



Research Paper

A comparison of systemic and local dexamethasone administration: From perilymph/cochlea concentration to cochlear distribution

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ARTICLE INFO

Article history:

Received 21 June 2018

Received in revised form

3 September 2018

Accepted 5 September 2018

Available online 7 September 2018

Keywords:

Dexamethasone

Intratympanic administration

High-performance liquid chromatography-mass spectrometry

Postaural administration

Systemic administration

ABSTRACT

Different types of inner ear diseases can damage different cochlear subsites by different mechanisms. Steroids administered by different methods are commonly used for treating inner ear diseases. There is reason to believe that dexamethasone (Dex) may reach cochlear subsite targets via different pathways after administration by different methods: Intratympanic (IT), postaural (PA), and intraperitoneal (IP). The purpose of this study was to explore the cochlear concentration and distribution of Dex after administration by different methods. High-performance liquid chromatography-mass spectrometry and immunofluorescence technology were employed to measure and compare the Dex concentration in the perilymph and cochlear tissue and the cochlear distribution of Dex. IT administration resulted in higher Dex concentrations in the perilymph and cochlear tissues than those with the other administration methods. Intratympanic and postaural administration could result in higher Dex concentrations in the organ of Corti than systemic administration, but systemic administration could result in higher Dex concentrations in the stria vascularis than the other administration methods. A decreasing basal-apical gradient of Dex uptake was present in the cochlea after IT but not IP or PA administration. These results indicate that different administration methods result in different Dex distributions, which can be attributed to features of the cochlear vascular system and intracochlear diffusion. Our results provide clinicians with an experimental basis for the use of different steroid injection routes to optimize the effects on inner ear diseases with different target organs.

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1. Introduction

The prevalence of inner ear diseases, such as sudden sensorineural hearing loss (SSNHL), Meniere disease (MD), and noise-induced hearing loss, is increasing due to an increase in life expectancy, noise exposure and the use of ototoxic medicines (Kim, 2017). Patients with inner ear diseases complain about hearing loss, vertigo or tinnitus. Different types of inner ear diseases can damage different cochlear subsites by different mechanisms (Creber et al., 2018). For example, the organ of Corti is the primary site of injury in noise-induced hearing loss and aminoglycoside ototoxicity (Hirose et al., 2005; Sato et al., 2010); however, the stria vascularis is primarily damaged in autoimmune hearing loss and

MD (Kariya et al., 2009; Lin and Trune, 1997; Ohlemiller et al., 2008; Tagaya et al., 2011).

Corticosteroid treatment for inner ear diseases such as SSNHL and MD is well accepted, commonly used, and has high efficacy, as suggested by many clinical trials (Garduno-Anaya et al., 2005; Stachler et al., 2012; Wilson et al., 1980). Steroids affect SSNHL in many ways, such as inhibiting immune responses, influencing the microvascular circulation, exerting mineralocorticoid effects and reducing the endolymphatic pressure (Mort and Bronstein, 2006; Schreiber et al., 2010). High-dose systemic steroids are the current standard treatment for SSNHL; however, this treatment may result in many adverse effects, such as partial inhibition of the hypothalamic-pituitary-adrenal axis, changes in mood, increased blood glucose or blood pressure, gastritis, and sleep disorders (Henzen et al., 2000; Stachler et al., 2012; Weinstein, 2012). Intratympanic (IT) administration of steroids to treat SSNHL is a promising method that maintains high steroid levels in the perilymphatic fluid while simultaneously avoiding the complications of systemic steroids (El

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et al., 2017; Rauch, 2008; Rauch et al., 2011). In 2012, the American Academy of Otolaryngology Head and Neck Surgery recommended IT steroids as an initial treatment rather than salvage therapy in patients with SSNHL (Stachler et al., 2012). Although IT steroids present less potential toxicity than systemic steroids, they can also cause many infrequent and transient complications, such as pain, persistent tympanic membrane perforation, and dizziness; IT steroids are also costly and require multiple visits (Rauch et al., 2011; Stachler et al., 2012). Postauricular (PA) steroid administration has been popular for treating SSNHL in China since it was first used for treating intractable low-frequency sensorineural hearing loss (Yang et al., 2007). PA steroids can not only avoid many side effects resulting from systemic and IT steroids but also present satisfactory therapeutic effects (Li et al., 2013). The Chinese Society of Otorhinolaryngology Head and Neck Surgery released its latest version of guidelines for sudden deafness in 2015, which recommended the use of PA corticosteroids for patients who do not recover with systemic corticosteroids. Although many clinical studies have been conducted to compare the efficacy of different administration methods, the results remain controversial (Ahn et al., 2008a,b; Ermutlu et al., 2017; Filipo et al., 2010; Stachler et al., 2012).

In recent years, many studies have been conducted to explore the pharmacokinetic concentration of dexamethasone (Dex) in perilymph using high-performance liquid chromatography (HPLC) and high-performance liquid chromatography-mass spectrometry (LC-MS) (Bird et al., 2011; Liu et al., 2006; Salt et al., 2012; Tobita et al., 2002; Wang et al., 2009; Yang et al., 2008). HPLC used to measure substances has many disadvantages, such as a long elution time and low sensitivity. LC-MS, which has a short analysis time and high efficiency for identification and separation, has been used to measure steroids and is currently considered the most accurate method for steroid quantification (Handelsman and Wartofsky, 2013; Lv et al., 2018; Wudy et al., 2018). Because the cochlear aqueduct allows the perilymph to mix with cerebrospinal fluid (CSF), it is possible that not all drugs in the perilymph arrive in cochlear tissue (Salt and Hirose, 2018). Investigators have recently demonstrated that IT drugs can reach the brain and spinal fluid in experimental animals (Dean et al., 2012; Lee et al., 2012; Zhang et al., 2012), meaning that the amount of drug in the perilymph does not reflect the actual value in cochlear tissue. In this study, we use LC-MS to simultaneously estimate and compare the cochlear and perilymphatic pharmacokinetics of Dex administered by three different methods (intraperitoneal (IP), IT, and PA).

Based on the current pathology, it is critical to choose the most appropriate method for administering Dex to treat inner ear diseases by understanding the pharmacokinetics and distribution of Dex in cochlear tissue and how they differ by administration method. In this study, (1) we used LC-MS to measure the pharmacokinetics of Dex in the perilymph and cochlear tissue and (2) immunofluorescence to explore the cochlear Dex distribution after injection by three different methods.

2. Methods

2.1. Design

The present study contained two parts. In part 1, we used LC-MS to explore the concentration of Dex in the perilymph and cochlear tissue at different times after administration by three different methods (IP, IT, PA) and determine the times when each regime resulted in the maximal Dex concentration in the cochlea. In part 2, we used immunofluorescence to investigate the cochlear distribution of Dex after IP, IT, and PA administration when each regime resulted in the maximal Dex concentration, according to the results of part 1.

2.2. Animal studies

The experiments were approved by the ethics committee of Peking University Peoples' Hospital (Beijing, China). The guidelines for the Care and Use of Laboratory Animals set by the China Association of Laboratory/Animal Care were also applied for these experiments.

Specific-pathogen-free male adult guinea pigs that were 7–8 weeks old and weighed 250–300 g were purchased from the Peking University Laboratory Animal Centre. Guinea pigs who had healthy external auditory canals and tympanic membranes examined with an automicroscope were employed in this study. They were individually raised at an appropriate temperature (20–22 °C) and humidity (55–65%) under a 12-h light/dark cycle with free access to standard water and feed. All animals were intraperitoneally anaesthetized with ketamine (60 mg/kg) and xylazine (4 mg/kg). The animals were divided into four groups according to the administration method employed: the control group (systemic saline administration) (n = 4); IP administration (n = 4); IT administration (n = 4); and PA administration (n = 4). The details of each administration were as follows.

IP: After the animals were anaesthetized, the animals received an intraperitoneal injection of Dex solution at 1 ml/kg.

IT: After the animals were anaesthetized, 10 mg/ml Dex was administered slowly through the anterosuperior quadrant of the right tympanic membrane using a surgical microscope. An approximate 50- μ l volume of Dex was injected until the middle ear was entirely full. After the injection, each animal was maintained in a right-ear-up position for 30 min.

PA: After the animals were anaesthetized, Dex at 1 ml/kg was administered slowly through the middle of the right retroauricular groove.

Control group: After the animals were anaesthetized, they received an intraperitoneal injection of saline at 1 ml/kg.

The formulation applied in our study is markedly different from those used in prior studies where dexamethasone-phosphate solution or a dexamethasone suspension was used as a conventional formulation (Salt et al., 2012; Wang et al., 2009). Dexamethasone has the shortcoming of low solubility. Although the polar molecular properties of dexamethasone phosphate confer higher aqueous solubility, this form is substantially less permeable through the round window membrane (RWM) and vasculature than dexamethasone (Salt and Plontke, 2018). Dimethyl sulphoxide (DMSO) is regarded as a polar amphipathic solvent and is used to dissolve hydrophobic substances. Moreover, 1% DMSO has been shown to cause no functional or morphological changes in the inner ear (Roldan-Fidalgo et al., 2014). In this study, Dex (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 1% DMSO at a concentration of 10 mg/ml. The total volume given for IP and PA administration was identical at approximately 1 ml/kg. The actual volume given to the IT group was 50 μ l (0.5 mg). The systemic and local doses in this study were selected because they are the standard formulations for patients with SSNHL in our clinic.

2.3. Part 1

In this experiment, the pharmacokinetics of Dex injected by three different methods in the perilymph and cochlear tissue were investigated in guinea pigs with a positive Preyer reflex. At 1 h, 2 h, 4 h, 6 h, 12 h, 1 day and 3 days after injection, all animals were intraperitoneally anaesthetized with ketamine (60 mg/kg) and xylazine (4 mg/kg). Perilymph samples were first collected, and the perilymph sampling process was described in detail in previous studies (Liu et al., 2006; Wang et al., 2011). After the animals were anaesthetized, the skin behind the ear was clipped

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