In vitro and in vivo transdermal iontophoretic delivery of naloxone, an opioid antagonist

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ABSTRACT

Aim: The feasibility of transdermal delivery of naloxone, an opioid antagonist, by anodal iontophoresis patches using Ag/AgCl electrodes was investigated.

Methods: To examine the effect of current strength, species variation and drug concentration on skin permeability of naloxone, in vitro skin permeation studies were performed using rat dorsal skin and porcine ear skin as the membrane. To determine in vivo transdermal absorption rate of naloxone, the iontophoretic patch system was applied to the dorsal skin of conscious rat with a constant current supply for 24 h.

Results: The in vitro steady-state skin permeation flux of naloxone current-proportionally (0–360 μA/cm²) increased without significant differences between these two different skin types. The in vitro delivery rate through the porcine skin was found to be independent of the concentration of naloxone hydrochloride dehydrate in the donor patch over the range from 1 to 10% (w/v). In the in vivo pharmacokinetic study, plasma concentrations of naloxone steadily increased and sustained steady-state levels from 4 h to 24 h after the initiation of current application. In vivo steady-state transdermal absorption rates at 90 and 180 μA/cm² were 136 and 305 μg/h/cm², respectively.

Conclusion: These results suggest that the transdermal delivery rates of naloxone by anodal iontophoresis are sufficient for the management of intoxication in opioid-overdosed patients.

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1. Introduction

Naloxone is a non-specific, competitive opioid receptor antagonist used for the treatment of opioid-overdose-induced respiratory depression, for the detoxification in opioid-dependent patients (Clarke et al., 2005; van Dorp et al., 2007), and for avoiding opioid-anesthesia-induced respiratory depression in patients treated with high-dose opioid agonists (Johnstone et al., 1974; Takahashi et al., 2004). However, oral formulation is less suitable for naloxone because of its extremely low bioavailability (2%) due to high first-pass effect (Panchagnula et al., 2005; Shibata et al., 2002). The elimination half-life of naloxone in plasma is between 30 and 100 min (Fishman et al., 1973). Since the duration of action of most available opioids exceeds that of naloxone, repeated intravenous or intramuscular administration (0.8–2 mg boluses, repeated as necessary up to 10 mg) and continuous intravenous infusion (4–8 μg/kg/h) have been required to prevent recurrence of respiratory depression in both opioid-overdosed patients and post-operative patients treated with opioid anesthesia (Clarke et al., 2005; Johnstone et al., 1974; Lasagna, 1964; Takahashi et al., 2004; van Dorp et al., 2007).

Iontophoresis, an active transdermal drug delivery technology, non-invasively delivers hydrophilic charged molecules across the skin via application of a small electric current on the skin, enables precise control of drug delivery kinetics according to the modulation of the intensity and duration of current application (Batheja et al., 2006; Dixit et al., 2007; Nair et al., 1999). As results, transdermal iontophoretic drug delivery system offers the potential benefits of simplicity, efficacy and patient acceptance by maintaining a constant blood drug concentration for an extended period of time with acceptable inter-patient variations. Anodal iontophoresis is the method whereby a cationic drug is delivered across an epithelial barrier when placed under a positively charged delivery electrode (anode) from which it is repelled. A counter electrode completes the circuit by drawing physiological anions (i.e. Cl⁻) from the body. Naloxone hydrochloride (Log P = 1.11 at pH 7.4, pKₐ₁ = 7.09, pKₐ₂ = 9.89) is a water-soluble drug and it exists as a cation in aqueous solution at pH 5–6. Hence, anodal iontophoresis is a desirable alternative administration route of naloxone for detoxication in opioid addiction and opioid anesthesia. However, to date...

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there have been no reports regarding transdermal iontophoretic delivery of naloxone.

The aim of the present study is to evaluate the feasibility of transdermal iontophoretic delivery of naloxone using anodal iontophoretic patches *in vitro* and *in vivo*. To examine the effect of current strength, species variation and drug concentration on skin permeability of naloxone, *in vitro* skin permeation studies were performed using rat dorsal skin and porcine ear skin as the membrane. To determine *in vivo* transdermal absorption rate of naloxone, the iontophoretic patch system was applied to the dorsal skin of conscious rat with a constant current supply for 24 h, and the transdermal absorption rate was determined by a constrained numeric deconvolution method (Fiset et al., 1995; Park et al., 1998; Verotta, 1989).

2. Materials and methods

2.1. Chemicals and animals

Naloxone hydrochloride dehydrate (Sigma–Aldrich, Inc., St. Louis, MO, USA) was dissolved in an aqueous solution with 3% (w/v) hydroxypropyl cellulose-H (HPC-H, Nippon Soda Co., Ltd., Tokyo, Japan) for iontophoretic experiments. Buspirone hydrochloride was purchased from LKT Laboratories, Inc. (St. Paul, MN, USA) for use as an internal standard in liquid chromatography tandem mass spectrometry (LC/MS/MS). High-performance liquid chromatography (HPLC) grade acetonitrile and ammonium acetate were purchased from Merck KGaA (Darmstadt, Germany) and Wako Pure Chemical Industries, Co., Ltd. (Osaka, Japan), respectively.

Fresh porcine ears collected from 6 to 7-month-old pigs were obtained from a local abattoir. Twelve-week-old male Sprague–Dawley rats weighing 351–398 g were purchased from Japan SLC, Inc. (Hamamatsu, Japan) and were used for both *in vitro* and *in vivo* studies. The rats were housed individually at room temperature (23 ± 2 °C), humidity 50 ± 20%, with a 12-h night/day cycle, and supplied with a standard pellet diet and water *ad libitum*. The protocols for animal use and care were approved by the Institutional Animal Care and Use Committee of TTI ellebeau, Inc.

2.2. Iontophoretic patch design

A proprietary iontophoretic patch used in present study was composed of an electrical high capacity sliver/silver chloride electrode (TCT®, Transcu Group Ltd., Singapore) and a reservoir retaining anodal or cathodal solution. Each electrode was housed in a reservoir and connected to an electric current controller (SDPS-518, Syrinx Inc., Tokyo, Japan). The reservoir was comprised of polyester non-woven material and housed in polyethylene foam to form an adhesive pad having flexibility to allow for animal movements. Volumes and active surface areas of the reservoir for *in vitro* and *in vivo* iontophoretic patches were 180 µL with 0.79 cm² (diameter: 1 cm) and 250 µL with 1.13 cm² (diameter: 1.2 cm), respectively.

2.3. In vitro protocol

2.3.1. Skin preparation

Porcine ear skin was prepared for skin permeation study according to the reported methods (Cazares-Delgadillo et al., 2010; Patel et al., 2007; Sylvestre et al., 2008). Ears were cleaned under running cold water and the hairs were shaved. The whole skin was removed carefully from the outer region of the ear and separated from the underlying cartilage with a scalpel. The skin was then dermatomed with an average thickness of 750 µm using a skin graft knife (PM-14701, Padgett Instruments, Inc., Kansas City, MO, USA). The pieces of skin obtained (3.5 cm × 3.5 cm) were individually wrapped in plastic films and stored for no more than 1 month at −80 °C until use. Fresh dermatomed porcine ear skin without frozen storage procedure was also used for *in vitro* skin permeation experiment to compare the skin permeation flux of naloxone between fresh and frozen skin. In the case of frozen skin, the required pieces of skin were thawed at room temperature for 30 min prior to the skin permeation experiment.

Rats were asphyxiated using carbon dioxide and the dorsal skins were shaved and excised. The excised skins were immediately dermatomed to a 750 µm-thickness using the skin graft knife, and used immediately for the skin permeation study.

2.3.2. Skin permeation study

The *in vitro* skin permeation study for naloxone hydrochloride by anodal iontophoresis was carried out using PermeGear side-by-side horizontal diffusion cells (orifice diameter: 10 mm, PermeGear Inc., Hellertown, PA, USA) with porcine ear skin and rat dorsal skin as the membrane. The anodal iontophoresis patch containing the aqueous solution of naloxone hydrochloride dehydrate was clamped between the skin and donor chamber, and tightly attached on the stratum corneum side of the skin. An AgCl electrode was placed in the sampling port of the receptor chamber as the cathode. The receptor chamber was filled with 3.4 mL of saline and temperature of the solution in donor and receiver chambers was maintained at 32 °C. Both anodal and cathodal electrodes were connected to the electric current controller, and constant current was applied for 5 h. No current applied group served as a control (passive condition group). Samples (200 µL) of the receiver chamber were collected with replacement of saline at 0, 60, 120, 180, 240 and 300 min, and stored at −20 °C until analyzed by HPLC. To examine the effect of increasing current intensity on the skin permeability of naloxone, the anodal patches containing 10% (w/v) naloxone hydrochloride dehydrate were used and four levels of current intensities (0, 90, 180 and 360 µA/cm²) were applied. To examine the effect of drug concentration, the anodal patches containing 1, 3 and 10% (w/v) naloxone hydrochloride dehydrate were used in combination with a current strength of 360 µA/cm².

2.4. In vivo protocol (pharmacokinetic study)

Two days before the iontophoretic delivery experiment, a cannula (silastic tube, Dow Corning Co. Ltd., Midland, MI, USA) was inserted into the jugular vein in rats under isoflurane anesthesia, and filled with heparinized saline until blood sampling. Prior to the application of iontophoretic patches, the hairs of the dorsal area were shaved. The iontophoretic anodal patch containing 10% (w/v) of naloxone hydrochloride dehydrate and cathodal patch containing saline were placed on the dorsal area of rat, separated by about 2 cm, and fixed onto position on the skin, using a medical elastic bandage (Multipore®M, 3 M, Tokyo, Japan). The electrodes in both patches were connected to the electric current controller and a constant current (90 and 180 µA/cm²) was applied. Animals with the naloxone-iontophoretic patches but no current applied served as control group (passive condition group). During the current application, the animals were housed individually in plastic cages (16 cm × 25 cm × 15 cm) in a conscious and freely-moving condition, and were supplied with a standard pellet diet and water *ad libitum*. Blood samples (150 µL) were collected via the cannula inserted into the jugular vein at 0.5, 1, 2, 4, 6, 8 and 24 h, and plasma fractions were stored at −20 °C until analyzed by LC/MS/MS. At 10 min and 24 h after the termination of current supply, macroscopic observation on the skin to which the patches were applied was performed in a single-blind manner. The animals with iontophoretic patches containing saline instead of naloxone hydrochloride dehydrate served as the reference group for macroscopic observation. Residues of naloxone in the used anodal patches
were extracted and measured by HPLC analytical method described below, and then the amounts of released naloxone from the patch and the release rate of naloxone from the patch were determined.

Pharmacokinetic parameters of naloxone after intravenous administration were required to calculate the transdermal absorption rate by the constrained numeric deconvolution method. Therefore, 0.2 mg/kg of naloxone hydrochloride dehydrate was intravenously injected via a hind limb vein in a conscious rat. Blood samples (150 μL) were collected via the cannula (pre-inserted into the jugular vein) at 5, 10, 20, 30, 60, 90, 120, 150 and 240 min, and the plasma fractions were stored at −20°C until used in the LC/MS/MS analysis.

2.5. Analytical methods

2.5.1. HPLC for in vitro samples

The samples were assayed using reverse phase HPLC. The HPLC system comprised an octadecyl, an L-2455 PDA detector, an L-2300 column oven, and L-2130 pump (Hitachi High-Technologies Co., Tokyo, Japan), and was equipped with a CAPCELL PAK C18 UG120 column (4.6 mm × 150 mm; particle size, 5 μm) purchased from Shimadzu Co., Ltd. (Tokyo, Japan). The mobile phase comprising 45% (v/v) acetonitrile with 0.1% (v/v) acetic acid (AcOH) and 55% (v/v) 10 mM sodium dodecyl sulfate solution with 0.1% (v/v) AcOH was delivered at a flow rate of 1 mL/min. The column oven was maintained at 50°C. The injection volume was 10 μL. Naloxone was detected at 285 nm by UV detection. Standard curves were linear over the range 10–1000 μg/mL (r² > 0.999), and the limit of detection (LOD) and quantification (LOQ) were 0.3 and 0.8 μg/mL, respectively.

2.5.2. LC/MS/MS for in vivo samples

A sample (20 μL) was transferred to a 1.5-mL polypropylene tube and then 150 μL of internal standard working solution (30 ng/mL buspirone acetone) and 80 μL of water were added. After vortex mixing for 10 s, the mixture was centrifuged at 4°C, 16,200 × g for 10 min. LC/MS/MS assay was performed according to the reported method with modifications (Shibata et al., 2002). The system included the prominence ultra fast liquid chromatography system (Shimazu Co., Kyoto, Japan) and API 4000 Mass Spectrometer with Turbo Ion spray, manufactured by Applied Biosystems/MD Sciex (Toronto, ON, Canada) operating in the positive ion mode. The chromatographic separations were performed on a TSK-GEL VMPPAK-25 column (2 mm × 150 mm; particle size, 7 μm) purchased from TOSOH Co. (Tokyo, Japan). Mobile phase A consisted of water with 10 mmol/L ammonium acetate and mobile phase B was 100% acetonitrile. The gradient was as follows: 0–0.50 min, solvent B maintain at 15% B; 0.50–2.00 min, linear gradient from 15 to 90% B; 2.00–4.00 min, maintain at 90% B. The flow rate was 0.25 mL/min and 5 μL was injected for each analysis. The column and autosampler were maintained at 30°C and 4°C, respectively. Quantitation was done using multiple reaction monitoring mode to monitor protonated precursor → product ion transition of m/z 328 → 310 for naloxone, and 387 → 122 for internal standard. Standard curves were linear over the range 0.05–150 ng/mL (r² > 0.99), and the LOQ was 0.05 ng/mL.

2.6. Data analysis

2.6.1. In vitro skin permeation study

Data were expressed as mean ± standard deviation (S.D.). The cumulative amount of naloxone permeated was plotted against time, and then the steady-state skin permeation fluxes were calculated from the straight line portion of the curve and the intercept of the straight line on the x-axis gave the lag time. Linear regression analysis was performed to examine correlation between the steady-state skin permeation flux and current intensity. Statistical analysis of the effects of current strength and drug concentration on the steady-state skin permeation flux and the lag time was performed using a one-way analysis of variance (ANOVA) followed by Bonferroni’s method. Effects of both current strength and species difference on the steady-state permeation fluxes were also analyzed by a two-way ANOVA. All statistic analyses were performed using STATISTICA 6.0j (StatSoft Japan Inc., Tokyo, Japan). P < 0.05 was considered to be statistically significant.

2.6.2. In vivo pharmacokinetic study

All pharmacokinetic data analysis was performed using WinNonlin™ V5.2.1 (Pharsight Inc., St. Louis, MO, USA). The plasma concentration of naloxone versus time profile after intravenous injection was fitted to a two-compartment model:

\[ C_P = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]

where \( C_P \) is plasma concentration of naloxone. Transdermal absorption rate (μg/h/cm²) during the iontophoretic delivery was determined based on the constrained numeric deconvolution method, a model-independent analytic deconvolution technique: intravenous data were analyzed as a first step of the deconvolution to estimate the naloxone disposition function, and then iontophoretic data were deconvolved in a second step to estimate the unknown transdermal input profile given the disposition function estimated in the first step (Fiset et al., 1995; Hung et al., 1995; Park et al., 1998; Verotta, 1989). Data were expressed as mean ± S.D.

3. Results and discussion

3.1. In vitro skin permeation study

Controlling plasma levels of naloxone is crucial in the medication of opioid-overdosed or opioid-dependent patients to avoid serious complications, because a rapid and remarkable elevation in blood levels of naloxone induced by high-dose administration and/or rapid intravenous infusion is supposed to cause catecholamine release and consequent pulmonary edema and cardiac arrhythmias (Clarke et al., 2005; van Dorp et al., 2007). One of benefits of transdermal iontophoresis is controlled drug delivery based on the percutaneous permeation of drug in proportion to current. The current application protocol (90, 180 and 360 μA/cm² for 5 h) used in the present study significantly and current-dependently enhanced the cumulative amount of percutaneously transported naloxone across both porcine ear skin and rat dorsal skin in vitro (Fig. 1). The steady-state skin permeation fluxes of naloxone across these two types of skin were also significantly and current-dependently increased (Table 1). As result of a linear regression analysis, excellent linear relationships were observed between naloxone percutaneous flux and current intensity (r² = 0.975 in the porcine skin experiments, r² = 0.998 in the rat skin experiments). These findings indicate that the enhancement of naloxone skin permeation can be governed directly by varying the current strength, and consequently, individual dose requirements in patients for antagonizing overdosed opioids can be defined and risks of complication can be also avoided.

To evaluate transdermal absorption of a molecule, the most relevant membrane is human skin, however, human skin specimens of sufficient size and quality are not readily accessible and only available in limited amounts. Porcine skin is readily obtainable from abattoirs and its histological and biochemical properties have been repeatedly shown to be similar to human skin (Barbero and Frasch, 2009; Dick and Scott, 1992; Godin and Touitou, 2007). Porcine ear skin is often used for permeation studies not only for passive-type transdermal formulation but also for active-type transdermal formulation (Dick and Scott, 1992; Patel et al., 2007;
One fresh fluxes were observed among these three concentrations (Fig. 2 and Table 2). It has been reported that in the absence of competing cations, iontophoretic flux is independent of concentration and dependent only on the ratio of diffusivities of the cation and the main counterion (usually Cl⁻) arriving in the donor compartment from beneath the skin (Kasting and Keister, 1989). In the present iontophoretic experiments using Ag/AgCl electrodes, naloxone was provided as a hydrochloride salt in aqueous solution without competing cations, therefore, Cl⁻ ions necessary for anodal reaction was likely sufficient in the donor solution. In the anodal iontophoresis of lidocaine hydrochloride (Marro et al., 2001) and hydromorphone

### Table 1

<table>
<thead>
<tr>
<th>Current strength (µA/cm²)</th>
<th>Skin permeation (µg/h/cm²)</th>
<th>Lag time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Porcine</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5.15 ± 6.24</td>
<td>2.93 ± 3.23</td>
</tr>
<tr>
<td>90</td>
<td>46.5 ± 16.9</td>
<td>3.17 ± 11.2</td>
</tr>
<tr>
<td>180</td>
<td>74.3 ± 39.2</td>
<td>7.05 ± 27.7</td>
</tr>
<tr>
<td>360</td>
<td>200 ± 44.2</td>
<td>135 ± 39.9</td>
</tr>
</tbody>
</table>

Mean ± S.D. [n=3–4]; ND: not defined.

* p < 0.05.

** p < 0.01, compared with 0 µA/cm²-group.
hydrochloride (Padmanabhan et al., 1990), in the absence of competing ions, it has been also shown that the iontophoretic flux is independent of the drug concentration in the donor compartment. The present result is consistent with these previous reports.

3.2. In vivo pharmacokinetic study

Plasma levels of naloxone after intravenous administration in rats were fitted to 2-compartment model (Eq. (1)) as reported in human subjects (Albeck et al., 1989; Goldfrank et al., 1986). The values of AUC, $A$, $B$, $\alpha$, $\beta$ and $T_{1/2}$ were listed in Table 3. The value of $A$, $B$, $\alpha$ and $\beta$ were used for the calculation of transdermal absorption rates during the iontophoretic administration of naloxone by the numeric deconvolution method. When the anodal iontophoretic patch system with the constant current application (90 and 180 $\mu$A/cm$^2$) was subjected on the dorsal skin in conscious rat, plasma concentration of naloxone elevated steadily, reached steady-state 4 h after the initiation of current supply and sustained stably for 20 h in each current application group (Fig. 3). Both AUC and the steady-state plasma concentration of naloxone increased in a current-proportional manner (Table 4), indicating both the systemic exposure and the plasma levels of naloxone are well-controlled by current intensity.

When applied the same current intensity, the steady-state transdermal absorption rate of naloxone was almost equivalent to the release rate of naloxone from the patches, and both of them also well-correlated increased with the applied current intensity (Table 4). The transport efficiency of naloxone (transport number: $t_d$), was calculated as follows: $t_d = I \times t_d/F \times z_i$, where $j_d$ is determined transdermal absorption rate or average release rate from the patch, $I$ is the total current, $t_d$ is the transport number of the ion, $F$ is the Faraday’s constant and $z_i$ is the valence of the ion (Sylvestre et al., 2008). As result, the transport number of naloxone determined using the transdermal absorption rate was 0.11–0.13, which was nearly identical to that determined using the average release rate from the patch (0.14–0.16). These findings demonstrate that the anodal iontophoretic patches efficiently delivered naloxone from the patch to the systemic circulation via skin in a current-correlated manner.

Only very slight erythema in the dorsal skin was observed in all rats applied with the constant current at 90 and 180 $\mu$A/cm$^2$ for 24 h in combination with naloxone patches or saline patches (incidence rate: 3/3 in each group), and these macroscopic changes were completely disappeared within 12 h after the removal of the patches. No erythema was observed at the site applied with the naloxone patch alone for 24 h without the current supply. Fig. 4 shows typical macroscopic observation of the rat dorsal skin treated with the iontophoretic patch (A: visual appearance of the patch, B: naloxone-containing patch without the current supply, C: saline-containing patch with current supply at 180 $\mu$A/cm$^2$, D: naloxone-containing patch with current supply at 180 $\mu$A/cm$^2$). Iontophoresis by itself is known to have a potential for skin irritation, especially at high current strength (Batheja et al., 2006). Because there was no apparent difference between naloxone patch applied groups and saline patch applied groups under the current supply, this reversible and very slight macroscopic changes observed in the present study is likely due to the long-lasting medium level (90–180 $\mu$A/cm$^2$) current application, but not due to the absorbed naloxone in the skin.

When compared the in vivo steady-state transdermal absorption rates in rat (Table 4) with the in vitro steady-state skin permeation flux in rats (Table 1), the former values were 5.09, 4.29 and 4.30 times higher than the later values at the current application of 0, 90 and 180 $\mu$A/cm$^2$, respectively. This result means the efficiency of transdermal delivery of naloxone is much higher in vivo than in vitro. Higher in vivo transdermal flux compared to in vitro flux has been reported for several molecules (Chaturvedula et al., 2005; Luzardo-Alvarez et al., 2003). Dermal blood supply has been found to play a significant role in the systemic and underlying tissue solute absorption during iontophoretic delivery (Cross and Roberts, 1995). These reports suggest that the faster percutaneous delivery of naloxone in vivo compared with the in vitro is likely due to intact cutaneous microcirculation in conscious rats.

Opioid addiction has become a serious medical and social problem, because addicts are likely to develop mental illness, to exhibit criminal behavior, and to be a risk for fatal overdose and various infectious diseases (Clarke et al., 2005; Stotts et al., 2009; van Dorp et al., 2007). Naloxone has been

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**Table 2**

Effect of concentration of naloxone hydrochloride dehydrate on the in vitro steady-state skin permeation flux of naloxone and lag time across porcine skin.

<table>
<thead>
<tr>
<th>Drug concentration (% (w/v))</th>
<th>Skin permeation flux ($\mu$g/h/cm$^2$)</th>
<th>Lag time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>142 ± 39.1</td>
<td>1.12 ± 0.18</td>
</tr>
<tr>
<td>3</td>
<td>169 ± 9.40</td>
<td>1.41 ± 0.13</td>
</tr>
<tr>
<td>10</td>
<td>189 ± 38.9</td>
<td>1.48 ± 0.32</td>
</tr>
</tbody>
</table>

Mean ± S.D. (n = 4–6).

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**Fig. 2.** Effect of concentration of naloxone hydrochloride dehydrate in the donor solution on in vitro skin permeation profiles of naloxone across previously frozen porcine ear skin. $\bullet$: 1, $\bigtriangleup$: 3 and $\triangle$: 10% (w/v) of naloxone hydrochloride dehydrate. Each point with bar represents the mean ± S.D (n = 4–6).

**Fig. 3.** Plasma concentration of naloxone during the transdermal iontophoretic administration in conscious rats. $\bullet$: 0 (n = 1), $\bigtriangleup$: 90 (n = 3) and $\triangle$: 180 $\mu$A/cm$^2$ (n = 3). Each point with bar represents the mean ± S.D.
Table 3
Pharmacokinetic parameters obtained from intravenous administration of naloxone hydrochloride hydrate in conscious rats.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AUC (h ng/mL)</th>
<th>A (ng/mL)</th>
<th>B (ng/mL)</th>
<th>α (1/h)</th>
<th>β (1/h)</th>
<th>T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>15.5 ± 3.98</td>
<td>64.2 ± 55.5</td>
<td>19.8 ± 11.7</td>
<td>18.0 ± 14.2</td>
<td>1.59 ± 0.45</td>
<td>0.53 ± 0.03</td>
</tr>
</tbody>
</table>

Mean ± S.D. (n = 3).

Table 4
AUC, the steady-state plasma concentration and transdermal absorption rate, and average release rate from the patch during transdermal iontophoretic administration of naloxone in conscious rats.

<table>
<thead>
<tr>
<th>Current strength (µA/cm²)</th>
<th>AUC (h ng/mL)</th>
<th>Plasma concentration (ng/mL)</th>
<th>Transdermal absorption rate (µg/h/cm²)</th>
<th>Average release rate (µg/h/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92.3 ± 3.82</td>
<td>31.9 ± 5.85</td>
<td>136 ± 21.3</td>
<td>191 ± 14.0</td>
</tr>
<tr>
<td>90</td>
<td>761 ± 130</td>
<td>71.3 ± 17.2</td>
<td>305 ± 50.7</td>
<td>395 ± 52.2</td>
</tr>
<tr>
<td>180</td>
<td>1731 ± 374</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± S.D. (n = 3).

References


