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Predicting patient exposure to nickel released from cardiovascular devices using multi-scale modeling

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ABSTRACT

Many cardiovascular device alloys contain nickel, which if released in sufficient quantities, can lead to adverse health effects. However, in-vivo nickel release from implanted devices and subsequent biodistribution of nickel ions to local tissues and systemic circulation are not well understood. To address this uncertainty, we have developed a multi-scale (material, tissue, and system) biokinetic model. The model links nickel release from an implanted cardiovascular device to concentrations in peri-implant tissue, as well as in serum and urine, which can be readily monitored. The model was parameterized for a specific cardiovascular implant, nitinol septal occluders, using in-vitro nickel release test results, studies of ex-vivo uptake into heart tissue, and in-vivo and clinical measurements from the literature. Our results show that the model accurately predicts nickel concentrations in peri-implant tissue in an animal model and in serum and urine of septal occluder patients. The congruity of the model with these data suggests it may provide useful insight to establish nickel exposure limits and interpret biomonitoring data. Finally, we use the model to predict local and systemic nickel exposure due to passive release from nitinol devices produced using a wide range of manufacturing processes, as well as general relationships between release rate and exposure. These relationships suggest that peri-implant tissue and serum levels of nickel will remain below 5 μg/g and 10 μg/l, respectively, in patients who have received implanted nitinol cardiovascular devices provided the rate of nickel release per device surface area does not exceed 0.074 μg/(cm^2 d) and is less than 32 μg/d in total.

Statement of significance

The uncertainty in whether in-vitro tests used to evaluate metal ion release from medical products are representative of clinical environments is one of the largest roadblocks to establishing the associated patient risk. We have developed and validated a multi-scale biokinetic model linking nickel release from cardiovascular devices in-vivo to both peri-implant and systemic levels. By providing clinically relevant exposure estimates, the model vastly improves the evaluation of risk posed to patients by the nickel contained within these devices. Our model is the first to address the potential for local and systemic metal ion exposure due to a medical device and can serve as a basis for future efforts aimed at other metal ions and biomedical products.

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1. Introduction

The presence of nickel in many of the metal alloys used to manufacture cardiovascular devices is metallurgically necessary to impart enhanced physico-chemical properties to the alloy that facilitate the successful function of these devices [1,2]. However, the presence of nickel in these alloys can give rise to concerns about adverse health effects that may occur if released from the device in sufficient quantities. Therefore, to identify the potential health risks associated with nickel ion release, it is necessary to characterize the dose of nickel that may be released from a nickel-containing medical device. While it is possible to estimate the extent of nickel ion release from the device using in-vitro test methods [3–5], it is not clear if the results of this testing are representative of the release characteristics in vivo. Further, in-vitro testing does not provide insight into the peri-implant or systemic distribution of nickel within the body following the release of

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nickel from the medical device. Therefore, it is not possible to leverage the in-vitro data alone to assess the extent and duration of internal site-specific exposures, such as levels in serum and peri-implant tissue. Experimental studies have assessed in-vivo corrosion of implanted nickel-containing alloys and evaluated site-specific exposure of tissues to metals released from implanted devices using animal models and explant studies [6–8]; however, these studies can be technically difficult to conduct, prohibitively costly and time consuming.

To overcome these challenges, modeling and simulation tools can provide a relatively straightforward means to predict both in-vivo ion release from the device and the subsequent patient exposure. For example, we previously developed a compartmental toxicokinetic model that linked nickel release from a cardiovascular device to serum and urine ion concentrations, analytical endpoints that can be measured with relative ease [9]. The results of this study also implied that toxicokinetic model could be used to estimate systemic exposure to nickel based upon in-vitro test data. However, the model was not sufficiently refined to resolve the concentration of metal ions in peri-implant tissue or the impact of the local tissue properties on ion release. Nevertheless, it should be possible to adopt a local tissue-specific transport model, such as those that have been employed to predict the local deposition of drugs from drug-eluting stents, to predict concentrations of nickel in tissues adjacent to an implant [10–12]. Coupling physics-based models for nickel release from a medical device alloy and transport within the local implantation environment with a systemic toxicokinetic model can provide a comprehensive representation of the potential exposure to nickel a patient may experience due to the presence of a cardiovascular device. Once parameterized and validated, this approach would enable the potential for systemic toxicity as well as toxicity in peri-implant tissues to be evaluated based solely on the results of in-vitro nickel release tests. Further, it may be possible to invert this hierarchy of models, allowing nickel ion release from a cardiovascular device and local tissue accumulation to be predicted in-vivo by using the model to estimate these quantities based upon serum or urine concentrations.

In this manuscript, we describe the development of a multi-scale exposure model for nickel release from implanted cardiovascular devices. Our approach combines physics-based models for nickel transport at the material and tissue level with a traditional toxicokinetic model to predict the extent and duration of both local and systemic nickel exposure. We note that the data needed to parameterize and validate these models are extremely limited. Most of the in-vitro efforts to characterize nickel release have focused on nitinol devices, due to the high nickel content and sensitivity of nickel release from this alloy on process history [3–5]. Further, relatively extensive, time-dependent measurements of nickel concentrations in serum and urine following implantation of a cardiovascular device have only been reported for a single family of nitinol devices, Amplatzer occluders, intended for the closure of atrial septal defects [13–15]. Therefore, we focused our model parameterization and validation efforts primarily on these devices. To obtain the necessary data to parameterize the model, we conducted ex-vivo analyses on porcine hearts to establish the transport properties of nickel in cardiac tissue. Once validated within this relatively limited scope, the model was used to predict worst-case estimates of local and systemic exposure for cardiovascular devices comprised of nitinol wire, by applying a set of worst-case assumptions.

2. Materials and methods

2.1. Model formulation

To develop the model, we consider the transport of nickel at three different length scales, specifically the material (microstructural), tissue, and system scales. This multi-scale approach is illustrated schematically in Fig. 1. At the material scale, the extent and rate of nickel release from nitinol is dictated by the physicochemical structure of the oxide layer, which is extremely sensitive to how the material is processed [3]. The presence of sub-micron nickel-rich regions within and beneath the primarily TiO_2 layer serve as a source for nickel release over time. Therefore, the number and distribution of these regions must be considered to accurately predict nickel release from a nitinol medical device. Previously, we have shown that the impact of oxide structure on nickel release is adequately captured over a wide range of process conditions by approximating the oxide layer as a "biphasic" material, shown schematically on the left- hand side of Fig. 1, with surface-connected (percolated) and fully embedded (bulk) nickel-rich regions that are both governed by diffusive transport [9]. This approximation of the surface oxide microstructure is consistent with electron microscopy characterization of cross-sections through nitinol surfaces prepared by focused ion beam (FIB) milling [16,17]. To model the biphasic nature of the oxide layer, we have adopted the approach previously described for drug-eluting stents [10–12], where the oxide layer is assumed to be comprised of two independent components, percolated and bulk nickel, with compositions expressed in mass concentration, C_p and C_b, respectively. The time t dependence of these composition fields within the oxide layer is then given simply as:

$$\frac{\partial C_i}{\partial t} = D_i \nabla^2 C_i, \tag{1}$$

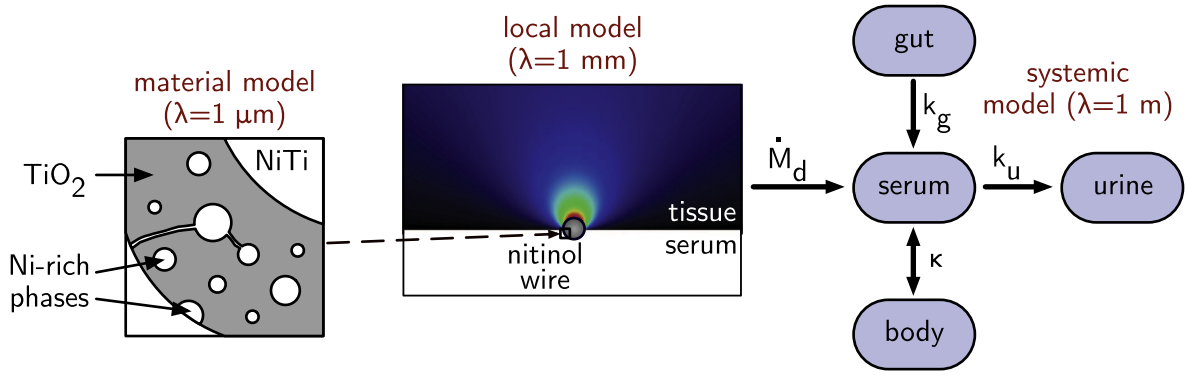

Fig. 1. Schematic representation of the multi-scale model at a hierarchy of length scales (λ). From left to right, we represent the microstructure of the nitinol oxide layer as a bi-phasic material. This representation is incorporated into a physics-based model for nickel transport within the local implant environment. Finally, the rate of nickel migration into the bloodstream predicted by the diffusion model is used in a compartment model to predict the systemic distribution and excretion of nickel.