Locoregional drug delivery

Locoregional drug delivery refers to the administration of therapeutic drugs directly to a specific localized region within the body. This approach is used to target a particular area or tissue while minimizing systemic exposure to the drug, reducing the risk of side effects, and improving the drug's efficacy at the intended site of action. Locoregional drug delivery is widely employed in various medical fields for the treatment of a range of conditions. Here are some common methods and applications of locoregional drug delivery:

Cancer Treatment:

Intratumoral Injections: Drugs are directly injected into tumor tissue. This method allows for a high drug concentration at the tumor site while minimizing systemic side effects. Chemoembolization: In cases of liver cancer, drugs are delivered directly into the hepatic artery, followed by the injection of embolic agents to block blood flow to the tumor. Pain Management:

Epidural and Intrathecal Injections: Analgesic medications, such as opioids or steroids, are injected into the epidural or intrathecal space to provide localized pain relief. Nerve Blocks: Local anesthetics or anti-inflammatory drugs are injected near specific nerves or nerve clusters to alleviate pain in a particular region of the body. Cardiovascular Interventions:

Drug-Eluting Stents: Stents implanted in blood vessels are coated with drugs that are slowly released to prevent restenosis (re-narrowing of the vessel) after angioplasty. Orthopedics and Rheumatology:

Intra-articular Injections: Medications, such as corticosteroids or hyaluronic acid, are injected directly into joints to treat conditions like osteoarthritis or rheumatoid arthritis. Tendon Injections: Drugs are injected into tendons to treat conditions like tendonitis or tendinosis. Ophthalmology:

Intravitreal Injections: Medications are injected directly into the vitreous humor of the eye to treat conditions like age-related macular degeneration (AMD) or diabetic retinopathy. Neurology and Neurosurgery:

Intracranial Drug Delivery: Implantable drug delivery systems, such as pumps or convection-enhanced delivery (CED), are used to treat brain tumors or neurological disorders. Intrathecal Drug Delivery: Pain medications or anti-spasticity drugs can be delivered directly into the cerebrospinal fluid via implanted devices. Dental and Oral Health:

Intraoral Injections: Local anesthetics are injected into the oral cavity to numb specific areas before dental procedures. Regenerative Medicine:

Stem Cell Therapy: Stem cells or growth factors are injected into damaged tissues or joints to stimulate tissue regeneration and repair. Gastrointestinal Conditions:

Intraluminal Drug Delivery: Medications can be administered directly into the gastrointestinal tract via localized delivery systems for the treatment of conditions like inflammatory bowel disease. Infections:

Intraperitoneal or Intrathoracic Antibiotics: Antibiotics can be delivered directly to the peritoneal or thoracic cavity to treat localized infections. The choice of locoregional drug delivery method depends on the specific medical condition, the drug being administered, and the desired therapeutic outcome. These approaches require precise placement and may involve specialized devices or techniques. Locoregional drug delivery is an important strategy for improving the effectiveness and safety of drug

therapy in a variety of clinical scenarios.

Locoregional drug delivery platforms offer an improved therapeutic index by achieving high drug concentrations in the target tissue with negligible systemic exposure. Intrathecal (intraventricular) [IT] and convection-enhanced delivery [CED] are two clinically relevant methods being employed for various CNS malignancies. Both of these standalone platforms suffer from passive post-administration distribution forces, sometimes limiting the desired distribution for tumor therapy. Focused ultrasound and microbubble-mediated blood-brain barrier opening (FUS-BBBO) is a recent modality used for enhanced drug delivery. It is postulated that coupling of FUS with these alternative delivery routes may provide benefits. Multimodality FUS may provide the desired ability to increase the depth of parenchymal delivery following IT administration and provide a means for contour directionality with CED. Further, the transient enhanced permeability achieved with FUS-BBBO is well established, but drug residence and transit times, important to clinical dose scheduling, have not yet been defined. The present investigation comprises two discrete studies: 1. Conduct a comprehensive quantitative evaluation to elucidate the effect of FUS-BBBO as it relates to varying routes of administration (IT and IV) in its capacity to facilitate drug penetration within the striatal-thalamic region. 2. Investigate the impact of combining FUS-BBBO with CED on drug distribution, with a specific focus on the temporal dynamics of drug retention within the target region.

Methods: Firstly, we quantitatively assessed how FUS-BBBO coupled with IT and IV altered fluorescent dye (Dextran 2000kD and 70 kDa) distribution and concentration in a predetermined striatal-thalamic region in naïve mice. Secondly, we analyzed the pharmacokinetic effects of using FUS mediated BBB disruption coupled with CED by measuring the volume of distribution and time-dependent concentration of the dye.

Results: Our results indicate that IV administration coupled with FUS-BBBO successfully enhances delivery of dye into the pre-defined sonication targets. Conversely, measurable dye in the sonication target was consistently less after IT administration. FUS enhances the distribution volume of dye after CED. Furthermore, a shorter time of residence was observed when CED was coupled with FUS-BBBO application when compared to CED alone.

1. Based on the findings, IV delivery coupled with FUS-BBBO is a more efficient means for delivery to deep targets (i.e. striatal-thalamic region) within a predefined spatial conformation compared to IT administration. 2. FUS-BBBO increases the volume of distribution (Vd) of dye after CED administration, but results in a shorter time of residence. Whether this finding is reproducible with other classes of agents (e.g., cytotoxic agents, antibodies, viral particles, cellular therapies) needs to be studied [1)].

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Cardenas RU, Laramee M, Dahmane N, Souweidane M, Martin B. Influence of focused ultrasound on locoregional drug delivery to the brain: Potential implications for brain tumor therapy. J Control Release. 2023 Aug 31:S0168-3659(23)00560-6. doi: 10.1016/j.jconrel.2023.08.060. Epub ahead of print. PMID: 37659767.