A REVIEW of pH AND OSMOLARITY

Marc Stranz, PharmD
Infusion Services Omnicare, Inc
Covington, Kentucky

Eric S. Kastango, RPh, MBA, FASHP
Clinical IQ, LLC
Madison, New Jersey

Pharmacists have been extemporaneously compounding medications to meet patient needs for centuries. After the industrial revolution, many compounding functions that had been performed by pharmacists were undertaken by pharmaceutical manufacturers, and the pharmacist's role gradually became primarily that of dispensing commercial mass-produced medications to patients. During the 1970s and 1980s, some pharmacists complemented dispensing with patient counseling.[1]

The demand for extemporaneously prepared medications in oral or parenteral dosage forms has increased significantly. Historically, pharmacy as a profession has applied the principles of secundum artem to ensure that only high-quality preparations were compounded. However, those principles have not adequately provided the most robust evidence-based decision-making tools in the past.

The delivery of pharmaceutical care requires specialized knowledge about many patient-related and medication-related considerations such as pharmacology, vascular access devices and their placement, compounding considerations (osmolarity, pH, stability, particulate matter), delivery systems, and patient management.[2] This article addresses patient morbidity and mortality associated with the effect of osmolarity and pH on compounded liquids for parenteral administration. Strategies that minimize the effects of osmolarity and pH are also presented.

Vascular damage (phlebitis) caused by infusates of incorrect pH and osmolarity occurs frequently. The development of phlebitis, which increases the patient's risk of local catheter-related infection, can be caused by mechanical trauma from catheter insertion, catheter material, catheter dwell time or duration of use, particulate matter, and chemically mediated factors.[3]

pH and OSMOLARITY

pH

The pH scale is a measurement of the concentration of hydrogen ions (H^+) in a solution. The scale ranges from 0 to 14; 0 is the most acidic, 7 is neutral, and 14 is the most alkaline (ie, basic). It is a logarithmic scale based on the power of 10; a change of 1 pH unit equals a 10-fold change in the concentration of hydrogen ions. The pH of human blood is about 7.35. Any changes in pH (even those that seem insignificant), effect great changes in the hydrogen ion concentration. In Table 1,[4] examples of common household and medication acids and bases and their relative pH and hydrogen ion concentrations are listed.

Which pH values damage cells? The degree of cellular damage from either low or high pH is determined by the type of tissue exposed to the pH and the duration of exposure. Phenytoin sodium (Dilantin) applied topically does not produce the same cellular toxicity as it does when administered parenterally. *In vitro* experiments have demonstrated that solution pH values of 2.3 and 11 kill venous endothelium cells on contact. The nearer the pH value is to 7.4, the less the damage that occurs. Limited research data, however, pertain to the effects of less extreme pH conditions.

Titratable Acidity

Although pH is a measure of hydrogen ion content, titratable acidity is a measure of the reservoir of hydrogen ions within a solution. Phlebitis is more likely to be caused by a solution with a high titratable acidity and a lower pH. Venous endothelial cells at sites distal to the catheter tip are subject to cellular insult because more time is required for the hydrogen ion content in the infusate to be neutralized by the blood. Titratable acidity has not been well-studied to date and requires further investigation.

Table 1. Common Acidic and Basic Medications and Household Products: pH and Hydrogen Ion Concentrations.

	H^+	pH	Household Products	Medications[5]
Acid	10,000,000	0	Hydrochloric acid	
	1,000,000	1	Stomach acid	
	100,000	2	Lemon juice	
	10,000	3	Vinegar	Dopamine HCl
	1,000	4	Soda	
	100	5	Rainwater	Potassium chloride[a]
	10	6	Milk	
Neutral	1	7	Pure water	
Base	1/10	8	Egg whites	Furosemide
	1/100	9	Baking soda	
	1/1,000	10	Tums antacid	
	1/10,000	11	Ammonia	Ganciclovir sodium
	1/100,000	12	Mineral lime - $Ca(OH)_2$	Phenytoin sodium
	1/1,000,000	13	Drano	
	1/10,000,000	14	Sodium hydroxide	

H^+ = Concentration of hydrogen ions compared to that in pure water.
[a] Abbott Laboratories, Abbott Park, Illinois.

Osmolality

Osmosis occurs when, to produce equilibrium, a substance in solution crosses a membrane from an area of lower concentration to an area of higher concentration. The concentration of particles dissolved in solution expressed as osmoles of solute per kilogram of solvent is referred to as "osmolality." In human plasma, the concentration of dissolved particles is about 290 x 10^{-3} M; therefore, its osmolarity is 290 mOsm/L (285 - 310 mOsm/L). Water, for example, flows from an area of low osmolarity to an area of high osmolarity at a rate directly proportional to the difference (gradient) in osmolality until equilibrium is reached.

The osmotic pressure of a solution can be expressed as either osmolality or osmolarity. Osmolality refers to the number of milliosmoles per kilogram of solvent. This value can be calculated or determined experimentally by osmometry. Osmolarity, which is the number of milliosmoles per liter of solution, is widely used in clinical practice because it expresses concentration as a function of volume. Osmolarity cannot be measured experimentally but must be calculated from osmolality by means of a conversion factor.

Solutions containing the same concentration of particles are iso-osmotic (isotonic). 0.9% Sodium chloride solution (normal saline solution) is iso-osmotic with blood and the venous endothelium; the solution causes no movement of water into or out of endothelial cells. Cellular damage does not occur when endothelial cells contact an iso-osmotic solution.

Solutions with a lower osmolality (a lower concentration of dissolved particles) than 0.9% sodium chloride solution are considered hypotonic. 0.45% Sodium chloride solution and sterile water for injection are examples of hypotonic solutions. Infused fluid is drawn into venous endothelial cells and blood cells, which have a relatively high osmolality. When those cells absorb too much water, they rupture or undergo hemolysis. Hypotonic solutions such as 0.45% sodium chloride are used to replenish water deficits or to reduce the final osmolarity of certain drugs in solution.

Solutions with a higher osmolality (a higher concentration of dissolved particles) than that of normal saline are considered hypertonic. 5% Dextrose and 0.9% sodium chloride injection, any type of amino acid solution, and 50% dextrose injection are examples of hypertonic solutions. The intravenous administration of hypertonic solutions draws fluid from the endothelium and blood cells, which causes the cells to shrink. That vascular insult renders cells susceptible to further damage. The degree and immediacy of that damage are determined by the osmolarity of the infused solution. Potassium chloride solution (2 mEq/mL) has an approximate osmolarity of 4000 mOsm/L.

Current recommendations from the United States Pharmacopeia for the labeling of intravenous fluids produced by pharmaceutical manufacturers require that osmolarity be stated on the product package, but there are no formal requirements for the determination of solution osmolarity.[6] Osmolarity labeling requirements for pharmacy-prepared intravenous admixtures do not exist. Osmolarity data for admixtures can be obtained only from the literature or by calculation from published osmolality values. The formula used to determine drug-solution osmolarity calculations is not accurate and is best determined by direct measurement via osmometry.[2]

Table 2. Infusion Nursing Society Recommendations for Minimization or Prevention of Vascular Damage from Extremes in Infusate pH or Osmolarity.

Vessel	Blood Flow (mL/min)[8]	Osmolarity (mOsm/L)	Solution pH
Superior vena cava	2000	> 900	< 5 or > 9
Subclavian vein and/or proximal axillary vein	800	500 - 900	< 5 or > 9
Cephalic and basilic veins in the upper arms	40 - 95	< 500	5 - 9

INFUSION NURSING SOCIETY RECOMMENDATIONS

To minimize or prevent vascular damage from extreme infusate pH or osmolarity, the Infusion Nursing Society (INS) has published recommendations based on a number of factors, including the physiologic location of the venous access device. In Table 2,[7] those recommendations are presented.

METHODS of COMPENSATION

Buffering Capacity

As mentioned earlier, the normal range of the pH of blood is between 7.35 and 7.45. That range is necessary for the normal functioning of critical metabolic processes. A pH not within that range is physiologically stabilized by three primary mechanisms: the action of buffer systems, respiratory control, and renal control. Buffer systems use proteins, hemoglobin, and bicarbonate-phosphate mixtures. The carbonic acid-bicarbonate system of the body is a chemical buffer mechanism that uses a weak acid and conjugate base to maintain the desired pH range. When acidic or basic drugs are infused, the carbonic acid-bicarbonate system releases the appropriate weak acid or conjugate base to maintain a pH near 7.4. As the infusate leaves the catheter tip, the pH is neutralized by the carbonic acid-bicarbonate system. The time required for neutralization of the pH is a function of the strength of the acid or base and its titratable acidity. The respiratory and renal pH control systems of the body monitor and compensate for pH via a series of complex processes.

Laminar Flow

"Laminar flow" refers to the movement of air or fluid in layers and without fluctuation or turbulence. Pharmacists are familiar with the concept of laminar flow because they use specialized equipment to create aseptic working environments for the preparation of parenteral products. Laminar flow can be applied to the infusion of solutions into the bloodstream.

According to the principle of laminar flow, infusate leaving the catheter travels in a layer parallel to but separate from the surrounding blood flow. Neutralization occurs during the slow diffusion of blood at the contact surface between the laminar blood flow and the laminar flow of the infused solution. As the infusate slows to the rate of blood flow, the infusate and blood mingle distal to the catheter tip. At that point, venous endothelial cells are exposed to the irritating solution, especially in smaller veins in which the amount of blood flow cannot further minimize the local effects of the infusate.

Animal studies[9] have shown evidence of venous lumen damage distal to the catheter tip. That finding is supported by studies indicating that increasing the infusion rate of irritating solutions reduces the potential for the development of phlebitis; cephalosporins and other antibiotics are irritating to peripheral veins but can be administered in an intravenous "push" without producing an increased incidence of phlebitis.[10-12] Attempts have been made to use the ratio of the infusion rate to the blood flow rate to estimate the risk of phlebitis caused by irritating intravenously administered solutions. Because the blood and the infusate flow in a laminar manner, the neutralization process and achieving osmotic equilibrium may take longer than expected. If that method of determining the risk of phlebitis is used, the location of the catheter tip and blood flow in the infused area must be known.

CHEMICAL PHLEBITIS In VIVO

Animal Models

To date, the effects of pH and osmolarity have been studied most effectively in animal models. According to Kuwahara et al,[13] the effects of infusions of solutions at various pH values and infusion times were studied. When the effects of 6-hour infusions through peripheral vessels were compared, a solution with a pH of 4.5 resulted in a 100% incidence of severe phlebitic changes, a pH of 5.9 caused mild-to-moderate phlebitic changes in 50% of the animal subjects, a pH of 6.3 caused mild damage in 20% of those subjects, and a pH of 6.5 caused no significant damage. When the pH value was 6.5, extending the duration of the infusion did not produce phlebitis.

Other trials[14,15] have indicated that a solution with a pH of 3 to 11 did not induce phlebitic changes when drugs were administered over a few minutes. When the same acidic solution volume was infused over 5 hours, 1 hour, or 30 minutes, fewer inflammation-related changes were noted after the more rapid infusions. No trials have studied the effect of slowing the infusion of highly acidic or basic infusates to increase dilution.

Both pH and titratable acidity must be considered when the administration of peripheral parenteral nutrition is required.[16] Animal studies[16,17] indicate that the higher the titratable acidity of an infusate, the greater the proximal and distal phlebitic changes. When the principles of laminar flow were applied, tolerance to osmolarity in peripheral veins was demonstrated in animal models. When other factors were controlled, those studies indicated that the peripheral tolerance was directly related to the osmolarity and duration of the infusion. The faster the infusion of hypertonic infusates, the greater the vein tolerance, which was 820 mOsm/kg for 8-hour infusions, 690 mOsm/kg for 12-hour infusions, and 550 mOsm/kg for 24-hour infusions.

Human Models

Human tolerance of pH and osmolarity has not been as well researched (or understood) as it has been in animal models; however, human tolerance to pH and osmolarity is similar to that of animals. There is a direct relationship between the pH and osmolarity of an infusate and the development of phlebitis. The incidence of phlebitis increases as infusate pH and osmolarity increase, and it decreases according to the baseline pH and osmolarity of blood. The exact point at which osmolarity and pH become significant risk factors in humans is not known.

The outcomes of human studies of osmolarity-induced phlebitis have been inconsistent. Gazitua et al[18] classified three risk levels of phlebitis caused by infusate osmolarity. The lowest risk of phlebitis occurred when a solution osmolarity lower than 450 mOsm/L was used, a moderate risk occurred at 450 to 600 mOsm/L, and the highest risk occurred when the solution osmolarity exceeded 600

mOsm/L. That study provided evidence-based science used by the INS to define an osmolarity of 500 mOsm/L as the outer limit of peripheral vein tolerance. The ability to tolerate different levels of infusate pH and osmolarity varies significantly among patients.

Few human trials have been conducted to measure the effect of pH on peripheral veins. Some studies[18-21] indicate that neutralizing the pH of the infusate to 7 to 7.4 significantly reduces the incidence of phlebitis. To date, no trial of human patients has identified a pH range that corresponds to the potential for the development of phlebitis. The physiochemical properties of medication indicate that very few drug infusions are stable at pH 7. The accepted pH range of 5 to 9 for solutions infused peripherally represents clinically significant variances from the ideal pH of 7.4. However, factors such as blood flow, infusion rate, venous access device, catheter tip location, and variations in patient tolerance to the pH of the infusate influence the occurrence of pH-induced phlebitis in spite of the challenges posed by the pH value of final drug admixtures.

Exceptions to the Rules

Some exceptions to the rules of pH and osmolarity cannot be easily explained. Certain isotonic, pH-neutral infusates (eg, amphotericin B, cladribine, erythromycin, foscarnet, imipenem, meropenem, pamidronate, nafcillin, oxacillin, chemotherapeutic drugs) cause phlebitis, perhaps because they can produce a direct cellular insult to the endothelial cells.

Secundum Artem

During manufacturing, the pH of many medications is adjusted with either hydrochloric acid and/or sodium hydroxide to ensure drug stability and a long shelf life. The solubility of weakly acidic or basic medications is a direct function of solution pH, which controls both the portion of medication that is in an ionized form (eg, that is metabolically active) and the solubility of the nonionized form of the medication.[6]

Sodium salts (phenobarbital, phenytoin, methotrexate) are considered weak acids and must be formulated at a high pH to ensure solubility. If, during the preparation of a solution, the pH is lowered, the aqueous solubility of the medication may be exceeded and the potential for precipitation exists. Medications that are considered weak bases are similarly affected; their formulation must result in a low pH to ensure solubility.

The effect of pH on solubility is best illustrated in parenteral nutrition solutions in which calcium salts (calcium gluconate or calcium chloride) interact with phosphates. The lower the pH of the final solution, the more stable the formulation, because the calcium and phosphate ions remain ionized. As the pH increases, the ions become less ionized, and precipitation can occur. Ready-to-use formulations of medications are not always isoosmotic or of neutral pH. Stability is the principle concern with those formulations. Premade frozen medications (eg, certain antibiotics) are formulated with sterile water or dextrose injection to produce better solution tonicity.

Diluting medications that are extremely acidic (vancomycin hydrochloride) or extremely alkaline (phenytoin sodium) in greater volumes of fluid to affect solution pH is not an effective method of mediating pH-induced effects. A solution that acts as a buffer must affect the titratable acidity of a medication by contributing either carbonic acid or hydroxide. Neither 5% dextrose injection nor 0.9% sodium chloride injection has an inherent buffering capacity; therefore the pH of the final infusate containing those substances is determined by the pH of the medication and not the base solution. Final osmolarity can be altered by using other base solutions such as lactated Ringer's solution, 5% dextrose injection, dextrose 5% in lactated Ringer's injection (D5LR), or 0.45% sodium chloride injection.

The osmolarity of most parenteral medication solutions (antibiotics, antineoplastics, etc) is usually less than 400

mOsm/L. Parenteral nutrition solutions usually have a much higher final osmolarity because of the number of cations and anions in solution.

CONCLUSION

The osmolarity of drug solutions should not be the primary consideration in the prevention of infusion-related phlebitis. Many approaches can be used to ensure that the osmolarity of an infusate (with the exception of parenteral nutrition solutions) remains below the recommended INS guideline of 500 mOsm/L.

According to data from anecdotal clinical practice and extensive studies of animal and human subjects, pH is the most significant cause of phlebitis. Current INS standards state that an infusate pH of 5 to 9 can be tolerated by peripheral veins. Animal and human data also suggest that variance from a pH of 7.4 causes damage to venous endothelium tissue. Other unknown mitigating factors prevent phlebitis from occurring in a large percentage of patients who receive infusions.

The best method of preventing patient morbidity and mortality caused by infusion therapy is to consider all primary and secondary factors that cause phlebitis, such as the dilution of the medication, the composition of the base infusate solution, the rate of infusion, and the type, size, material, and location of the venous access device and tip. Additional research on the principle of laminar flow must be conducted to identify methods (such as the intravenous push of antibiotics) of administering highly acidic or highly alkaline infusates.

References

1. RidgeRx Compounding. Available at: http://www.RidgeRx.com/story.ntml. Accessed January 12, 2002.
2. Kastango ES, Hadaway L. New perspectives on vancomycin use in home care. Part 1. *IJPC* 2001;6:465-469.
3. Pearson ML. Guideline for prevention of intravascular device-related infection. US Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, Georgia. Available online: http://www.cdc.gov/ncidod/hip/iv/iv.htm. 1999. Accessed January 12, 2002.
4. Carpi A. Acids and bases: An introduction. Available at: http://www.visionlearning.com/library/science/chemistry-2/CHE2.2-acid_base.htm. 2000.
5. Trissel LA. *Handbook of Injectable Drugs*. 11th ed. Bethesda, MD:American Society of Health-System Pharmacists; 2001.
6. CmcIssues: Consulting services for the pharmaceutical industry Website. Available online: http://www.cmcissues.com/Methods/osmolarity.htm. Accessed on January 10, 2002.
7. Intravenous Nurses Society. Intravenous nursing standards of practice. *J Intraven Nurs* 2000;23(suppl):S37-S38.
8. Kokotis K. Preventing chemical phlebitis. Nursing 98. Available at: http://www.springnet.com/ce/p118a.htm. Accessed May 28, 2001.
9. Kuwahara T, Asanami S, Tamura T, et al. Effects of pH and osmolarity on phlebitic potential of infusion solutions for peripheral nutrition. *J Toxicol Sci* 1998;23:77-85.
10. Poole SM, Nowobilski-Vasilios A, Free F. Intravenous push medications in the home. *J Intraven Nurs* 1999;22:209-215.
11. Nowobilski-Vasilios A, Poole SM. Development and preliminary outcomes of a program for administering antimicrobials by IV push in home care. *Am J Health Syst Pharm* 1999;56:76.
12. Vickery TR, Hatheway JG, Edgar SP, et al. Concentrated vancomycin and administration via central venous catheters in the alternate-care setting. Poster presented at: ASHP Midyear Clinical Meeting; 1990; Las Vegas, NV.
13. Kuwahara T, Asanami S, Kawauchi Y, et al. Experimental infusion phlebitis: Tolerance pH of peripheral veins. *J Toxicol Sci* 1999;24:113-121.
14. Simamora P, Pinsuwan S, Alvarez JM, et al. Effect of pH on injection phlebitis. *J Pharm Sci* 1995;84:520-522.
15. Hessov I, Bojsen-Mooller M. Experimental infusion thrombophlebitis. Importance of the infusion rate. *Eur J Intensive Care Med* 1976;2:103-105.
16. Kuwahara T, Asanamia T, Kubo S. Experimental infusion phlebitis: Importance of titratable acidity on phlebitic potential of infusion solution. *Clin Nutr* 1996;15:129-132.
17. Kuwahara T, Asanamia T, Kubo S. Experimental infusion phlebitis: Tolerance osmolarity of peripheral venous endothelial cells. *Nutrition* 1998; 14: 496-501.
18. Gazitua R, Wilson K, Bistrian BR, et al. Factors determining peripheral vein tolerance to amino acid infusions. *Arch Surg* 1979;114:897-900.
19. Fonkalsrud E, Pederson BM, Murphy J, et al. Reduction of infusion thrombophlebitis with buffered glucose solutions. *Surgery* 1968;63:280-284.
20. Eremin O, Marshall V. Complications of intravenous therapy: Reduction by buffering of intravenous fluid preparation. *Med J Aust* 1977;2:528-531.
21. Fujita M, Hatori N, Shimizu M, et al. Neutralization of prostaglandin E_1 intravenous solution reduces infusion phlebitis. *Angiology* 2000;51:719-723.

Address correspondence to: Marc Stranz, PharmD, 100 E. River Center Boulevard, Suite 1700, Covington, KY 41011. E-mail: marc.stranz@omnicare.com.