—Regular Articles—

Consideration on Prevention of Phlebitis and Venous Pain from Intravenous Prostaglandin E_1 Administration by Adjusting Solution pH: *In Vitro* Manipulations Affecting pH

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Prostaglandin E_1 (PGE_1; Alprostadil Alfadex) is a potent vasodilator and inhibitor of platelet aggregation used to treat patients with peripheral vascular disease. The main adverse effects of intravenous PGE_1 administration, phlebitis and venous pain, arise from the unphysiologically low pH of infusion solutions. When PGE_1 infusion solutions with a pH value greater then 6 are used, phlebitis and venous pain are considered to be avoidable. Beginning with a PGE_1 infusion solution with pH greater than 6, we add the amount of 7% sodium bicarbonate needed to bring the solution to pH 7.4 if phlebitis or venous pain develops. In the present study we established a convenient nomogram showing the relationship between the titratable acidity of various infusion solutions and the volume of 7% sodium bicarbonate required to attain pH 7.4 for preventing the phlebitis and venous pain associated with PGE_1 infusion.

Key words——prostaglandin E_1; phlebitis; venous pain; physiologic pH; titratable acidity

INTRODUCTION

Prostaglandin E_1 infusion (PGE_1; Alprostadil Alfadex) is widely used to treat peripheral circulatory disturbances based upon its ability to relax vascular smooth muscle[1] and thus increase blood flow. In addition to being a potent vasodilator, PGE_1 inhibits platelet aggregation.[2,3] Venous pain (occurrence, 3.50%), phlebitis (0.59%), infusion site pain (0.73%), and local erythema (4.41%) are the main side effects of intravenous PGE_1 administration. The infusion rate and PGE_1 concentration in the solution may not have an important influence on the occurrence of phlebitis.[4] Harrigan[5] reported that instead, adverse effects such as phlebitis and venous pain are caused by a low pH of the PGE_1 infusion solution relative to 7.4, the physiologic pH. Similarly, Ozaki *et al.*[6] pointed out that the occurrence of phlebitis and venous pain was decreased by adjusting the solution to pH 7.4.

PGE_1 treatment often requires more than 14 days of continued administration 1 to 2 times daily. However, the development of phlebitis and venous pain during PGE_1 infusion can cause considerable patient distress and interruption of treatment, decreasing the likelihood of complete remission. To avoid the development of phlebitis and venous pain, 20 ml of 7% sodium bicarbonate is often added to the PGE_1 infusion solution. However, excessive addition of sodium bicarbonate itself can give rise to venous pain, as well as causing alkalosis and increases in carbon dioxide levels. To determine the optimal addition of sodium bicarbonate, we established a convenient nomogram showing the relationship between the titratable acidity of each infusion solution and the volume of added 7% sodium bicarbonate required to bring the pH to 7.4. Thus using *in vitro* methods, we assessed possible problems associated with and optimal ways to carry out the addition of 7% sodium bicarbonate to prevent the phlebitis and venous pain associated with PGE_1 infusion.

MATERIALS AND METHODS

Materials Drugs tested included PGE_1 (Prostandin; Ono Pharmaceutical, Osaka, Japan) and 7% sodium bicarbonate (7% Meylon; Otsuka Pharmaceutical, Tokushima, Japan). Infusion solutions included normal saline (NS; Otsuka Normal Saline, Otsuka Pharmaceutical; and Isotonic Sodium Chloride Solution or ISC, Terumo, Tokyo, Japan); 2/3 normal saline (Solita-T No. 1, Ajinomoto Pharma, Tokyo, Japan; and Soldem 1, Terumo, Tokyo,

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Japan); 1/3 normal saline (Actit Injection, Kowa Pharmaceutical, Tokyo, Japan; KN Solution 3B, Otsuka Pharmaceutical; Solitax-H, Ajinomoto Pharma; and Soldem 3, Terumo); 1/4 normal saline (Solita-T No. 3, Ajinomoto Pharma; Soldem 3A, Terumo; and Solita-T No. 4, Ajinomoto Pharma); Ringer's solution (Physio 140, Otsuka Pharmaceutical; and Solita Shimizu, Ajinomoto Pharma); and 5% glucose solution (Otsuka Pharmaceutical). Table 1 shows the composition of each infusion solution used. Two-thirds, one-third, and one-fourth normal saline were distinguished by the quantity of sodium ion included in hypotonicity infusion solutions. Two-thirds, one-third, and one-fourth normal saline include 90 mEq/l, 45 to 50 mEq/l, and 30 to 35 mEq/l of sodium ion, respectively.

Methods Fluctuations in pH were monitored after adding 7% sodium bicarbonate to 200 ml or 500 ml of infusion solutions containing 40 μg of PGE_1. Infusion solutions tested were NS, ISC, Solita-T No. 1, Actit Injection, Solitax-H, Solita-T No. 3, Solita-T No. 4, and KN Solution 3B. Infusion solutions volumes of 40 ml or 100 ml containing 8 μg of PGE_1 were placed in a stoppered conical flask. Each of these samples represented 1/5 of the original solution volume. Then 0.01 to 4 ml of 7% sodium bicarbonate was added and the flask was shaken. A pH meter (Horiba Navi F-52, Horiba Ltd., Kyoto, Japan) was then used to measure pH. In additional experiments, pH was measured at 0, 2, 4, 6, 12, and 24 h in infusion solutions containing 40 μg of PGE_1.

Infusion solutions used were NS, ISC, Solita-T No. 1, Soldem 1, Soldem 3, Solita-T No. 3, Soldem 3A, Physio 140, Solita Shimizu, and 5% glucose solution. PGE_1 (7 or 2.8 μg) dissolved in 35 ml of infusion solution was placed in a stoppered conical flask. For original solution volumes of 200 ml, each sample volume represented 7/40; for original solution volumes of 500 ml, each sample volume represented 7/100. The flask was shaken, and pH was measured with the pH meter at 0, 2, 4, 6, 12, and 24 h.

RESULTS

Changes in pH after Adding 7% Sodium Bicarbonate Figure 1 shows the changes in pH after adding 7% sodium bicarbonate to 200 ml of infusion solution containing 40 μg of PGE_1, while Fig. 2 shows pH changes when the original infusion solution volume was 500 ml. Changes in pH varied between specific infusion solutions, and the volume of 7% sodium bicarbonate required to attain pH 7.4 varied between specific infusion solutions. The volume of 7% sodium bicarbonate required to reach pH 7.4 increased as the quantity of infusion solution increased.

Table 1. Composition of Infusion Solutions in this Study

Infusion solution	Glucose %	mEg/l									
		Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	$(Lactate)^-$	$(Acetate)^-$	$(Gluconate)^-$	$(Citrate)^{3-}$	$H_2PO_4^-$
Normal saline	0	154				154					
Soilta-T No. 1	2.6	90				70	20				
Soldem 1	2.6	90				70	20				
Actit Injection	M5	45	17		5	37		20			10
KN solution 3B	2.7	50	20			50	20				
Solitax-H	12.5	50	30	5	3	48	20				10
Soldem 3	2.7	50	20			50	20				
Solita-T No. 3	4.3	35	20			35	20				
Soldem 3A	4.3	35	20			35	20				
Solita-T No. 4	4.3	30				20	10				
Physio 140	1	140	4	3	2	115		25	3	6	
Solita Shimizu	4.3	130	4	3		109	28				
5% Glucose solution	5.0										

M: maltose.

NS, ISC, KN Solution 3B, Solita-T No. 1, Solita-T No. 3, and Solita-T No. 4 infusion solutions had a pH exceeding 8 after adding 20 ml of 7% sodium bicarbonate. The amount of 7% sodium bicarbonate needed to reach pH 7.4 depended on the specific infusion solution, while more 7% sodium bicarbonate was needed for larger amounts of infusion solution.

Table 2 shows the pH of 200 ml and 500 ml volumes of infusion solutions after adding 40 μg of PGE_1, titratable acidity of infusion solutions, and volumes of 7% sodium bicarbonate required to attain pH 7.4. The titratable acidity of infusion solutions was determined by measuring 0.1 N sodium hydroxide added until the pH of each infusion solution became 7.4. This titratable acidity was expressed as milliequivalents per liter of sodium hydroxide necessary for neutralization to pH 7.4.[7] Infusion solutions with low titratable acidity, such as NS, ISC, KN Solution 3B, Solita-T No. 1, Solita-T No. 3, and Solita-T No. 4, required small volumes of 7% sodium bicarbonate to reach pH 7.4. Adding 20 ml of 7% sodium bicarbonate to such a solution with low titratable acidity which contained 40 μg of PGE_1 resulted in a pH exceeding 8, as shown in Figs. 1 and 2. Infusion solutions with low titratable acidity required far less 7% sodium bicarbonate than 20 ml to attain pH 7.4, while infusion solutions with high titratable acidity, such as Actit Injection and Solitax-H required large volumes of 7% sodium bicarbonate to reach pH 7.4.

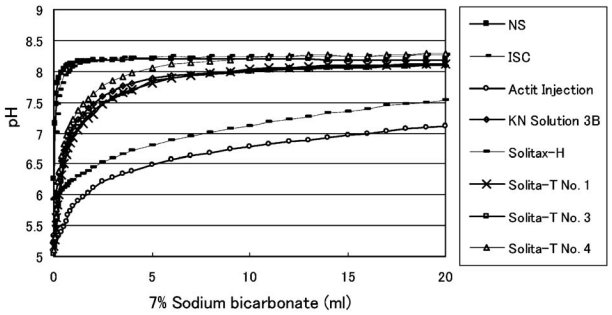

Fig. 1. Changes in pH after Adding 7% Sodium Bicarbonate to 200-ml Infusion Solutions Containing 40 μg of PGE_1

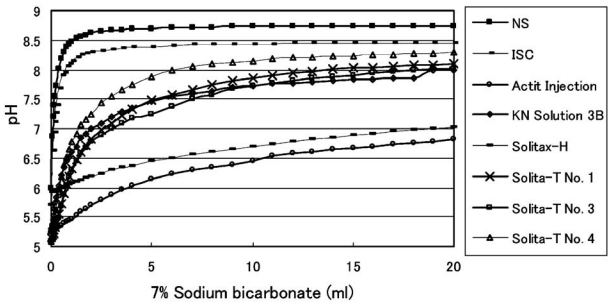

Fig. 2. Changes in pH after Adding 7% Sodium Bicarbonate to 500-ml Infusion Solutions Containing 40 μg of PGE_1

Stability of pH in Infusion Solutions Containing PGE_1 Figure 3 shows pH at 0, 2, 4, 6, 12, and 24 h after dissolving PGE_1 (40 μg) in 200 ml of infusion solutions including NS, ISC, Solita-T No. 1, Soldem 1, Soldem 3, Solita-T No. 3, Soldem 3A, Physio 140, Solita Shimizu, and 5% glucose solution. Figure 4 shows pH at 0, 2, 4, 6, 12, and 24 h with PGE_1 (40 μg) dissolved in 500 ml of infusion solution. The stability of pH with 40 μg of PGE_1 dissolved in the solution did not vary over time for either 200 ml or 500 ml solution volumes.

The results are summarized in Table 3. The pH of Solita Shimizu exceeded 6.5 with 40 μg of PGE_1. The pH of NS, Soldem 1, Soldem 3, Soldem 3A, or Phy-

Table 2. pH of Infusion Solutions after Adding 40 μg of PGE_1, Titratable Acidity of Infusion Solutions, and Volume of 7% Sodium Bicarbonate Required for the PGE_1 Solution to Reach pH 7.4

Infusion solution	pH of infusion solution with PGE_1 40 μg	Titratable acidity (mEq/l)	7% Sodium Bicarbonate (ml)	
			200 ml	500 ml
ISC	5.41	0.05	0.075	0.125
Solita-T No. 1	5.14	0.92	2.25	4.5
Actit Injection	5.1	9.87	27	49
KN solution 3B	5.44	0.55	1.3	4.5
Solitax-H	5.91	6.57	16.25	32.5
Solita-T No. 3	5.14	0.9	2.2	5
Solita-T No. 4	5.1	0.54	1.35	2.375

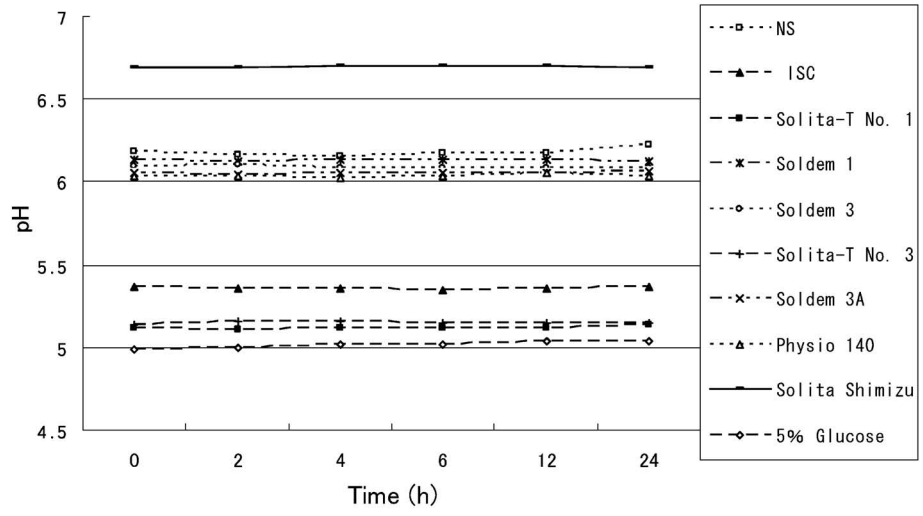

Fig. 3. Measured pH over Time in 200-ml Infusion Solutions Containing 40 μg of PGE_1

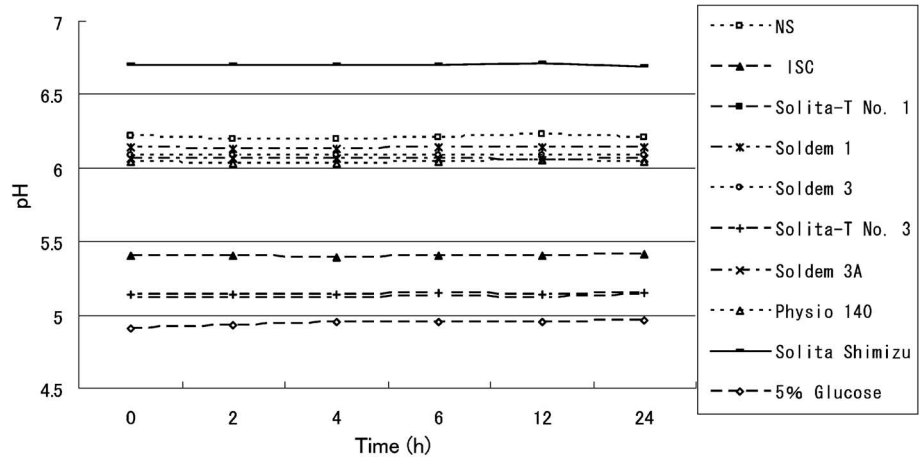

Fig. 4. Measured pH over Time in 500-ml Infusion Solutions Containing 40 μg of PGE_1

Table 3. pH of Solutions after Adding 40 μg of PGE_1

pH	Solution
$>$6.5	Solita Shimizu
6 to 6.5	NS, Soldem 1, Soldem 3, Soldem 3A, Physio 140
5 to 5.5	ISC, Solta-T No. 1, Solta-T No. 3
$<$5	5% Glucose solution

sio 140, each containing PGE_1, was 6.0 to 6.5. The pH of ISC, Solita-T No. 1, or Solita-T No. 3, each containing PGE_1, was 5.0 to 5.5. Even though NS and ISC both represented normal saline, the pH of NS containing PGE_1 differed from that of ISC. The pH for both 200 ml and 500 ml of 5% glucose solution containing PGE_1 was found to be less than 5.

DISCUSSION

The occurrence of phlebitis and venous pain has been attributed to the pH of infused fluid, osmotic pressure, titratable acidity, rate of administration, and drug reactions. *Standards for Infusion Therapy* published by the Royal College of Nursing (June 2007) state that peripheral vein infusion of a solution is permissible when the pH is 5 to 9, osmotic pressure is less than 500 mOsm/l, and known intimal damage is not present. According to the standards, the infusion solutions used in this study should pose no clinical problem after the addition of PGE_1 with respect to pH or osmotic pressure. Nonetheless, many patients have experienced side effects such as phlebitis and venous pain, which have proved to be related to an

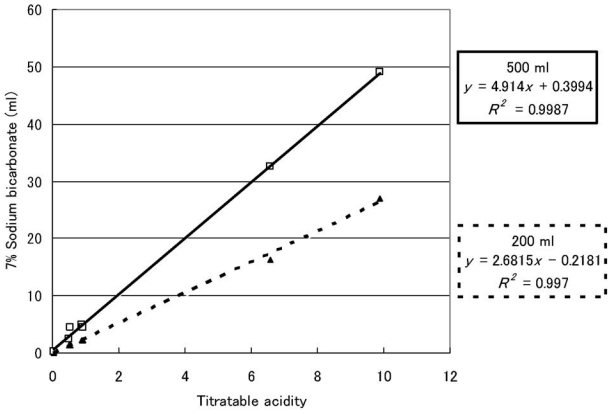

Fig. 5. Relationship between Titratable Acidity and Volume of Added 7% Sodium Bicarbonate Required to Attain pH 7.4

unphysiologically low solution pH.[5] Kuwahara *et al.*[8] reported that phlebitis was less likely when the solution of Plas-amino was neutralized to pH 5.93 when given to rabbits, and was nearly eliminated when the pH was raised further to 6.49. Thus the occurrence of phlebitis and venous pain may decrease when the pH of infusion solution is kept between 6.0 and 7.4. The pH of NS, Soldem 1, Soldem 3, Soldem 3A, Physio 140, or Solita Shimizu containing 40 μg of PGE_1 is greater than 6.0. When adverse effects such as phlebitis and venous pain develop with PGE_1, we consider adjusting the pH of the infusion solution to 7.4 with 7% sodium bicarbonate.[9] However, when 20 ml of 7% sodium bicarbonate is added to an infusion solution with a low titratable acidity, the pH of the solution rises to exceed 8. Table 2 shows the relationship between the titratable acidity of infusion solutions (quantity of 0.1 N of sodium hydroxide needed to neutralize to pH 7.4) and volume of 7% sodium bicarbonate required to reach pH 7.4. As shown in Fig. 5, the amount of additional sodium bicarbonate required correlated with the titratable acidity and volume of the infusion solution and could be determined graphically from a simple plot. The relationship between the titratable acidity (x) and volume of added 7% sodium bicarbonate (y) required to attain pH 7.4 can be calculated using the formulas:

$$y\,(\mathrm{ml}) = 2.6815x - 0.2181$$

for 200-ml solution volumes; and

$$y\,(\mathrm{ml}) = 4.914x + 0.3994$$

for 500-ml solution volumes.

The titratable acidity was clearly correlated with the volume of 7% sodium bicarbonate required to reach pH 7.4. This allowed us to estimate the amount of additional sodium bicarbonate graphically from a simple plot and facilitate the prevention of the phlebitis and venous pain associated with intravenous PGE_1.

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