THEORETICAL FRAMEWORK FOR THE DESIGN OF ORTHOPEDIC IMPLANTS AS DRUG-DELIVERY SYSTEMS

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Introduction: Different implant shapes have been proposed in the past years, as well as cemented implants and custom-shaped implants. However, the lifespan has not yet been improved enough to respond to the clinical use of implants for young patients. The principal cause of THR failures is aseptic loosening, often observed associated with peri-implant osteolysis. Implants failure rate is strongly related to the short-term quality of fixation. Our work is based on the hypothesis that implants releasing bisphosphonate molecules from their coating would protect the nearby bone from early osteolysis and therefore show an improved fixation.

A mathematical framework is needed to localize the drug and control its concentration for an optimal design [1]. The aim of this paper is, first, to develop a comprehensive mathematical model of implants used as bisphosphonate delivery system and, second, to verify it with in vivo experimental data of rats and osteoporotic sheep models.

Materials and Methods: Experimental

Titanium cylinders of 3mm diameter and 5mm length were coated with hydroxyapatite and loaded with different concentrations of zoledronate. Five ovariectomized sheep received these implants in the femoral condyle. After 6 months, the animals were sacrificed, the condyles extracted, sliced transversally and the bone density (BMD) was measured on the images obtained by backscattered scanning electron microscopy.

Mathematical model

The different events arising around the implant are distinct components of the global model. Each event is represented by a partial differential equation. The first element is the release and diffusion of the drug into the bone pores where it may fix on the bone material. This diffusion process is well represented by Fick’s law of diffusion, with a species-specific coefficient of diffusion. The effective diffusion coefficient was estimated with a custom numerical model of diffusion into porous bone. The second element is the biophysical effect of the drug on bone cells. Once it is fixed, the drug inhibits the osteoclasts activity. The effect of the drug was calculated indirectly at the implant surface, where the concentration was known. The model was implemented in a two-dimensional geometry and computed over a distance of 200μm from the implant for the rats and 800μm for the sheep. The effect of bisphosphonate-loaded implants was compared with that of control implants. All computations were realized with Mathematica (Wolfram Research).

Results: Equations of the rat model were solved numerically over a distance of 200 μm from the implant. The relative bone density φ(x) was evaluated and compared with in vivo results (figure 1a) for doses of 0.2, 2.1, 8.5 and 16μg of Zoledronate per implant and a Zoledronate-free control. The model fits the in vivo data for the control, 2.1μg, 8.5μg and 16μg conditions, with a maximum relative error of 9% on bone density. The model diverges from experimental data for the 0.2μg conditions after 100μm from the implant.

Equations of the osteoporotic sheep model were solved over the distance of interest of 800μm from the implant. The relative bone density φ(x) was evaluated and compared with in vivo results (figure 1b) for a dose of 2.1μg of Zoledronate per implant compared to control. The model fits the sheep in vivo data for the control and 2.1μg conditions, with a maximum relative error of 10% on bone density.

Discussion: Bisphosphonate-delivering implants were shown to increase the implant fixation. Peter et al showed that after three weeks, the peri-implants bone density was increased significantly with a dose of 2μg of drug per implant. Moreover the pullout force was increased by 20% with this later drug concentration [2].

The different biological effects of bisphosphonates on bone cells, osteoclasts activity inhibition and osteoblasts proliferation inhibition, lead to a complex pattern of bone density around the implant. Our model reflects this pattern with a very good accuracy for the different drug concentrations. The model parameters are species-dependent, but the model concepts are not. This mathematical model can be a very useful tool in the future to design and optimize bisphosphonate coated implants for human applications.


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Fig 1. Comparison of mathematical model (lines) with in vivo results (dots). (a) rats model, (b) sheep model.

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