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A rabbit model demonstrates the influence of cartilage thickness on intra-articular drug delivery and retention within cartilage.

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Abstract

For evaluation of new approaches to drug delivery into cartilage, the choice of an animal model is critically important. Since cartilage thickness varies with animal size, different levels of drug uptake, transport and retention should be expected. Simple intra-articular injection can require very high drug doses to achieve a concentration gradient high enough for drug diffusion into cartilage. New approaches involve nanoparticle delivery of functionalized drugs directly into cartilage; however, diffusion-binding kinetics proceeds as the square of cartilage thickness. In this study, we demonstrate the necessity of using larger animals for sustained intra-cartilage delivery and retention, exemplified by intra-articular injection of Avidin (drug-carrier) into rabbits and compared to rats in vivo. Penetration and retention of Avidin within cartilage is greatly enhanced by electrostatic interactions. Medial tibial cartilage was the thickest of rabbit cartilages, which generated the longest intra-cartilage half-life of Avidin ($\tau 1/2 = 154$ h). In contrast, Avidin half-life in thinner rat cartilage was 5-6 times shorter ($\tau 1/2 \sim 29$ h). While a weak correlation ($R(2) = 0.43$) was found between Avidin half-lives and rabbit tissue GAG concentrations, this correlation improved dramatically ($R(2) = 0.96$) when normalized to the square of cartilage thickness, consistent with the importance of cartilage thickness to evaluation of drug delivery and retention.