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Short Communication: In Vivo Evaluation of Microemulsion System for Oral and Parenteral Delivery of Rutaecarpine to Rats

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ABSTRACT Rutaecarpine-loaded microemulsion composed of 10.8% polyethylene glycol 400, 7.2% Tween 80, 20% caster oil, and 62% water were previously reported to be physically and chemically stable for at least 6 months. For the development of a Rutaecarpine-loaded microemulsion, here we studied the pharmacokinetic profiles of rutaecarpine after oral and intravenous administration of rutaecarpine-loaded microemulsion compared to suspension. The AUC of rutaecarpine from microemulsion after oral and intravenous administration increased about three-fold compared with that from suspension. Furthermore, the rutaecarpine-loaded microemulsion gave significantly higher AUC and C_{max} than did suspension, suggesting that the oral bioavailability of rutaecarpine in this microemulsion system could be enhanced due to the enhanced solubility of rutaecarpine by microemulsion. Thus, our results indicated that the microemulsion system composed of castor oil, polyethylene glycol 400, Tween 80, and water could be a more effective oral and parenteral dosage form for rutaecarpine.

KEYWORDS Microemulsion, Rutaecarpine, Pharmacokinetics

INTRODUCTION

Rutaecarpine, a bioactive component isolated from *Evodia rutaecarpa*, gave an antiplatelet activity and a vasorelaxing action (Sheu et al., 1996, 1998; Wang et al., 1999). However, it showed very low absorption, probably due to its poor water solubility. The solubility of rutaecarpine is about 0.05 ± 0.02 and 1358 ± 15 μg/mL in water and ethanol, respectively, which is insufficient to provide the desired amount in a solution for oral preparations (Choi et al., 2005). There have been many attempts to improve its solubility by applying various approaches such as co-solvency (Wang et al., 1999), surfactants (Adeel & Luthy, 1995; Shiau et al., 1994), dissolved organic matter (Rebhun et al., 1998), inclusion complexation (Archontaki et al., 2002) and solid dispersion (Verheyen et al., 2002; Watanabe et al., 2003).

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To improve the solubility of the poorly water-soluble drug rutaecarpine, a microemulsion system was formulated using castor oil, polyethylene glycol 400, Tween 80, and water (Choi et al., 2005). A recent report showed that the rutaecarpine (300 μg/g)-loaded microemulsion composed of 10.8% polyethylene glycol 400, 7.2% Tween 80, 20% caster oil, and 62% water was physically and chemically stable for at least 6 months. However, the previous studies focused on solubility of rutaecarpine and stability of the microemulsion as a fundamental experiment and there is a lack of information on the absorption of rutaecarpine from the microemulsion. Thus, in this study, we investigated the pharmacokinetic profiles of rutaecarpine after oral and intravenous administration of rutaecarpine-loaded microemulsion compared to rutaecarpine powder in aqueous suspension. Our results indicate that rutaecarpine-loaded microemulsion can improve the oral and intravenous bioavailability of the poorly water-soluble drug rutaecarpine.

MATERIALS AND METHODS

Materials

Rutaecarpine was supplied from the Institute of Organic Synthesis, College of Pharmacy in Yeungnam University (Kyungsan, South Korea). Polyethylene glycol 400 (PEG400), Tween 80, and castor oil were purchased from Yakuri Pure Chemicals Co. (Kyoto, Japan), Junsei Chemical Co. (Tokyo, Japan) and Sigma Aldrich Chemical Co. (Milwaukee, WI), respectively. All other chemicals were of reagent grade and used without further purification.

Preparation of Rutaecarpine-loaded Microemulsion

Rutaecarpine (30 mg) was thoroughly soluble in 20 g castor oil. The resulting oil phase was mixed with 10.8 g polyethylene glycol was mixed with 7.2 g Tween 80, added in 62% water and then passed through high-pressure homogenizer (Emulsiflex®-B3 Avestin Inc., Ottawa, Canada; Gao et al., 1998; Ko et al., 1994).

Pharmacokinetic Study

In vivo experiments–Male Sprague-Dawley rats weighing 250 ± 20 g were fasted for 24–36 hr prior to the experiments but allowed free access to water. Twenty-four rats were divided into four groups. Each group was orally or intravenously administered with rutaecarpine (300 μg/mL)-loaded microemulsion or suspension (1% povidone in water) containing rutaecarpine (300 μg/g), respectively. The rutaecarpine (300 μg/mL)-loaded microemulsion was composed of 10.8% PEG 400, 7.2% Tween 80, 20% caster oil, and 72% water. All animals care and procedures were conducted according to the Guilding Priciples in the Use of Animals in Toxicology, as adopted by the Society of Toxicology(USP) in 1989.

Administration–Each rat, anesthetized in an ether-saturated chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat. After recovering from anesthesia, rutaecarpine (300 μg/mL)-loaded microemulsion or suspension (1 mL/kg equivalent to rutaecarpine 300 μg/kg) was orally administered through a stomach sondle needle fitted on a glass syringe, respectively. Furthermore, rutaecarpine (300 μg/mL)-loaded microemulsion or suspension (1 mL/kg equivalent to rutaecarpine 300 μg/kg) was administered intravenously via femoral vein through the cannula. Half milliliter of blood was collected from the right femoral artery at various intervals and centrifuged at 3000 rpm for 10 min using a centrifuge 5415C (Eppendorf; Jiang et al., 2000).

Blood Sample Analysis

Plasma (100 μL) was mixed with 200 μL of acetonitrile solution containing ibuprofen (10 μg/mL), as an internal standard. It was then centrifuged at 3000 rpm for 10 min to precipitate the proteins. The supernatant layer (100 μL) was evaporated under N_2 (g). The residue was reconstituted in 50 μL of mobile phase. Then, the resulting solution analyzed by HPLC (Jasco PU-980) equipped with an Inertsil ODS-3 C_{18} column (GL science, 0.5 μm, 15 × 0.46 cm ID) and UV detector (Jasco UV-975). The mobile phase consisted of acetoniltrile, water, and orthophosporic acid (60:40:0.1, volume ratio). The eluent was monitored at 227 nm with a flow rate of 1 mL/min (Gao et al., 1998; Ko et al., 1994).

RESULTS AND DISCUSSION

The rutaecarpine (300 μg/g)-loaded microemulsion composed of 10.8% PEG 400, 7.2% Tween 80, 20%

caster oil, and 62% water was physically and chemically stable for at least 6 months (Choi et al., 2005). To investigate the oral and intravenous bioavailability of the microemulsion, the pharmacokinetic parameters of rutaecarpine were determined after oral and intravenous administration of rutaecarpine-loaded microemulsion or suspension (1% povidone in water), respectively.

Fig. 1 shows the change of mean plasma concentration after intravenous administration of rutaecarpine in rats. The plasma concentration of rutaecarpine after intravenous administration of rutaecarpine-loaded microemulsion and suspension decreased to ≤ 570 and 170 ng/mL by 120 min after the dose, respectively. The AUC of rutaecarpine from the microemulsion (min.μg/mL) increased about three-fold compared with that from suspension (Table 1). The K_{el} and $t_{1/2}$ values of rutaecarpine from microemulsion were not significantly ($p < 0.05$) different from those from suspension (Park & Kim, 1999; Von Corswant et al., 1998).

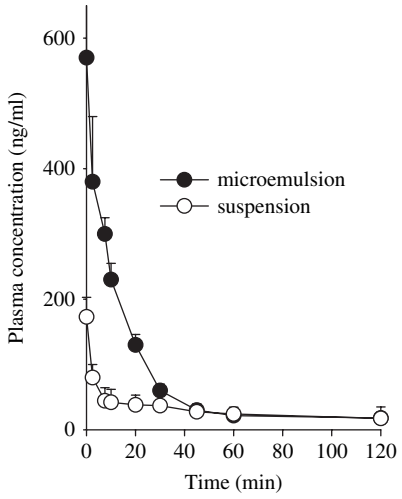

FIGURE 1 **Plasma Concentration-Time Profiles of Rutaecarpine After Intravenous Administration of Microemulsion and Suspension to Rats. The Rutaecarpine (300 μg/mL)-Loaded Microemulsion was Composed of 10.8% PEG 400, 7.2% Tween 80, 20% Caster Oil, and 62% Water. Each Value Represents the Mean + SD (n = 6). (*), p < 0.05 Compared to Suspension.**

TABLE 1 **Pharmacokinetic Parameters of Rutaecarpine After Intravenous Administration of Rutaecarpine-Loaded Microemulsion and Suspension**

Parameters	Microemulsion	Suspension
AUC (min.ng/mL)	14,400 ± 1720*	5,300 ± 1690
K_{el} (min^{-1})	0.005 ± 0.002	0.0010 ± 0.004
$t_{1/2}$ (min)	154.0 ± 66.7	78.1 ± 33.87

*p < 0.05 compared with suspension.
**Each value represents the mean ± SE (n = 6).

On the other hand, Fig. 2 shows the change of mean plasma concentration after oral administration of rutaecarpine in rats. The plasma concentrations of rutaecarpine in microemulsion were higher than those from suspension. In particular, in microemulsion, from 15 to 60 min, the plasma concentrations of rutaecarpine (30–60 ng/mL) were significantly higher than those in suspension ($p < 0.05$). However, from 90 min after the dose, the plasma concentrations of rutaecarpine in microemulsion were not significantly different from those in suspension (Jeng et al., 1995; Ko et al., 1994). These results indicated that the rutaecarpine-loaded microemulsion composed of castor oil, polyethylene glycol 400, Tween 80, and water improved the oral absorption of rutaecarpine. The AUC and C_{max} of rutaecarpine delivered by the microemulsion were higher than that delivered by suspension ($p < 0.05$; Table 2). In particular, the AUC of rutaecarpine from microemulsion increased about three-fold compared with that from suspension indicating that the rutaecarpine-loaded microemulsion composed of castor oil, PEG 400, Tween 80, and water could improve the oral bioavailability of rutaecarpine in rats due to the enhanced solubility of rutaecarpine by microemulsion (Choi et al., 2005). However, the T_{max}, K_{el}, and $t_{1/2}$ values of rutaecarpine from microemulsion were not significantly different from those from suspension.

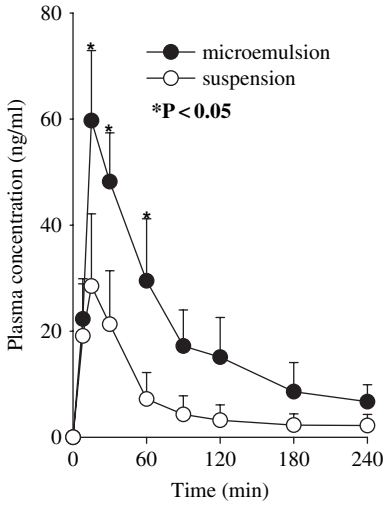

FIGURE 2 **Plasma Concentration-Time Profiles of Rutaecarpine After Oral Administration of Microemulsion and Suspension to Rats. The Rutaecarpine (300 μg/mL)-Loaded Microemulsion was Composed of 10.8% PEG 400, 7.2% Tween 80, 20% Caster Oil, and 62% Water. Each Value Represents the Mean + SD (n = 6). (*), p < 0.05 Compared to Suspension.**

TABLE 2 **Pharmacokinetic Parameters of Rutaecarpine After Oral Administration of Rutaecarpine-Loaded Microemulsion and Suspension**

Parameters	Suspension	Microemulsion
AUC (min. ng/mL)	1672.2 ± 944.4	4796.4 ± 1039.2*
T_{max} (min)	15 ± 9.6	15 ± 9.6
C_{max} (ng/mL)	28.50 ± 13.62	59.70 ± 13.21*
K_{el} (min^{-1})	0.0063 ± 0.0013	0.00767 ± 0.00367
$t_{1/2}$ (min)	111.6 ± 21.6	103.8 ± 35.4

*$p < 0.05$ compared with suspension.
**Each value represents the mean ± SE ($n = 6$).

CONCLUSION

It is concluded that the rutaecarpine-loaded microemulsion composed of castor oil, PEG 400, Tween 80, and water would be useful to deliver orally and intravenously rutaecarpine in a pattern that allows better absorption. It might be due to the enhanced solubility of rutaecarpine by microemulsion. The further study on the oral and intravenous bioavailability of rutaecarpine-loaded microemulsion in human subjects will be performed.

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