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Absorption behavior of etilefrine after buccal administration in rats

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ABSTRACT

Etilefrine hydrochloride (ET-HCl) is used in the treatment of hypotension. Dosage forms of orally administered tablets and parenteral injections are clinically available, but exhibit unfavorable characteristics, including cardiac toxicity, headaches, and damage at the injection site for the parenteral dosage form, and initially high plasma levels, fast elimination, and first-pass effects for its oral administration. Therefore, the buccal application of ET-HCl was herein investigated as an alternative to conventional administration routes. I.v., intragastric, and buccal administration were performed using rats, and absorption features were compared. Buccal application at open conditions for 1 h exhibited absolute bioavailability of more than 20%, while the intragastric administration gave much lower bioavailability (< 10%). The drug residue and drug distribution in the oral mucosa were investigated in order to clarify drug transfer behaviors. In the application of ET-HCl solution using a cotton ball, higher plasma concentrations and their maintenance at higher levels were achieved at 10 mg/kg than at 2.5 mg/kg. In addition, absorption was greater with a longer application (4 h) than with a shorter application (1 h). Etilefrine (ET) was rapidly absorbed using aqueous buffer of pH 9.5 as the solvent. Open application was appropriate for achieving and maintaining higher plasma levels. Thus, in the buccal application of ET-HCl aqueous droplets, a wide distribution throughout the mucosal surface is important for achieving rapid absorption and the maintenance of plasma levels. These findings suggested that the buccal application should be feasible administration of ET-HCl.

1. Introduction

High blood pressure (hypertension) is a high risk factor for brain infarction, cerebral hemorrhage, and cardiovascular events (Nyuyki et al., 2017; Moraes-Silva et al., 2017). However, low blood pressure (hypotension) often causes brain vascular disorders and heart diseases. Although hypotension does not directly result in a critical condition, physical and mental fatigue, such as vertigo and malaise, prevents the activities of daily living, indirectly leading to damage or diseases (Poon and Braun, 2005; Huang et al., 2017). The number of individuals with hypotension is very high and closely associated with age and physical condition (Rutan et al., 1992). Therefore, the prevention of or therapy for hypotension is of importance.

Etilefrine (ET) hydrochloride (HCl), named ET-HCl (Fig. 1), recorded in the Japanese Pharmacopoeia 17th Edition (JP17), is an agonist of and β adrenergic receptors, with constrictive effects on vascular smooth muscle and increased cardiac output being expected, respectively (Miller et al., 1973; Frost et al., 1977; Karasawa et al., 1992). Based on these functions of ET-HCl, it is used in the treatment of hypotension (Yamazaki et al., 1990; Bouaggad et al., 2000). ET-HCl is clinically available in dosage forms of orally administered tablets and parenteral injections (Hengstmann et al., 1975; Haustein and Hüller, 1985). The former is used in therapy for essential hypotension and orthostatic hypotension, while the latter is applied to the treatment of acute hypotension.

However, caution is needed regarding the use of these formally accepted dosage forms due to their pharmacokinetic characteristics and toxic features. The plasma half-life of this drug was previously reported to be approximately 2 h in humans (Hengstmann et al., 1975). Therefore, in the oral administration of ET-HCl, the drug must be taken three times per day, which may result in compliance issues. Furthermore, ET undergoes the first-pass effect (55% in humans) through gastrointestinal absorption (Hengstmann et al., 1975), which results in low bioavailability or an unstable supply of the drug. Parenteral injections of ET-HCl lead to high blood concentrations, resulting in toxic side effects due to its pharmacological function; for example, cardiac palpitations have been reported as an occasional side effect. Moreover, very high blood pressure is associated with the risk of cerebral hemorrhage or headache. Parenteral injections have also been shown to stimulate or damage tissues or nerves around the injection site, and may result in needle stick injuries or pain, which reduce the quality of life (QOL) of patients.

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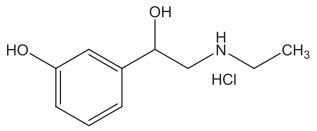

Fig. 1. Chemical structure of etilefrine hydrochloride (ET-HCl).

Due to these features of the conventional dosage forms described above, a gradual, sustained and non-invasive administration route is desirable for ET-HCl therapy. Novel administration routes to the mucosal membranes, such as rectal, nasal, or oral mucosa, have recently been attracting attention (Scott et al., 1999; Li et al., 2000; Owens et al., 2003) because they represent an alternative dosing route to intravenous (i.v.) injections (Campbell et al., 2012; Kaminsky et al., 2015). Mucosal absorption via these administration routes may achieve rapid absorption up to an effective plasma level (Ivaturi et al., 2013; Sakata and Onishi, 2013). Furthermore, mucosal administration is very useful for patients with diseases of the esophagus, stomach, or intestines. Oral mucosal delivery is very simple and easy to perform and may be appropriate as an alternative to oral administration or parenteral injections (Rossi et al., 2005; Onishi et al., 2014; Meng-Lund et al., 2016). Long-term medical therapy is needed for patients with hypotension, and further it is desirable for its therapy to be useful at the emergency of acute hypotension. In the present study, the potential of oral mucosal dosing with ET-HCl in ordinary or emergent therapies for hypotension was investigated *in vivo*. A dosage form of ET-HCl solution was used because rapid drug absorption was expected. Moreover, since ET-HCl may cause mouth dryness as a side effect, the application with this solution might be appropriate than dried dosage forms, power or tablet.

2. Materials and methods

2.1. Materials

ET-HCl (purity ≥ 98% (HPL assay), Lot No. EP J3672), phosphoric acid, glycine, 1-octanol (Oct), and urethane were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Saline with the JP17 preparation was purchased from Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). Cotton with the JP17 preparation was obtained from Suzuran Sanitary Goods Co., Ltd. (Nagoya, Japan). All other chemicals used were of reagent grade.

2.2. Animals

Male Wistar rats (7 weeks old, 200–210 g) were purchased from Tokyo Laboratory Animal Science Co., Ltd., and used in *in vivo* experiments. Animals were kept on the breeding diet MF supplied by Oriental Yeast Co., Ltd. (Tokyo, Japan) with water available *ad libitum* in a room in which temperature and relative humidity were maintained at 23 ± 1 °C and 60 ± 1%, respectively. The light–dark cycle was 12 h. The experimental protocol was approved by the Committee on Animal Research of Hoshi University (Tokyo, Japan), and animal experiments were performed according to the Guiding Principles for the Care and Use of Laboratory Animals of Hoshi University.

2.3. Partition experiments

As the initial step, 1/15 M phosphate buffers of pH 6, 7 and 8, 1/10 M carbonate buffers of pH 9 and 9.5, and 1/10 M glycine buffer of pH 9.5 were prepared. Saline and these aqueous buffers were used in partition experiments. Aqueous solvent (30 mL) and Oct (30 mL) were mixed and stirred magnetically at 25 °C for 24 h. The mixtures were then left to stand until the aqueous buffer and Oct phases became separated and clear. Both phases were taken separately and used as solvents in the partition experiment.

The aqueous phase containing ET-HCl at 11.5 μg/mL was prepared. Oct phase (2 mL) was then added to 2 mL of the drug aqueous solution. The mixture was stirred with a vortex mixer for 1 min, and shaken vigorously 100 times by hand. After centrifugation, the aliquot sample (50 μL) was taken from the aqueous phase. After the remaining mixture had been stirred overnight, 50 μL of the aqueous phase was collected in the same manner. Each sample (40 μL) was analyzed by HPLC.

2.4. HPLC assay

A Shimadzu LC-6AD pump equipped with a Shimadzu RF-10AXL fluorescence detector and a Shimadzu C-R7A plus chromatopac were used as the HPLC apparatus. A YMC Pack ODS-AM column (6 mm inner diameter × 150 mm length; YMC Co., Ltd., Kyoto, Japan) was used as the analytical column.

The concentration of ET in the plasma sample was measured by HPLC at room temperature. The mixture of 0.1% phosphoric acid and acetonitrile (20:1, v/v) was used as the mobile phase. Detection was performed with a fluorescent detector at excitation and emission wavelengths of 272 nm and 301 nm, respectively. The flow rate was 1 mL/min, and 40 μL of the sample was injected on the column. The concentration of ET was measured as that of ET-HCl by the absolute calibration curve method using ET-HCl. The recovery ratio from rat plasma was calculated as the ratio of the peak area obtained by the extraction experiment to the ideal peak area given by the standard dissolved in the mobile phase.

2.5. Preparations of dosing samples and methods of administration

Administration routes, doses, solvents used, and dosing methods are shown in Table 1. The corresponding administration routes were labeled with individual codes (dosing code), as shown in Table 1. These codes were used in the following methods and results.

The administration of ET-HCl was performed in the dosage forms of i.v., intragastrically (orally), and buccally. Regarding the i.v. injection, ET-HCl was dissolved in saline and injected via the jugular vein at 1 mg/kg (0.25 mL). This application code was IV(1).

Regarding oral administration, ET-HCl was dissolved in saline and dosing was performed intragastrically at 2.5 mg/kg (0.5 mL) and 10 mg/kg (0.5 mL). The dosing codes were PO(2.5)-S and PO(10)-S, respectively.

Buccal administration was conducted under the following conditions

1) ET-HCl was dissolved in saline, and a cotton ball was immersed in

Table 1
Dosing routes, conditions and manners in the administration of ET-HCl solution.

Administration route	Dose (mg/kg)	Solvent	Dosing manner	Dosing code*
Intravenous	1	Saline	Bolus	IV(1)
Intragastric	10	Saline	Bolus	PO(10)-S
	2.5	Saline	Bolus	PO(2.5)-S
Buccal	10	Saline	Open, 4 h applied	BU(10)-Op (4 h)-S
	2.5	Saline	Open, 4 h applied	BU(2.5)-Op (4 h)-S
	2.5	saline	Open, 1 h applied	BU2.5)-Op (1 h)-S
	2.5	Gly-buffer (pH 9.5)	Open, 1 h applied	BU(2.5)-Op (1 h)-G
	2.5	Gly-buffer (pH 9.5)	Closed, 1 h applied	BU(2.5)-Cl (1 h)-G

IV: intravenous, PO: intragastric, BU: Buccal; Op: open, Cl: closed; 4 h: 4 h application, 1 h: 1 h application; S: saline, G: glycine buffer of pH 9.5.