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ORIGINAL ARTICLE

Mechanism of drug interaction between a Kampo medicine, byakkokaninjinto, and tetracycline in rats

Kotaro Hitoshi · Miki Katoh · Yoshiteru Tanaka · Shunsuke Kurono · Kazuo Hotta · Hiroko Saito · Takaaki Hasegawa · Masayuki Nadai

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Abstract We have previously reported that concomitant oral administration of the Kampo medicine, byakkokaninjinto (TJ-34), in extract granules, reduced the plasma concentrations of tetracycline (TC) and ciprofloxacin in humans, which might be the result of forming a chelate with Ca^{2+}. In the present study, we investigated the effect of a chelating agent, ethylenediaminetetraacetic acid (EDTA), on the plasma concentration–time profiles of TC after coadministration of TJ-34 dried extract and TC in rats to clarify whether metal ions contained in the TJ-34 dried extract contribute to this interaction. TJ-34 dried extract significantly reduced the plasma concentration of TC. The values of maximum concentration (C_{max}), area under the plasma concentration–time curve and percentage of urinary recovery (f_e) of TC were reduced to 42%, 40%, and 45%, respectively. On the other hand, treatment with EDTA significantly counteracted the effect of TJ-34 dried extract to reduce absorption of TC, indicating that metal ions mainly account for the interaction. Next, we investigated the effect of staggered administration of TJ-34 dried extract and TC to avoid the drug interaction between them. Administration of TJ-34 dried extract 2 h before TC had no effect on plasma concentrations and pharmacokinetic parameters of TC. These results provide a precise mechanism of the interaction TJ-34 and TC, suggesting a safe and effective dosage regimen to coadminister TJ-34 and TC in clinical use.

Keywords Kampo medicine · Byakkokaninjinto · Tetracycline · Chelate · Drug interaction

K. Hitoshi · M. Katoh · Y. Tanaka · S. Kurono · M. Nadai (✉)
Department of Pharmaceutics, Faculty of Pharmacy,
Meijo University, 150 Yagotoyama, Tenpaku-ku,
Nagoya 468-8503, Japan
e-mail: nadai@meijo-u.ac.jp

K. Hotta · H. Saito · T. Hasegawa
Department of Pharmacy and Pharmacokinetics,
Aichi Medical University School of medicine, 21 Nagakute,
Aichi 480-1195, Japan

Introduction

Kampo medicine, a mixture of herbal medicines, is originated from Chinese medicines and has been modified and developed in Japan over more than a thousand years. It is possible for Kampo medicines to be coadministered with Western medicines because they are mainly prescribed for chronic diseases such as atopic dermatitis, bronchial asthma, hypertension, and diabetes for a long-term period. Because there is a considerable concern about the growing number of medicines prescribed along with an increase of lifestyle-related diseases such as hypertension and diabetes [1], it would be of great value in clinical practice to clarify drug interactions between Kampo medicines and Western medicines.

Many herb–Western medicines or Kampo medicines–Western medicines interactions have been discussed before [2–6]. Coadministration of St. John's wort, a herb extensively used as an antidepressant [7], potently inhibited the activities of major human drug-metabolizing enzymes [8]. There are also reports on Kampo medicines–Western medicines interaction represented by shosaikoto with interferon, which provoked interstitial pneumonia in humans [9].

It has been reported that 7% of the Kampo prescriptions involved concomitant use of antimicrobial agents in

clinical practice in Japan [10]. Kampo medicines, generally administered as an extract granule, are prepared by adding inactive ingredients, such as magnesium stearate as a lubricant, or lactose hydrate as an excipient, to the dried extract of the crude drugs. Because almost all Kampo medicines contain a small amount of metal cations as a lubricant, Hasegawa et al. [3, 4] has investigated the pharmacokinetic interactions of frequently prescribed Kampo medicines with quinolone antimicrobial agents, known to form insoluble chelate with cations such as Ca^{2+}, Al^{3+}, and Mg^{2+}. In their studies, extract granules of hochuekkito, rikkunshito, juzentaihoto, shosaikoto, rikkunshito, and saireito had no effect on the bioavailability of levofloxacin or ofloxacin in humans. These results indicated that metal cations contained in Kampo medicines as a lubricant had no effect on the bioavailability of quinolone antimicrobial agents. However, our previous study demonstrated that byakkokaninjinto (TJ-34) extract granules, which are mainly prescribed in patients with diabetic dry mouth and dermatosis, significantly reduce the plasma concentrations of tetracycline (TC) and ciprofloxacin in humans [11]. This phenomenon is speculated to be a result of reduced intestinal absorption of the antibiotics caused by the formation of insoluble chelate with cations contained in the TJ-34 extract granule, as it contains a large amount of Ca^{2+} compared to other Kampo medicines.

The purpose of the present study was to clarify the precise mechanism of the drug interaction between TJ-34 and TC, and to propose a safe and effective way to coadministrate them, using rats. The effects of a chelating agent, ethylenediaminetetraacetic acid (EDTA), on coadministration of TJ-34 dried extract and TC were investigated to clarify the contribution of metal ions contained in TJ-34 dried extract to the interaction between the two drugs. The effect of staggered administration of the two drugs was also investigated.

Materials and methods

Chemicals and reagents

TJ-34 extract granules (Lot No. AA5931) and TJ-34 dried extracts (Lot No. 2070034010) were kindly supplied by Tsumura & Co. (Tokyo, Japan). TJ-34 is composed of five crude drugs (summarized in Table 1) and the inactive ingredients magnesium stearate, lactose, and sucrose esters of fatty acids. Tetracycline hydrochloride (TC) and ethylenediaminetetraacetic acid disodium dehydrate (EDTA) were purchased from Nacalai Tesque (Kyoto, Japan). All other reagents were of analytical or highest grade commercially available.

Table 1 Composition of TJ-34

Crude drug	Amount (g)
Gypsum fibrosum	15.0
Oryzae radix	8.0
Anemarrhena rhizome	5.0
Glycyrrhiza radix	2.0
Ginseng radix	1.5

Nine grams of TJ-34 extract granules contain 5.0 g of a dried extract of the mixed crude drugs listed here

Analysis of cationic metals in TJ-34 extract granule and TJ-34 dried extract

Contents of Ca^{2+}, Mg^{2+}, Al^{3+}, Fe^{2+}, Zn^{2+}, and Mn^{2+} in TJ-34 extract granules and TJ-34 dried extract were analyzed by an X-ray fluorescence element analyzer (MESA-500; Horiba, Tokyo, Japan). A basic parameter method was used for quantitative analysis.

Animals

Eight- to 9-week-old male Wistar rats weighing 230–270 g were purchased from SLC Japan (Hamamatsu, Japan). Rats were housed under a controlled environmental temperature of 24°–25°C and a 12 h light/dark cycle with a commercial food diet ad libitum and free access to drinking water. All animal experiments were carried out according to the guidelines of the Faculty of Pharmacy, Meijo University for the Care and Use of Laboratory Animals.

Effect of TJ-34 dried extract on pharmacokinetics of TC

Following an overnight fast (16 h), 200 mg/kg TJ-34 dried extract ($n = 7$) was orally coadministered with 20 mg/kg TC. TJ-34 dried extract was suspended in distilled water at 100 mg/ml (containing 40 mM calcium), whereas TC was dissolved in distilled water at 10 mg/ml (20 mM). TJ-34 dried extract was administered 1 min before TC. Distilled water was orally administered 1 min before TC as a vehicle ($n = 10$). Blood samples (0.25 ml) were collected from a catheter implanted in the right jugular vein, at 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h after administration of TC using EDTA as an anticoagulant agent. Blood samples were immediately centrifuged at 11,000 *g* for 5 min at 4°C to yield plasma. Urine was collected into iced receivers over 24 h post dose using metabolic cages. Urine and plasma samples were stored at −20°C until analysis.