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# Intranasal delivery of ciprofloxacin to rats: A topical approach using a thermoreversible in situ gel

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ABSTRACT

Intranasal administration of antibiotics is an alternative and attractive delivery approach in the treatment of local infections such as chronic rhinosinusitis. This topical route has the advantage of delivering high drug concentrations directly to the site of infection when trying to eradicate the highly resistant bacterial biofilms. The purpose of this study was to assess and compare the pharmacokinetic parameters of ciprofloxacin following intranasal and intravenous administrations to rats in plasma, olfactory bulb and nasal mucosa of two different nasal regions. For intranasal administration a thermoreversible in situ gel was used to increase drug residence time in nasal cavity. Ciprofloxacin concentration time-profile in nasal mucosa of the studied anterior region (at naso- and maxilloturbinates level) was markedly higher after intranasal administration (0.24 mg/kg) than that following intravenous administration (10 mg/kg), while in nasal mucosa of the more posterior region (at ethmoidal turbinates level) ciprofloxacin concentrations were found to be higher after intranasal administration when the different dose administered by both routes is taken into account. A plateau in ciprofloxacin concentration was observed in nasal mucosa of both studied regions after intranasal administration, suggesting a slow delivery of the drug over a period of time using the nasal gel formulation. In plasma and olfactory bulb, concentration of ciprofloxacin was residual after intranasal administration, which demonstrates this is a safe administration route by preventing systemic and particularly central nervous system adverse effects. Dose-normalized pharmacokinetic parameters of ciprofloxacin exposure to nasal mucosa revealed higher values after intranasal delivery not only in the anterior region but also in the posterior nasal region. In conclusion, topical intranasal administration appears to be advantageous for delivering ciprofloxacin to the biophase, with negligible systemic and brain exposure using a 41.7-fold lower dose than intravenous administration. Therefore, it may represent a promising approach in the drug management of chronic rhinosinusitis.

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## 1. Introduction

Ciprofloxacin (CIP), a second-generation fluoroquinolone, is a synthetic antibiotic used in the treatment of a variety of bacterial infections particularly those of the respiratory, genitourinary and gastrointestinal tracts (Emmerson and Jones, 2003; Oliphant and Green, 2002; Sousa et al., 2010). Amongst respiratory diseases, chronic rhinosinusitis (CRS) continues to be a significant medical problem without any specific approved medication; however, several clinical studies have been conducted using fluoroquinolones including CIP to evaluate medical responses (Comstock et al., 2010; Vaughan, 2004).

CRS is a persistent symptomatic inflammation of the mucosa of the nasal cavity and paranasal sinuses, affecting 10–15% of adult European and USA population. Not only it represents a considerable economical burden in society due to direct costs in health service and indirect costs in productivity, but it also has a significant impact in patients' quality of life (Ramakrishnan et al., 2015; Suh and Kennedy, 2011). Although the exact aetiology and pathophysiology of CRS are still unclear, the theory of bacterial biofilms and its contribution to the recalcitrant and persistent nature of CRS are gaining prominence. Several studies have confirmed the presence of bacterial biofilms in the sinonasal mucosa of patients with CRS and some of the bacteria identified include *Streptococcus pneumonia*, *Haemophilus influenza*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, the latter two being the most prevalent in refractory CRS patients (Al-Mutairi and Kilty, 2011; Bendouah et al., 2006; Kilty and Desrosiers, 2008; Psaltis et al., 2008; Schwartz et al., 2016; Serralheiro et al., 2013; Suh and Kennedy, 2011). Current American and European guidelines for the management of CRS recommend with different grades the use of topical corticosteroids and broad-spectrum or cultured-directed oral antibiotics. Only patients who do not respond to these pharmacological therapies should be submitted to

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endoscopic sinus surgery (Fokkens et al., 2012; Rosenfeld et al., 2015; Schwartz et al., 2016). Studies have shown that bacterial biofilms are as high as 1000 times less susceptible to antibiotics than their corresponding planktonic form, which explains the lack of effectiveness of oral antibiotics in this clinical condition (Comstock et al., 2010; Desrosiers et al., 2007; Ramakrishnan et al., 2015). Increasing the concentration of antibiotics, especially those with concentration-dependent antibacterial activity such as fluoroquinolones, would overcome this drawback. However, high concentrations at the infected site are difficult to attain by traditional routes of administration (e.g. oral) without significant risks of systemic toxicity. Topical administration appears as an alternative approach to deliver high concentrations of antibiotics directly to the site of infection, using lower effective doses and thus minimizing systemic absorption and reducing the potential for systemic adverse effects (Comstock et al., 2010; Chiu et al., 2007; Chono et al., 2007; Desrosiers et al., 2007; Serralheiro et al., 2013). Presently, the information about topical intranasal (IN) administration of antibiotics in the management of CRS is scarce and often inconclusive (Lim et al., 2008; Wei et al., 2013). Evidence for clear benefits of topical antibiotics in patients with CRS is insufficient and therefore not recommended as first-line therapy; nonetheless, literature suggests that it is a reasonable treatment option for patients that are refractory to traditional oral antibiotics and surgical therapies (Lee and Chiu, 2014; Lim et al., 2008; Suh and Kennedy, 2011). Scheinberg and Otsuji (2002) conducted a clinical study where several antibiotics, including CIP and levofloxacin, were administered via nebulization to individuals with recalcitrant CRS. Based on a comparison of symptoms before and after treatment, they found that the use of nebulized antibiotics was effective and safe (Scheinberg and Otsuji, 2002). Furthermore, symptomatic and endoscopic data before and after nebulization with fluoroquinolones (e.g. CIP, levofloxacin and ofloxacin) to postsurgical CRS patients revealed a significantly longer average infection-free period (Vaughan and Carvalho, 2002).

CIP is the most potent of the currently marketed fluoroquinolones against *Pseudomonas aeruginosa*, which is known to be associated with recalcitrant CRS (Bendouah et al., 2006; Emmerson and Jones, 2003; Oliphant and Green, 2002; Zhanel et al., 2002). Therefore, IN administration of CIP is expected to be well succeeded as a cultured-directed therapy for refractory CRS patients, since it probably allows a topical antibiotic effect with lower potential for systemic toxicity. Presently, topical formulations of CIP are commercially available as ophthalmic and otic solutions/suspensions (Cilodex® SPC; Ciloxan® SPC; Ciprodex® Prescribing Information; Cetraxal® Prescribing Information). An otic suspension was tested by Sahin-Yilmaz et al. (2008) to deliver the antibiotic into sinonasal mucosa and no significant improvement on the bacterial infection was found probably because of the rapid nasal clearance of the drug (Sahin-Yilmaz et al., 2008). In situ gels have recently attracted a lot of attention as favourable delivery systems used to increase drug residence time, due to their viscosity and ability to undergo transition into a gel at the infection site. Indeed, several ophthalmic in situ gel forming systems for CIP have been designed with sol-gel transitions induced by a shift in pH, temperature, or ionic strength (Abdelkader and Mansour, 2014; Ahmed et al., 2014; Al-Kassas and El-Khatib, 2009; Makwana et al., 2015; Mansour et al., 2008; Varshosaz et al., 2008).

Following this line of research, a thermoreversible in situ gel containing CIP was used in the present work for IN administration to rats. CIP concentrations in plasma, olfactory bulb and nasal mucosa were determined and the pharmacokinetic parameters were assessed and compared, following IN and intravenous (IV) administrations to rats. To the best of our knowledge, only one in vivo study has been performed with IN gel formulations of CIP; however only data about plasma pharmacokinetic properties of CIP were given (Ozsoy et al., 2000). Thus, this is the first study that simultaneously characterizes the pharmacokinetic behavior of CIP delivered by IN route in nasal mucosa, plasma and olfactory bulb, giving key information about drug exposure at the biophase and also assessing the potential for systemic and brain drug exposure.

## 2. Materials and methods

### 2.1. Chemicals and reagents

CIP was purchased from Sigma-Aldrich (St. Louis, MO, USA) and gatifloxacin, used as internal standard (IS), was obtained from Biokemix (New Mills, Derbyshire, UK). Methanol and acetonitrile (both HPLC gradient grade) were purchased from Fisher Scientific (Leicestershire, UK). Ultrapure water (HPLC grade, 18.2 MΩ·cm) was prepared by means of a Milli-Q water apparatus from Millipore (Milford, MA, USA). Reagents such as fuming hydrochloric acid (37%), formic acid (98–100%) and triethylamine (TEA) were acquired from Merck KGaA (Darmstadt, Germany), and sodium hydroxide and trichloroacetic acid were obtained in solid state from Sigma-Aldrich (Steinheim, Germany). Potassium dihydrogen phosphate and *ortho*-phosphoric acid (85%), used to prepare 25 mM phosphate buffer pH 3.0 solution, were obtained from Merck KGaA (Darmstadt, Germany) and Panreac (Barcelona, Spain), respectively. Pluronic F-127 and propylene glycol were supplied by Sigma-Aldrich (St. Louis, MO, USA). Injectable solution of pentobarbital sodium was commercially available under the brand Eutasil® (200 mg/mL; Ceva Saúde Animal). Sodium chloride 0.9% solution was acquired from B·Braun Medical (Queluz de Baixo, Portugal).

### 2.2. Animals

Healthy adult male Wistar rats (RccHan:WIST; $n = 48$) weighing 290–340 g were used in this study and purchased from a professional stockbreeder (Harlan®, Barcelona, Spain). The animals were housed under controlled environmental conditions (12 h light/dark cycle; temperature 20 ± 2 °C; relative humidity 55 ± 5%) for a minimum of five days before the experiments. During this period, animals had free access to a standard rodent diet (4RF21, Mucedola®, Italy) and tap water. Rats were fasted overnight (12h) prior to drug administration and kept on fast during the first 4 h of the study. all experimental and care procedures were conducted in accordance with the European Directive (2010/63/EU) regarding the protection of laboratory animals used for scientific purposes and with the Portuguese law on animal welfare (Decreto-Lei 113/2013, 2013).

### 2.3. Preparation and optimization of ciprofloxacin formulations

For IN and IV administration, CIP was firstly dissolved at the concentration of 30 mg/mL in an aqueous acidic solution of 1% (v/v) of fuming hydrochloric acid (37%).

Pluronic F-127 (PF-127) was used to prepare the thermoreversible gel for IN administration by the cold method described by Schmolka (1972). A weighed amount of 9.6 g of PF-127 was slowly added to 40 mL of ultrapure cold water while providing gentle mixing and subsequent magnetic stirring to promote hydration of the flakes. The mixture was stored at 4 °C over night to achieve complete dissolution of PF-127 at 24% (w/v). A volume of 200 μL of the acidic CIP solution (30 mg/mL) previously prepared was then incorporated in 1800 μL of the thermoreversible gel (24% PF-127, w/v), leading to a final thermosensitive formulation with 3 mg/mL CIP and 21.6% (w/v) PF-127. Finally, the pH of this IN formulation was adjusted to 5.3–5.5 with minor amounts of 0.5 M NaOH in order to avoid nasal irritation. To ensure gelation of the thermoreversible gel at nasal physiological temperature, the percentage of PF-127 was optimized and three different concentrations of drug-free PF-127 gel were tested. Gelation temperatures were determined by the test tube inverting method described by Gilbert et al. (1987) and Mansour et al. (2008). A falcon tube containing 2 mL of the thermoreversible gel, sealed with parafilm, was immersed in a water bath. The temperature of the bath was increased by 2 °C from room temperature and left to equilibrate for 10 min at each new temperature. The sample was then examined for gelation, which is considered to have occurred if the meniscus no longer moves when tilted >90°. Tests were performed

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