ORIGINAL

Administration of Kampo medicine through a tube at an advanced critical care center

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Abstract : In emergency and critical care medical centers, tube administration is employed for patients who have difficulty swallowing oral drugs owing to decreased consciousness or mechanical ventilation. However, tube clogging due to drug injection is a concern. We compared the crushing method with the simple suspension method for the passage of amlodipine, an antihypertensive drug, in combination with rikkunshito, which has been used to treat upper gastrointestinal disorders such as functional dyspepsia and gastroesophageal reflux in emergency and critical care medical centers, to ascertain the effect of Kampo products on the passage of other drugs during tube administration. When the crushing method was employed, poorly water-soluble solid products were formed, while a uniformly dispersed suspension was obtained using the simple suspension method. In addition, the passage rate of amlodipine through the tube was 64% and 93% in the crushing and simple suspension methods, respectively, thereby indicating that the simple suspension method provided more favorable than the crushing method. The results of this study suggested that the passage rate of amlodipine for patients who received Kampo products concurrently was higher when the simple suspension method was used, and an appropriate drug amount might well be able to administered to patients using this method. J. Med. Invest. 65 : 32-36, February, 2018

Keywords **:** *Emergency and critical care medical center, Kampo product, simple suspension method, tube administration*

INTRODUCTION

Patients with severe brain damage or respiratory disorders are treated at emergency and critical care medical centers. Various drugs are required for treating these patients, but oral drug administration methods may not be possible owing to decreased consciousness levels or mechanical ventilation. Therefore, the preferred mode of administration is usually injection. However, if an injection formulation is unavailable, drugs are orally administered through a tube. In this form of administration, powdered medicines, granular medicines, tablets (after crushing), or capsules (after opening) are administered through a tube after dissolution in lukewarm or hot water (1). However, several pharmaceutical issues have been reported while crushing tablets or opening capsules, including alterations to the physicochemical stability of drugs, the loss of drugs due to adhesion to the crushing apparatus (2, 3), and variations in the compounding ratio when multiple drugs were simultaneously crushed (1, 4, 5).

Recently, the efficacy of Kampo medicines has drawn attention, and they have been used to stimulate immune function after surgery, during anticancer drug treatments, and to prevent peristalsis decrease in patients with gastrointestinal diseases (6). In the emergency and critical care medical center, gastric peristalsis decreases with critical illness. Thus, rikkunshito is frequently used for patients with acute gastrointestinal disorders presenting gastric content retention in order to increase peristalsis and vascular flow, protect the intestinal mucosa, and exert anti-inflammatory effects. However, the commercially available rikkunshito formulation is granular and poorly soluble in water. Therefore, while several attempts have been made at various facilities, clogging of the jejunum tube owing to rikkunshito administration has been reported, even after crushing the granules with a pestle prior to dissolution in water (7). Based on these facts, the passage of other drugs has become a concern in the emergency and critical care medical center, where rikkunshito is often administered with other drugs.

Many medical institutes are now replacing the conventional crushing method with the simple suspension method for tube drug administration (8). In the simple suspension method, drugs are suspended in hot water (about 55°C) and administered through the tube without grinding or opening of the tablet or capsules. The results showed that a decrease in the drug efficacy owing to light exposure or moisture absorption, as well as drug material loss which may have occurred during crushing, could be avoided using this method (9). Further, the passage of drugs while using multiple drugs has been examined (10). However, no study examining the effects of Kampo products, frequently used in the emergency and critical care medical center, on the passage of other drugs has been conducted.

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In this study, we examined the passage of amlodipine, an antihypertensive drug, in combination with rikkunshito, frequently used in the emergency and critical care medical center, to ascertain the effect of Kampo products on the passage of other drugs during tube administration.

METHODS

1. Study drugs and reagents

The study drugs used were Amlodin Tablets® (2.5 mg) and Rikkunshito Extract Granules® (7.5 g) purchased from Sumitomo Dainippon Pharma Co., Ltd. and Tsumura & Co., respectively. The mobile phase reagents methanol, acetonitrile, and trimethylamine were purchased from Wako Pure Chemical Industries, Ltd. Amlodipine besylate, which was used as the assay standard, was purchased from Sigma-Aldrich.

2. Preparation and quantification of sample solutions for tube administration and HPLC

The outline of the experimental method is shown in Figure 1. The sample solution used for the crushing method was prepared by mixing 1 ground tablet of Amlodin® (2.5 mg) and 1 package of Rikkunshito Extract Granules® (7.5 g, Tsumura & Co.), and crushing them together with a mortar and a pestle. After this, 20 mL of hot water (25°C) was added to prepare the suspension. The sample solution for the simple suspension method was prepared by putting 1 tablet of Amlodin® (2.5 mg) and 1 package of Rikkunshito Extract Granules® (7.5 g) in an injector without crushing, aspirating 20 mL hot water (55°C) into said injector, and leaving this mixture for 10 minutes to prepare the suspension. Sample solutions prepared using the above-mentioned methods were passed through a feeding tube (8 Fr, 120 cm ; manufactured by Kangaroo). Ultrasonication was performed after filtering both solutions by using a syringe. These solutions were then centrifuged and the amlodipine concentrations were quantified using HPLC. After the solutions were passed, the tube was flushed with 20 mL of hot water (55°C) in accordance with the treatment procedure specified in each ward. Lavage fluid generated after flushing was also collected and used for quantification of amlodipine concentrations by HPLC.

Sample solution that was passed through the tube in each experiment was collected at the same location. The uniformity of all obtained suspensions was ensured by agitation with a vortex mixer. After collecting 1 mL of suspension from each sample solution, 1 mL of the mobile phase was added and ultrasonication was performed. The mobile phase for HPLC was prepared under the following conditions after referencing the Japanese Pharmacopoeia documents for amlodipine to obtain a peak detection of amlodipine even with the presence of rikkunshito ingredients : the measurement wavelength was 237 nm, the column was C18-Supersphar® (4 μm, 50 mm×2.1 mm), the column temperature was 25°C, a constant flow rate was set at 1.0 mL/min, and the mobile phase was methanol/acetonitrile/0.7% triethylamine (7 : 3 : 10).

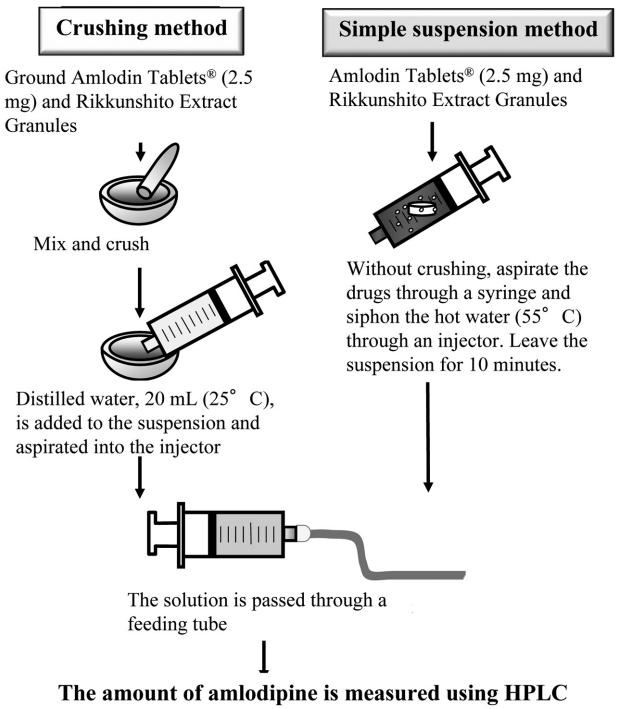

Figure 1. Outline of the experimental method.

3. Statistical analysis

The results of these experiments were presented as the mean ± standard error. Student's t-test was used to examine statistical significance, and a significance level of < 5% indicated a significant difference.

RESULTS

1. HPLC measurement conditions for simultaneous suspension of rikkunshito and amlodipine

In order to compare the amount of amlodipine passing through the tube with concomitant rikkunshito use when the crushing and simple suspension methods were used, we first examined the mobile phase and found that the HPLC-detected peaks for amlodipine and rikkunshito did not overlap, and no confounding peaks were detected (Figure 2). The measurement time was 15 minutes. We performed various examinations under these HPLC conditions.

Figure 3 shows the calibration curve of amlodipine. The calibration curve was found to be favorably linear with the equation y = 33976x - 3317.2, with a correlation coefficient of 0.9979 over a concentration range between 0 and 100 mg/L. Using this calibration curve, the passage of amlodipine administered with rikkunshito after using either the crushing method or simple suspension method was quantified by HPLC.

2. Conditions of simultaneous suspension of rikkunshito and amlodipine after using the crushing method and the simple suspension method

The appearance of the sample rikkunshito/amlodipine solutions after grinding was compared after utilization of the crushing method and the simple suspension method (Figure 4). Poorly water-soluble solid products were produced when the compounds were manipulated using the crushing method, while a uniformly dispersed suspension was obtained using the simple suspension method. Furthermore, residual solid matter was observed in the tube after the crushing method, while no such matter was found after the simple suspension method. No tube clogging was observed in either sample solution during the course of the experiment.

3. Comparison of the amount of amlodipine passed after using the crushing method and the simple suspension method

The passage rate of the rikkunshito/amlodipine suspension through the tube was compared between suspensions generated using the crushing method and the simple suspension method, and

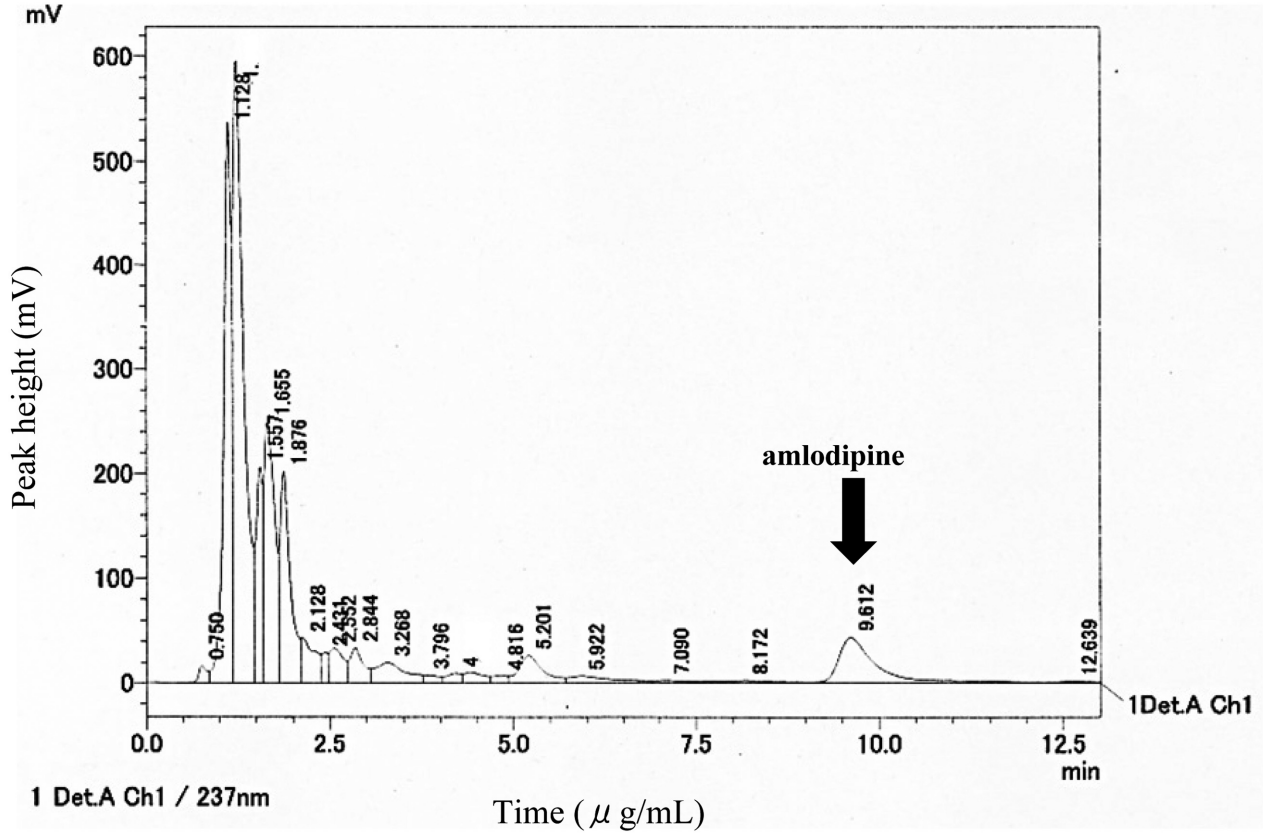

Figure 2. Typical chromatogram of the Amlodin® + Rikkunshito suspension.

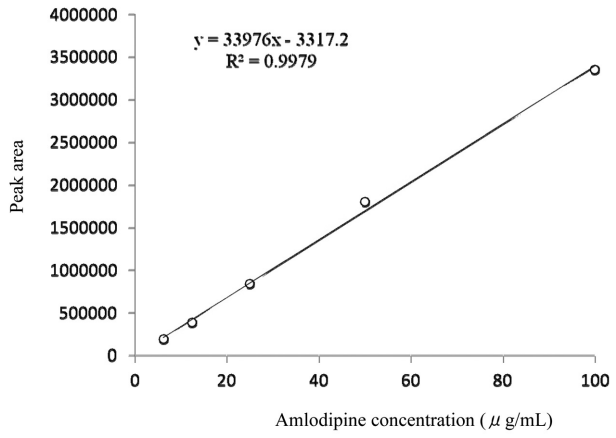

Figure 3. Calibration curve of amlodipine.

was found to be 64% in the crushed suspension and 93% when the simple suspension method was used, thereby indicating that the simple suspension method was more effective for the passage of amlodipine through the tube than the crushing method (Figure 5).

DISCUSSION

Drugs are often administered through a tube in emergency and critical care medical centers, and thus, the appropriate methodology for tube drug administration is essential during emergency medical care. However, tube clogging due to drug injection is a concern in clinical practice, since clogging has been reported to occur between 6% and 38% of the time (11). Hence, employment of appropriate evidence-based drug administration techniques is required. In this study, we examined the passage of amlodipine during concomitant use of rikkunshito, since this combination is frequently used in emergency medical care. Our results demonstrated the efficacy of the simple suspension method.

During analysis of Kampo medicines using HPLC, peaks indicating impurities must be distinguished from those of the other active ingredients. Therefore, the mobile phase was examined to ensure that the amlodipine and rikkunshito peaks did not overlap. Rikkunshito consists of 8 herbal medicines : ginseng, *Atractylodes lancea* (soujutsu), pinellia (hange), bukuryo, zizyphi fructus (taiso), tangerine peel (chenpi), Chinese licorice (gan cao), and ginger, all with various peaks detected by HPLC. We examined various mobile phases to avoid peak overlap with that of amlodipine, and found that the amlodipine peak did not overlap with other peaks in the mobile phase under the following conditions : methanol/acetonitrile/0.7% triethylamine. The calibration curve of amlodipine was plotted under these analytical conditions and a favorable linearity was obtained.

Gastric peristalsis in patients with acute gastrointestinal disorders decreases with high invasion of critical illness, resulting in gastric content retention, which in turn results in increased risk of aspiration pneumonia caused by gastroesophageal reflux disease and ventilator-associated pneumonia. Furthermore, metabolic abnormalities occur due to increased fluid discharge from the nasogastric tube, leading to intractable disease conditions. In recent

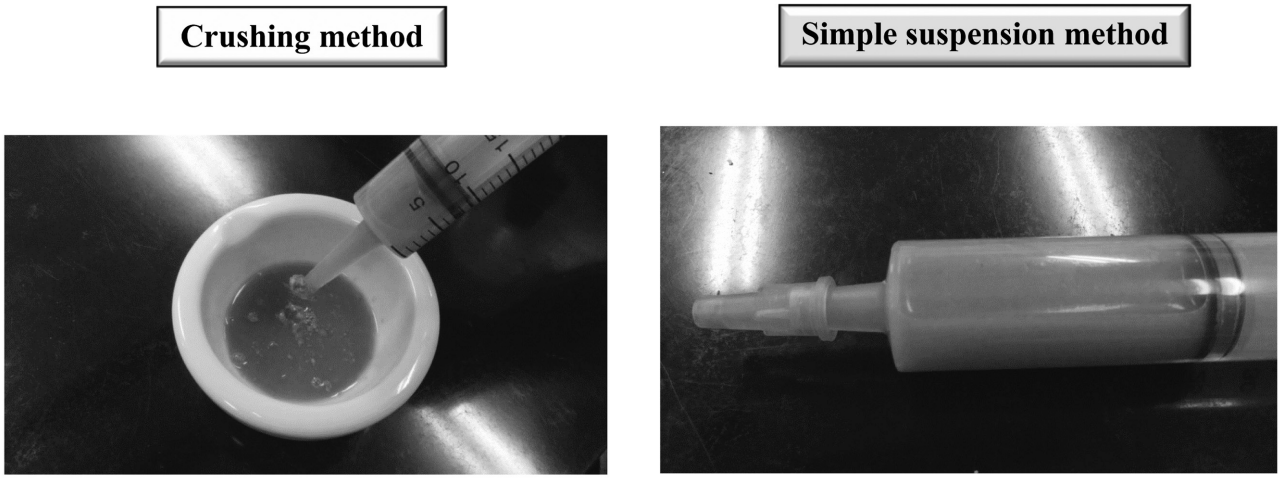

Figure 4. Sample solution.

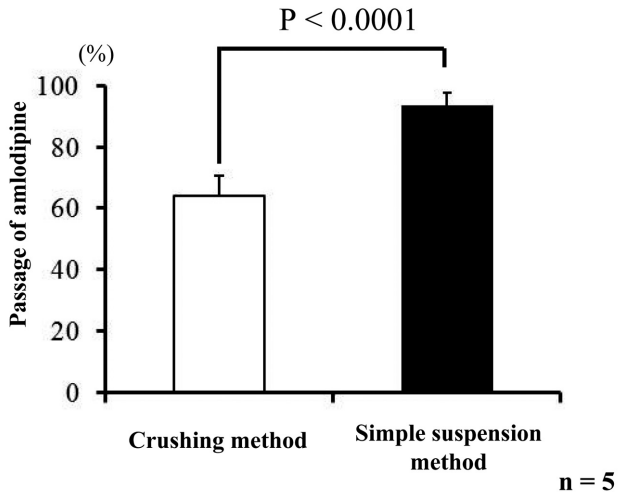

Figure 5. Comparison of the passage amounts of amlodipine between the crushing method and simple suspension method.

years, studies using molecular biological methods have revealed the effects of rikkunshito on these disease conditions, including improvement of gastric emptying and accommodation and promotion of ghrelin secretion. Therefore, rikkunshito has been widely used for patients with decreased gastric peristalsis in emergency intensive care (12, 13).

When hot water (55°C) was added after crushing rikkunshito and amlodipine, the drugs adhered to the mortar and pestle and solidified. Conversely, no solidification was observed during and after employment of the simple suspension method. The Instruction sheet of Rikkunshito Extract Granules® (Tsumura & Co., revised in November 2014) states that rikkunshito is highly susceptible to moisture, and caking is likely to occur when the moisture content in the drug is at or greater than 7%. Hence, caking may be enhanced due to an increase in the powder surface area due to crushing. In the simple suspension method, no caking occurred, as there was no crushing. Examination of drug passage using HPLC revealed that the simple suspension method was superior to the crushing method in preventing amlodipine loss. The aforementioned results suggest that drug administration concomitant with rikkunshito using the simple suspension method was more useful than crushing the compounds. Unlike general hospital wards, a rapid, safe, and efficacious tube administration method is required in emergency and critical care medical centers. Therefore, these findings could potentially increase administration efficacy.

The results of this study suggested that appropriate drug administration to patients might well be able to achieved by a combination of rikkunshito, a Kampo product frequently used in emergency medical care, and amlodipine through a tube by using the simple suspension method, which resulted in decreased drug loss compared to the crushing method. Since only two drugs were studied, further investigation with more concomitant drugs may be required in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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