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Tissue Distribution of a therapeutic monoclonal antibody determined by large pore microdialysis

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Abstract

Therapeutic monoclonal antibodies (mAbs) exhibit limited distribution to the target tissues. Determination of target tissue interstitial concentration of mAbs is an important aspect in the assessment of their pharmacokinetic/pharmacodynamics (PK/PD) relationship especially for mAbs targeting membrane bound receptors. The pharmacokinetics of R7072, a full length mAb (IgG) targeting human insulin like growth factor-1 receptor (IGF-1R) was evaluated following a single intravenous (IV) dose at 1, 6.25 and 25 mg/kg in healthy female SCID-beige mice. R7072 showed linear pharmacokinetics over the dose range tested and was characterized by low systemic clearance and long terminal half-life. Further, interstitial distribution of R7072 was evaluated in liver, skin, kidney and muscle tissues using large pore microdialysis (MD) after IV administration of 10 mg/kg dose in mice. The relative recoveries of R7072 were consistent and similar between in vitro and in vivo MD experiments. The tissue and/or interstitial concentrations were significantly lower compared to serum concentrations and found to be highest in liver and lowest in muscle. The interstitial concentrations of R7072 were approximately 2-4 fold lower than corresponding total tissue concentrations. Large pore MD appears to be an attractive approach for direct measurement of pharmacologically relevant concentrations of therapeutic mAbs in tissue interstitial fluid.

Introduction

Monoclonal antibodies (mAbs) are an important class of therapeutic drugs in various disease areas. The majority of therapeutic mAbs are designed to target either cell surface antigens or soluble ligands such as cytokines[1,2]. The pharmacokinetic properties of mAbs are different from small molecules and are mainly characterized by low clearance and volume of distribution. Due to their large molecular size and physico-chemical properties, they distribute only to a small extent to target tissues[3]. Interstitial fluid in between the outer endothelial lining and the plasma membranes of cells is the most relevant biological compartment for mAbs targeting cell surface antigens. Although challenging, the determination of interstitial tissue concentrations is an important aspect in assessment of receptor occupancy and PK/PD of therapeutic mAbs. The currently available methods to collect interstitial fluids such as wick technique and centrifugation suffer from technical limitations and have not been widely used. The other approach relies mainly on systemic concentrations and estimate interstitial concentrations using physiologically based pharmacokinetic (PBPK) models.