

RESEARCH ARTICLE

The Development of Transdermal Ketamine Patch

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Abstract**Objective**

We prepared the transdermal ketamine patch, determined the size of the patch to yield proper plasma ketamine level due to human skin permeability and the amount of residual ketamine in the patch, and estimated the utility of this ketamine transdermal patch when it will be applied to patients.

Methods

A ketamine patch was prepared with ketamine hydrochloride intramuscular solution (3.0mg/cm²). The ketamine patch was put on the skin samples taken from the human. The solutions of the diffusion cell were examined every two hours after the application until 30 hours. The amount of ketamine that has penetrated into the skin was measured by using HPLC system, and Flux of transdermal ketamine patch was defined.

Results

The cumulative ketamine permeation amount was found to be 785.6 µg/cm² at the 30-hour sampling, showing a stable Flux of 30.1 µg/cm²/hr during the period from 10 to 30 hours of sampling.

Conclusion

We have been attempting to formulate transdermal ketamine patches at a size of 155 cm² to yield a plasma ketamine level of 50 ng/mL for use in the clinical practice setting. The patch may become a formulation of choice as an analgesic adjuvant for combined use with opioids.

Key words: ketamine, transdermal patch, skin permeability, flux

Introduction

Ketamine is a dissociative anesthetic endowed with both analgesic and anesthetic effects. It exerts its analgesic effect by acting as a non-competitive antagonist of the N-methyl D-aspartate (NMDA) receptor. At low doses, ketamine exerts an obvious analgesic effect against neuropathic pain refractory to morphine. Ketamine has been administered by the IV and IM routes for obtaining analgesia. There are no commercially available formulations except for injection, so liquid formulation is prepared for in-hospital use (1). The efficacy of ketamine administered alone or in combination with opioids is anticipated, particularly in patients with terminal-stage cancer in whom opioid medication alone fails to provide satisfactory relief. Recently, it is also said that ketamine might be effective in the treatment of depression.(2-3) However, the pharmacokinetic profile of ketamine in humans, has not yet been clarified, nor has the appropriate dosage schedule been established. Further, there exist problems inherent to the use of injectable preparations, which can hardly be prescribed to patients wishing home care, and liquid formulations, which are unsuitable for patients incapable of oral intake.

We have investigated and confirmed the pharmacokinetics of ketamine and its active metabolite, norketamine after oral administration of liquid formulation of ketamine (4). We formulated a ketamine transdermal patch and applied it to hairless rats, and demonstrated that the pharmacokinetic profile of this formulation was similar to that of ketamine intravenous infusion (5). The transdermal patch is

expected to become a novel, clinically applicable dosage form of ketamine. Although Azevedo *et al.* indicated that transdermal ketamine was effective as an adjuvant of epidural lidocaine for postoperative analgesia, and prolonged the duration of analgesia, the appropriate dosage and pharmacokinetics of ketamine was not determined (6). Therefore, we prepared the transdermal ketamine patch, determined the size of the patch to yield proper plasma ketamine level due to human skin permeability and the amount of residual ketamine in the patch, and estimated the utility of this ketamine transdermal patch when it will be applied to patients.

Methods

1. Preparation of the Transdermal Ketamine Patch

Partially neutralized polyacrylate (0.60 g), aluminum stearate (0.48 g) and ketamine hydrochloride (0.48 g) were mixed by slow stirring. Concentrated glycerin (2.10 g), 1,3-butylene glycol (2.10 g), isopropyl myristate (0.30 g), diisopropanolamine (0.96 g), lactic acid (0.06 g) were added to the mixture and stirred until it equalized. 10% Methyl vinyl ether maleic anhydride copolymer dissolved in ethanol solution (6.00 g) added to the mixture and stirred until it equalized. The mixed suspension removed air was spread on the release layer of polyethylene terephthalate using a knife coater (Kodaira Seisakusho Co., Ltd. Japan) to contain about 3.0 mg of ketamine hydrochloride per cm². The film was dried at 60°C for 1 hour and covered with the backing layer of polyethylene terephthalate, and heated at 100°C for 1hour. The

ketamine hydrochloride used in the above formulation was lyophilized hydrochloride ketamine (Ketalar[®]) for Intramuscular Injection (Daiichi-Sankyo Co., Ltd, Tokyo).

2. *In vitro* Human Skin Permeability Study

2.1. Materials

Caucasian human abdominal skin (BIOPREDIC International, France) was used. The skin specimens were surgically collected skin sections, preserved at -80°C until use in the test. Six pieces of skin were cut out of two 12-cm^2 skin specimens from the same individual and used for the tests on normal skin and tape-stripped skin. The dermal stripping for removal of the stratum corneum was carried out by repeatedly applying surgical tape to the skin surface about 30 times.

2.2. Sampling and analysis

A human skin specimen with a round patch, 1 cm in diameter, containing 2.49 mg of ketamine hydrochloride was mounted in a diffusion cell (available diffusion area, 0.785 cm^2 ; volume of receiver cell, 2.8 mL). The receiver cell was filled with phosphate buffered saline. During the experiments the solution in receptor side was maintained at 37°C and stirred using a magnetic stirrer. At each of all the 15 time-points (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30 hrs) after the start of the stirring, 500 μL of the receiver solution was sampled and the same volume of fresh receiver solution was pipetted to fill up the complement. To 200 μL of the sampled solution, the same volume of a 0.05-mg/mL tulobuterol hydrochloride solution in methanol was added as the

internal standard, and the resultant mixture was stirred in a vortex mixer and analyzed by a high performance liquid chromatography (HPLC) system to determine the amount of ketamine that had penetrated the skin. The HPLC conditions were as follows: pump, LC-10AD; detector, SPD-10A; auto injector, SIL-10A_{XL}; column oven, CTO-10AC (Shimadzu Co. Ltd., Japan); column, Purospher RP-18e ($125\text{ mm}\times 4\text{ mm}$, $5\mu\text{m}$; Merk Co. Ltd., Germany); column temperature, 40°C . The mobile phase consisted of acetonitrile and 0.03 mol/L phosphate buffer at ratios of 1 : 1. The flow rate was 1mL/min. The absorption wavelength was determined at 210 nm (7).

After completion of the permeability study, the skin was processed with 20 mL of methanol solution to extract ketamine, followed by analysis performed in the same manner as that in the permeability study, to verify the amount of residual ketamine in the skin. The rate of ketamine residue in the skin was calculated from the amount of residual ketamine to the amount of ketamine content in the patch.

2.3. Indicator of skin permeability

The amount of drug that has penetrated the skin (stratum corneum, epidermis, and dermis) per unit area of the patch per unit time was defined as the percutaneous drug permeability rate (Flux). This variable was calculated from the gradient of the steady-state cumulative permeation amount of drug determined from the permeability study.

3. Verification of the Amount of Residual Ketamine in the Patch after the Human Skin Permeability Study

3.1. Materials

Six ketamine hydrochloride patches (1 cm in diam., 0.785 cm²) that had been applied to test human skin specimens for 30 hours in the human skin permeability study and three unused ketamine hydrochloride patches (1 cm in diam., 0.785 cm²) were used. All these patch preparations were weighed prior to use and those that were still unused were checked for the weight of the drug-containing plaster base material (drug reservoir) (g) [Weight of drug product (g) – Mean weight of liner/support (g)].

3.2. Ketamine extraction and analysis

One used or unused ketamine patch was immersed in 100 mL of a water: methanol solvent mixture (1:1 v/v%) to which 1 mL of 1N hydrochloric acid and 1 mL of a 5-mg/mL tulobuterol hydrochloride solution in methanol, as the internal standard, had been added, and allowed to stand overnight, followed by shaking for 3 hours to extract the ketamine from the patch. The resultant mixture was filtered and analyzed by a HPLC system under the same conditions as those described for the human skin permeability study.

4. Method of calculation of the amount (%) of the residual drug

The percentage of the amount of ketamine per unit weight of the drug reservoir of a used patch was calculated from the amount

of residual ketamine in an unused patch. The ketamine content of a test patch used in the skin permeability study was estimated from the weight of the drug reservoir of the test patch prior to use. The ketamine residual rate (%) at 30 hours of application was calculated from the estimated ketamine content and the residual amount in the used patch.

$$\text{Weight of drug reservoir (g)} = \text{Weight of drug product (g)} - \text{Mean weight of liner/support (g)}$$

$$\text{Ketamine concentration (\%)} = \text{Ketamine content (mg)} / \text{Weight of drug reservoir (g)}$$

$$\text{Estimated ketamine content (mg)} = \text{Weight of drug reservoir (g)} \times \text{Ketamine concentration in unused drug product (\%)}$$

$$\text{Residual rate (\%)} = \text{Amount of residual ketamine (mg)} / \text{Estimated ketamine content (mg)} \times 100$$

Results

1. *In vitro* Human Skin Permeability Study

Ketamine was released from the patch into the diffusion cell at 2 hours after the start of sampling in the case of normal skin, and the cumulative ketamine permeation amount was 2.3 µg/cm² at the 2-hour sampling. It was found to be 201.5 ± 30.4 µg/cm² at the 10-hour and 785.6 ± 4.6 µg/cm² at the 30-hour sampling, showing a stable Flux of 30.1 µg/cm²/hr during the period from 10 to 30 hours of sampling (Fig. 1). The amount (%) of residual ketamine in the skin was 2.3 ± 0.3% after 30 hours of patch application.

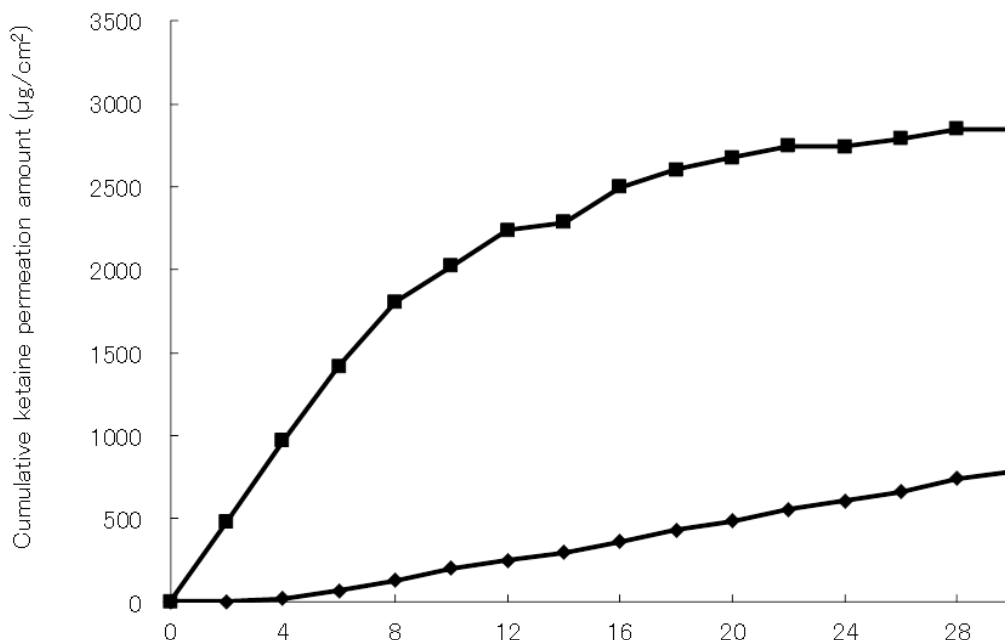


Figure 1. The Cumulative ketamine permeation amount through the human skin. Symbols: normal skin(●) stripping skin (■)

In the case of stripped skin, the cumulative ketamine permeation amount was $2844.8 \pm 606.7 \mu\text{g}/\text{cm}^2$ at the 30-hour sampling, showing a Flux of $227.3 \mu\text{g}/\text{cm}^2/\text{hr}$ during the first 8 hours of sampling. The amount (%) of residual ketamine in the skin was $1.4 \pm 0.1\%$.

2. Verification of the Amount of Residual Ketamine in the Patch after the Human Skin Permeability Study

In the skin permeability study carried out using human normal skin, the estimated ketamine content of the transdermal patch (0.785cm^2) was $2.04 \pm 0.05 \text{ mg}$ ($n = 4$), and the quantity of residual ketamine in the patch after use was $1.32 \pm 0.07 \text{ mg}$. The residual rate (%) of ketamine in the patch after 30 hours of application was $64.9 \pm 3.1\%$ (Table1). The estimated ketamine content of the transdermal patch

in the test with stripped skin was $2.16 \pm 0.15 \text{ mg}$ ($n = 2$), the quantity of residual ketamine in the patch after use was $0.09 \pm 0.02 \text{ mg}$, and the residual rate of ketamine in the patch was $4.3 \pm 0.5\%$.

Discussion

Ketamine, which is endowed with both analgesic and anesthetic effects, is administered as an analgesic not solely by intravenous or intramuscular injection, but also in the liquid formulation prepared for in-hospital use for the treatment of cancer pain, etc. Other dosage forms of ketamine such as tablets, capsules, nasal spray and suppositories are also reported. However, the pharmacokinetics of those preparations are not yet well established, and their analgetic effects and safety profiles remain to be investigated in detail (8-11).

Table 1. The amount of residual ketamine in the transdermal patch after the human skin permeability study

subject No	Weight of drug reservoir (g)	Estimated ketamine content (mg)	Amount of residual ketamine (mg)	Residual rate (%)
A	0.036	2.03	1.27	62.4
B	0.036	1.98	1.26	63.6
C	0.365	2.04	1.41	69.3
D	0.038	2.10	1.35	64.2
Ave	0.12	2.04	1.32	64.9
SD	0.16	0.05	0.07	3.1

We have formulated a ketamine transdermal patch as a novel dosage form and verified the pharmacokinetic profile and skin permeability of the patch following application to hairless rats (5). The Flux of the ketamine patch was found to be 46.7 $\mu\text{g}/\text{cm}^2/\text{hr}$ in the skin permeability study conducted in the hairless rats, and the drug absorption rate of a test patch containing ketamine at 56 $\text{mg}/16 \text{ cm}^2$ was 33.3 $\mu\text{g}/\text{cm}^2/\text{hr}$.

The Flux determined in the present human skin permeability study was 30.1 $\mu\text{g}/\text{cm}^2/\text{hr}$,

indicating that the human skin permeability of ketamine was equivalent to 64.4% of the rat skin permeability of this compound. The drug absorption rate in the hairless rats corresponded to 71.3% of the Flux. Assuming that ketamine might show an essentially same absorption rate in humans as well, it was presumed that the drug absorption rate in humans might be 21.5 $\mu\text{g}/\text{cm}^2/\text{hr}$ (Fig. 2). It has thus become feasible to estimate the steady-state plasma level in humans by using Flux, clearance and patch area.

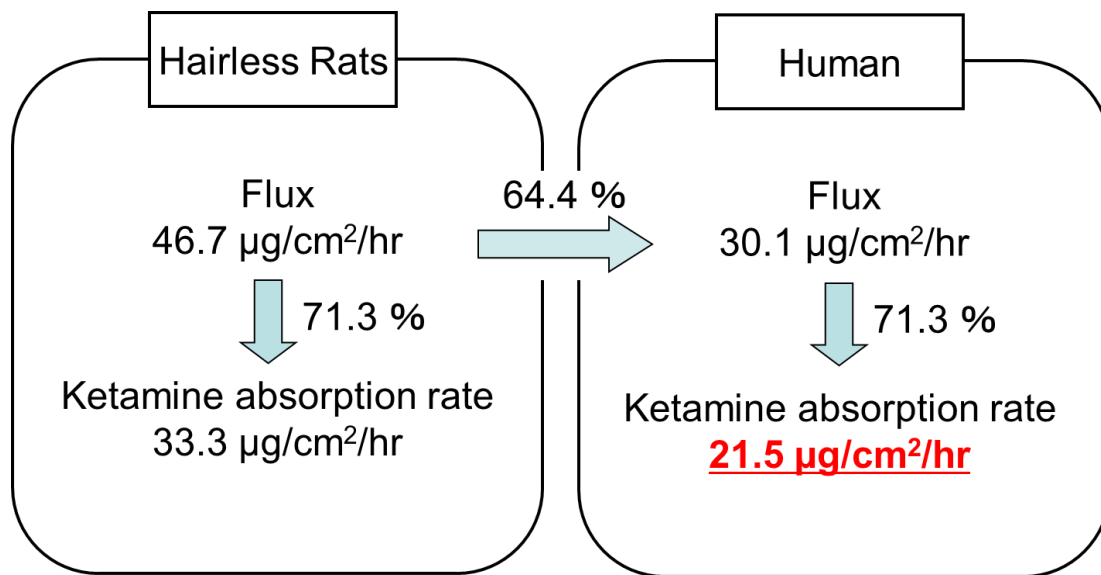


Figure 2. Estimation of ketamine absorption rate in human skin

It has been reported by Schmid et al., that an adequate analgesic effect of the drug may be expected, without its producing any central nervous system-related adverse reactions, as long as the plasma ketamine level does not exceed 50 ng/mL, when ketamine hydrochloride is administered concomitantly with opioids (12). According to a report by Persson and colleagues, intolerable adverse reactions occurred at a frequency of 65% when the plasma S(+)-ketamine concentration exceeded 100 ng/mL in patients receiving intravenous injections of ketamine (13). Therefore, we decided to formulate the ketamine patch, designed to yield a target plasma level of 50 ng/mL, at which an adequate analgesic effect may be expected without any significant adverse reactions.

Figure 3 indicates how to decide the appropriate size of ketamine patch. The area size of the test patch for use in humans was calculated using the drug absorption-steady-state plasma concentration relational expression: $J_{ss} = C_{ss} \times CL / S$ (J_{ss} , drug absorption rate; CL , clearance; and S , area of drug application), where J_{ss} , as estimated from the results of the human skin permeability test, was $21.5 \mu\text{g}/\text{cm}^2/\text{hr}$, the C_{ss} was 50 ng/mL, being the target plasma ketamine concentration, and CL was 18.5 mL/kg/hr as reported by Yajima et al.(14); the patch was assumed to be applied to patients weighing 60 kg. As a result, the patch area for achieving an anticipated plasma level of 50 ng/mL was determined to be 155.24cm^2 when the patch size was $12 \times 13 \text{ cm}$ as almost square.

The Relationship between the Ketamine Absorption Rate and Steady-State Concentration

$$J_{ss} = C_{ss} \times CL / S$$

[J_{ss} : Drug absorption rate CL : Clearance S : Supplied area]

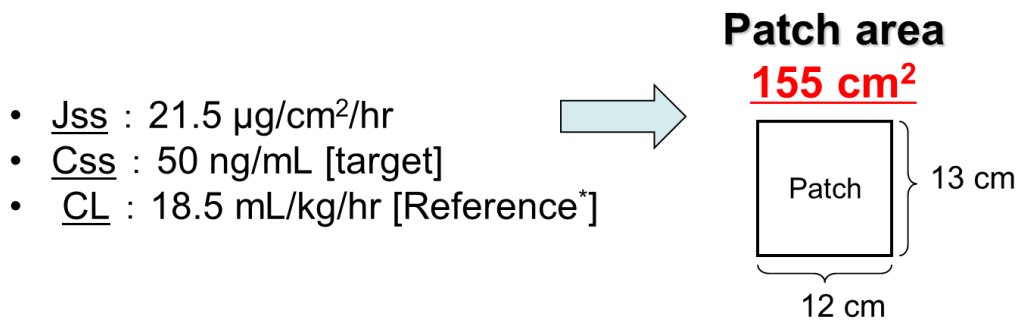


Figure 3. The estimated therapeutic size of ketamine patch

$J_{ss} = C_{ss} \times CL / S$ (J_{ss} , drug absorption rate; CL , clearance; and S , area of drug application), where J_{ss} , as estimated from the results of the human skin permeability test, was $21.5 \mu\text{g}/\text{cm}^2/\text{hr}$, the C_{ss} was 50 ng/mL, being the target plasma ketamine concentration, and CL was 18.5 mL/kg/hr as reported by Yajima et al.(14); the patch was assumed to be applied to patients weighing 60 kg. As a result, the patch area for achieving an anticipated plasma level of 50 ng/mL was determined to be 155.24cm^2 when the patch size was $12 \times 13 \text{ cm}$ as almost square.

The amount (%) of residual ketamine in patches that had been applied to human normal skin in the permeability study was 64.9%, indicating that about 35% of the ketamine that had been applied transdermally was absorbed. The cumulative amount of ketamine permeating the skin up to 30 hours of application corresponded to about 30% of the ketamine content of the patch, and did not contradict the outcome of the human skin permeability study. Furthermore, it was suggested from the amount (%) of residual ketamine, that the drug was scarcely retained in the skin. Although no one reported that the availability of ketamine patch, the permeability of fentanyl was influenced by various factors, and the systemic availability of transdermal fentanyl patch was about 30% (15-16).

Results of the test with skin specimens stripped of the stratum corneum, i.e., stripped skin, showed that the cumulative permeation amount of the drug was 3.6-fold greater and the Flux 7.6-fold higher as compared to that observed for the case of normal skin, suggesting a high permeability of ketamine. The stratum corneum functions as a barrier against intrusion of foreign matter from outside, and the present results suggest that the stratum corneum exerts substantial influence upon the skin permeation process and constitutes a rate-controlling step in the percutaneous absorption process of the drug.

We have been attempting to formulate transdermal ketamine patches at a size of 155 cm² to yield a plasma ketamine level of 50 ng/mL for use in the clinical practice setting. Transdermal therapeutic systems have been paid attention and thought to be greatly useful in patients due to advanced technology in enhancement of skin

permeation and decreased side effect on the skin after the patch was removed. Fentanyl patch for the narcotic analgesics, tulobuterol tape for the asthma treatment and oxybutynin patch for the urine incontinence treatment are useful (17).

We will conduct a single-dose administration study of the ketamine transdermal patch at a size of 155 cm² for use in the clinical practice setting and confirm the safety and pharmacokinetics of the patch preparation.

Conclusion

Use of the ketamine transdermal patch is not complicated to administer and less invasive than use of formulations requiring administration by other routes. The transdermal ketamine patch was prepared, and the size of the patch to yield proper plasma ketamine level was determined in this study.

Conflict of Interest: None

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