

# The Implications of Osmolality, Osmolarity and pH in Infusion Therapy

Marc Stranz, PharmD

---

## Outline

Points to be addressed include the INS parameters for pH and osmolality tolerance, the definition of pH and osmolality, the pH and osmolality of common drugs, the feasibility of controlling pH and osmolality, and changing the pharmacists' perspective on pH and osmolality.

The scope of this presentation is limited to the pharmaceutical aspects of controlling the pH and osmolality of infusates. Damage induced by ions (pH) and osmolality rarely occurs as an isolated event. Rather it is part of an orchestra of insults to the vein during infusion therapy. The singular impact of either pH or osmolality should be known, but the practitioner must consider the synergistic effect of all factors. There are many confounding circumstances in the etiology of phlebitis, including mechanical, material, duration, infection, particulate, and chemical factors. Others have addressed these topics.

## INS

To prevent or reduce vascular complications, INS standards recommend that vascular access be determined by the pH and osmolality of the infusion. Infusions with a pH outside the range of 5 to 9 and/or an osmolality greater than 500 should be administered through an access device that delivers the infusate into a blood vessel with a high rate of blood flow. Those vessels include the subclavian and superior vena cava.

Histopathological changes in the vein caused by chemical irritation include loss of venous endothelial cells, inflammatory cell infiltration, edema, and thrombus. The damage can be proximal and distal to the catheter tip.

## Review of pH and osmolality

**Osmolality.** If a semi-permeable membrane like a cell wall is used to separate solutions of different solute concentrations, a phenomenon known as osmosis occurs in which water crosses the membrane from lower to higher concentration to establish concentration equilibrium. The concentration of particles dissolved in each solution is referred to as its osmolality. In human plasma the concentration of dissolved particles is about  $290 \times 10^{-3} \text{ M}$ , so its osmolality is 290 mOsm/L (285 - 310 mOsm/L). Water flows from a low osmolality to a high osmolality at a rate directly proportional to the difference (gradient) in osmolality until it reaches equilibrium. The phenomenon of water osmotic flow is well known, but the reasons that osmosis occurs are poorly understood.

Solutions containing the same concentration of particles are called iso-osmotic. The term isotonic is used interchangeably with the term iso-osmotic. Normal Saline is iso-osmotic/isotonic with blood and the venous endothelium, meaning there is no net gain or loss of water by the endothelial cells, or other change in those cells, when in contact with the solution. Solutions containing fewer particles (lower osmolality) than Normal Saline are called hypotonic ( $\frac{1}{2}$  Normal Saline) and solutions containing more particles (higher osmolality) are called hypertonic (Dextrose 5% & Normal Saline). Intravenous administration of hypotonic solutions results in fluid moving into the more concentrated venous endothelial cells and blood cells. When the cells draw in too much water, they rupture. Hypertonic solutions draw fluid from the endothelium and blood cells, causing the cells to shrink, making them susceptible to further damage.

Osmotic pressure of a solution can be expressed as either osmolality or osmolarity. Osmolality is defined as the number of milliosmoles per kilogram of solvent. This value can be calculated using sodium chloride equivalents or determined experimentally by osmometry. Osmolarity is defined as the number of milliosmoles per liter of solution. This term has gained wide acceptance in clinical practice because it expresses concentration as a function of volume. Osmolarity cannot be measured experimentally but must be calculated from osmolality determinations using a conversion factor.

Current USP recommendations for labeling of intravenous fluids require that osmolarity be stated on the package, but there is no such requirement for extemporaneously prepared intravenous admixtures.

---

# The Implications of Osmolality, Osmolarity and pH in Infusion Therapy

Marc Stranz, PharmD

Osmolarity data for admixtures can be obtained only if they appear in the literature or are calculated from published osmolality values.

For those who need to know:

Osmolality =  $[\sum(C_i E_i) \times 0.58/1.86] \times 1000$  where C = grams of solute per 100ml of solution, E = the sodium chloride equivalent, and  $\sum(C_i E_i)$  = the sum of the products of (C X E) for each solute in the solution. When the sodium chloride equivalents are unknown, the following equation is used to determine a value for E:  $E = 17 \times (L_{iso}/MW)$  where  $L_{iso}$  is a value that takes into account the nonideal behavior of ionic solution and depends on the nature of the solute and MW is molecular weight. An  $L_{iso}$  value of 4.3 is used for disodium salts and a value of 3.4 for all other drugs. Sodium chloride equivalent values for many drugs are available from reference sources.

$$\text{Osmolarity (mOsmol/liter)} = \frac{\text{wt. Of substance (g/liter)}}{\text{Molecular weight}} \times \text{number of species (ions)} \times 1000$$

As the concentration of the solute increases, interactions among solute particles increases and actual osmolar values decrease when compared to ideal (calculated) values. Deviation from calculated values is slight in dilute solutions, but increases as concentration increases. For example, the calculated osmolarity of 0.9% sodium chloride solution is  $9/58.4 \times 2 \times 1000 = 308$  mOsmol/liter. The measured value (osmometer) is about 286 mOsmol/liter. The theoretical value of some complex admixtures cannot be calculated but must be measured. Molecular weight can be obtained from most drug package inserts.

**pH.** The pH scale is a measurement scale used to quantify the concentration of hydrogen ions,  $H^+$ , in a solution. The scale runs from 0 to 14, 0 being the most acidic, 7 neutral, and 14 being the most alkaline or basic. It is a logarithmic scale, based on the power of 10, so that 1 pH unit change equals a 10-fold change in  $H^+$  ion concentration. Human blood pH is about 7.35. What is critical to understand is that small changes in pH can signify large changes in  $H^+$  ion concentration. Consider that a change from pH 7.35 to pH 7.15 is a 2% drop in pH but equals a 24% change in  $H^+$  ion concentration.

These are common examples of acids and bases:

	$[H^+]$	pH	Example
Acids	$1 \times 10^0$	<b>0</b>	HCl
	$1 \times 10^{-1}$	<b>1</b>	Stomach acid
	$1 \times 10^{-2}$	<b>2</b>	Lemon juice
	$1 \times 10^{-3}$	<b>3</b>	Vinegar
	$1 \times 10^{-4}$	<b>4</b>	Soda
	$1 \times 10^{-5}$	<b>5</b>	Rainwater
	$1 \times 10^{-6}$	<b>6</b>	Milk
	$1 \times 10^{-7}$	<b>7</b>	Pure water
Neutral			
Bases	$1 \times 10^{-8}$	<b>8</b>	Egg whites
	$1 \times 10^{-9}$	<b>9</b>	Baking Soda
	$1 \times 10^{-10}$	<b>10</b>	Tums <sup>®</sup> antacid
	$1 \times 10^{-11}$	<b>11</b>	Ammonia
	$1 \times 10^{-12}$	<b>12</b>	Mineral Lime - $Ca(OH)_2$
	$1 \times 10^{-13}$	<b>13</b>	Drano <sup>®</sup>
	$1 \times 10^{-14}$	<b>14</b>	NaOH

**Titrateable acidity** is a quality of some infusion solution that increase the phlebotic potential. Titrateable acidity is essentially a measure of the reservoir of  $H^+$  ion in the solution. An infusate with low titrateable acidity is immediately neutralized by very little blood. A high titrateable acidity means that as soon as the blood eliminates the  $H^+$  ions, they are replaced by more  $H^+$  from the infusate. A solution with a high

# The Implications of Osmolality, Osmolarity and pH in Infusion Therapy

Marc Stranz, PharmD

---

titratable acidity is likely to irritate venous endothelial cells over a longer distance from the catheter tip. Significant titratable acidity is common to parenteral nutrition, but is also found in some drug formulations.

**What pH damages cells?** Some pH examples appear not to be injurious, such as vinegar, but the closest equivalency is not vinegar on the skin, but vinegar in the eye. So what pH damages the venous endothelium? pH's of 2.3 and 11 have been shown to kill these cells on contact. There is little information on the effect of less extreme pH, other than the knowledge that as the pH moderates, the cells survive for a longer time period. One trial showed that cell cultures at pH 4 survived for 10 minutes.

## Mitigating factors

**Buffering systems.** When the blood is exposed to a pH outside the normal range, it uses its buffers to stabilize the pH. A buffer is a mixture of two compounds that protect the pH of a solution from undergoing large changes when small amounts of acid or base are added. The bicarbonate system is a chemical buffer that keeps blood pH near 7.35. When acidic or basic drugs are infused, the bicarbonate system works to return the pH to 7.35. As the infusate leave the catheter tip, the bicarbonate system begins to neutralize the pH. The time it takes to neutralize the pH is a function of the strength of the acid or base and the titratable acidity.

**Laminar flow.** Some have tried to estimate the phlebotic potential of irritating solutions using the diluting ratio of the infusion rate and the blood flow rate. Because the blood and the infusate flow a laminar manner, the neutralization process as well as attaining osmotic equilibrium may take longer than expected. As the infusate leaves the catheter, it travels in a layer parallel to but separate from the surrounding blood flow (laminar flow). A solution infused into a vein undergoes neutralization by slow diffusion of blood at the contact surface between the laminar blood flow and the laminar flow of the infused solution. Thus, the venous endothelial cells downstream from the catheter tip are exposed to the irritating solution. As the infusate slows to the rate of blood flow, the two mingle distally to the catheter tip. Animal studies show a predominance of damage on the lower part of the venous lumen. This concept may support the finding that increasing the infusion rate of irritating solutions reduces their phlebotic potential.

## Intrinsically toxic drugs

Certain infusates produce phlebotic changes despite being isotonic and pH neutral. This appears to be the result of an immediate toxic effect on the endothelial cells. The manifestation is a sterile inflammation that increases expression of factors that cause granulocyte adhesion to the endothelium (thrombosis). The changes are related to the drug and the drug concentration. Few drugs have been tested, but among those, macrolides (erythromycin) produce the greatest changes and penicillins the least. The list of drugs that associated with these changes include amphotericin B, cladribine, erythromycin, foscarnet, imipenem, meropenem, pamidronate, nafcillin, oxacillin, and many chemotherapy drugs.

## Chemical Phlebitis in vivo

Animal data best define the traumatic effect of pH and osmolality, as these parameters can be isolated. Comparing six hour infusions through peripheral vessels, a solution at a pH of 4.5 resulted in a 100% incidence of severe phlebotic changes, at a pH of 5.9 caused mild to moderate phlebotic changes in 50%, at a pH of 6.3 caused mild damage in 20%, and at a pH of 6.5 caused no significant damage<sup>1</sup>. This trial also showed that when the pH was 6.5, extending the duration of the infusion did not produce phlebitis. Another trial showed that solution pH ranging from 3 to 11 did not induce phlebotic changes when the drugs were given over a few minutes<sup>2</sup>. When the same acidic solution volume was infused over 5 hours, 1 hour, or 30 minutes, the inflammatory changes were less after the more rapid infusions<sup>3</sup>. No trials have studied the effect of slowing the infusion of highly acidic or basic infusates to increase dilution.

When considering peripheral parenteral nutrition, not only the pH but the titratable acidity (acid reservoir) must be considered<sup>4</sup>. Animal data shows that the higher the titratable acidity, the greater the proximal and distal phlebotic changes.

---

# The Implications of Osmolality, Osmolarity and pH in Infusion Therapy

Marc Stranz, PharmD

---

Tolerance osmolarity of peripheral vessels has also been demonstrated in animals. Controlling for other factors, the peripheral tolerance was directly related to the osmolarity and the duration of the infusion. The faster the infusion of hypertonic infusates, the greater the vein tolerance. Tolerance levels were 820 mOsm/kg for 8 hours, 690 mOsm/kg for 12 hours, and 550 mOsm/kg for 24 hours<sup>5</sup>.

## Phlebitis in Humans

Human tolerance of pH and osmolarity will differ from that of animals, but the relationships remain. The incidence of phlebitis increases as infusate pH and osmolarity differs from that of the blood. The exact point at which osmolarity and pH become a liability in humans is unknown because of the variables involved in that determination. Those variables include not only the factors known to cause phlebitis, but also the determination of solution osmolarity.

Human studies of osmolarity-induced phlebitis have arrived at different conclusions, but the most often cited reference found the lowest risk of phlebitis occurred with solution osmolalities under 450 mOsm/L, moderate risk at 450 to 600 mOsm/L and the highest risk over 600 mOsm/L<sup>6</sup>. This was key research in establishing 500 mOsm/L as the outer limit of peripheral vein tolerance. There is significant interpatient variability in results of these trials.

Human trials measuring the impact of pH on peripheral veins found that neutralizing the pH to 7 - 7.4 significantly reduced the incidence of phlebitis<sup>7,8,9</sup>. There are no human trials that control for the phlebitic potential of a range of pH values. There are ophthalmic trials demonstrating that the pH range necessary to prevent corneal damage is 6.5 to 8.5. Unfortunately, few drug infusions are stable at pH 7. The accepted range of 5 to 9 for peripheral veins represents clinically significant variances from ideal pH. However, factors such as blood flow, the infusion rate, and patient variability influence pH-induced phlebitis, permitting a more encompassing range of final drug admixture pH values.

## Typical pH and osmolarity profile

When plotted by pH and osmolarity, the chart of common infusion drugs shows that most drugs fall within an acceptable osmolarity. Most drugs also fall within the pH range of 5 to 9. There are exceptions to both and those drugs are listed. The list also noted those drugs listed as "phlebitic" in a search of a large drug database (Drugdex<sup>10</sup>).

## Modifying pH and osmolarity

Osmolarity is not the primary cause of infusion phlebitis. The osmolarity of most infusions other than parenteral nutrition is less than 400 mOsm/kg and few are above 500 mOsm/kg (see Chart). Products can be compounded in diluents to reduce osmolarity, such as sterile water or ½NS. Ready-to-Use doses have been created to be isotonic when possible. Frozen antibiotics use sterile water or dextrose to create an isotonic pH because dextrose has a lower tonicity than normal saline. Furthermore, the dextrose is titrated to the desired osmolarity instead of using D5W (range of 0.6% to 5%). Ready-to-Use drugs are popular because they save labor and reduce waste.

The pH profile of a drug will determine the pH at which the product is formulated. This usually correlates to the pH of maximum stability, but can be a pH to enhance solubility. Significant variance from the ideal pH can lead to drug decomposition or precipitation. Ready-to-Use products are not neutral because optimum drug stability is usually found at the extremes of pH. Drug manufacturers all stated that their products are as close to physiologic norms as the pharmaceutical parameters permit.

Dextrose solutions are acidic because dextrose decomposition increases as the pH rises. Saline solutions are stable at a neutral pH, but are made acidic to enhance drug additive stability. The degree of saline acidity differs by country, with the US establishing a pH of 5 and Japan setting it at 6.

# The Implications of Osmolality, Osmolarity and pH in Infusion Therapy

Marc Stranz, PharmD

---

Parenteral nutrition solutions are acidic to enhance electrolyte solubility. For example, calcium phosphate precipitation increases as pH increases. Neutralization makes the formulation highly unstable.

Co-infusion of drugs with running hydration solutions will reduce the osmolarity of those solution. However, the pH of the final dilution was determined by the pH of the drug, not the hydration solution<sup>11</sup>.

One can increase the pH of drugs if necessary by changing the diluent. A drug with a pH of 4.7 in either NS or D5W would likely have a pH of 4.9 in D5RL, a pH of 5.0 in D5Plasmalyte 56, and a pH of 5.5 in Sodium Lactate. That type of drug compounding requires significant changes to routine pharmacy dispensing procedures and may reduce drug stability.

The less stable a drug solution is, the more frequently it must be compounded and the greater the waste if the product is not used. Those costs and risks might be greater than those associated with placing central lines for drug administration.

## Summary

Osmolality of drug solutions is not the primary concern when considering the overall causes of peripheral phlebitis. There are many options available to keep infusate osmolality below 500 mOsmol/L, excepting peripheral parenteral nutrition.

pH is and will remain a significant cause of phlebitis in peripheral veins. One might call it **pHlebitis**. INS standards suggest a range of pH 5 to 9 as peripherally tolerable. Animal and human data suggest that lesser variance from a pH of 7.4 causes damage, but the mitigating effect of short duration infusions has not been determined.

Furthermore, one cannot ignore the influence of cannula material, cannula size, vein size, and vein site upon the effect of pH and osmolarity.

Pharmacists use charts to decide on dilution, stability, and infusion rates. The addition of pH and osmolarity to these charts will assist in identifying candidates for central catheters.

---

<sup>1</sup> Kuwahara T, Asanami S, Kawauchi Y, Kubo S. Experimental infusion phlebitis: tolerance pH of peripheral veins. *J Toxicol Sci* 1999; 24: 113-121

<sup>2</sup> Simamora P, Pinsuwan S, Alvarez JM, Myrdal PB, Yalkowsky SH. Effect of pH on injection phlebitis. *J Pharm Sci* 1995;84:520-522

<sup>3</sup> Hessov i, Bojsen-Mooller M. Experimental infusion thrombophlebitis. Importance of the infusion rate. *Eur J Intensive Care Med* 1976;2:103-105

<sup>4</sup> 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

<sup>5</sup> Kuwahara T, Asanamia T, Kubo S. Experimental infusion phlebitis: tolerance osmolarity of peripheral venous endothelial cells. *Nutrition* 1998; 14: 496-501

<sup>6</sup> Gazitua R, Wilson K, Bistran BR, Blackburn GL. Factors determining peripheral vein tolerance to amino acid infusions. *Arch Surg* 1979; 114: 897-900

<sup>7</sup> Fonkalsrud E, Pederson BM, Murphy J, Beckerman JH. Reduction of infusion thrombophlebitis with buffered glucose solutions. *Surgery* 1968; 63:280-284

<sup>8</sup> Eremin O, Marshall V. Complications of intravenous therapy: reduction by buffering of intravenous fluid preparation. *Med J Aust* 1977; 2: 528-531.

<sup>9</sup> Fujita M, Hatori N, Shimizu M, Yoshizu H et al. Neutralization of prostaglandin E1 intravenous solution reduces infusion phlebitis. *Angiology* 2000; 51:719-723

<sup>10</sup> Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Englewood, Colorado 2001

<sup>11</sup> Leff RD, Roberts RJ. Effects of intravenous fluid and drug solution coadministration on final-infusate osmolality, specific gravity, and pH. *AHJP* 1982; 39:468-471

---