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Short communication

Kinetics of charged antibiotic penetration into human intervertebral discs: A numerical study

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ABSTRACT

Little quantitative information exists on the kinetics of charged antibiotic penetration into human intervertebral discs (IVD). This information is crucial for determining the dosage to use, timing of administration, and duration of treatment for infected IVDs. The objective of this study was to quantitatively analyze the transport of various charged antibiotics into human lumbar IVDs. Penetration of charged and uncharged antibiotics into a human lumbar disc was analyzed using a 3D finite element model. The valence (z) of the electrical charge of antibiotics varied from $z=+2$ (positively charged) to $z=-2$ (negatively charged). An uncharged antibiotic ($z=0$) was used as a control. Cases with intravenous (IV) administrations of different charged antibiotics were simulated. Our results showed that the electrical charge had great effects on kinetics of an antibiotic penetration into the IVD; with higher concentrations and uptakes for positively charged antibiotics than those for negatively charged ones. This study provides quantitative information on selecting antibiotics for treating intervertebral disc infections.

1. Introduction

Intervertebral disc (IVD) infections are caused by the seeding of bacteria into the disc space as a result of bacteremia or following spine operations or other spine procedures (Silber et al., 2002). Although the incidence of IVD infection is low, varying from 0.02–4% (Silber et al., 2002), it will usually cause severe spine pain and may cause major disabilities including paralysis if treated inadequately with antibiotics that do not penetrate into the IVD (Silber et al., 2002). Antibiotics are used for the treatment of IVD infections and for perioperative prophylaxis. Due to the avascular nature of the IVD, antibiotics have to transport by diffusion into the IVD from blood vessels at disc boundaries. After age 16, there are no blood vessels which go into the IVD. Penetration of antibiotics into IVD has been studied in animals (Currier et al., 1994; Eismont et al., 1987; Fraser et al., 1989; Riley et al., 1994; Scuderi et al., 1993; Thomas et al., 1995; Walters et al., 2006b) and humans (Gibson et al., 1987; Lang et al., 1994; Tai et al., 2002; Walters et al., 2006a). These studies have suggested that the ability of antibiotics to penetrate into IVDs depends on several factors, such as antibiotic molecular weight (size), antibiotic charge, IVD porosity, etc. (Currier et al., 1994; Eismont et al., 1987; Gibson et al., 1987; Riley et al., 1994; Thomas et al., 1995; Urban et al., 1977).

A number of experimental studies have indicated that electrical charge plays a significant role in penetration of antibiotics into discs (Conaughty et al., 2006; Gibson et al., 1987; Riley et al., 1994; Scuderi et al., 1993; Tai et al., 2002; Thomas et al., 1995). Gibson et al. (1987) reported that despite high levels of flucloxacillin and cephadrine in serum, little antibiotic could be detected in AF or NP harvested 30 minutes to 4 hours after intravenous (IV) administration in the 12 adolescent patients (Gibson et al., 1987). Tai et al. (2002) examined the penetration of negatively charged cefuroxime and positively charged gentamicin into patients and they found that gentamicin diffused into discs much easier than cefuroxime (Tai et al., 2002). In a rabbit model of IVD infection with methicillin-resistant Staph aureus, Conaughty et al. (2006) found that intravenous treatment with positively charged vancomycin was much more effective than treatment with negatively charged linezolid in resolving the infection. They stated that differences in the electrical charge between the two molecules may affect the penetration of the molecules into the discs (Conaughty et al., 2006). Riley et al. (1994) studied the penetration of positively charged gentamicin and negatively charged penicillin into a rabbit IVD model and reported that penicillin has less ability than gentamicin to penetrate into the negatively charged nucleus pulposus (NP) (Riley et al., 1994). Thomas et al. (1995) found that uptake of positively charged aminoglycosides was higher than that

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of the negatively charged penicillins and cephalosporins, and the uncharged ciprofloxacin showed an intermediate degree of uptake in a mouse disc model (Thomas et al., 1995). Results from these studies either directly suggested or indicated that positively charged antibiotics have easier access to or higher uptake in the discs than the negatively charged ones.

Though many experimental data on antibiotic penetration into the disc have been reported, there is a lack of analytic tools to predict kinetics of charged antibiotic transport in the IVD. Thus, the objective of this study was to quantitatively analyze and compare the penetration of differently charged antibiotics into human lumbar discs with a finite element method, to understand the effect of electrical charge on the kinetics of antibiotic penetration into the IVD. This numerical model can be used to provide quantitative guidance on dosage to use, timing of administration, and duration of treatment for disc infections.

2. Methods

2.1. The theoretical framework

A multiphysics model for IVD has been developed based on the triphasic continuum mixture theory (Lai et al., 1991). In this model, the disc was modeled as an inhomogeneous, porous, mixture consisting of a charged solid phase, a fluid phase, and a solute phase (with multiple species of solutes). The fixed charge density, hydraulic permeability, solute diffusivities were nonlinearly coupled with tissue deformation (or tissue hydration). The interactions among tissue deformation, electrical charge, fluid and solute transport were taken into consideration in the model. The mass balance equation for an antibiotic (A) is given as

$$\partial(\phi^w c^A)/\partial t + \nabla\cdot(\mathbf{J}^A + \phi^w c^A \mathbf{v}^s) = 0, \tag{1}$$

where ϕ^w is the water volume fraction (or water content), c^A is the molar concentration (per unit fluid volume) of the antibiotic, $\mathbf{J}^A$ is the molar flux of the antibiotic (relative to the solid phase), and $\mathbf{v}^s$ is the velocity of the solid phase.

The molar flux of the antibiotic can be expressed as:

$$\mathbf{J}^A = H^A c^A \mathbf{J}^{\mathbf{w}} - \frac{\phi^w c^A D^A}{\varepsilon^A}\nabla\varepsilon^A, \tag{2}$$

where H^A is the convection coefficient of the antibiotic, $\mathbf{J}^w$ is the volume flux of water relative to the solid phase, D^A is the diffusivity of the antibiotic in the disc tissue. ε^A is the modified (electro)chemical potential of the antibiotic, which is related to the molar concentration (per unit fluid volume) of the antibiotic c^A by the following equation:

$$c^A = \frac{\varepsilon^A}{\gamma_A}\left[\exp\left(z^A\frac{F_c\psi}{RT}\right)\right]^{-1}, \tag{3}$$

where γ_A is the activity coefficient of the charged antibiotic in tissue, z^A is the valence of the net electrical charge of the antibiotic, F_c is the Faraday constant, ψ is the electrical potential within the disc, R is the gas constant, T is the absolute temperature. The electrical potential ψ can be solved with the electro-neutrality equation (Ateshian et al., 2013):

$$\sum_\alpha z^\alpha c^\alpha = 0, \tag{4}$$

where z^α is the valence of the charged solutes or fixed charge in the disc, and c^α is the concentration of the corresponding solute or fixed charge. For the solutes considered in this study (i.e., Na^+, Cl^-, antibiotics), Eq. (4) reduces to,

$$c^+ - c^- + z^A c^A - c^F = 0. \tag{5}$$

Other governing equations for the solid deformation, fluid flow, ions and nutrients transport can be found in our recent publication (Zhu et al., 2012).

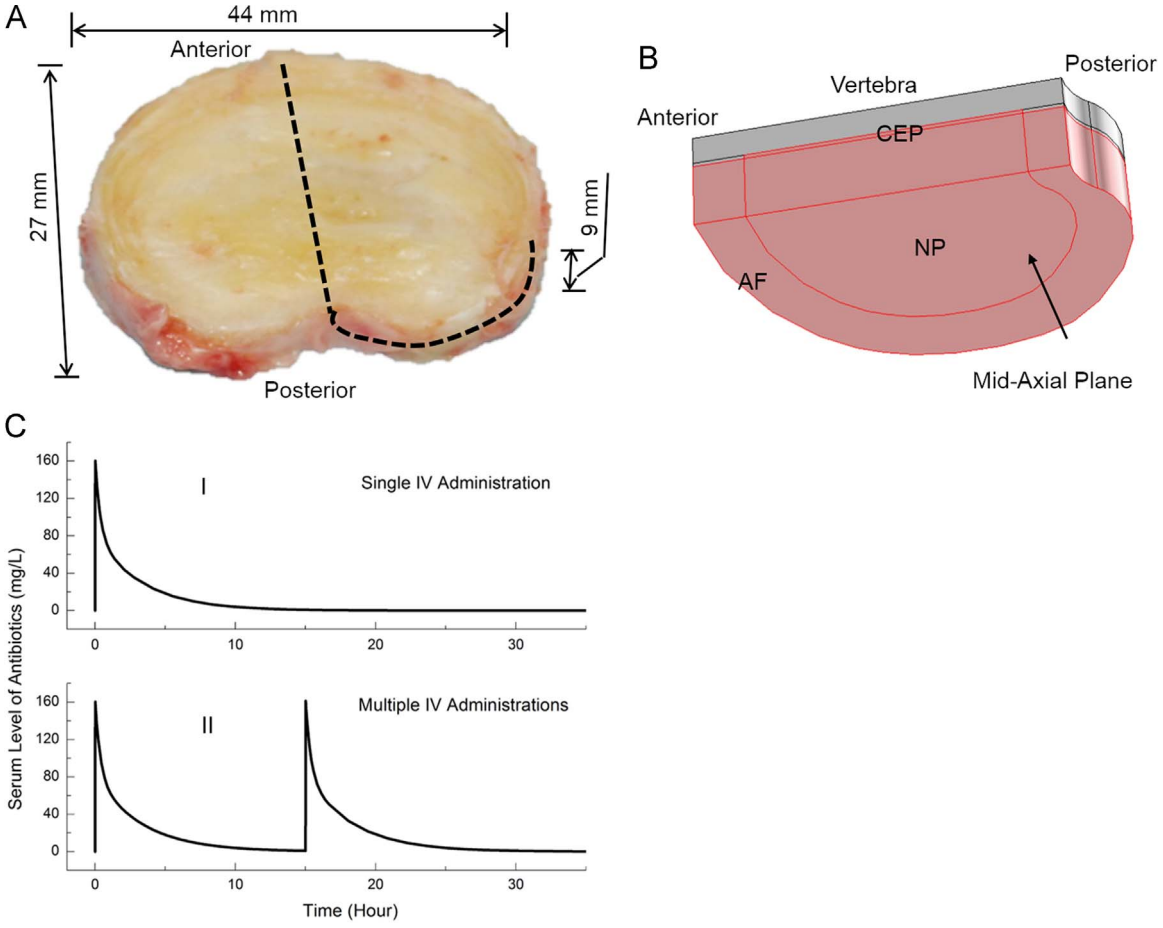

Fig. 1. (A) Picture of a human lumbar intervertebral disc (IVD, L2-3, non-degenerated). (B) Schematic of a quarter of the IVD-vertebra segment used in the FEM analysis (due to symmetry). NP: Nucleus pulposus. AF: Annulus fibrosus. CEP: Cartilaginous endplate. (C) The variation of antibiotic level in serum with time: (I) post an IV administration, and (II) post multiple IV administrations.

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