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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.

Keywords

intervertebral disc; antibiotic penetration; transport phenomena; mixture theory; finite element analysis; 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

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Conflict of interest statement

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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 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

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

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:

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

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:

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

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):

$$\sum_{\alpha} z^{\alpha} c^{\alpha} = 0 \quad , \quad (4)$$

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), equation (4) reduces to,

$$c^+ - c^- + z^A c^A - c^F = 0 \quad (5)$$

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

2.2 Finite element model

A 3D finite element model for IVDs was developed based on the framework stated above. The IVD height was 10 mm and the cartilaginous endplate (CEP) thickness was 0.6 mm [based on a human L2-3 disc (Jackson et al., 2011; Zhu et al., 2012)], see Figure 1A. The IVD was modeled as an inhomogeneous structure with three regions: NP, annulus fibrosus (AF), and CEP. The disc was attached to a part of the vertebra (Fig. 1B) and the displacement boundary condition was applied on the top of the vertebra surface. The vertebra was modeled as a single-phase, linear elastic solid. Due to symmetry, only the upper-right quarter of the disc-vertebra segment was modeled (Fig. 1B). COMSOL software (COMSOL 4.3b, COMSOL, Inc., MA) was used to solve a system of partial differential equations (Gu et al., 2014; Zhu et al., 2012).

The material properties (including the mechanical properties, transport properties, and electrochemical properties) used in this study were similar to those used in Gu et al (Gu et al., 2014) for the disc and vertebral bone, and in Zhu et al (Zhu et al., 2012) for CEP, see Table 1.

Three groups of antibiotics were investigated: a positively charged group, a negatively charged group, and a neutral group. To eliminate the effects of differences in molecular characteristics on the transport of antibiotics into discs, all the antibiotics are assumed to have the same molecular properties [e.g., molecular weight (400 g/mol), diffusivity in water at 37 °C (6.2×10^{-10} m²/s), hydraulic radius (0.53 nm), and blood-disc partition coefficient], except electrical charge. Note that the values of the molecular properties (except charge) are “averaged” ones based on the properties of commonly reported antibiotics. For example, the molecular weight of commonly used antibiotics are in the range of 330 g/mol (ciprofloxacin) to 549 g/mol (ceftazidime), and we used the value of 400 g/mol for the molecular weight of the antibiotics in our simulations. The uptake of the antibiotics by the cells was not considered in the current study.

In this study, the antibiotic concentration in the blood was assumed to peak (i.e., 160 mg/L) at 30 seconds after a single IV administration, then decline exponentially (Fig. 1C-I) (Currier et al., 1994; Pinto et al., 2011; Shi et al., 2010; Walters et al., 2006a). The blood-disc partition coefficient was assumed to be unity for each antibiotic studied, and the antibiotic concentration was neglected in Eq (5) due to its low concentration. Cases with single and multiple IV administrations of antibiotics (Fig. 1C) were simulated.

3. Results

3.1 Effects of electrical charge on kinetics of antibiotics transport into the disc

It was predicted that concentrations of positively charged antibiotics were higher than those of negatively charged ones at each time point after the single IV administration (Fig. 2). The peak concentrations (averaged over the disc) were 29.4%, 16.1%, 8.3%, 4.2%, and 2.1% (of its peak concentration in the serum, i.e., 160 mg/L) for antibiotics with $z=+2$, $z=+1$, $z=0$, $z=-1$, and $z=-2$, respectively (Fig. 2A). The time to achieve peak value of overall concentration in the disc (averaged over whole disc) was found to be different (Fig. 2A), with 5.56 hr, 4.44 hr, 3.89 hr, 2.78 hr, 2.22 hr for antibiotics with valance $z=+2$, $z=+1$, $z=0$, $z=-1$, and $z=-2$, respectively. Similar results were found at the center of the disc (Fig. 2B). Assuming the minimum inhibitory concentration (MIC) to be the same for all antibiotics, say, 1 mg/L, the treated regions (defined as drug concentration higher than MIC) in the disc at 2 hours after IV administration was predicted to be much larger by using positively charged antibiotics than negatively charged ones (Fig. 3).

3.2 Single IV administration vs. multiple IV administrations

Our simulated results showed that multiple IV administrations of the same antibiotic would effectively maintain the concentration level higher than the MIC (assumed to be 1 mg/L in this study) for a prolonged period of time (Fig. 4). For example, the duration of the antibiotic (negatively charged, $z=-2$) concentration at the levels above the MIC at the disc center increased from ~19 hours to ~37 hours after a second administration was issued at 15 hrs (Fig. 4). Comparison of the spatial distribution of the antibiotic ($z=-2$) in the disc between the single IV administration and double IV administrations were shown in Fig. 5.

4. Discussion

The driving force for the transport of charged antibiotics is the combination of electrical potential gradient and concentration gradient. Due to the existence of fixed negatively charged groups in the disc, the electrical potential inside the disc is lower than outside the disc. Thus, the direction of the driving force caused by electrical potential difference for negatively charged antibiotics is outward, whereas it is inward for positively charged antibiotics. The direction of the driving force caused by concentration gradient varies with time, and is inward initially. When the driving force caused by electrical potential gradient is balanced by the driving force caused by concentration gradient, the antibiotic concentration within the disc reaches its peak value in time. Due to the Donnan's effect, the concentration of negatively charged antibiotics within the negatively charged disc is much lower (Conaughty et al., 2006; Riley et al., 1994; Thomas et al., 1995)

The multiple IV administrations of antibiotics could effectively maintain the high antibiotic concentration in the disc for a prolonged duration (Figs. 4 and 5). The pattern of concentration change with time for the second IV administration is similar to the first one, indicating the patterns are repeatable for subsequent IV administrations. This phenomenon is useful for estimating the number of IV administrations needed in order to maintain antibiotic concentration above the therapeutic level for a period of time.

In this study, only the charge effect on transport of antibiotics in IVD was investigated. Effects of daily cyclical loading on the antibiotic penetration has not been considered in this study. Nor does the binding effect on antibiotic transport in the disc because of very limited information on binding kinetics of antibiotics available in the literature.

In conclusion, this study is primarily a parametric analysis with the focus on investigating the effect of electrical charge on antibiotics penetration into human IVD. Our results indicate that electrical charge has great influences on both the concentration level and the kinetics of antibiotics in the disc, with much higher concentration and longer time to reach the peak value for positively charged antibiotics than those for the negatively charged ones. This numerical model can be used to provide quantitative guidance on dosage, timing of administration, and duration of treatment for disc infections.

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Figure 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.

Figure 2.

Effect of electrical charge on antibiotic concentrations in a single IV administration: (A) over the disc, and (B) at the disc center. z is the valence of the antibiotics. All the concentrations were normalized to the peak value of the concentration in serum (i.e., 160 mg/L).

Figure 3.

Spatial distributions of antibiotic concentrations at 2 hours post a single IV administration. z is the valence of the antibiotics. Regions with concentration higher than the minimum inhibitory concentration (MIC) [e.g., 1 mg/L (Tai et al., 2002; Walters et al., 2006a)] were colored in Crimson.

Figure 4.

Comparison of the antibiotic ($z=-2$) concentration profiles between single IV administration and double IV administration cases: (A) averaged over the disc and (B) at the disc center. The concentration was normalized to the peak value in serum (i.e., 160 mg/L). MIC: minimum inhibitory concentration, e.g., 1 mg/L.

Figure 5.

(A) Spatial distributions of a negatively charged ($z=-2$) antibiotic in the disc at 15th hour after the single IV administration. Variations of spatial concentration distributions of a negatively charged ($z=-2$) antibiotic in the disc with (B) a single IV administration, and (C) double IV administrations. Regions with concentration higher than 1 mg/L were colored in Crimson.

Table 1

Material properties of the IVD and vertebra in the finite element analysis

IVD Properties		
Reference water content ϕ_0^w ^a	CEP	0.6
	NP	0.85
	AF	linearly decreased from 0.85 (innermost) to 0.7 (outermost)
Thickness (mm)	CEP	0.6
	NP	10
	AF	10
c^F (mol/m ³) ^b	CEP	90
	NP	342.5
	AF	linearly decreased from 342.5 mM (innermost) to 163.4 mM (outermost)
Parameters for diffusivity ^c $\frac{D^\alpha}{D_0^\alpha} = \exp \left[-A \left(\frac{r^\alpha}{\sqrt{k}} \right)^B \right]$	CEP	A=1.29 B=0.372
	NP	A=1.25 B=0.681
	AF	A=1.29 B=0.372
Parameters for permeability ^d $k = a \left(\frac{\phi^w}{1 - \phi^w} \right)^n$	CEP ^e	a=0.0248 nm ² n=2.154
	NP	a=0.00339 nm ² n=3.240
	AF	a=0.00044 nm ² n=7.193
Mechanical properties (Lame constant) ^f	CEP	$\lambda=100$ kPa $\mu=200$ kPa
	NP	$\lambda=15.6$ kPa $\mu=0.18$ kPa
	AF	λ linearly increased from 15.6 kPa (innermost) to 300 KPa (outermost) μ linearly increased from 0.18 kPa to 100 KPa (outermost)
Vertebra properties		
Thickness (only a part of the vertebra modeled)	5 mm	
Mechanical properties (Lame constant) ^g	$\lambda=86.5$ MPa, $\mu=57.5$ MPa	

^aFrom (Antoniou et al., 1996; Magnier et al., 2009; Urban and Maroudas, 1979).^bFrom (Esko et al., 2009; Urban and Maroudas, 1979).^cFrom (Gu et al., 2004).^dFrom (Gu et al., 2003).^eFrom (Jackson et al., 2011).^fFrom (Cloyd et al., 2007; Iatridis et al., 1999; Iatridis et al., 1997).^gFrom (Goldstein, 1987).