**Introduction:** There is actually a trend to propose total hip replacement (THR) to younger and more active patients; therefore orthopedic implants with extended life spans are needed. Different implant shapes have been proposed in the past years. 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.

In this study we assess the innovative concept of orthopedic implant as bisphosphonate-delivery system. This concept relies on the fact that implants failure rate is strongly related to the short-term quality of fixation. Our hypothesis is that the drug release from the implant would prevent early osteolysis.

Bisphosphonates are molecules that inhibit osteoclasts activity and decrease bone resorption [1]. Bisphosphonates also inhibit osteoblasts maturation at higher doses. Therefore it is crucial to localize the drug and control its concentration for an optimal result [2].

The aim of this paper is, first, to develop a mathematical model of implants used as drug delivery system and, second, to verify it with in vivo experimental data of rats and osteoporotic sheep models.

**Materials and Methods:**

**Experimental**

The experimental method was developed in [3]. Briefly, Ti cylinders of diameter 3mm and length 5mm 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 and the bone density (BMD) was measured 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 second element is the effect of the drug on bone cells. Once it is fixed, the drug inhibits the osteoclasts activity. This 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.

**Results:** The rat model was solved numerically over a distance of 200 μm from the implant. The relative bone density was evaluated and compared with in vivo results (figure 1) 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, 2.1, 8.5 and 16μg conditions, with a maximum relative error of 9% on bone density. The model diverges from the data for the 0.2μg condition after 100μm from the implant.

For the osteoporotic sheep model, the distance of interest was 800μm from the implant. The relative bone density was evaluated and compared with in vivo results (figure 2) for a dose of 2.1μg of Zoledronate per implant compared to control. The model fits the sheep in vivo data for both conditions, with a maximum relative error of 10% on bone density.

**Discussion:** Peter et al have shown that bisphosphonate-delivering implants increase the implant fixation [3]. 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.

The bone density around an implant used as drug delivery system is not linearly related to the dose of drug on the implant. The balance between the coupled effects, osteoclasts activity inhibition and osteoblasts proliferation inhibition, leads to a complex pattern of bone density around the implant.

Our model reflects this pattern with a very good accuracy for most 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 optimize bisphosphonate coated implants for human applications.


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