Abstract. Malignant gliomas tend to recur in the vast majority of cases. Recurrent gliomas may arise from vital tumor cells present in this zone around the resection margin. It appears promising to combine tumor resection with local chemotherapy using an antineoplastic, but non-toxic agent. Taurolidine exerts a selective antineoplastic effect by induction of programmed cell death and has anti-angiogenic activity. Fibrin sealant is completely degradable and firmly adheres to brain tissue, suggesting that it would provide a suitable matrix for taurolidine delivery – a Taurolidine-Fibrin-Sealant-Matrix (TFM) – in the local treatment of brain tumors. The potential of local delivery of taurolidine out of a fibrin sealant matrix was investigated. Taurolidine could be suspended homogeneously in both the thrombin and the procoagulant protein components of the fibrin sealant. The fibrin sealant matrix was a suitable carrier for the suspension of taurolidine at a concentration that ensured the release of therapeutically effective amounts of the drug over a period of 2 weeks in vitro. The antineoplastic action of taurolidine was not affected by embedding in the fibrin sealant matrix. The described drug delivery system may be suitable for local taurolidine treatment of brain tumors following complete or partial resection or of tumors that are non-resectable because of their location.

Malignant gliomas invade surrounding tissue and, therefore, tend to recur in the vast majority of cases even after apparently complete gross resection. Gliomas recur within 2 cm of the original resection margin in 80-90% of cases (1, 2). This suggests that recurrent gliomas arise from vital tumor cells present in this zone around the resection margin, as observed by some authors (1, 2). These results are corroborated by prospective studies showing that the extent of tumor resection correlates with postoperative survival (3, 4). Furthermore, metastases from malignant gliomas are very rare and primarily extracerebral in location (5, 6).

Based on these observations, it appears promising to combine total or partial tumor resection with local chemotherapy using an agent with a selective antineoplastic activity without damaging normal brain tissue. This led us to develop a method for delivering the drug into the brain to enable close contact to the tumor or the walls of the resection cavity. The method should allow the delivery of the drug in therapeutically effective concentrations with minimal toxic effects on healthy brain tissue. Moreover, the method of delivery should be devoid of the risk of infection and leave no residues that may cause local complications.

Taurolidine is used as an adjuvant in treating bacterial infections (7). Recently, the antineoplastic activity of taurolidine on different brain tumor cell lines has been reported (8-12). The antitumor activity of taurolidine is attributed to the induction of programmed cell death and it also has anti-angiogenic activity (8, 9, 11-13). Initial experience with the intravenous administration of taurolidine in patients with glioblastoma was promising (10). Fibrin sealant is often used for intracerebral haemostasis in neurosurgery. It is easy to handle, completely degradable and firmly adheres to brain tissue, suggesting that fibrin sealant could provide a suitable matrix for taurolidine delivery – a Taurolidine-Fibrin-Sealant-Matrix (TFM) – in the local treatment of brain tumors. Therefore the potential of a local delivery system for taurolidine using TFM was investigated.

Materials and Methods

The fibrin sealant matrix was prepared using the Tisseel kit (Immuno AG, Vienna, Austria, kindly provided by Baxter Deutschland GmbH, Heidelberg, Germany) according to the
from a glioblastoma were seeded in 150-cm$^3$ plastic cell culture vessels. DMEM medium and cell lines were kindly provided by Prof. Karl Frei, Dept. of Neurosurgery, University of Zurich, Switzerland. DMEM medium was purchased from Gibco, Basel, Switzerland.

Taurolidine suspension in the matrix. Taurolidine was added to the two components of fibrin sealant – thrombin and procoagulant protein. The suspension was prepared at 25°C using the following concentrations of taurolidine (mg/ml): 10, 25, 50, 100, 150, 200 and 250. We examined the maximum concentration of taurolidine which forms a homogeneous suspension in the fibrin sealant.

Coagulation time of TFM. Taurolidine was suspended in thrombin and procoagulant protein at 25°C at the following concentrations (mg/ml): 20, 40 and 80. The two components were mixed and filled into 2-ml vials. The coagulation time was measured three times for each concentration and compared to that of a sample of fibrin sealant without taurolidine.

Kinetics of diffusion-controlled taurolidine release from the matrix. The kinetics of taurolidine release was investigated using a "limited-sink" model with an acceptor medium volume of 400 µl, which is the same as that of the drug-carrying matrix. The taurolidine concentration in the acceptor medium was zero.

Different concentrations of taurolidine were homogeneously suspended in the two components of the fibrin sealant. The two components were then mixed in wells of a 24-multiwell plate to prepare matrices with identical total volumes of 400 µl per well, containing final taurolidine concentrations (mg/ml) of 10, 20, 40 and 80. The resulting thickness of the matrix was 2 mm ± 0.4 mm. In addition, matrices with volumes of 400 µl and 800 µl containing 10 mg/ml or 40 mg/ml of taurolidine were prepared to investigate the effect of matrix size on taurolidine release. The 800-µl matrix had a thickness of 4 mm ± 0.3 mm. Matrices of identical volume and thickness without taurolidine served as controls. Supernatants of 400 µl phosphate-buffered saline (PBS) were added to each well after solidification. The multiwell plates were incubated at 37°C. The supernatants were pipetted off at 24-hour intervals over a period of 7 days and replaced by identical amounts of fresh PBS.

The long-term release kinetics of taurolidine were investigated by homogeneously suspending different concentrations of taurolidine in the two components of the fibrin sealant in such a way that the final concentrations (mg/ml) of 10, 40 and 80 were achieved per 400 µl of matrix per well. The resulting matrix thickness was 2 mm ± 0.4 mm. The multiwell plates were incubated at 37°C, the supernatants pipetted off and replaced by 400 µl of fresh PBS at 24-hour intervals over a period of 14 days. The supernatants from the wells containing identical taurolidine concentrations were pooled. The taurolidine concentrations in the supernatants were determined by means of a colorimetric reaction (7).

Effect of released taurolidine on tumor cell proliferation. To determine whether the antineoplastic activity of taurolidine is affected by embedding in the matrix, the glial tumor cell lines LN18, LN229 and U87MG and ex vivo cells from a freshly isolated glioblastoma were incubated with taurolidine released from the matrices at different periods.

The LN18, LN229 and U87MG tumor cells and ex vivo cells from a glioblastoma were seeded in 150-cm$^3$ plastic cell culture flasks until a cell confluency of 80% was reached. Following detachment of the cells by trypsinization, cell counts were performed. The resulting cell suspensions were centrifuged at 1200 rpm for 5 min and then diluted to yield cell suspensions containing 5 x 10$^6$ cells per ml. Aliquots of 200 µl of the cell suspensions were pipetted into the wells of a 96-multiwell plate.

After 12 hours, when the cells were adherent, the medium was removed and replaced by fresh medium. The cells were incubated for 24 hours with the taurolidine solution released at different time intervals from the matrices loaded with different taurolidine concentrations. Tumor cells incubated with the same volume of supernatant from fibrin sealant matrix without taurolidine were used as negative controls. Identically treated cells to which Fas-ligand at a concentration of 25% was added served as positive controls.

After incubation for 24 hours, the supernatants were removed and 100 µl of crystal violet staining solution (0.5% crystal violet in 19.5% methanol and 80% distilled water) added. The solution was removed after 10 minutes and residual dye rinsed off with tap water. The plates were then left to air-dry for 12 hours followed by counting in a microplate counter at 540 nm.

Modeling of diffusion-controlled taurolidine release kinetics. The theoretical assumptions underlying the diffusion-controlled release of taurolidine from the fibrin sealant matrix were reviewed. Using a model of local taurolidine metabolism, the factors affecting the diffusion-controlled release of taurolidine from the matrix were investigated.

Application of the TFM. The two components of the fibrin sealant containing the suspended taurolidine were sprayed through a single nozzle at 1.5 bar by means of filter-sterilized compressed air. The highest possible concentration of taurolidine in the matrix was investigated. Whether a uniform distribution of the TFM can be achieved was determined.

Results

Taurolidine suspension in the matrix. Taurolidine can be suspended homogeneously in both the thrombin and the procoagulant protein components of the fibrin sealant at

Figure 1. Cumulative release of taurolidine over a 7-day period from a 400-µl matrix containing different taurolidine loading concentrations (mg/ml).
concentrations of up to 80 mg/ml. Higher concentrations resulted in faster deposition or inhomogeneous suspension. At taurolidine concentrations of 10 mg/ml and above, taurolidine crystals started to settle down in both components of the fibrin sealant after 25 ± 12 seconds. It is therefore necessary to agitate the components shortly before administration in order to ensure homogeneity of the suspension.

Coagulation time of TFM. The coagulation time of the fibrin sealant without taurolidine addition was 5.2 ± 0.5 seconds. Adding taurolidine at concentrations (mg/ml) of 20, 40 and 80 prolonged the solidification time to 16.6 ± 1.2 seconds, 24.3 ± 1.8 seconds, and 35.5 ± 2.4 seconds, respectively.

Kinetics of diffusion-controlled release of taurolidine from the TFM. The investigation of taurolidine release from the fibrin sealant matrix over a period of 1 week showed an exponential increase of the cumulative amount of taurolidine released (Figure 1).

The cumulative amounts of taurolidine released into the supernatant at different concentrations of taurolidine loading differed statistically significantly [analysis of variance (ANOVA), Kruskal-Wallis-test; \( p < 0.001 \)]. The exponential course of cumulative taurolidine release from the matrix means that the largest amounts of taurolidine are released within the first days (Figure 1).

The temporal course of percentage taurolidine release was determined in relation to the initial taurolidine load of the matrix. The results suggested that, irrespective of the initial taurolidine concentration, about 50% of the total taurolidine was released from the matrix within the first 2 days (54.7 ± 1.44%) and about 75% within 6 days (75.2 ± 6.64%). The percentage release rates did not differ significantly for the different taurolidine loading concentrations in the TFM (ANOVA, Kruskal-Wallis-test; \( p = 0.522 \)).

Effect of TFM volume on the taurolidine release. Cumulative taurolidine release differed significantly for constant concentrations of taurolidine but different matrix volumes (ANOVA and Holm-Sidak-test; \( p < 0.001 \)), while no statistically significant differences in cumulative taurolidine release were seen for identical initial amounts of taurolidine in different matrix volumes (analysis of variance and Holm-Sidak-test; \( p = 0.934 \) (initial amount of 8 mg) and \( p = 0.159 \) (initial amount of 32 mg) (Figure 2).

The loaded amount of taurolidine in the matrix seems to be the crucial determinant of release. Apparently, the thickness of the matrix does not have an important role in controlling taurolidine release. This observation is crucial for the practical application of the fibrin sealant matrix since it is not possible to ensure an uniform matrix thickness in all cases.
Long-term release of taurolidine. A long life-span of the TFM is desirable to ensure local therapy over an adequate period of time. The life-span of a fibrin matrix is limited by the onset of fibrinolysis. The data available so far suggest that the in vivo life-span can at most be extended to 12-14 days when an antifibrinolytic such as aprotinin is added (14). Moreover, the rate at which the fibrin sealant matrix is degraded varies with the proteolytic activity at the site of application.

We therefore investigated whether taurolidine is released throughout the maximum life-span of the matrix of 14 days. In the experimental model used here, antineoplastically effective amounts of taurolidine were released throughout the 14-day observation period at the loading concentrations of taurolidine to 25 mg/ml, or above. Loading concentrations of 50 mg/ml or higher resulted in the release of over 100 ìg/ml of taurolidine on day 14 (Figure 3). This taurolidine level is above the EC_{50} of acute cytotoxicity for most of the cell lines tested with taurolidine before (9, 13).

The temporal course of taurolidine release was investigated for different loading amounts of taurolidine in the matrix over a period of 14 days. Irrespective of loading concentrations, 98.93% ± 0.33 of the taurolidine had been released from the matrix after 10 days and almost 100% (99.99% ± 0.02) after 14 days (Figure 4). The percent release did not change for the different loading concentrations of taurolidine (ANOVA, Kruskal-Wallis test; p=0.830).

Effect of released taurolidine on tumor cell proliferation. The proliferation of all the tumor cell lines investigated and of the ex vivo glioblastoma cells was inhibited in a concentration-dependent manner (Figure 5, Table I). Taurolidine released on day 13 from TFM with an initial taurolidine loading concentration of 10 mg/ml (c_{10}) had no further effects on tumor cell proliferation. This is in accordance with the concentration of taurolidine released from the matrix at this time (Table I). In contrast, taurolidine released on day 13 with a loading concentration of 100 mg/ml was found to reduce cell counts by at least 60%.

Modeling of diffusion-controlled taurolidine release kinetics. The taurolidine-loaded fibrin sealant matrix is applied intraoperatively after removal of the tumor in a way such as to ensure close binding to the wall of the cavity and filling out of all the surface irregularities. Taurolidine then diffuses from the matrix compartment into the brain compartment along the diffusion gradient, which is the main force...
underlying taurolidine release (turnover constant $k_1$). At the same time, the process of elimination of taurolidine from the brain area adjacent to the matrix starts; by metabolism ($k_2$), on one hand, and by diffusion into deeper brain areas ($k_3$), on the other hand (Figure 7).

In addition to these processes, taurolidine may enter and get distributed in the cerebrospinal fluid (CSF) space ($k_{4a}$, $k_{4b}$, $k_5$). This distribution is driven by diffusion through the matrix surface facing the resection cavity and enhanced by CSF convection, particularly when the resection cavity remains ‘open’. To counteract these undesired losses, the authors suggest application of a multilayer matrix with the top layer consisting of fibrin sealant without taurolidine (Figures 6, 7). This extra layer reduces the loss of drug due to diffusion and convection of CSF. Losses of drug by this route are taken into consideration by using a safety factor in calculating taurolidine delivery.

Since most of the taurolidine compound is suspended in the matrix, the kinetics of taurolidine release is most adequately depicted by the Higuchi model (15). The TFM undergoes fairly little dissolution or erosion and therefore releases the suspended drug it carries primarily by diffusion. The release is dominated by the diffusion velocity of the drug from the matrix into surrounding tissue (15). The release rates under these conditions are in linear relationship to the square root of time. The amount of drug released from the matrix can be calculated by the equation given below if the assumptions described by Higuchi (15) hold:

$$M = A \cdot \sqrt{D \cdot c_0 \cdot \left(\frac{2 \cdot M_0}{V} - c_s\right) \cdot t}$$

with $M$=cumulative amount of drug released [mg]; $A$=diffusion area [cm$^2$]; $D$=diffusion coefficient [cm$^2$/s]; $c_0$=initial drug concentration in the matrix [mg/ml]; $c_s$=saturation concentration of the drug in the matrix [mg/ml]; $t$=time [s]; $V$=volume of the matrix [cm$^3$]; and $M_0$=amount of drug in the matrix at time $t=0$ [mg]. Assuming that $c_0 >> c_s$, the following equation holds:

$$c_0 = \frac{M}{V} - c_s, \quad \text{and} \quad M = A \cdot \sqrt{2 \cdot c_0 \cdot c_s \cdot D \cdot t}.$$  

The amount of taurolidine released from the matrix is directly proportional to the diffusion area $A$. Therefore, a proportionality factor for the different initial concentrations of taurolidine in the matrix is determined, which then can be used to calculate taurolidine release as a function of time and diffusion area.

Using the Higuchi model (15), the equation for slope $k_d$ is used to determine the diffusion coefficient:

$$k_d = 2 \cdot A \cdot c_0 \cdot \sqrt{\frac{D}{\pi}},$$

solving for $D$ yields: $D = \frac{kd^2}{4 \cdot A \cdot c_0 \cdot \pi}$.

The following diffusion coefficients were calculated according to the Higuchi model (15) using the experimental results. These are dependent on the loading concentration of taurolidine in the matrix: $D_{20}=2.897 \cdot 10^{-8}$ mg/$\sqrt{\text{sec}}$ for $c_0=20$ mg/ml; $D_{40}=4.917 \cdot 10^{-8}$ mg/$\sqrt{\text{sec}}$ for $c_0=40$ mg/ml; and $D_{80}=9.011 \cdot 10^{-8}$ mg/$\sqrt{\text{sec}}$ for $c_0=80$ mg/ml.

The effective diffusion area $A_{\text{eff}}$ is calculated from the in vitro data using the Higuchi equation: (16, 17):

$$A_{\text{eff}} = \frac{M}{\sqrt{2 \cdot c_0 \cdot c_s \cdot D \cdot t}},$$

with $A_{\text{eff}}$=effective diffusion area [cm$^2$]; $M$=cumulative amount of taurolidine released [mg]; $D$=diffusion coefficient [cm$^2$/sec]; $c_0$=initial taurolidine concentration in the TFM [mg/ml]; $c_s$=saturation concentration of taurolidine in the TFM [mg/ml]; $t$=time [sec].

Comparison with the experimental diffusion area of 1.9 cm$^2$ yields a correction factor which is determined to compensate for differences between the saturation concentration of taurolidine in water (10 mg/ml at 25°C), which is used in the calculation, and that in the matrix,
which cannot be determined directly, and to compensate for other approximations of the Higuchi (15) model. The following effective diffusion areas were calculated on the basis of the in vitro data: 2.96 cm² for an initial concentration of \( c_0 = 80 \text{ mg/cm}^3 \), \( A = 2.59 \text{ cm}^2 \) for \( c_0 = 40 \text{ mg/cm}^3 \); and \( A = 2.11 \text{ cm}^2 \) for \( c_0 = 20 \text{ mg/cm}^3 \).

The correction factor \( k_c \) adapts the calculated effective diffusion area according to the experimental data and is calculated as:

\[
k_c = \frac{A_{\text{eff}}}{A}
\]

For the experimental diffusion area of \( A = 1.9 \text{ cm}^2 \) and \( c_0 = 80 \text{ mg/cm}^3 \), the calculated effective diffusion area is \( A_{\text{eff}} = 2.955 \text{ cm}^2 \), yielding a \( k_c = 1.556 \). For \( c_0 = 40 \text{ mg/cm}^3 \) and \( c_0 = 20 \text{ mg/cm}^3 \), the \( k_c = 1.364 \) and \( k_c = 1.109 \), respectively.

The cumulative amount of taurolidine released from the matrix for a given diffusion area, initial taurolidine loading concentration, the taurolidine saturation concentration in the matrix, and the diffusion coefficient is calculated as:

\[
M = A_B \cdot f \cdot k_c \cdot \sqrt{2 \cdot D \cdot c_s \cdot c_0 \cdot t},
\]

where \( M \) = cumulative amount of taurolidine released [mg]; \( A_B \) = diffusion area in the brain [cm²]; \( k_c \) = correction factor; \( D \) = diffusion coefficient [mg/sec]; \( c_0 \) = initial taurolidine concentration in the TFM [mg/ml]; \( c_s \) = saturation concentration of taurolidine in the TFM [mg/ml]; \( t \) = time [sec].

The term \( f = \sqrt{2 \cdot D \cdot c_s \cdot c_0 \cdot t} \) is constant for a given time and \( c_0 \). The multiplication of \( f \) with the correction factor \( k_c \) leads to the proportionality factor \( F \), which is constant for a given release time and \( c_0 \). The factor \( F \) permits calculation of the cumulative amount released according to: \( M = F \cdot A_B \), where \( M \) = cumulative amount of taurolidine released [mg]; \( F \) = proportionality factor for a given \( c_0 \) and \( t \); \( A_B \) = diffusion area in the brain [cm²]. For a release time of 14 days, the factors are: \( c_0 = 20 \text{ mg/ml} \); \( F_{20} = 4.16 \); \( c_0 = 40 \text{ mg/ml} \); \( F_{40} = 9.42 \); \( c_0 = 80 \text{ mg/ml} \); \( F_{80} = 20.54 \).

**Simulation of in vitro release kinetics by model calculation.** Model prediction of the in vitro conditions by calculating the requisite parameters using the equation \( M = F \cdot A \) showed very good correlation with the actual experimental release kinetics of taurolidine. The experimental results and the calculated data showed no statistically significant differences for any of the initial taurolidine concentrations investigated (\( t \)-test; \( c_0 = 20 \text{ mg/ml} \): \( p = 0.628 \); \( c_0 = 40 \text{ mg/ml} \): \( p = 0.481 \); \( c_0 = 80 \text{ mg/ml} \): \( p = 0.628 \) (Figure 8).

**Intraoperative application.** The present data show that TFM releases of taurolidine are sufficient in concentration to exert antitumor activity over 14 days if the matrix is loaded with an adequate concentration. The results of the in vitro experiments suggest that an initial taurolidine concentration of 80 mg/ml is appropriate. Intraoperative application of the drug delivery system involves the following steps:

1. **Determination of the volume of the tumor resection cavity**, \( V_R \). The volume of the tumor resection cavity, \( V_R \), is determined by filling the cavity with physiologic saline solution after removal of the tumor.

2. **Calculation of the surface of the resection cavity by approximation.** The shape of the resection cavity is idealized as a sphere to calculate diffusion area \( A \) as the surface of a sphere according to the equation: \( A = 4 \cdot \pi \cdot \left( \frac{3 \cdot V_R}{4 \cdot \pi} \right)^{\frac{2}{3}} \).

3. **Calculation of the cumulative amount of taurolidine released.** Based on the preceding calculations, the cumulative amount of taurolidine released over a period of 14 days can be calculated as it is directly proportional to diffusion area \( A \): \( M = 20.54 \cdot A \) for \( c_0 = 80 \text{ mg/ml} \).

4. **Calculation of the required matrix volume.** The required matrix volume is calculated from the amount of taurolidine released and the initial taurolidine concentration, \( c_0 \), according to the equation: \( V_{\text{TFM}} = \frac{M}{c_0 \cdot (1+k_c)} \).
where $V_{TFM}$ = required TFM volume [ml]; $M$ = cumulative amount of taurolidine released [mg]; $k_s$ = safety factor; $c_0$ = initial taurolidine concentration in the TFM [mg/ml]. The safety factor is introduced to compensate for diffusion losses into the fibrin sealant cover layer and subsequent losses by convention. The safety factor chosen here is 1.

**Spray application of TFM.** The TFM was applied to the resection cavity by spraying. Application by spraying ensures even distribution of the matrix on the walls of the resection cavity. Suspension of taurolidine in the two components of the fibrin sealant and spraying of the drug delivery system posed no problems for initial taurolidine loading concentrations of up to 80 mg/ml. It was possible to apply TFM very homogenously and even in multiple layers due to the short coagulation time.

**Discussion**

In systemic chemotherapy, the antineoplastic agent is unspecifically distributed throughout the body via circulation. Proliferating cells in healthy organs are thus exposed to the same concentrations of the agent as tumor cells. Moreover, intratumoral distribution of the agent may be prevented by different hemodynamic factors in the tumor (18). The antineoplastic action of most chemotherapeutic agents depends on the difference in proliferation rates between normal cells and tumor cells. When these rates are the same, dose-limiting adverse events may occur. It is generally assumed that the effectiveness of chemotherapy increases with the concentration of the agent within the tumor and the duration of exposure. On the other hand, systemic administration is limited by the severity of adverse events.

An approach to overcome this problem is to administer chemotherapeutic agents locally, relying on diffusion for their distribution. In local therapy, the antineoplastic agent is introduced into the tumor itself or the area around the tumor. The resulting pressure gradient leads to diffusion of the antineoplastic agent into the tumor. This mode of administration not only increases the concentration of the agent within the tumor but also results in much lower concentrations in other tissues compared to systemic administration.

Various materials such as collagen or biodegradable polymers or silicones are used in local drug delivery systems. The materials serve as matrices by means of which embedded local cytostatic agents such as BCNU (19), mitoxantrone (20), or cisplatin (21) are introduced into the tumor resection cavity. Moreover, silicones have been used for local delivery of antineoplastic agents (22). Potential problems with this mode of drug administration may arise when the carrier matrix contains components that undergo complete degradation after a very long time only or not at all. Another risk is the uncontrolled distribution of the antitumor agent in the CSF which, moreover, makes it difficult to accurately determine the concentration at the target. The postoperative changes in the shape and size of the tumor resection cavity associated with edema formation may preclude complete filling of the cavity with the drug-carrying wafers. The resulting inhomogeneous distribution of the agent can lead to pronounced local increases in drug concentration that may have toxic effects on adjacent healthy tissue.

Another approach of local tumor treatment is so-called convection-enhanced drug delivery (CEED) in which the drug is infused into the tumor or the surrounding brain. The drug is distributed by convective transport (23). However, this mode of administration requires placement of a catheter in most cases, which increases the risk of infection and the incidence of postoperative CSF fistula formation. Furthermore, it is better suited in cases of non-resected tumors. It can hardly be applied following tumor resection.

These limitations of local drug administration can be overcome by the method of taurolidine administration in a fibrin sealant matrix as presented here. This matrix is sprayed over the walls of the resection cavity after total or partial tumor resection. During coagulation, fibrinogen is converted into fibrin and forms covalent bonds with surrounding proteins, resulting in a layer of hemostatically active sealant that is subsequently degraded by proteolytic activity. This matrix has hemostatic effects necessary after surgery. On the other hand, covalent bonding to surrounding proteins ensures that the matrix stays exactly where it has been applied. This is crucial since the displacement of brain structures after tumor resection and postoperative edema formation change the size and the shape of the resection cavity.

The experimental results demonstrate that taurolidine is released from the TFM under infinite-sink conditions over 2 weeks in concentrations that have definitive antineoplastic effects on the tumor cell lines and *ex vivo* tumor cells.
investigated here. A study investigating the release of antibiotics from a fibrin matrix suggests that the limited-sink model is most suitable to describe the in vivo conditions (24). The experiments using different tumor cell lines and ex vivo glioblastoma cells show that the antitumor activity of taurolidine is not affected by its embedding in the fibrin sealant matrix. Taurolidine is known to have no cytotoxic effects on normal cells (25). Earlier cell culture experiments using neuronal and glial brain cells obtained from rat fetuses on day 15 of gestation showed that taurolidine has no cytotoxic effects on these cells (9). A taurolidine concentration of 80 mg per ml of fibrin sealant can be homogeneously suspended in the matrix.

Conclusion

A fibrin sealant matrix is a suitable carrier for the suspension of taurolidine at a concentration that ensures the release of therapeutically effective amounts of the drug over a period of 2 weeks in vitro. The antineoplastic action of taurolidine is not affected by embedding in and release from fibrin sealant matrix. Higuchi’s model (15) of drug release from matrices provides a suitable approximation for describing the diffusion-controlled release of taurolidine from the fibrin sealant matrix.

The described drug delivery system may be suitable for local taurolidine treatment of brain tumors following complete or partial resection or of tumors that are non-resectable because of their location.

References


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