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RESEARCH ARTICLE

Comparison of plasma pharmacokinetics of Tanreqing solution between intratracheal aerosolization and intravenous injection in rats

Cui Li[1,2] | Siyu Liu[3] | Gan Luo[2] | Guohua Wang[2] | Baoxian Zhang[2] | Qixia Nie[2]

[1] China Academy of Chinese Medical Sciences, Beijing, China

[2] Institute of Chinese Material Medica, China Academy of Chinese Medical Sciences, Beijing, China

[3] The Institutes of Biomedical Sciences of Shanghai Medical School, Fudan University, Shanghai, China

Correspondence
Baoxian Zhang and Qixia Nie, Institute of Chinese Material Medica, China Academy of Chinese Medical Sciences, Beijing, China.
Email: zhangbaoxian925@tom.com; qxnie@icmm.ac.cn

Abstract

A rapid ultra high performance liquid chromatography tandem mass spectrometry method was developed for the simultaneous analysis of baicalin, oroxylin A-7-*O*-*β*-D-glucoronide and chlorogenic acid in rat plasma, and applied to comparison of pharmacokinetics of Tanreqing solution between intratracheal aerosolization and intravenous injection. Results of the analytical method validation assay showed high sensitivity, accuracy and suitable recovery. Results of pharmacokinetics showed similar decline phases for baicalin, oroxylin A-7-*O*-*β*-D-glucoronide and chlorogenic acid in two different delivery routes. The half-lives of intratracheal aerosolization and intravenous injection were 0.90 and 1.22 h for baicalin, 0.47 and 0.17 h for oroxylin A-7-*O*-*β*-D-glucoronide and 0.22 and 0.13 h for chlorogenic acid, and this implies that compounds were retained in the lung for a relatively short time. This study was the first to provide important pharmacokinetics information for traditional Chinese medicine delivery to the lung.

KEYWORDS

intratracheal aerosolization, intravenous injection, plasma pharmacokinetics, Tanreqing solution, UHPLC–MS/MS

1 | INTRODUCTION

Ever since the successful development of inhaled insulin, drug delivery via lung administration has become an attractive route to treat diseases (Patton & Byron, 2007). Drug delivery to the lung is advantageous to avoid the extensive first-pass metabolism, increasing the bioavailability and reducing the time of pharmacological onset of activity (Brillault, Tewes, Couet, & Olivier, 2017; Dugas et al., 2013; Gaspar et al., 2015; Patton & Byron, 2007). As a noninvasive and easy drug administration route, drug delivery via lung administration also has the potential to minimize toxicity without compromising efficacy and improve patient compliance (Fu & de Lannoy, 2002). Nowdays, it is preferably used in the treatment of pulmonary disease such as respiratory tract infections, asthma and chronic obstructive pulmonary disorder in the clinic (Li et al., 2016; Nahar et al., 2013).

Abbreviations: MRM, multiple reaction monitoring; MRT, mean residence time; TRQ, Tanreqing solution.

Traditional Chinese medicines have been used to treat respiratory diseases for thousands of years (Wong, Lam, & Fong, 2012; Zhang et al., 2014). Although the enormous gas-exchange surface of the lung represents a versatile and highly promising market, exploitation of this route for drug delivery of traditional Chinese medicine has been rare until recently. Traditional Chinese medicine Tanreqing solution (TRQ) is a famous traditional Chinese medicine prescription. Consisting of five kinds of traditional Chinese medicines: Radix Scutellariae, *Forsythia suspense*, Flos Lonicerae, bear gall powder and Cornu Gorais. In clinical practice TRQ is mainly utilized to cure upper respiratory tract infections (Dong, Zhong, Yang, Xiong, & Mao, 2013; Wang et al., 2011, 2016). In this work, TRQ was selected as the research object for drug delivery via lung administration. Baicalin, oroxylin A-7-*O*-*β*-D-glucoronide and chlorogenic acid are the main active compounds in TRQ (Liu et al., 2014; Zhang, Sun, Gao, Chen, & Chai, 2016). These compounds are associated with a variety of biological activities, including anti-inflammatory, antipyretic and anti-tumor (Farah, Monteiro, Donangelo, & Lafay, 2008; Liao et al., 2005; Wei et al., 2017; Zhou et al., 2013). A rapid ultra-high-performance liquid chromatography

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tandem mass spectrometry (UHPLC–MS/MS) method was developed for the simultaneous analysis of baicalin, oroxylin A-7-*O*-*β*-D-glucoronide and chlorogenic acid in rats plasma, and used for pharmacokinetics studies of both drug delivery to the lung and intravenous administration of TRQ. By evaluating plasma pharmacokinetics data from intravenous and inhalational administration of TRQ, our aim was to increase the mechanistic understanding of the lung absorption processes and provide support for the clinical potential of traditional Chinese medicine in the inhalation route.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

Both baicalin and chlorogenic acid were purchased from the National Institutes for Food and Drug Control (Beijing, China). Oroxylin A-7-*O*-*β*-D-glucoronide and apiin were obtained from Jiangsu Yongjian Pharmaceutical Technology Co. Ltd (Jiangsu, China). The purities of all standard drugs were >98% and met the requirements of ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) analysis. The chemical structures of all compounds are shown in Figure 1. HPLC-grade acetonitrile, formic acid and methanol were purchased from Fisher Scientific (FairLawn, NJ, USA). Ultrapure water was supplied by a Cascada™ IX water purification system obtained from Pall Corporation (Port Washington, NY, USA). Tanreqing solution was supplied by Shanghai Kaibao Pharmaceutical Co. Ltd (Shanghai, China). A 10% chloral hydra solution was purchased from Beijing Dingguochangsheng Biotecnology Co. Ltd (Beijing, China). All other chemicals were analytical grade and implemented without further purification.

2.2 | Animals

All male Sprague–Dawley rats (210–220g) were supplied by Vital River Laboratories (Beijing, China), and were kept in a temperature- and humidity-controlled environment with free access to food and water in a 12 h light–dark cycles. All experimental procedures were approved by the Committee on Animal Care and Usage of the China Academy of Chinese Medical Sciences. All of the operations in experiments followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.3 | Size of the particles of TRQ

TRQ was delivered to the lung as particles. The size of the particles is the major factor that affects the deposition. A miniature liquid aerosolizer (Beijing Huironghe Technology Co. Ltd, Beijing, China) was used in the study. The size of the particles was measured on a Spraytec laser diffraction system from Malvern Instruments Ltd (Worcestershire, UK). All measurements were made at room temperature (25°C) at a relative humidity close to 60% (Dayal, Shaik, & Singh, 2004; Nahar et al., 2013). The focal length of the lens was 1.0 m, which has a particle size range of 0.5–200 mm. Measurements were conducted at 1 cm from the laser beam six times. Data was reported as Dv50, defined as 50% of the cumulative volume undersize.

2.4 | Pharmacokinetics study

Twelve rats were evenly divided into two groups, and were anesthetized using an intraperitoneal injection of 3 mL/kg body weight 10% chloral hydrate. TRQ was analyzed by Shanghai Kaibao Pharmaceutical Co. Ltd. The concentrations of baicalin, oroxylin A-7-*O*-*β*-D-glucoronide and chlorogenic acid in TRQ were 853.75, 44.24 and 6.28 μg/mL. Group 1 was given an intravenous bolus injection of TRQ in a tail vein at a dose of 1 mL/kg of body weight. Group 2 was set on the operating table at 20° angle, and then was treated intratracheally with aerosolized TRQ using a miniature liquid aerosolizer at a dose of 1 mL/kg of the body weight. TRQ was atomized via the trachea of rats into the lung as previously described (Sakagami, 2006). A blood sample (0.3 mL) was collected from the ocular fundus veins of rats before administration and after 10, 20, 30, 45 min, 1, 1.5, 2, 3, 6, 12 and 24 h. To prevent blood from clotting, all collected blood samples were placed in a plastic centrifuge tube prefilled with EDTA anticoagulant. Then blood samples were centrifuged at 4000 rpm for 15 min at 4°C, and stored in a low-temperature refrigerator (−20°C) until analysis.

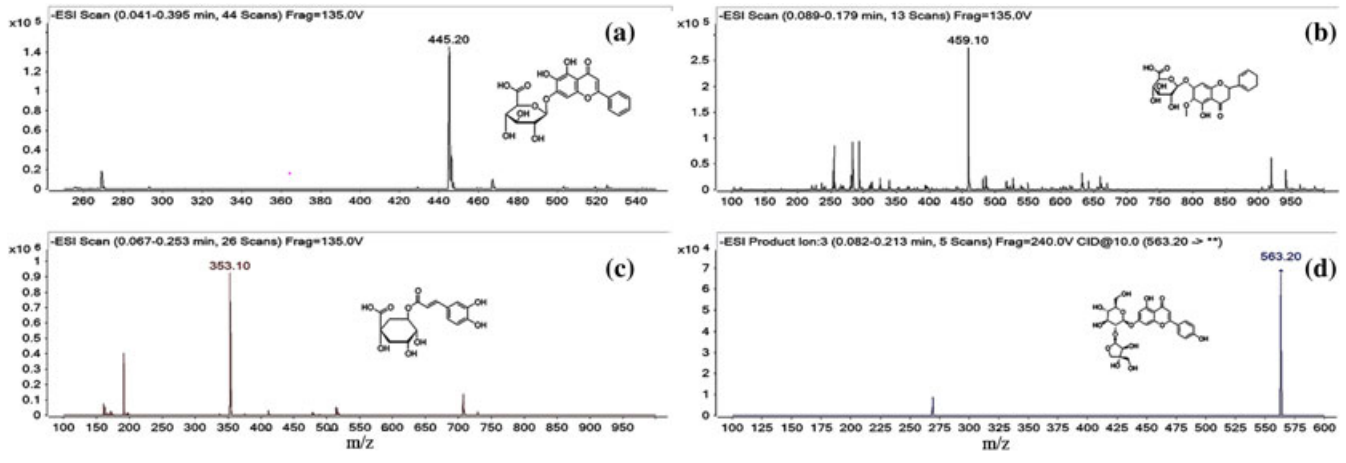

FIGURE 1 MS spectra and chemical structures of baicalin (a), oroxylin A-7-*O*-*β*-D-glucoronide (b), chlorogenic acid (c) and apiin (d)