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In vitro transdermal permeation and *in vivo* transdermal absorption of domperidone cream formulations compounded from tablets as a hospital formulation

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This study aimed to evaluate the transdermal absorption of domperidone cream formulations compounded from a tablet formulation. The creams were prepared to simulate hospital formulations, and skin permeation was evaluated *in vitro* and *in vivo*. *In vitro* steady-state permeation flux (*J*) values determined of each domperidone solution (19 types) was evaluated using Franz diffusion cells. Cream formulations containing 0.1% domperidone were prepared by mixing N-methyl-2-pyrrolidone (NMP) and commercially available cream bases (hydrophilic, absorptive and urea (10%)-containing cream). *In vitro* skin permeation of the creams was evaluated under non-occlusive and occlusive conditions. The plasma concentrations of domperidone 24 h after application of the creams were determined. The *J* value of NMP solution of domperidone was the highest among that of the tested solutions. The *J* values of the 0.1% domperidone hydrophilic and absorptive creams were lower than that of the urea-containing cream under non-occlusive conditions. However, the occlusive dressing technique (ODT) increased the *J* values of the hydrophilic and absorptive creams such that they were similar to that of the urea-containing cream. In *in vivo* absorption studies using ODT, the plasma concentrations of domperidone 24 h after application of the absorptive and urea-containing creams were 0.94±0.13 and 1.68±0.45 ng/mL, respectively. However, it was not detected after application of the hydrophilic cream. The 0.1% domperidone creams, prepared using commercially available cream bases, showed significant *in vivo* absorption.

1. Introduction

Nausea and vomiting are observed in acute gastroenteritis including an infection caused by rotavirus and norovirus (Offit and Rubin 1982; Kerwat et al. 2011), and mainly as side effects of anticancer drugs (Lindley et al. 1992; Scotté et al. 2019). Domperidone is a selective peripheral dopamine antagonist at the dopamine D2 receptor, used in the prevention and symptomatic relief of acute nausea and vomiting (Wilson and Dundee 1979; Barone 1999; Reddymasu et al. 2007). The product of domperidone, Nauzerin has been used in many countries including Japan. Domperidone is currently available in oral dosage forms, such as tablets, orally disintegrating tablets and powders, or as suppositories. It is difficult to administer these formulations to patients with acute nausea, vomiting, and diarrhea. A transdermal drug delivery system (TDDS) has many advantages over drug delivery *via* conventional routes (Prausnitz et al. 2004; Karande and Mitragotri 2009). A TDDS is usually well accepted, easy to apply, and a convenient alternative when oral dosage forms are difficult to swallow or the patient is experiencing nausea or vomiting. Therefore, transdermal delivery of domperidone could overcome these limitations of oral administration in such patients.

The aim of this study was to prepare transdermal formulations of domperidone and evaluate their transdermal absorption *in vitro* and *in vivo*. In this study, domperidone ointments and creams were compounded from the pulverized commercially available tablet of the drug as a hospital formulation. The formulation using pulverization of the tablets is considered to be safer than bulk, and such a formulation is classified as a "lower risk class" hospital formula-

Table 1: Solubility and *in vitro* skin permeation flux of domperidone simple solutions

Solvent	Solubility (mg/mL)	J ($\mu g \cdot cm^{-2} \cdot h^{-1}$)
Buffer		
Phosphate buffered saline (pH 4.0)	0.10 ± 0.05	0.19 ± 0.70
Phosphate buffered saline (pH 5.6)	0.07 ± 0.01	0.43 ± 0.39
Phosphate buffered saline (pH 8.2)	0.01 ± 0.01	0.18 ± 0.18
Alcohols		
Ethanol (EtOH)	0.95 ± 0.24	0.21 ± 0.05
Isostearyl alcohol (ISAL)	0.46 ± 0.09	0.08 ± 0.05
Lauryl alcohol (LAL)	0.34 ± 0.24	0.11 ± 0.03
2-Octyl-1-dodecanol (OD)	0.24 ± 0.03	0.22 ± 0.20
Oleyl alcohol (OAL)	0.40 ± 0.03	0.20 ± 0.08
Benzyl alcohol (BA)	6.11 ± 0.03	1.12 ± 0.48
Polyols		
Propylene glycol (PG)	2.74 ± 0.26	0.32 ± 0.21
Dipropylene glycol (DPG)	5.28 ± 0.04	0.18 ± 0.17
Polyethylene glycol 300 (PEG300)	6.05 ± 0.01	n.d.
Esters		
Polyoxyethylene alkyl ether (PGM)	0.57 ± 0.09	0.29 ± 0.26
Isopropyl myristate (IPM)	n.d.	n.d.
Diisopropyl adipate (DIA)	0.09 ± 0.02	0.14 ± 0.03
Propylene carbonate (PC)	0.17 ± 0.02	n.d.
Ethers		
Polyoxyethylene (2) oleyl ether (Oleth-2)	0.54 ± 0.04	0.03 ± 0.02
Others		
N-Methyl-2-pyrrolidone (NMP)	7.03 ± 0.38	14.6 ± 5.38
Triacetin (TA)	0.11 ± 0.02	n.d.

Each value represents the mean ± S.D. of 3 determinations.
n.d., not detected.

tion in the guidelines of Japanese Society of Hospital Pharmacists. In addition, we selected creams and ointments for TDDS in this study, because they are commonly used in clinical practice.

2. Investigations, results and discussion

2.1. Domperidone solubility and in vitro transdermal absorption of domperidone solutions

The solubility of domperidone in benzyl alcohol (6.11 mg/mL), propylene glycol (2.74 mg/mL), dipropylene glycol (5.28 mg/mL), polyethylene glycol 300 (6.05 mg/mL), and NMP (7.03 mg/mL) was higher than that in other solutions (Table 1). The permeation flux values of domperidone was the highest when domperidone was administered as an NMP solution (14.6 $\mu g \cdot cm^{-2} \cdot h^{-1}$).

2.2. In vitro skin permeation study of domperidone ointments and creams under non-occlusive condition

Ointment or cream formulations containing 0.1% domperidone were prepared by mixing NMP solutions of domperidone and commercially available ointment or cream bases (10:90, w/w). Since the concentration of NMP used as a pharmaceutical additive was up to 10% (Abolghasem et al. 2010), skin permeation of domperidone using 10% NMP was studied. The *J* values of domperidone ointments and creams based on the *in vitro* skin permeation study under non-occlusive condition are shown in Table 2.

Table 2: *In vitro* skin permeations of domperidone ointments and creams

Ointment and cream	J ($\mu g \cdot cm^{-2} \cdot h^{-1}$)
Simple ointment	0.11 ± 0.04
Hydrophilic vaseline	0.19 ± 0.04
Absorptive cream	0.12 ± 0.06
Hydrophilic cream	0.10 ± 0.04
Solbase	n.d.
Pastaron soft ointment	0.15 ± 0.03
Urepearl cream	0.21 ± 0.07
Hirudoid soft ointment	0.18 ± 0.07
Hirudoid cream	0.18 ± 0.13

Each value represents the mean ± S.D. of 3 (absorptive cream, hirudoid soft ointment), 4 (simple ointment, hydrophilic vaseline, hydrophilic cream, urepearl cream 10%, hirudoid cream) and 5 (pastaron soft ointment 10%) determinations.
n.d., not detected

It was the highest in 0.1% domperidone urepearl cream. It was thought that urea contained in urepearl cream promoted the transdermal permeation of domperidone. Urea is a physiological component and a natural moisturizing factor in the skin; its mild keratolytic effect could have promoted the permeation (Wong et al. 1988). In order to evaluate the influence of the base, a hydrophilic cream, having the same base as that of urepearl cream, and another similar absorptive cream were selected.

2.3. In vitro skin permeation of the domperidone cream preparation under an occlusive and non-occlusive conditions

Cumulative domperidone concentrations from the different bases, under occlusive and occlusive conditions in the *in vitro* permeation study, revealed notable permeation of the drug after 24 h (Fig. 1). Under the occlusive condition, the urepearl cream showed the highest domperidone permeation, followed by hydrophilic and absorptive creams (Fig. 1a). However, the absorptive cream showed highest domperidone permeation, followed by the urepearl and hydrophilic creams under the non-occlusive condition (Fig. 1b).

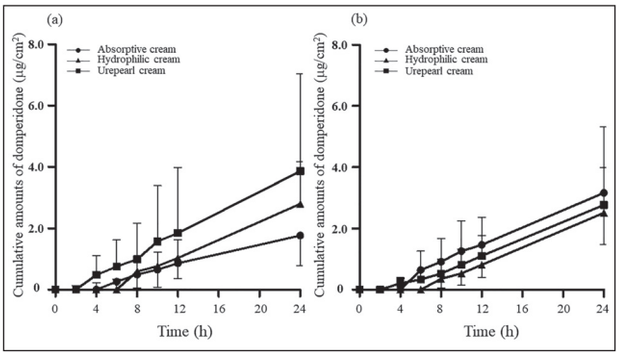

Fig. 1: *In vitro* skin permeation profile after application of domperidone creams under occlusive (a) or non-occlusive (b) conditions. Data are presented as mean±S.D of 3 (absorptive cream, hydrophilic cream in occlusive condition) and 4 (hydrophilic cream in non-occlusive condition, urepearl cream) determinations.

ODT is a method in which an ointment or a cream is applied to the skin and covered with a dressing material; it has been reported to promote the absorption of drugs (Berardesca et al. 1992; Kennish and Reidenberg 2005). Because of the occlusion by ODT, the *J* values of hydrophilic and absorptive creams increased by 1.6 and 1.5 times of that under the non-occlusive condition (Fig. 2). However, the urepearl cream exhibited similar permeations under both non-occlusive and occlusive conditions. Occlusion increases the water content in the stratum corneum by preventing water transpiration from the skin, thereby promoting percutaneous absorption of the drugs (Hotchkiss et al. 1992; Treffel et al. 1992). In hydrophilic and water-absorbing creams, this mechanism is thought to increase the absorption of domperidone.

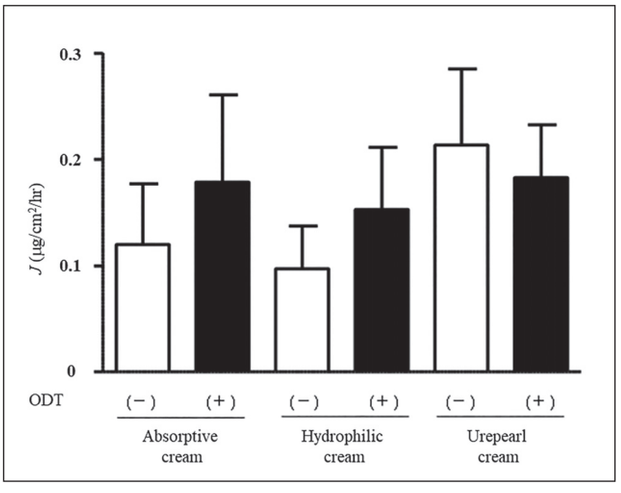

Fig. 2: *In vitro* skin permeation flux of domperidone creams under occlusive (closed columns; ODT, −) or non-occlusive (open columns; ODT, +) conditions. Data are presented as mean±S.D. of 3 (absorptive cream, hydrophilic cream in occlusive condition) and 4 (hydrophilic cream in non-occlusive condition, urepearl cream) determinations.

However, urea in the urepearl cream also increases the water content in the stratum corneum (Chong et al. 1993), by altering its ultrastructure and leading to the formation of large hydrophilic diffusion channels; consequently, permeability of the stratum corneum increases (Björklund et al. 2013). We hypothesized that domperidone permeation from the urepearl cream was not influenced by ODT because the cream itself saturated the stratum corneum with water.

2.4. In vivo transdermal absorption of domperidone cream under the occlusive condition

We studied the *in vivo* absorption of domperidone in rats, and domperidone concentrations in plasma, 24 h after the application

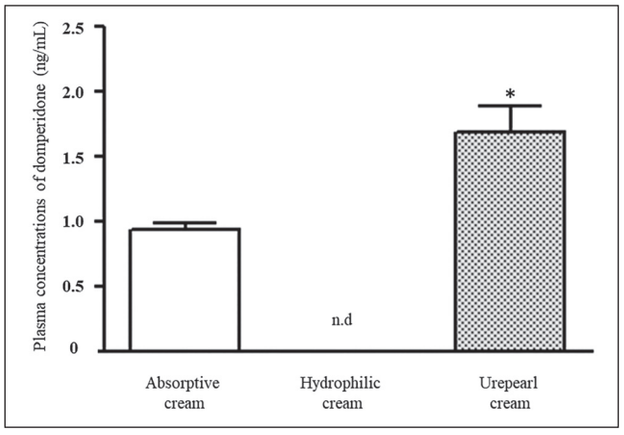

Fig. 3: *In vivo* skin absorption of domperidone cream under the occlusive condition in rats. Data are presented as mean±S.D. of 8 and 7 rats treated with absorptive and urepearl creams, respectively. The plasma concentration of domperidone was not detected in rats treated with hydrophilic cream (n=3). *Significant difference between absorptive cream and urepearl cream with Student's t-test, $*p < 0.001$.
n.d., not detected.

of the absorptive and urepearl creams of domperidone under the occlusive condition, were 0.94±0.13 and 1.68±0.45 ng/mL, respectively (Fig. 3). The difference of plasma concentrations in absorptive and urepearl creams was statistically significant ($p < 0.001$).

Therapeutic plasma levels of domperidone are ranging from 1–10 ng/mL in humans (Heykants et al. 1981). Although the plasma drug concentration 24 h after the administration of urepearl cream formulation was lower than the therapeutic range of the drug, the drug concentration could increase to the steady-state level after several times of dosing, and reach the range.

2.4. Conclusion

Domperidone (0.1%) in creams prepared using commercially available cream bases showed significant *in vivo* absorption. Transdermal delivery of domperidone may be a suitable route for the treatment of nausea and vomiting.

3. Experimental

3.1. Materials

Domperidone was purchased from Toronto Research Chemicals Inc. (Toronto, Canada). Domperidone tablets (Nauzerin) were purchased from Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan). Simple ointment, hydrophilic cream, and hydrophilic vaseline were purchased from Mylan Inc. (Tokyo, Japan). Absorptive cream base was purchased from Nikko Pharmaceutical Co., Ltd. (Gifu, Japan). Macrogol ointment base (Solbase) was purchased from Meiji Yakuhin Co., Ltd. (Tokyo, Japan). Urea cream (Urepearl cream, 10%) was purchased from Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan). Urea ointment base (Pastaron soft ointment, 10%) was purchased from Sato Pharmaceutical Co., Ltd. (Tokyo, Japan). Heparinoid cream (Hirudoid cream, 0.3%) and heparinoid ointment (Hirudoid soft ointment, 0.3%) were purchased from Maruho Co., Ltd. (Osaka, Japan). All other chemicals used were of reagent grade.

3.2. Preparation of domperidone solutions

Domperidone solutions were prepared by pulverizing tablets of domperidone and adding 1.65 g of the powder (150 mg of domperidone) to 5 mL of the 19 different solvents listed in Table 1. The solutions were stirred by vortex mixing for 1 min, sonicated for 30 min, and stored at 30 °C overnight (15–20 h). Further, the solutions were centrifuged at 4,000 rpm for 20 min and filtered through a 0.45 μm filter (Toyo Roshi, Tokyo, Japan). The concentration of domperidone in the solution was determined by HPLC, and its solubility was calculated.

3.3. Preparation of domperidone ointment or cream

The domperidone solution (10 mg/mL, 2 g) of N-methyl-2-pyrrolidone (NMP) was added to commercially available ointment or cream bases (18 g) and mixed well with a pestle. The ointments or creams used were heparinoid cream and heparinoid ointment, urea cream and urea ointment, macrogol ointment, simple ointment, hydrophilic vaseline, absorptive cream, and hydrophilic cream.

3.4. In vitro permeation of domperidone solution and ointment or cream

The *in vitro* skin permeation of domperidone formulations was measured using Franz diffusion cells (effective diffusional area: 3.14 cm^2, receptor volume: 17 mL), as previously reported with minor modification (Matsui et al. 2014). The receptor cell (dermis side) was filled with PBS at pH 7.4, stirred with a magnetic stirrer bar, and maintained at 37 °C in order to hold the temperature on the stratum corneum surface at 37 °C. The skin of male Sprague-Dawley (SD) rats (7–8 weeks, Japan SLC Inc.) was placed on the receptor cell with the stratum corneum facing upwards. The amount of domperidone solution applied was 5 mg/cm^2 (formulation per unit effective diffusional area of the stratum corneum), and the amount of domperidone in each ointment or cream applied was 134 μg/cm^2. In the experiment of occlusive condition, the domperidone cream formulations were covered with a sheet of film dressing (Tegaderm, 3M Healthcare, Tokyo, Japan). Cumulative amounts of permeated domperidone were measured by HPLC and concentration-time profiles from 0 to 24 h were plotted.

3.5. In vivo absorption following application of domperidone ointment or cream

To evaluate transdermal absorption, the dorsal hair of SD rats (7–8 weeks) were trimmed with clippers under pentobarbital (40 mg/kg, i.p.) anesthesia. Domperidone ointment or cream was homogeneously applied (8 × 5 cm^2 area) on the dorsal surface and kept under an occlusive condition with a sheet of Tegaderm that was fixed to the skin with Eraspore (Nichiban, Tokyo, Japan). To evaluate skin absorption, a clinically feasible and relevant dose of 5.36 mg (134 μg/cm^2) of domperidone as each ointment or cream in was applied on the skin of rats under anesthesia. Blood samples (400 μL) were withdrawn from the subclavian vein 24 h after transdermal administration. Plasma samples, isolated from whole blood samples by centrifugation, were stored at -20 °C until determination of the domperidone concentration. At the end of the collection period, rats were euthanized by use of pentobarbital. All animal experiments were approved by the Institutional Animal Care and Use Committee of the University of Shizuoka (approval number: 156157) and adheres to the Japanese animal experiment guidelines.

3.6. Measurement of domperidone by HPLC

The concentration of domperidone in the *in vitro* permeation study was determined using an HPLC system (LC-10, Shimadzu, Kyoto, Japan), with a packed column (Capcell Pak C18 MGIII, 3 μm, 3 mm i.d. × 150 mm, Shiseido, Tokyo, Japan). The mobile phase was acetonitrile:water (35:65, v/v) containing 6.5 mM sodium 1-octanesulfonate and 0.1% phosphoric acid. The flow rate was 0.5 mL/min; detection was based on UV absorbance at 287 nm.

3.7. Measurement of plasma concentration of domperidone in rats

The plasma concentration of domperidone was determined using LC-MS. Briefly, 100 μL of celiprolol (1 μg/mL), as an internal standard, and 4% ammonia solution (400 μL) was added to the rat plasma sample (250 μL). After centrifugation at 10,000 ×g for 5 min, the supernatant was subjected to solid-phase extraction (OASIS HLB 96-well microelution plate; Waters, Milford, MA, U.S.A.). The eluate (50 μL) was treated with 1 mL of 0.1% formic acid in methanol. After desiccating the collected extract, the pellet was treated with 50 μL of 0.1% formic acid and stirred in vortex mixer for 30 s. After centrifugation at 3,000 rpm, the supernatant (20 μL) was filtered through a 0.2-μm filter (Millipore) and the eluate (10 μL) was injected into the chromatographic system for LC-MS analysis.

The plasma concentration of domperidone was measured by LC (Alliance 2695 system, Waters Co.) with a mass spectrometer (Micromass ZQ mass spectrometer; Waters Co.). A separation column, Atrantis T3 (using 150 mm × 2.1 mm, 3 μm, Waters) at 40 °C, was used. The mobile phase consisted of acetonitrile:formic acid (0.1%) in a ratio of 25:75 at a flow rate of 0.3 mL/min. The mass spectrometer was operated in the positive ion mode at *m/z* 426 and 380 for domperidone and celiprolol, respectively. The limit of quantitation was 0.4 ng/mL and the intra-assay coefficient of variation was < 7%.

3.8. Data analysis

The apparent steady-state permeation flux (J) in the *in vitro* permeation study was calculated using the cumulative amount of domperidone. The J value was calculated up to 24 h. The least-squares method using the solver tool of Microsoft® Excel 2003 was used. All data are presented as mean±standard deviation (S.D.). The GraphPad Prism software (version 5.0, GraphPad, San Diego, CA, USA) was used for statistical analysis. The statistical analysis of the data was performed with a Student's t-test and Tukey's test. Statistical significance was accepted at $p < 0.05$.

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