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Polymeric controlled release of dexamethasone in normal rat brain

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Controlled release polymeric implants may improve delivery of anti-edema agents to the central nervous system. Ethylene-vinyl acetate copolymer (EVAc) matrices containing dexamethasone (35% w/w) were implanted either intracranially or intraperitoneally in Fisher 344 rats. Selective extraction and high performance liquid chromatography were used to quantify tissue concentrations after implantation of the drug-loaded polymer or intraperitoneal injection of an equivalent dose. Dexamethasone was detected in brain for up to 21 days after intracranial polymer implantation, with peak levels of 4.0 ± 0.7 μg/g tissue measured in the ipsilateral hemisphere. Concentrations in the contralateral hemisphere and peripheral circulation were measurable for the first 12 h only (peak level at 1 h of 0.5 ± 0.2 μg/g in the contralateral hemisphere). By contrast, intraperitoneal bolus administration of dexamethasone in control animals resulted in minimal brain levels (peak at 1 h of 0.8 ± 0.4 μg/g) and very high plasma levels (peak at 4 h of 23.6 ± 6.0 μg/g). No drug was detected in the brains of animals with intraperitoneal dexamethasone-EVAc implants. Measured dexamethasone concentrations were compared to a one-compartment pharmacokinetic model. The experimental results are best described by assuming diffusion-limited release of dexamethasone from the polymer (characteristic release constant of 0.5 μg $h^{-\frac{1}{2}}$) and first order drug elimination (half-life of 16 h).

Keywords: Targeted drug delivery; Dexamethasone; Controlled release; Brain edema; Polymer; Pharmacokinetic modeling

Introduction

The synthetic corticosteroid dexamethasone is widely used in the treatment of neurological disease, especially to reduce cerebral edema associated with tumors [1]. Because of its limited ability to cross the blood–brain barrier, dexamethasone must be administered in high systemic doses to achieve therapeutic brain levels. Prolonged systemic administration is associated with serious side effects such as diabetes, hemorrhagic ulcers, skin atrophy, myopathies, osteoporosis and psychosis [2].

Several recent communications described the

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advantages of using local, controlled release polymers to deliver substances to the brain [3–11]. Because the implants are placed directly in the brain tissue, drugs do not have to cross the capillary wall to produce a pharmacological effect. The objective of this study was to determine whether dexamethasone administration by intracranial controlled release polymer matrices provides sustained local concentrations of this drug while avoiding high systemic levels. Polymer matrices that release controlled quantities of dexamethasone were implanted in the brains of normal rats and the resulting concentrations were measured in various tissues for up to 21 days following polymer implantation. We compared the drug levels in brain and plasma following polymer implantation to those resulting from conventional systemic administration. Dexamethasone levels in brain and plasma were quantitated by extraction [12], followed by reverse phase high performance liquid chromatography (HPLC). While a variety of methods for analyzing dexamethasone in plasma, cerebrospinal fluid, brain tumor fragments, and urine have been reported [12–23], this is the first study of dexamethasone levels in normal brain.

Materials and Methods

Materials

Adult Fisher 344 male rats (150–260 g) were purchased from Harlan Sprague-Dawley, Inc. (Indianapolis, IN, U.S.A.). Dexamethasone was from Sigma Chemical Company (St. Louis, MO, U.S.A.) and dexamethasone sodium phosphate injectable (10 mg/ml, 8.33 mg dexamethasone/ml) was obtained from Elkins-Sinn, Inc. (Cherry Hill, NJ, U.S.A.). All solvents and the sodium acetate were HPLC grade; sodium hydroxide was analytical reagent grade. Ethylene vinyl acetate (EVAc, ELVAX 40 W) was purchased from DuPont (Dover, DE, U.S.A.).

The anesthetic contained 25 ml ketamine hydrochloride (100 mg/ml, Ketalar, Parke-Davis, Morris Plains, NJ, U.S.A.), 2.5 ml xylazine (100 mg/ml, Rompun, Mobay Company, Shawnee, KA, U.S.A.), 14 ml 100% ethanol, and 58 ml of 0.9% NaCl. The solution was filter sterilized.

Methods

Polymer preparation

EVAc was cleaned with absolute ethanol for 35 days at room temperature [24]. Dexamethasone was encapsulated in EVAc by solvent evaporation [25], as follows. EVAc was dissolved in methylene chloride (10% w/v) and enough solid particles of dexamethasone were added to the EVAc solution to obtain a 35% mass fraction of dexamethasone (mass dexamethasone/(mass dexamethasone+mass polymer)). The dexamethasone/EVAc solution was thoroughly mixed; 0.5-ml aliquots were transferred into glass cylindrical molds (5 mm diameter×27 mm) previously cooled over dry ice. Upon solidification (20 min) the device was removed from the mold. Methylene chloride was evaporated from the polymer matrices in a −35°C freezer for 3 days and then under vacuum at room temperature for 2–3 days, at which time the polymers were reduced to about one half their original size. The polymers were stored in glass vials in a conventional freezer (−20°C) until needed. At time of use, the polymers were cut to 14 mg (2.5 mm diameter×2.2 mm), and sterilized by exposure to ultraviolet light for 1 h. Control implants containing 100% EVAc were prepared by the same technique except that no drug was added to the methylene chloride/EVAc solution.

In vitro release study

The release of dexamethasone from polymer matrices was monitored for a period of incubation in sodium phosphate-buffered water at 37°C. The samples were shaken during the entire incubation period. The polymers were immersed in 5 ml of 0.2 M phosphate-buffered water (pH 7.4) with an antibacterial agent (0.01% sodium azide). At specific times following immersion the buffer solution was replaced with fresh solution and the concentration of dexamethasone was determined in the solution by spectrophotometry at 240 nm.

Surgery

Surgery was performed under aseptic conditions. Intraperitoneal injections of 3.0 to 3.5 ml of anesthesia solution/kg of animal weight were used for all procedures. Each rat was weighed at the end of the polymer implant procedure and at time of euthanasia. An intracerebral polymer was placed 3.5 mm posterior for the bregma and 3.5 mm lateral to the sagittal suture as previously described [11]. A 3-mm deep cortical incision was made and the polymer was inserted. To place the intraperitoneal implants, a small incision was made on the midline through the peritoneum, and the polymer was inserted in the lower right quadrant of the abdominal cavity.

The rats were anesthetized as described and euthanized by exsanguination. Blood samples were collected in heparinized syringes by direct cardiac puncture.

Experimental design

Three treatment groups were studied. Group 1 animals ($n=30$) received an intracranial dexamethasone-EVAc implant (14.3 ± 0.3 mg) containing 5 mg of dexamethasone, an intraperitoneal implant of pure EVAc, and an intraperitoneal injection of normal saline. Group 2 animals ($n=9$) received an intracranial implant of pure EVAc, an intraperitoneal implant of dexamethasone-EVAc matrix, and an intraperitoneal injection of normal saline. Group 3 animals ($n=9$) received intracranial and intraperitoneal implants of pure EVAc and an intraperitoneal bolus dose of 5 mg dexamethasone phosphate injectable (4.16 mg dexamethasone). A final control group ($n=3$) with pure intracranial and intraperitoneal EVAc implants and a bolus injection of normal saline was studied for the presence of endogenous interfering steroids.

Sample preparation and extraction

To determine dexamethasone concentration in brain tissue, the polymer was carefully removed and the cerebrum was divided into right and left hemispheres. Each hemisphere was weighed and placed in 10 ml Potter-Elvehjem homogenizer tubes. Normal saline was added to make 2 ml and the tissue was homogenized. The samples were pipetted into 1.5 ml tubes and frozen at $-35°C$ until analysis. The time from animal euthanasia to sample freezing was about 5–10 min. Plasma was obtained by centrifugation and then stored with the brain samples at $-35°C$. Dexamethasone standards ranging in concentration from 0.1 to 5 μg/ml were prepared in brain homogenate and plasma obtained from untreated male Fisher 344 rats. Prednisolone was used as the internal standard because it has a similar structure, ultraviolet absorbance, and elution time as dexamethasone.

Plasma and brain homogenates were extracted by the method of Cham et al. [12]. Briefly, 1-ml samples were washed with heptane under alkaline conditions. The heptane layer was discarded and 1 μg of internal standard (10 μl of 0.1 mg/ml prednisolone in methanol) was added to the aqueous phase, which was then extracted with 10 ml of methylene chloride. After aspirating the upper aqueous layer, the organic phase was transferred to a clean glass centrifuge tube, leaving the tissue residue on the walls of the first tube. Finally, the solvent was evaporated at 45°C under a stream of nitrogen gas. The tubes were capped and stored at 4°C until analysis.

Chromatography

All chromatography was performed with the following instruments (all from Waters Associates, Inc., Milford, MA, U.S.A.): prepacked reverse phase columns (uBondapak C18), high pressure pumps (Model 6000A), automatic sample injector (WISP, Waters Intelligent Sample Processor), and UV absorbance detector (Model 440). All separations were performed at ambient temperature.

The isocratic delivery system for the brain samples consisted of two eluents: 60% sodium acetate buffer (2 mM) and 40% acetonitrile. The acetate buffer was prepared in distilled water, adjusted to pH 4.8 with glacial acetic acid, and filtered through a 0.2 μm nylon filter. The flow rate of the mobile phase was 2 ml/min and the effluent was monitored at 254 nm. To eliminate an interfering endogenous peak, a continuous gradient system (20–60% acetonitrile in 2 mM acetate buffer (pH 4.8) over 30 min) was used

for the chromatography of plasma samples. The flow rate of the mobile phase was 1 ml/min.

At the time of HPLC analysis, 80 μl of tetrahydrofuran were added to reconstitute the sample residue. The dissolved sample was filtered with a 0.45 μm nylon syringe filter and 25 μl were injected into the sample loop of the liquid chromatograph. After reconstituting samples from numerous experiments in this manner, we experienced problems due to precipitation on the column of residual material that was soluble in tetrahydrofuran but insoluble in the aqueous mobile phase. Reconstitution of the sample was modified by adding 80 μl acetonitrile and 80 μl buffer to the original sample solution in tetrahydrofuran and then filtering. The volume injected was increased from 25 μl to 75 μl to compensate for this change.

Retention times of prednisolone and dexamethasone in brain samples were 2.35 and 2.80 min, respectively (isocratic chromatography), and 15.82 and 18.60 min for plasma (gradient chromatography). The elution time ratio of dexamethasone to internal standard was 1.27 ± 0.1 for brain and 1.20 ± 0.03 for plasma over the course of the experiment. The limit of detectability with these methods is about 50 ng dexamethasone/ml tissue sample. In the rest of this paper, measured concentrations are reported as the mean ± the standard deviation.

Pharmacokinetic model

A one-compartment model was used to predict dexamethasone levels in the brain following release from an intracranial polymeric device. The single compartment represented the brain hemisphere containing the implant (Fig. 1). Assuming that dexamethasone is released by diffusion through the polymer, the rate of release of dexamethasone decreases with the square root of time [25,27].

$$\frac{dM_t}{dt} = \frac{A_r}{\sqrt{t}} \qquad (1)$$

where M_t is the cumulative mass of dexamethasone released from the polymer (μg), A_r is a constant that depends on the properties of the implant (μg/h$^{-\frac{1}{2}}$), and t is the time following implantation (h). Integration of equation (1) with respect to time yields:

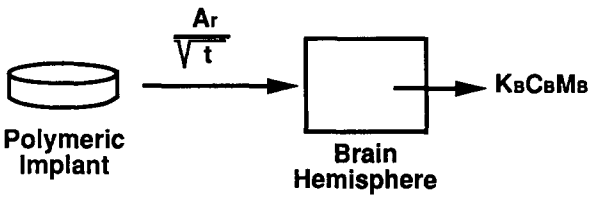

Fig. 1. Compartmental model predicting dexamethasone concentration in normal rat brain following release from an intracranial polymeric implant. The single compartment represents drug concentration in the brain hemisphere containing the implant. The model assumes that the rate of dexamethasone release from the polymer decreases linearly with the square root of time and that the elimination kinetics are first order.

$$M_t = 2A_r\sqrt{t} \qquad (2)$$

In the absence of mass transfer limitations at the polymer-tissue interface, the release constant, valid for the first 60% of dexamethasone released, can be predicted [26]:

$$A_r = 2M_0\sqrt{\frac{D_{eff}}{\pi L^2}} \qquad (3)$$

where M_0 is the initial mass of dexamethasone in the polymer (μg), L is the thickness of the implant (cm), and D_{eff} is the effective diffusion coefficient of the drug in the polymeric device (cm^2/sec).

Assuming first-order elimination of dexamethasone from the brain tissue yields:

$$E_r = K_B C_B M_B \qquad (4)$$

where E_r is the total elimination rate of dexamethasone from the brain tissue (μg/h), K_B is the first order rate constant (h^{-1}), C_B is the concentration of dexamethasone in the brain hemisphere containing the implant (μg/g), and M_B is the mass of the brain hemisphere (g). We emphasize that K_B is a lumped parameter intended to describe drug elimination by several mechanisms including dexamethasone metabolism in the tissue and partitioning into the microcirculation.

A mass balance over the entire brain hemisphere gives:

$$M_B \frac{dC_B}{dt} = \frac{dM_t}{dt} - E_r \quad (5)$$

Substituting eqns. (1) and (4) into eqn. (5) yields:

$$M_B \frac{dC_B}{dt} = \frac{A_r}{\sqrt{t}} - K_B C_B M_B \quad (6)$$

Assuming no dexamethasone is present in the brain initially, the solution to eqn. (6) is:

$$C_B = \frac{2A_r e^{-K_B t}\sqrt{t}}{M_B} \sum_{n=0}^{\infty} \frac{(K_B t)^n}{n!(2n+1)} \quad (7)$$

For short times ($t \ll 3/K_B$) equation (7) can be approximated by:

$$C_B = \frac{2A_r e^{-K_B t}\sqrt{t}}{M_B} \quad (8)$$

Eqn. (7) provides the dexamethasone concentration in the brain as a function of time; concentrations predicted by this equation can be compared to those measured experimentally. Adjustable parameters, A_r and K_B, were determined by minimizing the sum of the squares of the errors between concentrations predicted by eqn. (7) and concentrations measured experimentally in the brain tissue.

Results

In vitro release

The release of dexamethasone from 35% loaded EVAc matrices was measured in phosphate-buffered water at 37°C for over 120 days (Fig. 2). At the end of the 4 month experiment only 24% of the original drug mass had been released into the water. The slope of the line of best fit in Fig. 2B is 100 μg day$^{-\frac{1}{2}}$ which by comparison to eqn. (2), yields a value of A_r of 10.2 μg h$^{-\frac{1}{2}}$.

Effect of mode of administration

Concentrations of dexamethasone in brain and plasma were measured for the three treatment groups at 1, 4 and 12 h after administration as shown in Table 1.

Peak ipsilateral brain levels for rats receiving an intracranial dexamethasone-EVAc implant (Group 1) were measured at 4 h after implantation: 4.3 ± 0.7 μg dexamethasone/g tissue. Drug levels were low (< 0.6 μg/g) to undetectable in the contralateral hemisphere and plasma throughout the course of the experiment.

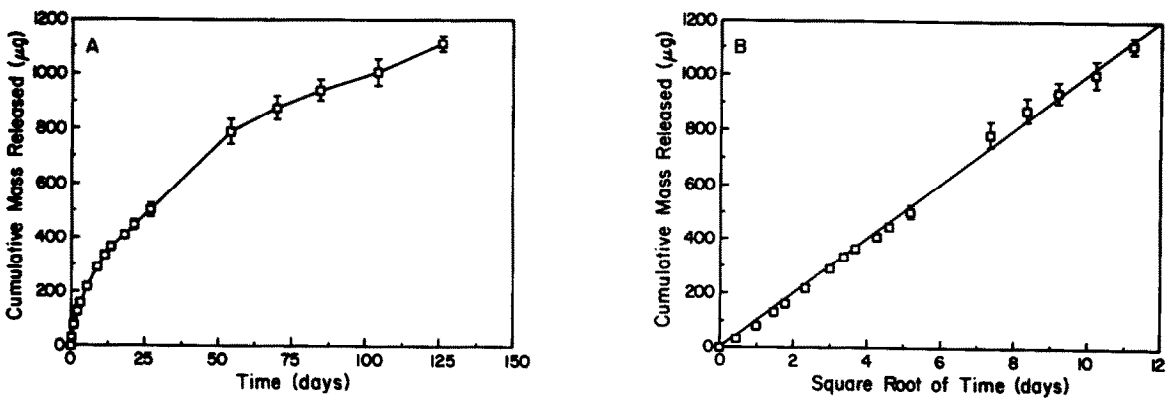

Fig. 2. Dexamethasone release into a well-stirred reservoir. Each value represents the mean of 3 matrices (±SD). In Fig. A, the cumulative mass of dexamethasone released from dexamethasone-EVAc cylindrical matrices (35% dexamethasone – 2.5 mm diameter × 2.2 mm, 14 mg) into 0.2 M phosphate buffered water at 37°C is plotted versus time. Each point represents the total mass released into 5 ml of phosphate buffer since time zero. Fig. B is the same data plotted versus the square root of time. The solid line in B represent a linear regression line of best fit with a slope of 100 μg day$^{-\frac{1}{2}}$ and a correlation of 0.999. For those data points where no error bars are evident, the standard deviation is smaller than the symbols.

TABLE 1

Effect of mode of administration

Group and time (h)	Dexamethasone concentration (μg dex./g tissue)		
	Implanted hemisphere	Contralateral hemisphere	Plasma
1. Dex. EVAc implant-IC			
1	3.4±0.05	0.5±0.2	0.8*
4	4.0±0.7	n.d.	0.4±0.05
12	3.3±0.6	n.d.	0.15 (n=1)
2. Dex. EVAc implant-IP			
1	n.d.	n.d.	n.d.
4	n.d.	n.d.	0.2±0.1
12	n.d.	n.d.	0.2±0.04
3. Dex. bolus injection-IP			
1	0.8±0.4	0.3*	18.8±8.0
4	0.8±0.03	0.6±0.1	23.6±5.7**
12	n.d.	n.d.	0.6±0.4

n.d., not detectable; IC, intracranial; IP, intraperitoneal; dex. dexamethasone; EVAc, ethylene vinyl acetate. Values shown represent the mean (±SD) of three animals (except where noted).
*Only 1 of the 3 samples had detectable dexamethasone levels; **the value at 4 h is not statistically different from 1 h (P=0.36).

Four hours after intraperitoneal injection of 5 mg dexamethasone phosphate (Group 3), we measured peak brain and plasma levels of 0.8±0.03 and 23.0±6.0 μg/g tissue, respectively. By 12 h, brain levels in both hemispheres were undetectable and the plasma concentration dropped to 0.6±0.4 μg/g tissue. At that time, ipsilateral brain concentration in rats with a dexamethasone-EVAc intracranial implant (Group 1) was 3.3±0.6 μg/g.

Animals with intraperitoneal dexamethasone-EVAc matrices of the same size as those implanted intracranially (Group 3) exhibited very low (<0.3 μg/g) to undetectable drug levels in both brain and plasma.

In vivo long-term release

During the first 14 days after dexamethasone-EVAc implantation, the concentration in the ipsilateral hemisphere dropped from 3.30±0.46 to 1.17±0.17 μg dexamethasone/g tissue. The drug concentration in the contralateral hemisphere and plasma was either very low (0.1±0.10 μg/g tissue at 3 days), or undetectable during the period of study.

In chromatograms obtained with plasma and brain samples from control rats receiving pure EVAc polymers, no endogenous steroids with the same retention times as dexamethasone or the internal standard were found.

Pharmacokinetic model

Fig. 3 shows experimental dexamethasone concentrations in the brain hemisphere containing an intracranial implant. The solid line indicates the concentrations predicted by eqn. (7). The root mean squared error between experimental and predicted concentrations was 29.8% with A_r equal to 0.53 μg h$^{-\frac{1}{2}}$ and K_B equal to 0.043 h^{-1}. This elimination constant corresponds to a dexamethasone half-life ($t_{1/2}=\ln 2/K_B$) of 16 h in the brain tissue. It should be noted that the half-life does not correspond to the time required for the concentration to fall by a factor of two because one must account for the changing rate of drug introduction to the tissue from the implant.

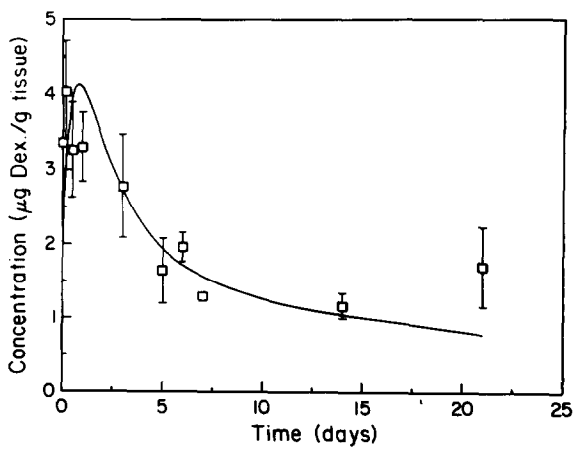

Fig. 3. Dexamethasone concentration in the brain hemisphere containing an intracranial dexamethasone-EVAc implant. Drug levels in the ipsilateral brain (±SD) were measured from 1 h to 21 days. Peak levels were seen at 4 h (4.03±0.68 μg dexamethasone/g brain tissue). Plasma concentrations were negligible to undetectable 4 h after implantation. Drug levels were determined by HPLC. The solid line represents the concentrations predicted by a one-compartment model (Eqn. (7), A_r=0.53 μg h$^{-\frac{1}{2}}$, K_B=0.043 h^{-1}, and M_B=0.67 g).

Discussion

Steroids have proven useful in the management of cerebral edema, but their use is limited by their profound systemic effects. We have explored an alternate means of administering steroids to the brain – the local application of steroids utilizing a polymer for controlled release. We have found that intracranial controlled release of dexamethasone is a more efficient means of delivering dexamethasone to the brain than conventional systemic therapy. High drug concentrations were consistently measured in the brain hemispheres containing dexamethasone-EVAc devices from 1 h to 21 days after polymer insertion, the duration of the experiment. Studies in our controlled system, however, suggest that drug release from these implants could be extended for several months.

When immersed in a well-stirred reservoir, the rate of dexamethasone release from EVAc matrices was very slow: (after 21 days only 450 μg of the 5 mg of dexamethasone originally encapsulated in the device had been released). Nevertheless, ipsilateral dexamethasone brain levels were consistently higher than those achieved with a large systemic dose. Twelve hours after bolus intraperitoneal injection of 5 mg of dexamethasone phosphate (4.16 mg dexamethasone), no drug was detectable in the brain and only 0.6 ± 0.4 μg dexamethasone/g tissue was detectable in the plasma. By contrast, the concentration in the ipsilateral hemisphere of the animals with intracranial implants was 3.3 ± 0.6 μg/g tissue after 12 h. A small quantity of dexamethasone was found in the contralateral hemisphere following intracranial implantation: this was probably due to acute changes in cerebrospinal flow following surgery.

One hour after blank polymer implantation and bolus intraperitoneal injection of dexamethasone (Group 3), the concentration of the implanted hemisphere was initially higher than the drug level measured in the contralateral hemisphere. This difference may be due to the acute breakdown of the blood-brain barrier resulting from the surgical procedure. In these same animals, plasma concentration increased over the first 4 h, however, the contralateral brain concentration increased only slightly because of the barrier to penetration by the intact capillaries on the normal side of the brain.

An empirical pharmacokinetic model was used to describe the general trend of dexamethasone concentration in the cerebral hemisphere containing the implant. Although the model does not include specific physiological mechanisms of drug elimination, model results are useful in predicting the effects of similar, but different, treatment regimens. Based on this model, the rate of dexamethasone release from the polymer in the brain was nearly twenty times less than the rate measured in a well-stirred reservoir. There are several possible reasons for this difference. (1) Additional resistance to drug diffusion: because drug molecules must diffuse through brain tissue after release from the polymer, they will accumulate near the polymer/brain interface. Increased dexamethasone concentration near the interface may decrease the release rate from the implant [28]. (2) Partitioning: it is possible that most of the dexamethasone is eliminated in an aqueous phase. The low first order rate constant and long half-life in rat brain tissue (16 h) – compared to a half-life in plasma of 2–3 h in humans [29] – may be caused by partitioning of dexamethasone into phospholipid membranes or some other anatomical compartments. Since partitioning makes some fraction of the dexamethasone unavailable for elimination, the overall elimination rate and the lumped first order partition constant must decrease (increasing the half-life).

Rats treated with dexamethasone-EVAc intracranial devices showed progressive weight loss over the course of the experiment. From 1 to 14 days after implantation, the rats lost 8 to 26% of their original weight. Rats with implants for 21 days showed a weight loss of 12%. The weight loss was probably a reflection of systemic toxicity, for example, it could be due to the diuresis seen in diabetes. Regardless of the etiology, it is likely that the weight loss observed may be minimized by optimizing the rate of drug release from the polymer.

The optimal brain level of dexamethasone needed for maximum control of peritumoral brain edema is unknown. Recent results from our laboratory suggest that dexamethasone-EVAc polymers implanted intracranially are as effective in reducing peritumoral edema in the rat 9L gliosarcoma tumor model as is the delivery of large systemic doses [9,30]. Concentrations of dexamethasone in brain measured by HPLC showed a local concentration almost 20 times higher with intracranial dexamethasone-EVAc polymers than from bolus intraperitoneal administration [30]. As in the present study, very low to undetectable drug levels were measured in the contralateral hemisphere of animals with intracranial dexamethasone-EVAc implants and tumors. Sparing of this region is desirable since vasogenic edema (in the case of brain tumors and cold lesions) has not been demonstrated to cross the corpus callosum either in clinical conditions or in animal experimental models [31–33], except when invaded by tumor.

Polymeric intracranial drug delivery has many advantages over conventional forms of drug administration [4,10,11]. Pharmacologically active drug molecules can be continuously released to localized areas of the brain for long periods of time [5,6,28]. Localized delivery may provide therapeutic levels at the desired target site while minimizing systemic drug levels and consequent side effects. The polymeric devices used in this study are easily fabricated, non-inflammatory [24], economical, and have been shown to release drugs for many months [27,34,35].

We hope that by delivering high levels of steroid directly into the brain for prolonged periods of time we will gain a better understanding of the effect of dexamethasone on the brain and further improve the clinical utility of this drug by reducing the systemic exposure.

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References

1 R.E. Maxwell, D.M. Long and L.A. French, The clinical effects of a synthetic gluco-corticoid used for brain edema in the practice of neurosurgery, in: H.J. Reulen and K. Schürmann (Eds.), Steroids and Brain Edema, Springer-Verlag, Berlin, 1972, pp. 219–232.

2 J.C. Melby, Systemic corticosteroid therapy: pharmacology and endocrinology considerations, Ann. Intern. Med., 81 (1974) 505–512.

3 H. Brem, Polymers to treat brain tumors, Biomaterials, 11 (1990) 699–701.

4 H. Brem, Delivery of drugs to the brain by use of a sustained release polyanhydride polymer system, in: G. Gregoriadis (Ed.), Targeting of Drugs: Optimization Strategies, Plenum Publishing Co., London, 1990, pp. 155–163.

5 M.J. During, A. Freese, B.A. Sabel, W.M. Saltzman, A. Deutch, R.H. Roth and R. Langer, Controlled release of dopamine from a polymeric brain implant: *in vivo* characterization, Ann. Neurol., 25 (1989) 351–356.

6 A. Freese, B.A. Sabel, W.M. Saltzman, M.J. During and R. Langer, Controlled release of dopamine from a polymeric brain implant: *in vitro* characterization, Exp. Neurol., 103 (1989) 234–238.

7 S.A. Grossman, C.S. Reinhard, H. Brem, R. Brundrette, M. Chasin, R. Tamargo and O.M. Colvin, The intracerebral delivery of BCNU with surgically implanted bioerodible polymers: a quantitative autoradiographic study, Proc. Am. Soc. Clin. Oncol., 7 (1988) 84.

8 E. Powell, M.R. Sobarzo and W.M. Saltzman, Controlled release of nerve growth factor from a polymeric implant, Brain Res., 515 (1990) 309–311.

9 A.K. Sills, R.J. Tamargo and H. Brem, Reduction in peritumoral brain edema by an intracranial polymer implant, Surg. Forum, 41 (1990) 516–518.

10 R.J. Tamargo, J.J. Epstein, C.S. Reinhard, M. Chasin and H. Brem, Brain biocompatibility of a biodegradable controlled release polymer in rats, J. Biomed. Mat. Res., 23 (1989) 253–266.

11 M.B. Yang, R.J. Tamargo and H. Brem, Controlled delivery of 1,3-bis(2-chloroethyl)-1-nitrosourea from ethylene-vinyl acetate copolymer, Cancer Res., 49 (1989) 5103–5107.

12 B.E. Cham, B. Sadowsky, J.M. O'Hagan, C.N. de Wytt, F. Bochner and M.J. Eadie, High performance liquid chromatographic assay of dexamethasone in plasma and tissue, Ther. Drug. Monit., 2 (1980) 373–377.

13 F.J. Frey, B.M. Frey and L. Benet, Liquid chromatographic measurement of endogenous and exogenous glucocorticoids in plasma, Clin. Chem., 25 (1979) 1944–1947.
14 D. Lamiable, R. Vistelle, M. Nguyen-Khac and H. Millart, High-performance liquid chromatographic determination of dexamethasone in cerebrospinal fluid and plasma in the rabbit, J. Chromatogr., 434 (1988) 315–319.
15 D. Lamiable, R. Vistelle and H. Millart, High-performance liquid chromatographic determination of dexamethasone in human plasma, J. Chromatogr., 378 (1986) 486–491.
16 S. Lasic', N. Bobarevic' and B. Nikolin, Simultaneous determination of prednisone, prednisolone, cortisol and dexamethasone in plasma by high-performance liquid chromatography, J. Pharm. Biomed. Anal., 7 (1989) 777–782.
17 E.S. Lo, G. Huttinot, M. Fein and T.B. Cooper, Direct radioimmunoassay procedure for plasma dexamethasone with sensitivity at the picogram level, J. Pharm. Sci., 78 (1989) 1040–1044.
18 S. Mingawa, Y. Kasuya and S. Baba, Determination of dexamethasone in human plasma and urine by electron-impact mass spectrometry, J. Chromatogr., 343 (1985) 231–237.
19 P. Plezia and P. Berens, Liquid-chromatographic assay of dexamethasone in plasma, Clin. Chem., 31 (1985) 1870–1872.
20 J.Q. Rose and W.J. Jusko, Corticosteroid analysis in biological fluids by high-performance liquid chromatography, J. Chromatogr., 162 (1979) 273–280.
21 M.D. Smith, Determination of synthetic adrenocorticosteroids in pharmaceutical preparations and biological fluids by HPLC, in: M.P. Kautsky (Ed.), Steroid Analysis by HPLC, Marcel Dekker, Inc., New York, 1981, pp. 105–144.
22 S.E. Tsuei, R.G. Moore, J.J. Ashley and W.G. McBride, Disposition of synthetic glucocorticoids. I. Pharmacokinetics of dexamethasone in healthy adults, J. Pharmacokinet. Biopharm., 7 (1979) 249–264.
23 S.E. Tsuei and J.J. Ashley, Quantitation of dexamethasone in biological fluids using high-performance liquid chromatography, J. Chromatogr., 145 (1978) 213–220.
24 R. Langer, H. Brem and D. Tapper, Biocompatibility of polymeric delivery systems for macromolecules, J. Biomed. Mat. Res., 15 (1981) 267–277.
25 W.D. Rhine, D.S.T. Hsieh and R. Langer, Polymer for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics, J. Pharm. Sci., 69 (1980) 265–270.
26 D.R. Paul and S.K. McSpadden, Diffusional release of a solute from a polymer matrix, J. Membr. Sci., 1 (1976) 33–48.
27 W.M. Saltzman and R. Langer, Transport rates of proteins in porous materials with known microgeometry, Biophys. J., 55 (1989) 163–171.
28 W.M. Saltzman and M.L. Radomsky, Drugs released from polymers: diffusion and elimination in brain tissue, Chem. Eng. Sci. (1991), in press.
29 M.J. Eadie, T.R.O'R. Brophy, G. Ohlrich and J.H. Tyrer, Dexamethasone: pharmacokinetics in neurological patients, Clin. Exp. Neurol., 20 (1984) 107–118.
30 R.J. Tamargo, A.K. Sills, C.S. Reinhard, M.L. Pinn, D.M. Long and H. Brem, Interstitial dexamethasone delivery in the brain for the reduction of peritumoral edema, J. Neurosurg., (1991) Vol. 74(6).
31 A.R. Cowley, Influence of fiber tracts on the CT appearance of cerebral edema: Anatomic-pathologic correlations, AJNR, 4 (1983) 915–925.
32 A. Monajati and L. Heggeness, Patterns of edema in tumors vs. infarcts; visualization of white matter pathways, AJNR, 3 (1982) 251–255.
33 K.G. Rieth, K. Fujiwara, G. DiChiro, I. Klatzo, R.A. Brooks, G.S. Johnston, C.M. O'Connor and L.G. Mitchell, Serial measurements of CT attenuation and specific gravity in experimental cerebral edema, Radiology, 135 (1980) 343–348.
34 R. Langer, New methods of drug delivery, Science, (1990) 1527–1533.
35 R. Langer and N.A. Peppas, Present and future applications of biomaterials in controlled drug delivery systems, Biomaterials, 2 (1981) 201–214.