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Antibiotic loaded poly(ε-caprolactone) microspheres functionalized with poly(aspartic acid) as bone targeting delivery system to treat infection

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INTRODUCTION: The recurrence rate of chronic osteomyelitis in adults is close to 30% [1]. Bacteria are known to migrate deeper into bone tissue through canaliculi and evade common systemic- and local-antibiotic therapies [2]. By fabricating antibiotic loaded poly(ϵ-caprolactone) (PCL) microspheres conjugated with the bone-chelator poly(aspartic acid) (PAA) we aim to prolong the microsphere residency near the site of infection, increasing bactericidal potential.

METHODS: Hydrophobic Gentamicin-dioctyl sulfosuccinate (Gen-AOT) loaded PCL microspheres were made by oil/water emulsion methods. In vitro antimicrobial properties were tested by zone of inhibition (ZOI) in a serial plate transfer test with S. aureus. In vivo antimicrobial efficacy of 1 mg of microspheres was tested in a femoral defect in rats (n =5), infected with $2 \cdot 10^6$ colony forming units (CFU) of bioluminescent Xen-29 a week prior to treatment. In a 2nd study, the PCL microspheres underwent conjugation with PAA by carbodiimide chemistry. Interaction with bone mineral was assessed in the same model as above. IR780 iodide loaded PCL or PCL-PAA microspheres (1 mg) were injected in the bone defect and traced using an in vivo imaging system (IVIS Lumina III, Perkin Elmer).

RESULTS & DISCUSSION: ZOI of Gen-AOT loaded PCL was measurable for 5 days, while a ZOI for bactericidal collagen-sheets was visible for 3 days. The Gen-AOT loaded PCL microspheres caused an 81% reduction in CFU compared to untreated control. In vivo, a brighter signal was measured for PCL-PAA compared to PCL microspheres, validating the hypothesis that PAA-grafted PCL resides longer in bone as control PCL.

CONCLUSIONS: In the presented animal model, a monotreatment of 1 mg PCL microspheres caused an 81% CFU reduction. PCL-PAA microspheres enhance bone affinity by chelation of the PAA to bone mineral at the femoral defect. Further work is required to optimize the bone-targeted drug delivery system to bone.

ACKNOWLEDGEMENTS: Project funding was received from AO Trauma.

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