Convection-enhanced delivery

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The use of convection-enhanced delivery (CED) as a method for delivering therapeutic agents in patients with disorders of the brain is a technique that has been increasingly studied over the last 2 decades. The primary reasons for using this method are poor passage of drugs across the blood-brain barrier (BBB), the limited efficacy of other methods of drug delivery in targeting specific areas of the brain, and the lack of similarly promising alternative treatment options. Investigations regarding CED in laboratory and human studies have improved our understanding of the variables important for successful CED, and have also revealed some of the limitations of this technique. Further work is needed to better define these aspects of CED and advance its use in humans. Toward this end, Ksendzovsky et al. provide evidence that large nanoparticles can be safely administered via CED. The volume of distribution (Vd) of M13 bacteriophage was assessed with real-time MRI to evaluate coinfused Gd, and the results were confirmed histologically. This work may expand the therapeutic alternatives that could be investigated for a variety of CNS disorders, including drug-loaded microspheres, monoclonal antibodies, and liposomes to the CNS. By applying a pressure gradient to establish bulk flow during interstitial infusion, the Vd is a linear function of the volume of infusion (Vi).

Multiple properties of CNS diseases contribute to the difficulty in developing effective therapies. Therapeutic agents are most commonly given by mouth or by intravenous injection. However, the BBB limits the ability of therapeutic agents to cross from the circulation into the brain to reach target cells, thus reducing the efficacy of some forms of systemic drug delivery. Certain drugs or particles that have shown promise in laboratory models may not translate to similar clinical success in humans when administered via standard oral or intravenous methods, or may not be candidates for these routes of delivery. Several approaches have been proposed to bypass the BBB and deliver therapeutic agents directly to the brain, thereby increasing drug concentrations, improving targeting to the cells of interest, and reducing associated systemic toxicity. In brain tumors, these methods have included intratumoral bolus injection, surgical implantation of drug-loaded polymer matrices in the brain, intraarterial injection, and CED of drugs via catheters placed into the tumor and/or surrounding brain. For degenerative neurological disorders such as Parkinson disease (PD), recent experimental drug delivery approaches include intracerebroventricular delivery of the glial-derived neurotrophic factor protein and CED of genetic material to increase expression of specific proteins to compensate for loss of dopaminergic neurons. Minimization of systemic exposure to a therapeutic compound may be especially important when treating a patient with gene therapy or toxic chemotherapy compounds. The CED method may represent the best alternative of these drug delivery options based on current understanding and technology, but further refinements in this technique are needed.

In addition to allowing for bypass of the BBB, possible advantages of CED include targeted delivery to a specific area in the brain and the potential for modification of the properties of infusion based on variables such as the size and location of the region of interest. In patients with PD, current treatments are oral medications that are not specifically targeted. Oral medications and the other main treatment, deep brain stimulation, treat symptoms, but the disease continues to progress due to continued loss of dopaminergic cells. The CED method can be targeted to a specific site such as the substantia nigra or putamen, and may be able to halt or reverse disease progression with delivery of gene therapy vectors.
Although CED is a promising method for drug delivery in patients with PD, clinical results reported thus far have not fully lived up to expectations. Design flaws in previous CED techniques may have played a role in these failures. Continued improvements in CED techniques may increase its viability as a treatment option in humans and allow for reinvestigation of compounds that demonstrated efficacy in the laboratory, but failed in clinical trials. Refinements in catheter design have helped reduce reflux and backflow of infusate along the catheter track. Real-time fluorescence imaging of CED has demonstrated that the larger nanoparticles (100 nm) had an increased tendency to use perivascular spaces for convective transport compared to smaller (24-nm) nanoparticles. Other advances include use of real-time MRI with confusion of a contrast agent, advanced stereotactic techniques, and use of CED simulation models. In the present study, evaluation of CED of very large particles pushes the boundaries of this technique, and possibly allows for a broader spectrum of treatment options. Further laboratory and clinical work will help refine CED techniques to optimize delivery of therapeutic agents to target tissue.

At our institution, experience with CED is primarily in the form of brain tumor therapy, rather than treatment for degenerative CNS disorders. Laboratory studies and human clinical trials have investigated CED of the chemotherapy agent carboplatin as well as CED of a genetically engineered oncolytic herpes simplex virus. The efficacy of our CED technique has improved as our understanding of factors important for infusion has evolved, allowing for optimization of a variety of variables. Further laboratory efforts and clinical trials in both areas at our institution will make use of future studies that continue improving on CED techniques.

The use of larger nanoparticles may provide the opportunity for designing increasingly sophisticated treatment strategies. Larger particles may have the capacity to deliver more complex genetic material, or could be designed to contain multiple therapeutic and diagnostic compounds. The increased surface area of these particles could be populated with a variety of targeting molecules specifically tailored to a patient’s disease and designed to optimize targeting specificity. However, the use of larger particles may also present new problems, because CED implies a pressure gradient driving the distribution of infusate. Larger, irregularly shaped nanoparticles could possibly be damaged by this process. The role of properties such as shape and surface charge may be different for such large particles. Although histological evidence of distribution was provided, evidence of retained efficacy of these particles would be important to determine. Recent work suggests differences in convective paths based on perivascular spaces for different sizes of nanoparticles. This may also play a role in the design of a nanotherapeutic molecule.

Understanding the advantages and limitations of CED will help define its ultimate role in treating CNS disorders. Toward this goal, Ksendzovsky et al. have demonstrated that CED can be used to deliver M13 bacteriophage, which is nearly 1 micron in length. This represents a significant increase in size compared to previous data on CED, which is largely limited to particles up to 100 nm, and this is potentially an important step toward new areas of CED-based investigations.

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Disclosure

The authors report no conflict of interest.

References

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