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Herb–drug interaction of *Evodia rutaecarpa* extract on the pharmacokinetics of theophylline in rats

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Abstract

The extract of *Evodia rutaecarpa* fruit and its preparation were used for the treatment of gastrointestinal disorders and headache. To assess the possible herb–drug interaction, the ethanol extract of *Evodia rutaecarpa* fruit (1 and 2 g/kg/day, p.o.) and the herbal preparation Wu-Chu-Yu-Tang (1 and 5 g/kg/day) were given to rats daily for three consecutive days and on the fourth day theophylline was administered (2 mg/kg, i.v.). Theophylline concentration in blood was measured by a microdialysis coupled to a liquid chromatographic system. Pharmacokinetic data were calculated by noncompartmental model. The results indicate that the theophylline level was significantly decreased by the pretreatment with the extract of *Evodia rutaecarpa* and herbal preparation Wu-Chu-Yu-Tang with dose-related manner. It is suggested that the herb–drug interaction may occur through the induction of the metabolism of theophylline.

Keywords: *Evodia rutaecarpa*; Microdialysis; Pharmacokinetics; Theophylline; Traditional Chinese medicine

1. Introduction

Theophylline is a potent bronchodilator that has been widely used in the treatment of acute asthma. Almost entirely 90% of theophylline is metabolized in the human liver by the cytochrome P450 (CYP) with its members CYP1A2 and CYP2E1 (Ogilvie, 1978). It was also reported (Teunissen et al., 1985) that theophylline was metabolized to 1,3-dimethyluric acid (1,3-DMU) via CYP1A2 and CYP2E1 and to 1-methylxanthine via CYP1A2 which was further metabolized to 1-methyluric acid (1-MU) via xanthine oxidase in rats. Hence, it could be expected that the pharmacokinetic parameters of theophylline could be changed in the pretreatment of herbal medicine which affects the activity of CYP1A2 and CYP2E1. Theophylline has been characterized by a narrow therapeutic index with the therapeutic concentration ranges of 5–20 μg/ml. Therefore, drug–drug or herb–drug interaction may sensitively affect the therapeutics of theophylline.

The dried unripened fruits of *Evodia rutaecarpa* (Chinese name: Wu-Chu-Yu) are a traditional Chinese herbal medicine that has been used as a remedy for gastrointestinal disorders, headache, amenorrhea, and postpartum hemorrhage for a long time (Liao et al., 1981; Sheu, 1999). Recent reports indicate that *Evodia rutaecarpa* is a potent inducer of CYP1A (Ueng et al., 2001, 2002b). Rutaecarpine, an active ingredient, was originally isolated from *Evodia rutaecarpa* (Asahina and Kashiwaki, 1915) and total synthesized (Chavan and Sivappa, 2004) which possesses antihypertensive (Chiou et al., 1994), anti-platelet (Sheu et al., 1998) and antithrombotic (Sheu et al., 2000) activities. In addition, rutaecarpine has been identified as a potent inhibitor of CYP1A2 in both mouse and human liver microsomes (Ueng et al., 2002a). Wu-Chu-Yu-Tang (Goshuyu-to in Japanese Kampo medicine) is a

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traditional Chinese preparation for the treatment of migraine and vomiting which contains four herbs with *Evodia rutaecarpa*, Ginseng Radix, Zingiber Rhizoma, Zizyphi Fructus (Kano et al., 1991).

Microdialysis is a biological fluid sampling technique with a principle of passive diffusion processes through semi-permeable membrane. The mass transport through the membrane is governed by diffusion and forced by concentration gradient. Microdialysis sampling from blood vessels is applied to investigate the protein-unbound sample with no blood loss. Due to the constriction of blood volume, pharmacokinetic studies are often limited by the temporal resolution for a small experimental animal. With minimum disturbance of physiological function of the body, microdialysis compensate the disadvantage of blood withdrawing and increase the temporal resolution.

Few published data are available concerning the *Evodia rutaecarpa* related herb–drug interaction on the perspective of pharmacokinetics (Ueng and Wang, 2003). The purpose of this paper is to explore the effect of *Evodia rutaecarpa* and the herbal preparation Wu-Chu-Yu-Tang pretreatment on the pharmacokinetics of theophylline to rats with a microdialysis application.

2. Materials and methods

2.1. Chemicals and reagents

Theophylline was purchased from Sigma Chemicals (St. Louis, MO, USA). Rutaecarpine (purity 99.5%, by HPLC, Fig. 1) was isolated from *Evodia rutaecarpa* (Juss) Benth (Rutaceae) (Lin et al., 1991). Dried fruit of *Evodia rutaecarpa* (600 g) was collected at Lishan, Taichung, Taiwan. A voucher specimen (No. 700191) has been deposited in the National Research Institute of Chinese Medicine, Taipei, Taiwan. Fruits were powdered using a crushing machine (Yu Chi Machinery Co., Taiwan). The powder was immersed in deionized water–ethanol (1:1, v/v) overnight and then shaken at 50 °C, 200 rpm for 1 h. The mixture was filtered through filter paper (Advantac #1, Tokyo, Japan). The filtrate was concentrated using a rotary vacuum evaporator. Extracts were lyophilized (169 g; yield 28.17%) and then stored at room temperature. The herbal extract preparation, Wu-Chu-Yu-Tang was purchased from Sheng Chang Pharmaceutical Co., Taipei, Taiwan. Nine gram of Wu-Chu-Yu-Tang extract contain starch:concentrate herbal decoction (3.8:5.2, w/w). The concentrate herbal decoction was prepared from 7.5 g Evodia Fructus, 4.5 g Ginseng Radix, 9 g Zingiber Rhizoma and 6 g Zizyphi Fructus and the extraction yield of the decoction was 19.26%. Chromatographic solvents were obtained from Mallinckrodt Baker Inc. (Phillipsburg, NJ, USA). Triple deionized water from Millipore (Bedford, MA, USA) was utilized for all preparations.

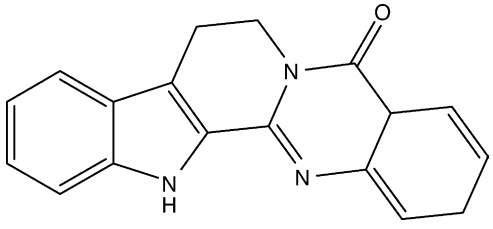

Fig. 1. Chemical structure of rutaecarpine.

2.2. Liquid chromatography

HPLC was performed with a chromatographic pump (BAS PM-80, West Lafayette, IN, USA), a Rheodyne Model 7125 injector equipped with a 10 μl sampling loop and an ultraviolet detector (Varian, Walnut Creek, CA, USA). Separation was achieved by a Phenomenex LUNA microbore Phenyl-Hexyl column (150 mm × 1 mm i.d.; 5 μm, Torrance, CA, USA) (Tsai and Liu, 2004). The mobile phase consisted of acetonitrile–methanol–10 mM monosodium phosphate (pH 3.0) (10:20:70, v/v), with a flow rate of 0.05 ml/min, and the wavelength was 270 nm. Output data from the detector were integrated using an EZChrom chromatographic data system (Scientific Software, San Roman, CA, USA).

2.3. Animals

The institutional animal experimentation committee of the National Research Institute of Chinese Medicine reviewed and approved all experimental protocols involving animals. Male, specific pathogen-free Sprague–Dawley rats were obtained from the Laboratory Animal Center of the National Yang-Ming University, Taipei. The animals had free access to food (Laboratory rodent diet #5P14, PMI Feeds Inc., Richmond, IN, USA) and water until 18 h prior to being supplied for experiments, at which time only food was removed. The rats were initially anaesthetized with urethane 1 g/ml and α-chloralose 0.1 g/ml (1 ml/kg, i.p.), and remained anaesthetized throughout the experimental period. The femoral vein was exposed for further drug administration. The rats' body temperature was maintained at 37 °C with a heating pad during the experiment.

2.4. Microdialysis experiment

Blood microdialysis system was comprised of a CMA/100 microinjection pump (CMA, Stockholm, Sweden) and microdialysis probes. The dialysis probe for blood (10 mm in length) was made of silica capillary in a concentric design (Tsai et al., 1999). Their tips were covered by dialysis membrane (Spectrum Lab., 200 μm inner diameter with a cut-off at nominal molecular weight of 13,000, Laguna Hills, CA, USA) and all unions were cemented with epoxy. At least 24 h was allowed for the epoxy to dry. The blood microdialysis probe was located within the jugular vein/right atrium and then perfused with anticoagulant dextrose (ACD) solution (citric acid 3.5 mM; sodium citrate 7.5 mM; dextrose