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DOI: 10.5582/ddt.2023.01091

Comparison of the physicochemical properties of branded and generic glucose-added maintenance hypotonic infusion fluids to assess the potential for phlebitis and incompatibility with other drugs

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SUMMARY In Japan, the switch from branded to generic infusion fluids has been promoted as a national policy. Recently, as generic products have been in short supply, the switch from generic to branded infusion fluids has increased. However, certain additives for injectable infusion fluids, such as nonvolatile acids like acetic acid and hydrochloric acid, are not required to be listed in the package insert. We hypothesized that the addition of nonvolatile acids may be one of the reasons for the differences in physicochemical properties between the branded and generic infusion fluids. We have previously reported that in other types of electrolyte infusion fluids, a variation in pH can cause incompatibility with other drugs, and variation in titratable acidity and osmolality can lead to phlebitis. Glucose-added maintenance hypotonic infusion fluid (listed as type-3G) is commonly used as a maintenance solution when energy support is needed. However, nonvolatile acid is added to prevent the caramelization of glucose, resulting in higher osmolality and titratable acidity and lower pH. Therefore, we hypothesized that both phlebitis and incompatibility with other drugs are likely to occur; hence, we measured and evaluated the physicochemical properties of branded and generic type-3G infusion fluids. We show that the osmolality, pH, and titratable acidity of all evaluated branded and generic products differed significantly and that these properties should be evaluated together to avoid phlebitis and incompatibility with other drugs when switching between branded and generic type-3G infusion fluids.

Keywords infusion fluids, titratable acidity, pH, osmolality, phlebitis, incompatibility

In Japan, four types of hypotonic infusion fluids with different compositions are used according to their specific purposes. Some additives for injectable infusion fluids that are intended to adjust pH or make the infusion fluid isotonic are not required to be listed on the package insert (*1*). Of these, weakly acidic nonvolatile acids, such as acetic, do not fully dissociate in the infusion fluids due to their weakly acidic pH. However, they almost completely dissociate in blood, which is weakly basic. Consequently, the concentration of hydrogen ions in these weakly acidic nonvolatile acids is not indicated by the pH of the infusion but is represented by the titratable acidity, which measures the hydrogen-ion concentration in the infused solution within the bloodstream. Titratable acidity is defined as the amount of base (NaOH) required to neutralize the pH of 100 mL of an infusion fluid to physiological pH (7.4) (*2*). Based on these facts, we hypothesized that differences in additives may contribute to differences in the physicochemical properties, such as pH, titratable acidity, and osmolarity, between branded and generic infusion fluids. Variations in pH lead to possible incompatibility with other drugs (*3*), while changes in pH (*4-7*), titratable acidity (*6,7*), and osmolarity (*5,8-10*) can lead to phlebitis. In our previous studies, we measured the pH, titratable acidity, and osmolality of isotonic electrolyte infusion fluids and three types of hypotonic electrolyte infusion fluids to determine any differences, and reported properties that should be evaluated when switching between branded and generic infusion fluids (*11-14*). In this study, we measured the pH, titratable acidity, and osmolarity of branded and generic glucose-added maintenance hypotonic infusion fluids (listed as type-3G), which are commonly used as

maintenance solutions when energy support is needed, and we considered which physicochemical properties should be evaluated when switching between branded and generic type-3G infusion fluids.

Experiments were performed using four branded infusion fluids (labeled "Brand 1", "Brand 2", "Brand 3", and "Brand 4"), and the generic version of each (labeled "Generic 1", "Generic 2", "Generic 3", and "Generic 4"). Table 1 lists the constituents of each infusion fluid. All measurements were performed on five preparations each of formulations with the same lot numbers. Normality was confirmed using Shapiro-Wilk's W test. Two-group comparisons were performed using the two-sided Student *t*-test or Wilcoxon rank-sum test. All statistical analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA), and results with $P < 0.05$ were considered statistically significant.

The results are shown in Table 2. There were significant differences in osmolality between the branded and generic versions in each group. The osmolality of Generic 1 was ~1.02-fold higher than that of Brand 1, that of Brand 2 was ~1.01-fold higher than that of Generic 2, that of Generic 3 was ~1.01-fold higher than that of Brand 3, and that of Brand 4 was ~1.01-fold higher than that of Generic 4. There were significant differences in pH between the branded and generic versions in each group. The pH of Generic 1 was ~0.4 higher than that of Brand 1, that of Generic 2 was ~0.44 higher than that of Brand 2, that of Generic 3 was ~0.04 higher than that of Brand 3, and that of Brand 4 was ~0.12 higher than that of Generic 4. There were significant differences in the titratable acidity between the branded and generic versions in each group. The titratable acidity of Brand 1 was ~2.35-fold higher than that of Generic 1, that of Brand 2 was ~1.29-fold higher than that of Generic 2, that of Brand 3 was ~1.04-fold higher than that of Generic 3, and that of Generic 4 was ~1.44-fold higher than that of Brand 4.

Although there is insufficient evidence for tolerable osmolality in phlebitis, there have been scattered reports recommending a threshold of 600 mOsm/kg (5,8,10).

Table 1. Composition of type-3G infusion fluids

Classification	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Branded
Labeled name	Brand 1	Generic 1	Brand 2	Generic 2	Brand 3	Generic 3	Brand 4	Brand 4
Components*								
Na^+ (mEq/L)	35	35	40	40	35	35	35	35
K^+ (mEq/L)	20	20	35	35	20	20	20	20
Ca^{2+} (mEq/L)	–	–	–	–	5	5	–	–
Mg^{2+} (mEq/L)	–	–	–	–	3	3	3	3
Cl^- (mEq/L)	35	35	40	40	28	28	38	38
$Lactate^-$ (mEq/L)	20	20	20	20	–	–	20	20
$Acetate^-$ (mEq/L)	–	–	–	–	20	20	–	–
$Gluconate^-$ (mEq/L)	–	–	–	–	5	5	–	–
$Citrate^{3-}$ (mEq/L)	–	–	–	–	–	–	–	–
P (mmol/L)	–	–	8	8	10	10	–	–
Glu (%)	7.5	7.5	10	10	10	10	10	10

* Data on constituents were obtained from the infusion fluid package insert of each preparation.

Table 2. Comparison of the osmolality, pH, and titratable acidity of branded and generic infusion fluids

Classification	osmolality		pH		titratable acidity	
Labeled name	mean ± SD* (mOsm/kg)	*P* value	mean ± SD* or median [IQR]**	*P* value	mean ± SD* or median [IQR]** (mEq/L)	*P* value
Group 1		< 0.0001		0.0109		0.0117
Brand 1	543 ± 2*		5.35 [5.35-5.37]**		0.532 [0.531-0.534]**	
Generic 1	552 ± 1*		5.75 [5.72-5.75]**		0.226 [0.226-0.236]**	
Group 2		0.0005		< 0.0001		0.0122
Brand 2	762 ± 3*		5.18 ± 0.002*		9.050 [9.033-9.082]**	
Generic 2	753 ± 1*		5.62 ± 0.005*		7.013 [6.820-7.018]**	
Group 3		0.0017		< 0.0001		< 0.0001
Brand 3	728 ± 1*		5.02 ± 0.004*		15.156 ± 0.150*	
Generic 3	738 ± 3*		5.06 ± 0.006*		14.536 ± 0.054*	
Group 4		< 0.0001		< 0.0001		< 0.0001
Brand 4	732 ± 1*		4.74 ± 0.005*		1.879 ± 0.006*	
Generic 4	723 ± 2*		4.62 ± 0.008*		2.715 ± 0.019*	

* Continuous variables are presented as mean ± standard deviation (SD). ** Continuous variables are presented as median [interquartile range].

Furthermore, regarding the relationship between tolerable osmolality of peripheral veins and the duration of administration, it has been reported that the upper limit of osmolality that can be administered through a peripheral vein is approximately 820, 690, and 550 mOsm/kg for 8, 12, and 24 h, respectively. Furthermore, the longer the duration of administration, the lower the tolerable osmolality in the peripheral veins (*9*). In the current study, there were clear differences in osmolality between the branded and generic infusion fluids in all groups; however, except for Group 1, all groups had an osmolality greater than 600 mOsm/kg. Therefore, the possibility of phlebitis is high, and avoidance measures are necessary regardless of switching in Groups 2-4. In contrast, type-3G infusion fluids contain potassium ions and glucose, each with a dosage rate limitation (*15,16*). The time required to administer 2,000 mL to a 60-kg patient, the average weight of a Japanese patient (*17*), within this dosing rate limit is more than 5 h for Group 1 and more than 7 h for Groups 2-4. Compared to the data on the duration of administration and peripheral venous tolerable osmolality reported in previous studies (*18*), our estimate suggests that Group 1 can be safely administered for up to 24 h, whereas Groups 2-4 are safe for administration within an approximate 8-h window. These estimates indicate that switching between branded and generic infusion fluids should not be a problem within these timeframes. Based on these findings, we determined that osmolality should be evaluated along with the duration of administration when switching between branded and generic type-3G infusion fluids to avoid phlebitis.

Differences in pH can cause incompatibility with other drugs (*3*) and phlebitis (*4,6,7,9*). The present study revealed significant differences in pH between branded and generic type-3G infusion fluids in each group investigated. If 4 mg of bromhexine hydrochloride (Bisolvon® Injection 4 mg) (*19*) is administered through the side tube for Brand 4 (pH 4.74) and Generic 4 (pH 4.62), no change is expected for Generic 4, whereas the solution is expected to become cloudy for Brand 4. Bisolvon® Injection is formed by adding hydrochloric acid to bromhexine, a weakly basic substance, to produce the hydrochloride salt. Based on the results of experiments conducted by the manufacturer (*19*), it is anticipated that the proportion of insoluble molecular forms will increase and the solution may become turbid if the pH of the solution is higher than 4.71.

Based on previous studies that showed that the upper limit of pH tolerated for phlebitis is approximately 6.5 (*4*), all products evaluated in the current study are likely to cause phlebitis. Okamura *et al*. (*6*) examined the effects of pH and titratable acidity on phlebitis in hospitalized patients using two parenteral nutritional infusion fluids with nearly identical osmolality but different pH and titratable acidity (pH 5.1 and titratable acidity 17.5 *vs.* pH 6.7 and titratable acidity 7) and found that products with lower pH and higher titratable acidity had a significantly higher incidence of phlebitis. Kuwahara *et al*. (*7*) evaluated the same formulations pathologically in animal studies and reported results similar to those of Okamura *et al*. (*6*), and further reported that for equally low pH, the higher the titratable acidity, the higher the likelihood of phlebitis.

The titratable acidity of branded and generic infusion fluids may differ due in part to non-volatile acids. Moreover, titratable acidity is equivalent to a value that indicates the total amount of dissociated and undissociated acid in the infusion fluid and is not predictable from the pH. When infusion fluids with high titratable acidity are administered to blood, hydrogen ions are supplied by both dissociated and undissociated acids in the infusion fluid and are more difficult to neutralize. Therefore, infusion fluids with high titratable acidity are more likely to irritate venous endothelial cells with hydrogen ions for a longer period and cause phlebitis than infusion fluids with low titratable acidity (*20*). In the present study, the pH of all products was below 6.5 (*4*), the upper tolerable pH limit for phlebitis, and there was a significant difference in titratable acidity between the branded and generic infusion fluids in each group. Considering the above-mentioned studies by Okamura *et al*. (*6*) and Kawahara *et al*. (*7,20*) on infusion pH and titratable acidity, the potential for phlebitis is more likely in Brands 1–3 and Generic 4. Based on these findings, we determined that titratable acidity and pH are important when switching between branded and generic type-3G infusion fluids because they allow for more accurate avoidance of phlebitis.

In conclusion, the present showed that pH, titratable acidity, and osmotic pressure are the physicochemical properties that should be evaluated when switching between branded and generic type-3G infusion fluids. Our results from the present and previous studies (*11-14*) highlighted physicochemical properties that should be evaluated when switching between branded and generic electrolyte infusion fluids for all types. We believe that it is our urgent task to integrate the results of this study with our previous studies (*11-14*) to provide practical information that can be used in clinical practice.

Acknowledgements

We express our sincere gratitude to Associate Professor Keisuke Imada of Tokyo University of Pharmacy and Life Sciences for their guidance in this study, and all laboratories for their support and cooperation in advancing the research.

Funding: None.

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

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Received November 22, 2023; Revised February 16, 2024; Accepted February 18, 2024.

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Released online in J-STAGE as advance publication February 21, 2024.