Original Article

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Physicochemical properties of brand and generic infusion fluid preparations (Part 3): Investigation of type 1 hypotonic infusion fluids

Sawako Takei[1,*], Soh Katsuyama[2], Yusuke Hori[1]

[1] Center for Experimental Pharmacy Practice, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan;
[2] Clinical Pharmaceutical Sciences Course, Department of Pharmaceutical Sciences, Nihon Pharmaceutical University, Kitaadachi-gun, Saitama Prefecture, Japan.

SUMMARY In Japan, the increasing use of generic drugs has led to a reduction in drug prices, which affect the steady supply of drugs. A "basic drug" system was introduced to rescue these drugs by eliminating gaps in drug prices among preparations with the same constituents. "Type 1" hypotonic infusion fluids, which are potassium-free and commonly used to treat dehydration, meet the definition of a "basic drug" in Japan, and there are no drug price gaps. However, there is a lack of information on the physicochemical properties of "type 1" hypotonic infusion fluids, making it difficult to identify differences among them. Extracellular fluid-replacement solutions and "type 3" hypotonic infusion fluids have different pH and titratable acidity. Here, we measured the pH, titratable acidity, and osmolality of six different "type 1" hypotonic infusion fluids and compared the results with respect to risk avoidance considering metabolic acidosis, changes upon mixing, and vascular pain. There was a significant difference, or trend toward significance, in titratable acidity, which is a risk factor for metabolic acidosis in patients with impaired renal function, and pH, which is a risk factor for change upon mixing, among all combinations except one of the infusion fluids. Thus, the selection of "type 1" hypotonic infusion fluids for children with immature renal function, elderly patients with impaired renal function, and patients with unknown pathophysiology, considering titratable acidity and pH, is an effective strategy for risk avoidance.

Keywords Titratable acidity, pH, risk avoidance, impaired renal function, elderly patients, metabolic acidosis

1. Introduction

In Japan, the use of generic drugs is encouraged as a part of fiscal reforms of the national medical insurance system (*1*). As of March 2021, generic drug use by volume was 79.6% in Japan, rapidly closing in on the 80% target for 2020 (*2*). Owing to frequent reductions in drug prices, introduced by national health insurance price revisions, an increasing number of drugs have become unprofitable despite a high demand for their use as a part of insured medical care, their long-term widespread use in clinical settings, and their established safety and efficacy. Thus, there is a need to ensure a continuous and stable supply of these drugs that have become unprofitable. A provisional system was introduced with the 2016 drug pricing reforms to designate these as "basic drugs," and to offer support before they are subject to "repricing of unprofitable products" or become "minimum-priced products" (*3*). Currently, because "type 1" hypotonic infusion fluids in Japan meet the definition of an unprofitable product, all such generic and Brand versions of "type 1" hypotonic infusion fluids are designated "basic drugs" (*4*), and there is no drug price gap between them (*5*). However, as generic preparations intended for intravenous administration undergo fewer tests during development than Brand versions, they are subjected to fewer submission requirements when applying for approval (*6*).

Previously, we showed that pH, titratable acidity, osmolality, and insoluble microparticle levels differ between Brand and generic versions of extracellular fluid replacement solutions (*7*) and "type 3" hypotonic infusion fluids (*8*). Additionally, these differences contribute to metabolic acidosis, changes upon mixing, and vascular pain (*7,8*). Information on titratable acidity, osmolality, and insoluble microparticles need not be included in drug package inserts or pharmaceutical interview forms. Additionally, information on these items is not available

in the Information Package of Quality of Prescription Drugs (the so-called Blue Book) (*9*). However, besides pH, titratable acidity influences the acid-base equilibrium of blood and changes upon mixing, osmolality can cause vascular pain, and insoluble microparticles can induce adverse events (*e.g.*, phlebitis and pulmonary fiber embolism) (*10,11*). Even among preparations with the same constituents, examining the differences in these parameters is an effective strategy for risk avoidance when deciding whether a preparation is indicated (*7,8*).

In this study, we evaluated pH and other physicochemical properties (titratable acidity and osmolality) that need not be included in drug package inserts or pharmaceutical interview forms. We aimed to ascertain information that should be evaluated from the perspective of risk avoidance when deciding if a "type 1" hypotonic infusion fluid is indicated.

2. Materials and Methods

2.1. Experimental materials

Experiments were performed using two brand-equivalent drugs (labeled "Brand 1" and "Brand 2"), three brand-equivalent versions of brand 1 (labeled "Generic 1-1," "Generic 1-2," and "Generic 1-3"), and one brand-equivalent version of brand 2 (labeled "Generic 2"). Note that preparations classified as "Brand drugs" before the introduction of the "basic drugs" system are herein referred to as "brand-equivalent drugs." Similarly, preparations classified as "generic drugs" before the introduction of the "basic drugs" system are referred to as "generic-equivalent drugs."

Generic 1-2 contains the same constituents, raw drug materials, and additives as Brand 1; it is produced using the same method under license from the manufacturer of Brand 1 and approved for national health insurance coverage. Table 1 indicates whether each preparation is a brand-equivalent or a generic-equivalent drug, and includes the indicated name, constituents, and manufacturer.

2.2. Measurement of pH and physicochemical properties

Titratable acidity was determined using a TUA-701 automatic analyzer (DKK-TOA Corporation, Tokyo, Japan). Neutralization of titratable acidity was measured using 0.1 N NaOH (Hayashi Pure Chemical, Osaka, Japan) with the endpoint set to pH 7.4. pH was determined using a TUA-701 automatic analyzer (DKK-TOA Corporation). Osmolality was determined using the freezing point depression method (*12*) with supercooling using Osmostat™ OM-6040 (Arkray Factory, Inc., Shiga, Japan). Each sample was analyzed five times for each measured parameter.

2.3. Statistical analysis

Normality was confirmed using Shapiro-Wilk's W test. Two-group comparisons were made using the two-sided Student t-test or Kruskal-Wallis test. Either Tukey-Kramer test or Steel-Dwass test was used for multiple-group comparisons. All statistical analyses were performed using JMP® 14 (SAS Institute Inc., Cary, NC, USA), and results with $p < 0.05$ were considered statistically significant.

3. Results

3.1. Titratable acidity

3.1.1. Comparison among Brand 1, Generic 1-1, Generic 1-2, and Generic 1-3

There was a significant difference in titratable acidity between Generic 1-1 and Generic 1-2 (median [IQR]: 0.77 [0.77-0.78] *vs*. 0.39 [0.38-0.39], respectively, $p = 0.043$), Generic 1-1 and Generic 1-3 (median [IQR]: 0.77 [0.77-0.78] *vs*. 0.11 [0.11-0.14], respectively, $p = 0.049$), and Generic 1-2 and Generic 1-3 (median [IQR]: 0.39 [0.38-0.39] *vs*. 0.11 [0.11-0.14], respectively, $p = 0.044$). A significant difference was also observed between Generic 1-1 and Brand 1 (median [IQR]: 0.77 [0.77-0.78] *vs*. 0.41 [0.39-0.45], respectively, $p = 0.052$), and between Brand 1 and Generic 1-3 (median [IQR]: 0.41 [0.39-0.45] *vs*. 0.11 [0.11-0.14], respectively, $p = 0.053$). There was no significant difference in titratable activity

Table 1. Brand- and Generic-equivalent drugs evaluated in the current study

Classification	Labeled name	Constituents**			
		Na^+ (mEq/L)	Cl^- (mEq/L)	Lactate$^-$ (mEq/L)	Glucose (%)
Brand-equivalent drugs*	Brand 1	90	70	20	2.6
Generic-equivalent drugs*	Generic 1-1	90	70	20	2.6
Generic-equivalent drugs*	Generic 1-2	90	70	20	2.6
Generic-equivalent drugs*	Generic1-3	90	70	20	2.6
Brand-equivalent drugs*	Brand 2	77	77	–	2.5
Generic-equivalent drugs*	Generic 2	77	77	–	3.5

*Although designated a "basic drug" in 2020, preparations classified as "Brand drugs" before the introduction of the "basic drugs" system are referred to as "brand-equivalent drugs" and "generic drugs" are referred to as "generic-equivalent drugs." **Data on constituents were obtained from the drug package insert of each preparation.

between Brand 1 and Generic 1-2 (median [IQR]: 0.41 [0.39-0.45] *vs*. 0.39 [0.38-0.39], respectively, $p = 0.235$).

The titratable acidity of Generic 1-1 was ~1.8-fold higher than that of Generic 1-2, ~7-fold higher than that of Generic 1-3, and ~1.9-fold higher than that of Brand 1. The titratable acidity of Brand 1 was ~3.8-fold higher than that of Generic 1-3 and that of Generic 1-2 was ~3.5-fold higher than that of Generic 1-3 (Figure 1A).

3.1.2. Comparison between Brand 2 and Generic 2

There was a significant difference in titratable acidity between Brand 2 and Generic 2 (mean ± SD: 0.04 ± 0 *vs*. 0.11 ± 0.01, respectively, $p < 0.0001$). The titratable acidity of Generic 2 was ~2.8-fold higher than that of Brand 2 (Figure 1B).

3.1.3. Comparison between Brand 1 and Brand 2

There was a significant difference in titratable acidity between Brand 1 and Brand 2 (mean ± SD: 0.42 ± 0.03 *vs*. 0.04 ± 0, respectively, $p < 0.0001$). The titratable acidity of Brand 1 was ~10.5-fold higher than that of Brand 2 (Figure 1C).

3.2. pH

3.2.1. Comparison among Brand 1, Generic 1-1, Generic 1-2, and Generic 1-3

There was a significant difference in pH between Generic 1-3 and Generic 1-2 (median [IQR]: 6.06 [6.01-6.06] *vs*. 5.47 [5.47-5.48], respectively, $p = 0.043$), Generic 1-3 and Brand 1 (median [IQR]: 6.06 [6.01-6.06] *vs*. 5.46 [5.46-5.47], respectively, $p = 0.049$), Generic 1-3 and Generic 1-1 (median [IQR]: 6.06 [6.01-6.06] *vs*. 5.18 [5.18-5.19], respectively, $p = 0.043$), Generic 1-2 and Generic 1-1 (median [IQR]: 5.47 [5.47-5.48] *vs*. 5.18 [5.18-5.19], respectively, $p = 0.038$), and Brand 1 and Generic 1-1 (median [IQR]: 5.46 [5.46-5.47] *vs*. 5.18 [5.18-5.19], respectively, $p = 0.044$). There was no significant difference between Brand 1 and Generic 1-2 (median [IQR]: 5.46 [5.46-5.47] *vs*. 5.47 [5.47-5.48], respectively, $p = 0.108$). The pH of Generic 1-3 was ~0.59-fold higher than that of Generic 1-2, ~0.60-fold higher than that of Brand 1, and ~0.88 higher than that of Generic 1-1. The pH of Generic 1-2 was ~0.29-fold higher than that of Generic 1-1 and the pH of Brand 1 was ~0.28-fold higher than that of Generic 1-1 (Figure 2A).

3.2.2. Comparison between Brand 2 and Generic 2

There was a significant difference in pH between Brand 2 and Generic 2 (mean ± SD: 4.98 ± 0.02 *vs*. 4.63 ± 0.02, respectively, $p < 0.0001$). The pH of Brand 2 was ~0.35-fold higher than that of Generic 2 (Figure 2B).

3.2.3. Comparison between Brand 1 and Brand 2

There was a significant difference in pH between Brand

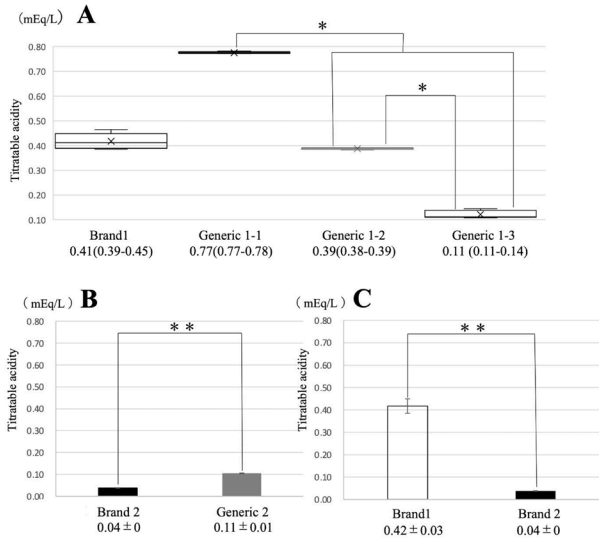

Figure 1. Comparison of titratable acidity between brand-equivalent drugs and generic-equivalent drugs. (A) Comparisons among Brand 1, Generic 1-1, Generic 1-2, and Generic 1-3. Data are presented as median, and the upper and lower ends of the box represent the third and first quartiles, respectively. **(B)** Two-group comparisons between Brand 2 and Generic 2 and **(C)** between Brand 1 and Brand 2. For parts **(B)** and **(C)**, data are presented as mean ± SD. *$p < 0.05$, **$p < 0.01$.

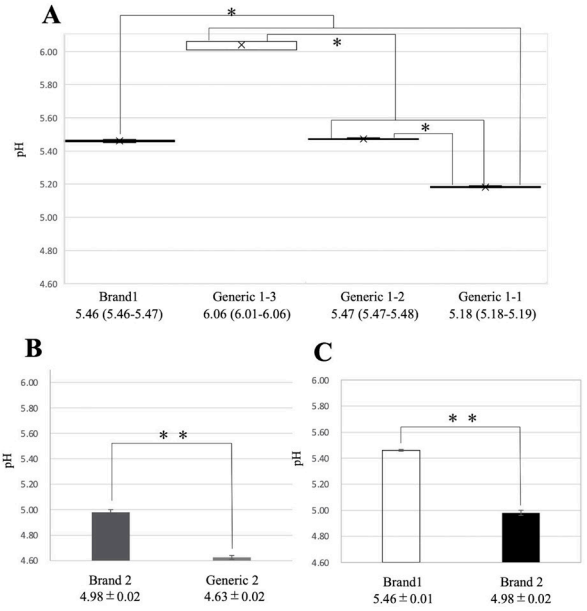

Figure 2. Comparison of pH between brand-equivalent drugs and generic-equivalent drugs. (A) Multiple comparisons among Brand 1, Generic 1-3, Generic 1-2, and Generic 1-1. Data are presented as median, and the upper and lower ends of the box represent the third and first quartiles, respectively. **(B)** Two-group comparisons between Brand 2 and Generic 2 and **(C)** between Brand 1 and Brand 2. For parts **(B)** and **(C)**, data are presented as mean ± SD. *$p < 0.05$, **$p < 0.01$.

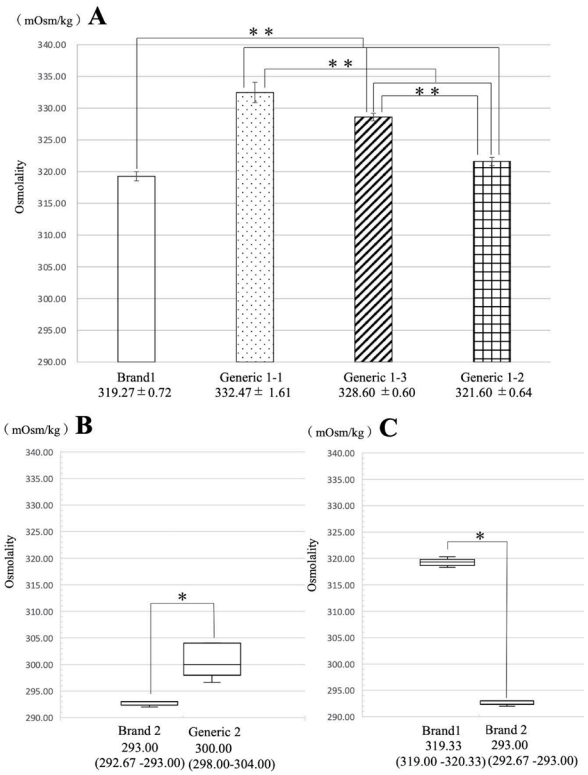

Figure 3. Comparison of osmolality between brand-equivalent drugs and generic-equivalent drugs. (A) Comparisons among Brand 1, Generic 1-1, Generic 1-3, and Generic 1-2. Data are presented as mean ± SD. **(B)** Two-group comparisons between Brand 2 and Generic 2 and **(C)** between Brand 1 and Brand 2. For parts **(B)** and **(C)**, data are presented as median, and the upper and lower ends of the box represent the third and first quartiles, respectively. $^{*}p < 0.05$, $^{**}p < 0.01$.

1 and Brand 2 (mean ± SD: 5.46 ± 0.01 *vs*. 4.98 ± 0.02, respectively, $p < 0.0001$). The pH of Brand 1 was ~0.48-fold higher than that of Brand 2 (Figure 2C).

3.3. Osmolality

3.3.1. Comparison of Brand 1, Generic 1-1, Generic 1-2, and Generic 1-3

There was a significant difference in osmolality between Generic 1-1 and Generic 1-3 (mean ± SD: 332.47 ± 1.61 *vs*. 328.60 ± 0.60, respectively, $p < 0.0001$), Generic 1-1 and Generic 1-2 (mean ± SD: 332.47 ± 1.61 *vs*. 321.60 ± 0.64, respectively, $p < 0.0001$), Generic 1-1 and Brand 1 (mean ± SD: 332.47 ± 161 *vs*. 319.27 ± 0.72, respectively, $p < 0.0001$), Generic 1-3 and Generic 1-2 (mean ± SD: 328.6 ± 0.60 *vs*. 321.60 ± 0.64, respectively, $p < 0.0001$), Generic 1-3 and Brand 1 (mean ± SD: 328.6 ± 0.60 *vs*. 319.27 ± 0.72, respectively, $p < 0.0001$), and Generic 1-2 and Brand 1 (mean ± SD: 321.60 ± 0.64 *vs*. 319.27 ± 0.72, respectively, $p = 0.009$).

The osmolality of Generic 1-1 was ~3.87 mOsm/kg higher than that of Generic 1-3, ~10.87 mOsm/kg higher than that of Generic 1-2, and ~13.20 mOsm/kg higher than that of Brand 1. The osmolality of Generic 1-3 was ~7.00 mOsm/kg higher than that of Generic 1-2 and ~9.33 mOsm/kg higher than that of Brand 1. The osmolality of Generic 1-2 was ~2.33 mOsm/kg higher than that of Brand 1 (Figure 3A).

3.3.2. Comparison of Brand 2 and Generic 2

There was a significant difference in osmolality between Brand 2 and Generic 2 (median [IQR]: 293.00 [292.67-293.00] *vs*. 300.00 [298.00-304.00], respectively, $p = 0.011$). The osmolality of Generic 2 was ~7.00 mOsm/kg higher than that of Brand 2 (Figure 3B).

3.3.3. Comparison of Brand 1 and Brand 2

There was a significant difference in osmolality between Brand 1 and Brand 2 (median [IQR]: 319.33 [319.00-320.33] *vs*. 293.00 [292.67-293.00], respectively, $p = 0.011$). The osmolality of Brand 1 was ~26.33 mOsm/kg higher than that of Brand 2 (Figure 3B).

4. Discussion

In Japan, drug package inserts, pharmaceutical interview forms, and pharmaceutical product information outlines are common sources of information when using pharmaceuticals (*13,14*). In 2018, the Generic Pharmaceutical Quality Information Study Committee published the Information Package of Quality of Prescription Drugs (Blue Book) (*9*) to provide information on and ensure the quality of generic pharmaceuticals. Since then, this "Blue Book" has become a useful source of information. The Tokyo Metropolitan Government also reported that, based on the results of a 2019 questionnaire concerning generic pharmaceuticals, Pharmaceutical and Medical Device Delivery Services (PMDA Medi-Navi) and pharmaceutical company websites are common sources of information on generic drugs (*15*). However, it is difficult to obtain information on titratable acidity, osmolality, and insoluble microparticles from these information sources. This information need not be included in drug package inserts or pharmaceutical interview forms.

Titratable acidity is calculated by titrating the acidity of a material with a standard base; in clinical terms, it can be described as the amount of base (0.1 mol/L NaOH) needed to titrate the infusion fluid preparation to the pH of human blood (7.4) (*16*). Although fixed acids affect the titratable acidity of these preparations, information on some fixed acids such as acetic acid need not be included in the drug package insert (*17*). Therefore, for example, adding acetic acid to an infusion fluid preparation will have a limited effect on pH, but it will increase titratable acidity. For this reason, adding fixed acids that need not be mandatorily included in drug package inserts results in different titratable acidities among preparations with the same constituents. Furthermore, because fixed

acids are processed by the kidneys, administering preparations with high titratable acidities increases the risk of metabolic acidosis in patients with impaired renal function, elderly patients, and children with immature renal function (*18*).

The results of the present study revealed a significant difference, or trend toward significance, in titratable acidity among all combinations of "type 1" hypotonic infusion fluids with the same constituents, except between Brand 1 and Generic 1-2. Humans produce fixed acids at a rate of 1 mEq/kg/d (*19*). If 1,000 mL of Generic 1-1, which presented the highest titratable acidity, is administered over 1 d, the kidneys of a person weighing 50 kg will process 50.78 mEq of fixed acids or 1.02-times their normal acid-processing capacity. This would be considered a low risk in patients with a normal renal function. However, in Japan, such "type 1" hypotonic infusion fluids do not contain potassium and can be administered to patients with unknown pathophysiology. Therefore, assuming "type 1" hypotonic infusion fluids will be administered to patients with impaired renal function, the indications of a patient for these preparations must be determined by evaluating the risk posed by different titratable acidities among preparations with the same constituents.

Differences in pH may affect the occurrence of pH-dependent changes upon mixing. The results of this study revealed a significant difference in pH among all combinations of "type 1" hypotonic infusion fluids with the same constituents, except between Generic 1-2 and Brand 1. This is illustrated by examining the likelihood of a pH change upon mixing when Omepral® injection 20 (omeprazole sodium hydrate) is administered from a side tube of Brand 1 or Generic 1-1, both of which have significantly different pH. The pH variability of Omepral® injection 20 (*20*) and data gathered in the present study indicate that because the pH change point of Omepral® injection 20 is 5.29 (*20*), it can be administered from a side tube of Brand 1 (pH 5.46), but not from a side tube of Generic 1-1 (pH 5.18), owing to the likelihood of pH change upon mixing (Figure 4). This is also illustrated by examining the likelihood of pH change upon mixing when Dormicum® injection 10 mg (change point pH of 4.72) (*21*) is administered from a side tube of Brand 2 (pH 4.98) or Generic 2 (pH 4.63). Based on pH variability testing of Dormicum® injection 10 mg (*21*) and the results of the present study, Dormicum® Injection 10 mg cannot be administered from a side tube of Brand 2 owing to the likelihood of pH change upon mixing. However, it can be administered from a side tube of Generic 2 (Figure 5).

Whether the risk posed by a difference in pH, as

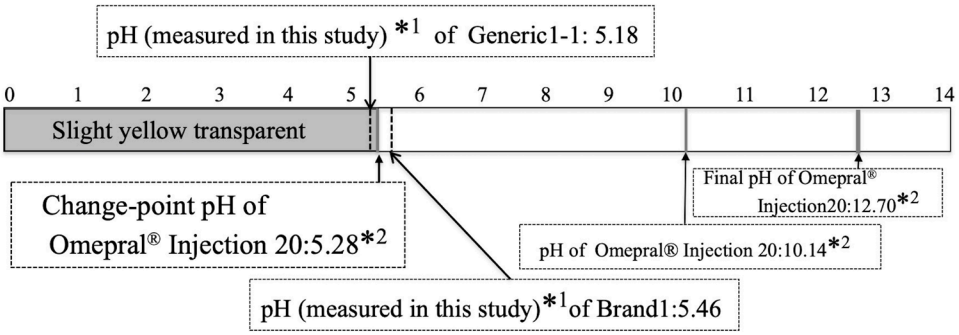

Figure 4. Predicting whether Omepral® Injection 20 (omeprazole sodium hydrate) can be mixed with Brand 1 and Generic 1-1. *1 pH values measured in this study were used as the pH values for Brand 1 and Generic 1-1. *2 The pH, final pH, and change-point pH of the Omepral® Injection 20 were obtained from pH variability test results in the Omepral® Injection 20 pharmaceutical interview form. ® represents trademark.

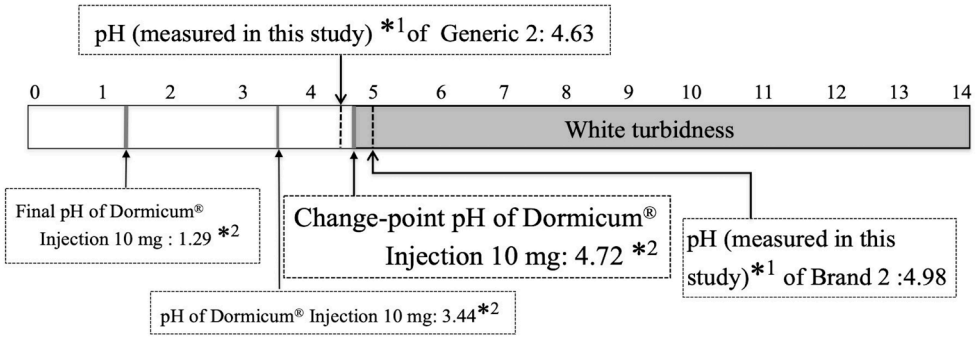

Figure 5. Predicting whether Dormicum® Injection 10 mg (midazolam) can be mixed with a Brand 2 and Generic 2. *1 pH values measured in this study were used as the pH values for Brand 2 and Generic 2. *2 The pH, final pH, and change point pH of Dormicum® Injection 10 mg were obtained from pH variability test results in the Dormicum® Injection 10 mg pharmaceutical interview form. ® represents trademark.

illustrated above, can be attributed to titratable acidity, as previously discussed, is not clear. Consequently, the indications of a patient for "type 1" hypotonic infusion fluids with the same constituents must be determined by evaluating the risk posed by the differences in pH, in addition to the differences in titratable acidity. Note that pH variability is tested by adding small amounts of 0.1 M hydrochloric acid or 0.1 M sodium hydroxide into 10 mL of infusion fluid to identify pH-dependent changes in appearance. The change-point pH is defined as the pH at which a change in appearance occurs, and the final pH is defined as the pH measured after adding 10 mL of 0.1 M hydrochloric acid or 0.1 M sodium hydroxide when there is no change in appearance (*22*).

Vascular pain is commonly reported at osmolalities of approximately 600 mOsm/kg (*23*). Although a significant difference in osmolality was observed in the present study among all combinations of "type 1" hypotonic infusion fluids with the same constituents, the measured osmolalities ranged between 300 and 333 mOsm/kg, suggesting no clinically important risk of vascular pain.
There are two forms of "type 1" hypotonic infusion fluid, and the results of the present study revealed a significant difference in titratable acidity, pH, and osmolality among these Brand-equivalent drugs. Recognizing the differences in titratable acidity, pH, and osmolality even among preparations of the same type (in this case, "type 1" hypotonic infusion fluids) is an effective strategy for risk avoidance when considering patient indications.

"Type 1" hypotonic infusion fluids do not contain potassium and can, therefore, be administered to children with immature renal function, elderly patients with impaired renal function, and patients with unknown pathophysiology. Furthermore, utilizing the findings of this study when considering prescription questions and other evaluations of appropriate usage will aid the safe and effective provision of medical care.

Previously, we reported that differences in insoluble microparticles between Brand and generic pharmaceuticals are risk factors associated with extracellular fluid replacement solutions (*7*) and "type 3" hypotonic infusion fluids (*8*). However, in this study, we did not investigate insoluble microparticles. Insoluble microparticles must be removed from these preparations based on multiple reports showing that they accumulate in the body following intravenous administration (*24,25*). In addition, glass fragments and other foreign substances generated during administration and mixing operations need to be removed (*26*). Such particles can be effectively removed with a filter during administration (*27-29*). When administering a preparation that is absorbed by or interacts with the filter, changing the filter diameter, filter material, or method of administration is an effective strategy for risk avoidance (*30,31*). We considered that it was necessary to use a filter when administering the injection, regardless of the presence or absence of existing insoluble microparticles in the preparation. For this reason, we did not examine the insoluble fine particles in this study.

In conclusion, we revealed that differences in pH and titratable acidity are risk factors associated with "type 1" hypotonic infusion fluids. Because the physicochemical properties that pose such risks differ by infusion fluid type, the same tests should be performed by strictly adhering to a unified procedure for other hypotonic infusion fluids (types 2 and 4), "type 3" hypotonic infusion fluids with added glucose, and nutritional infusion fluids. Findings from such studies must continue to be applied in clinical settings.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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**Address correspondence to:*
Sawako Takei, Center for Experimental Pharmacy Practice, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan.
E-mail: takei@toyaku.ac.jp

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