to medical devices as some may think. Various types of hemostat, shunts, and clips are already used in certain neurological conditions, but the way seems clear for a more active phase of device intervention in these matters of the brain.

References

l. D.F. Williams, "Below the Belt: The Technology of Incontinence; Medical Device Technology, 6(2),8-12 (1995).
2. D.F. Williams, "Molecular Ambiguity - The Difference Between Drugs and Devices," Medical Device Technology, 5(7),12-14 (1994).