New Routes for Delivery of Anti-Epileptic Medications

Robert S. Fisher and David K. Chen

Abstract- Use of novel drug delivery methods might enhance efficacy and reduce toxicity, in comparison with currently existing oral anti-epileptic drugs (AEDs). Novel methods aim to deliver optimal drug concentration more specifically to the seizure focus or foci. In this review, we first consider unconventional routes of drug delivery to the peripheral system, then potential new methods of targeted CNS drug delivery. Intrathecal or intraventricular AEDs might circumvent systemic toxicity. Drug-eluting wafers could be surgically positioned over an epileptogenic region of brain. Drug can be delivered to a seizure focus by an implanted catheter and subcutaneous pump. Inactive prodrugs, given systemically, can be made active only at the seizure focus, by interaction with locally-released substances. Liposomes and polysomes are engineered slow-release storage vehicles for drugs. Targeting components can hold liposomes near a region of interest, provided that they can penetrate the blood brain barrier. Lastly, we discuss future prospects for the use of transplanted cells and genes as potential vehicles for local delivery of renewable anti-epileptic regimen.

Key Words: Anti-epileptic drugs, Seizure treatment, Drug delivery, Targeted, Routes, Methods

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INTRODUCTION

Many options currently exist for oral medication to treat epilepsy, but none are ideal. Adequate control with acceptable side effects is achieved only in approximately two out of three patients[1]. When patients present with acute seizures, oral medication is not an option, and establishment of intravenous access may entail delays. Therefore, to potentially obtain a better therapeutic-to-toxic ratio, interest has been expressed in alternative routes to treat seizures. Table 1 lists other potential routes.

This paper provides an update of material originally presented in Fisher and Ho[2].

UNCONVENTIONAL ROUTES TO THE PERIPHERAL SYSTEM

Among the delivery routes listed in Table 1, only the rectal route of administration is approved currently in the United States[3]. In some circumstances, administration to the nasal mucosa can be more practical and con-

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Table 1. *Non-oral routes of antiepileptic drug delivery*

Rectal
Skin
Nasal / Buccal
Inhaled
Direct delivery to CNS

Table 2. *Possible methods for direct delivery of AEDs to brain*

CSF delivery
Drug wafers
Local perfusion
Seizure-activated drugs
Liposome-microsomes
Cell transplants
Gene therapy

venient than is delivery to rectal mucosa[4]. Additionally, nasal spray to deliver drug does not run the risk of aspiration pneumonia or bite injuries presented by oral/sublingual/ buccal administration of a drug during a seizure. Several studies have explored intranasal administration of the water-soluble benzodiazepine, midazolam[5]. Although effects of intranasal midazolam are slower than those of intravenous diazepam in terms of time to peak effects, this delivery route may in actuality stop seizures faster from time of arrival at a hospital, since no time is required for establishment of an intravenous line.

Skin presents the most accessible organ for administration of medications, provided that they are designed to penetrate the epidermis and into the blood-rich dermal layer. Many medications, such as hormones, scopolomine for nausea, nitroglycerin and others are delivered dermally. One study has looked at the efficacy of dermally delivered lidocaine for seizures[6]. In 19 patients suffering seizures in association with gastroenteritis, application of lidocaine tape to the skin caused rapid remission of recurrent seizures in 13 seizure episodes. In this study, serum lidocaine levels were low, generally in a range from being undetectable to 0.5 micrograms per milliliter (therapeutic range is approximately from 1.6 to 6 micrograms per milliliter).

The inhalation route exposes alveoi to the drug, and has been an accepted delivery route for bronchodilators, corticosteroids and antibiotics[7]. Recently, clinical trials have demonstrated feasibility of delivering insulin[8] and heparin[9] by inhaled routes. It is possible that antiepileptic medications may be delivered by the pulmonary route, but technical problems with delivering the bolus of drug at inhalation will first require some thought, since respirations can be shallow and irregular during a seizure.

DRUG DELIVERY METHODS TO THE CNS

The 16th century philosopher, Paracelsus, pointed out that it is only the drug dose that differentiates a poison from a therapeutic drug. With the possible exception of anticancer chemotherapy agents, this concept is nowhere as true as it is with antiepileptic medication. Direct delivery of AEDs to the central nervous system theoretically provides for the possibility of a therapeutic-toxic ratio greater than that found with systemic drug delivery. Inadvertent adverse reactions, such as kidney stones, liver toxicity, skin rash, or blood dyscrasias would not occur with direct delivery to the CNS. Side effects resulting from toxicity within the CNS might still remain, but also could be limited by regional brain distribution. Table 2 shows possible methodologies for direct delivery of drug to the central nervous system.

DELIVERY TO CSF

CSF delivery can be intraventricular or intrathecal. The intrathecal route is easier and safer, since the medication can be administered into the CSF without need for any surgical trauma to the brain. However, drugs administered by this route may not penetrate ventricular fluids, and therefore have limited distribution throughout the brain. At the present time, commercially-available infusion pumps are used in conjunction with catheters to deliver morphine into the epidural or subarachnoid spaces of the spinal cord, respectively, for treatment of intractable pain or spasticity. Plans were well advanced for an intrathecal trial of a selective NMDA antagonist from the conus snail, named CGX-1007; however, toxi-

cology issues delayed the trial. A drug to be used with direct brain infusion need not demonstrate good oral absorption or ability to penetrate the blood brain barrier. In addition, infusion eliminates the important compliance issue present with oral medications.

An unresolved question pertaining to intrathecal or intraventricular administration of medications is the degree of drug penetration into brain tissue. How far need a drug travel and at what concentration in order to prevent seizures? Medications move very slowly through brain by direct diffusion, but may penetrate faster when under pressure, or moving via bulk convection[10-11].

IMPLANTED DRUG-ELUTING WAFERS

A drug wafer is a polymer matrix with interwoven drug. As a polymer dissolves, it slowly releases medication over a period of time, typically weeks, months or even a few years. Drug releasing wafers have become well-known to neurologists and neurosurgeons from the BCNU-containing Gliadel wafer, which is left in the bed of tumor resection[12]. Tamargo and colleagues[13] explored the efficacy of intracerebrally administered phenytoin using such a controlled release polymer in their colbalt-induced rat model of epilepsy. A relatively constant amount of phenytoin was released from the polymer daily for a period of almost four months. Compared to animals receiving implantation of empty polymer matrices, those given phenytoin improved on a behavioral seizure scale and on two measures of EEG. Another group[14] delivered thyrotropin releasing hormone to the right amygdala of a rat, and showed that it delayed development of amygdala kindling. Potential disadvantages of therapy with polymer wafers include the low solubility of most current antiepileptic drugs, as well as their low potencies, which would require a bulky wafer. As polymers age *in-situ*, release of drug becomes considerably nonlinear. This may not be critical for chemotherapy agents, but could be for an anti-seizure medication with a narrow therapeutic ratio. In addition, craniotomies at intervals would be required to replenish the wafer.

LOCAL PERFUSION BY CATHETER

Local perfusion refers to delivery of a medication via an implanted catheter attached to a pump. The pump can be programmed to infuse medication at a constant ratio, a variable ratio, or upon demand for detection of a seizure. In some experiments, anti-epileptic medication can be infused first, in order to see whether it can prevent seizures. The current author and colleagues[15] demonstrated proof-and-principal of this approach in a rat model of epilepsy. A small bone window was made in the left parietal region of a rat, and the convulsant antagonist, bicuculline methiodide, was injected to produce epileptiform spikes. Local infusion of diazepam also can shorten (Fig. 1) or prevent ongoing seizures produced by application of convulsant chemicals[16-18].

To be practical, cerebral infusion of medication must take place without ongoing human intervention. Either the implanted pump can be programmed to deliver specified rates of medication over time, or a computerized detection algorithm can instruct the pump to release a bolus of medication upon detection of a seizure[16]. Infusion on the basis of seizure prediction, with ongoing monitoring of the EEG, would in theory be even more useful, but such prediction currently works only in a limited manner[19].

What would be the best medication to infuse in order

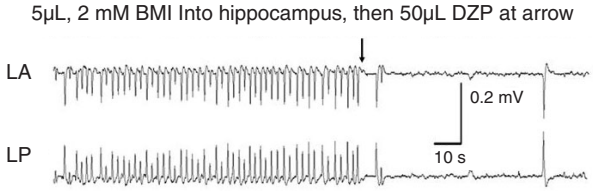

Figure 1. Cortical EEG is recorded in an adult rat via bone screw electrodes, shown for two channels (left anterior, LA and left posterior, LP) recorded with respect to a midline electrode over the frontal sinus. A seizure focus is produced by injection of 2 mM, 5 μL bicuculline methiodide (BMI, a GABA antagonist) into left hippocampus. The arrow shows time of injection of diazepam 50 μL into the left hippocampus, with termination of the epileptiform EEG activity.

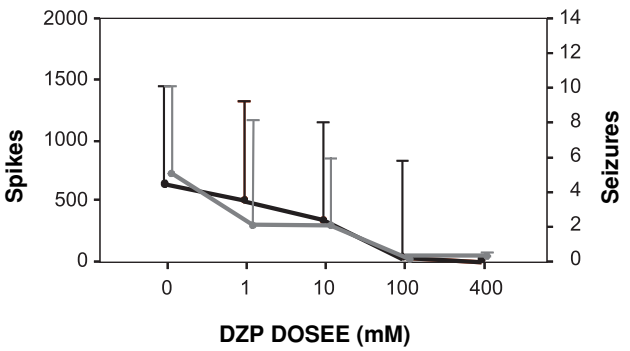

Figure 2. Numbers of spikes (left bars of pairs) and seizures (right bars of pairs) in the 15 minutes after injection of bicuculline methiodide (0.01 ml of 0.1 mM) into the left hippocampus of a rat, following by 5 minutes a prophyactic dosage of 0.02 ml of diazepam dissolved in DMSO. A dose-related suppression of both spikes and seizures is produced by prior injection of diazepam. Vertical bars encompass 75% of the range. Data obtained by Anschel D and Fisher RS, see Anschel et al.[18] for experimental details.

to stop or prevent seizures? Diazepam is not likely the best medication, since it has a pH of approximately 11, and can suppress respirations when in contact with the brain stem. Other possibilities that have been considered, but not studied systematically are midazolam, pentobarbital, phenobarbital, lidocaine, potassium, muscimol, vigabatrin, adenosine, and the range of other conventional antiepileptic drugs. Among these possibilities, adenosine has some attractive features. It is an endogenous neuromodulator, released during seizures[20]. Via the A1 receptor, adenosine suppresses synaptic activity. Fig. 2 shows latency to the first EEG spike and to the electrocorticographically-recorded seizure in control rat (labeled 0 on the dose scale) and with four different concentrations of adenosine infused into hippocampus prior to administration of hippocampal bicuculline methiodide[18]. Adenosine increases latency significantly for both spikes and seizures in a concentration-dependent manner.

Anti-epileptic medication infusion might be tailored to the anatomical sites known to be involved in the generation of a particular seizure type. For example, the nucleus reticularis of thalamus and the ventrobasal relay nuclei are known to be substantially involved in pathophysiology of spike-waves in animal model systems of epilepsy[21], with communication in this network relying strongly on the GABAB receptor. Application of a GABAB antagonist within thalamic nuclei partially inhibits epileptiform spike-waves in the rat model system.

Safety and tolerably of intracerebral infusion remains a substantial issue. Inhibitory medication might transiently depress a function of underlying cortex, thereby trading seizures for undesirable absence of function. Excess drug could produce toxic local effects or spread to portions of the brain involved in control of respiration and blood pressure. The long-term effect of such infusion is uncertain. Would receptors continuously exposed to medications down-regulate or up-regulate in a way that might lead to a lower seizure threshold, especially if the medications suddenly were withdrawn?

SEIZURE-ACTIVATED DRUGS

In this strategy, an inactive precursor drug is activated by a substance released at the seizure focus. This results in a highly specific concentration of drug at the seizure focus, with little drug effect at other brain or systemic sites. One drug utilizing this strategy is DP-VPA[22], which is an analog of valproic acid. With the phosphono group attached, the drug is without effect. When a seizure occurs, elevated activity of the enzyme phospholipase-A2 cleaves the phosphono moiety and generates locally high concentrations of valproic acid. The extent to which a seizure needs to be underway before activating a drug, as well as intrinsic characteristics of the drug itself may determine its utility in real clinical situations.

LIPOSOMES-POLYSOMES

A liposome is a fatty bubble, filled with a medication of interest. More precisely, liposomes are colloidal particles composed of phospholipid molecules assembled in a cell membrane-like bilayer or a multilayer sheet-disk configuration. Polysomes use artificial poly-

mers, such as polysorbate, to package the drug. Chemists can vary the characteristics of the membranes and the preparation medium in order to produce a variety of different types of liposomes or polysomes. The aim usually is to produce delivery vehicles that are able to steadily release the drug regionally over a period of days-to-weeks. Attached to the liposome may be a targeting agent that uses specific receptor binding or antibody affinity to link the liposome to a region of interest. For example, daunorubicin is a chemotherapy agent useful in treating breast cancer, but it can be cardiotoxic. Attachment of an antibody directed against the HER-2 receptor found in some breast cancers can enhance aggregation of liposomal daunorubicin in cancer tissues, relatively sparing other tissues such as the heart[23].

Delivery of liposomally-prepared antiepileptic drugs to specific sites in brain where seizures are occurring would be an attractive strategy. Several problems, however, have made this strategy difficult to achieve in practice thus far. First, the preparation must be able to penetrate the blood-brain-barrier. Most liposomes would not. One strategy suggested by Bickel and associates[24] is to link a liposome to the transferrin receptor, via a monoclonal antibody, named OX26. The transferrin receptor transports iron across the blood-brain-barrier, and can be shown to carry contents of a linked liposome into brain tissue. In order to be useful specifically against seizures, further strategies will be required to maintain steady release and activity of a desired antiepileptic drug, and to deliver it specifically to needed regions in brain.

CELL TRANSPLANTS AND GENE THERAPY

Discussion of cell transplants and gene therapy is beyond the scope of this brief review, but the topics should be mentioned as possible strategies for insight to renewable local delivery of chemical compounds. Cells can be engineered to release neurotransmitters, neuromodulators or other compounds. If such cells can survive in the central nervous system, then they might provide a renewable source for seizure-altering medication.

Cell transplants in brain can be free or encapsulated[25-27]. Free cells can form synapses with native neurons, which are readily subjected to attack from the native immune system. Encapsulated neurons cannot make synapses, but can release local factors that might favorably influence seizure threshold. One type of encapsulation is demonstrated in the technique of Schneider and associates[28], in which C2C12 myoblasts injected into hollow-fiber polyethylene fibers are genetically-engineered to release chemical factors. Adenosine, released from these myoblasts into rat lateral ventricle, can inhibit development of kindled seizures. Laboratory workers have utilized several different cell transplants, to affect animal models of seizures (Table 3).

Table 3. *Laboratory studies of cell transplants to treat seizures*

Locus ceruleus	Noradrenaline	Bengzon et al.[29]
Septal	Acetylcholine	Ferencz et al.[30]
Fetal raphe	Serotonin	Clough et al.[31]
Fetal striatal eminence	GABA	Loscher et al.[32]
Fibroblasts in polymers	Adenosine	Huber et al.[33]

Gene therapy could repair defective genes, replace missing gene products, protect neurons during seizures, or produce regional excitation-inhibition modulators. Many laboratories are working on such strategies, with virus vectors designed to enhance production of GABAergic drugs or other neuromodulators[34]. Often, the transfection rate is low, and the effect too temporary for practical use in chronic epilepsy. Immune reaction to the vector can sometimes be severe. Alteration of neuronal or glial genes remains a very interesting strategy for renewable local drug delivery, but much more work will be required before it can be considered practical.

CONCLUSION

Current oral epilepsy therapy has the regrettable tendency to distribute a medication to wide regions of the brain and body, including where it is not needed to stop seizures, and where it may produce adverse effects. Targeted drug delivery could improve the therapeutic/toxic ratio, by delivering high concentrations of drug where it is needed. Such targeted strategies might include: intrathecal administration of drug, poly-

mer wafers containing medications able to be implanted surgically into brain tissue, inactive prodrugs that are activated at a seizure focus, catheter administration of medication via a programmable implanted infusion pump, and chemically-engineered liposomes or polysomes containing drugs, perhaps with targeting mechanisms. In the future, transplanted cells and genes might be used to produce renewable local delivery of antiepileptic medications. No such targeted delivery of drug to brain is yet available for use in treating patients with seizures, but the level of promise is high.

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